HIV and the Brain

New Challenges in the Modern Era

Edited by

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Ned Charlton Sacktor, MD
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Humana Press

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Series Editor's Introduction

It is now more than a quarter century since the appearance of the first reported cases of the acquired immunodeficiency syndrome (AIDS). Although successful treatments with highly active antiretroviral therapies have made a major impact on survival, there still remains no vaccine for prevention and the available therapies do not cure the disease. As a result, AIDS has been transformed into a chronic, lifelong disease which requires continuous antiretroviral drug treatment together with ongoing treatment of the associated systemic medical complications. It appears that as survival improves, the prevalence of chronic central nervous system involvement may be increasing. As pointed out by the editors of this volume, this shift in emphasis requires further examination of how AIDS affects the brain in terms of cognitive function, neuropsychiatric manifestations, activities of daily living, and quality of life. They also go on to ask the interesting question of how AIDS involvement of the brain interacts with normal aging.

In *HIV and the Brain*, Drs. Paul, Sacktor, Valcour, and Tashima have assembled an impressive international team of experts to summarize the current state of knowledge concerning brain function in AIDS. Early chapters review epidemiology, pathophysiology, neuropathology, neuroimaging, and HIV genetics followed by a series of chapters concerning the neuropsychological, behavioral, and neuropsychiatric aspects of the disease. Finally, several chapters are devoted to examining the interaction of the aging brain on the expression of AIDS-related cognitive impairment. This volume is largely directed to a clinical audience with the hope of advancing multidisciplinary translational research that may serve to increase the understanding of how HIV affects the brain. The sobering statement by the editors that AIDS may be the most common cause of dementia among people under age 40 should lend impetus to the importance of more effectively dealing with this most dreaded complication of the disease.

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Preface

The history of human immunodeficiency virus (HIV) is very familiar to clinicians and researchers invested in this field, and a number of excellent texts have been published that provide contemporary summaries of the disease. This remains true in terms of the impact of the virus on the brain, which is an area of focus that has been appreciated since the early period of the HIV epidemic. Based on this, one may ask why yet another book is needed that specifically focuses on HIV and the brain. Below we answer this question and in the process establish the rationale, purpose, and scope of this important and timely contribution to the field.

Although treatment of HIV with highly active antiretroviral therapy (HAART) has become standard in the developed world, and more common in the developing countries, no current therapies "cure" HIV. This has resulted in HIV transitioning from a time-limited, fatal disease to a chronic condition that requires constant medical intervention. As such, whereas in the past clinical care providers and the scientific community may have largely focused on efforts to prevent mortality prior to the availability of HAART, there is now a greater focus on addressing factors that negatively impact overall quality of life among individuals infected with HIV who are surviving the disease in the context of chronic treatment. This paradigm shift has brought brain function associated with HIV into the clinical forefront because the impact of the virus on the brain is directly related to cognitive capacity, the expression of neuropsychiatric symptoms, independence in activities of daily living (including medication adherence), and ultimately patients' perceived ratings of quality of life.

In addition to the general recognition noted above that brain function is now an important aspect of both HIV-related clinical care and research, new areas of emphasis have emerged in the modern era of the HIV pandemic that warrant an update on HIV and the brain. In part, these changes reflect outcomes associated with a population of patients who are living longer, such as the impact of HIV on the brain in the context of chronic, long-term treatment with HAART, as well as the potential synergistic effects of HIV and advanced age on cognitive outcomes. The HIV population is aging, in part due to the longer survival times associated with treatment and there is concern that HIV, like many other medical factors, may interact with the aging process to increase cognitive burden among patients. Finally, a focus on international studies of brain dysfunction in the context of HIV has

emerged within the last decade, and this work may offer important insights into the neuropathogenesis of brain impairment associated with the virus. HIV includes multiple genetic strains (clades), and reports suggest potential differences in biological properties and neurovirulence across these clades. Answering these issues is complicated by the global geographic distribution of the clade subtypes, and the inherent need to conduct cross-cultural studies of neuropsychological function. Several chapters in this book review this literature and provide guidance and insight for future studies.

The purpose of this edited volume is to summarize the extant knowledge of brain function in the context of chronic treatment, interactions between age and HIV on the brain, and international studies of brain involvement with an emphasis on clade diversity. Scientific authorities in each of the three areas have provided comprehensive and insightful reviews of the literature. Each chapter is written with a clinical audience in mind, and while the science is of sufficient rigor to serve as an important resource for basic scientists, a major goal of this book is to present the science in a manner that is ultimately useful to both bench scientists as well as clinical researchers and clinical-care providers. Ideally, a book that is attractive to these audiences will facilitate the development of future transdisciplinary and translational studies to further develop our understanding of HIV and the brain. Given current estimates that HIV may be the most common cause of dementia worldwide among individuals under the age of 40, the research reviewed and guidelines proposed within this book are both timely and important in a global and international context.

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Neurocognitive Changes in AIDS: Evolution of Treatment of HIV Infection

Erna Milunka Kojic and Charles C.J. Carpenter

The acquired immunodeficiency syndrome (AIDS) was first identified as a distinct clinical entity in June 1981 when the CDC reported the occurrence of five cases of *Pneumocystis pneumonia* (PCP), accompanied by severe wasting, in young men who had sex with men (MSMs) in Los Angeles (1). This was quickly followed by reports of several cases of Kaposi's sarcoma, also associated with severe wasting, in 25 young MSMs in New York City and California (2). Of these cases, six developed pneumonia (confirmed in four cases as PCP), one had central nervous system (CNS) toxoplasmosis, and another had cryptococcal meningitis and extensive mucosal candidiasis. Since past experience with both *Pneumocystis pneumonia* and Kaposi's sarcoma in young individuals was almost entirely limited to persons with severe immunodeficiency, these observations suggested that immunodeficiency, of uncertain origin, provided the background for development of these usually fatal illnesses in previously healthy young men. Following the initial reports from Los Angeles and New York City, similar observations were reported in the MSM community in San Francisco, and extensive investigations were carried out to attempt to determine the basis for the immunodeficiency in these individuals.

Over the next 12 months, many additional cases of PCP pneumonia, Kaposi's sarcoma, and cryptococcal meningitis were identified in young MSMs, especially in major US cities on the East and West coasts. In most cases, the individuals had no prior indication of immunodeficiency, which provided the basis for nomenclature of AIDS that was applied to this syndrome by the CDC in 1982.

In September 1982, three men with hemophilia were observed to develop severe PCP, and immunological studies were similar to those in the MSM population with AIDS (3). Each of these men had received infusions of exogenous Factor VIII derived from plasma pools collected from up to 1,000 donors. These collective

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observations in MSM populations and in hemophiliacs suggested that the severe underlying insufficiency was caused by an infectious agent, which was transmitted both sexually and parenterally in a manner similar to that of the hepatitis B virus. The subsequent recognition of AIDS occurrence in both male and female intravenous drug users (13% of reported cases of AIDS by September 1982) added further credence to the concept that an infectious agent, most likely a virus, was responsible for the rapidly expanding epidemic of AIDS. The death in late 1982, from an AIDS-like illness, of a 20-month-old child who had received multiple blood transfusions, appeared to confirm transmission of an infectious agent by blood. Experience in Western Europe and Australia demonstrated that AIDS was also spreading, largely in the same population groups in which it had been recognized in the United States.

In late 1983, a viral agent, initially called human T lymphocyte virus III, was identified by Dr. Luc Montagner (4). This virus, now called HIV-1, was confirmed as the etiologic agent of AIDS by Dr. Robert Gallo in 1984 (5). These two investigators and their colleagues were independently successful in developing an enzyme-linked immunosorbent assay (ELISA), which could detect antibodies in persons infected by HIV-1. Application of this assay made it possible to identify individuals at an earlier, preclinical, state of HIV infection. Further studies of the commercial test (ELISA), in large numbers of "at-risk" individuals (intravenous drug users and MSMs) in 1985, indicated that the majority of persons who had been infected by the HIV virus were not yet symptomatic. Subsequent cohort observations, notably the Multicenter AIDS Cohort Study (MACS) initiated in 1984, have indicated that the average individual who acquires HIV infection remains asymptomatic, but at risk of transmitting the virus by either sexual or intravenous infection route, for an average of 9–10 years before developing distinctive infections or neoplasms associated with immunodeficiency.

With the development of the diagnostic test, it became clear that the HIV-1 infection was even more prevalent in sub-Saharan Africa, and that HIV-1 was the etiologic agent of "slim disease," a wasting illness that has been identified in Central and West Africa in the late 1970s. Epidemiologic observations in Africa, as well as increasing identification of HIV-1 infection in sexual partners of intravenous drug users in Europe and the United States, confirmed that the HIV virus could be transmitted heterosexually, and this has been the predominant route of HIV transmission worldwide.

Thus, by 1985, the etiologic agent for AIDS had been identified and persons living asymptomatically with the virus could be detected. This led to increasing major efforts by the pharmaceutical industry to develop effective antiretroviral agents.

The first potential antiretroviral agent to which the HIV virus showed in vitro susceptibility was the reverse transcriptase inhibitor (RTI) azidothymidine (AZT), subsequently known as zidovudine. Zidovudine, which has originally been developed as a potential chemotherapeutic agent for the treatment of cancer, was found to be effective in inhibiting the growth of HIV-1 in vitro. Extensive field trials of this agent were initiated in 1986 by the newly established NIH-supported AIDS

Clinical Trials Group (ACTG). Initial randomized controlled trials of this agent indicated a significant decrease in mortality in HIV-infected individuals who received this agent for 24 weeks (6). On this basis, and with additional support from subsequent studies by the ACTG, the FDA approved in 1989 the use of AZT for persons living with HIV infection who had a CD4 cell count of <500.

During the first 2 years this agent was employed (most often in doses of 600 mg but sometimes in doses as great as 1,500 mg/day), side effects, especially nausea, headache, and anemia, were common. Follow-up studies over several years demonstrated that the clinical benefit of monotherapy with zidovudine was transient. In 1990, a state-of-the-art panel convened by the NIH suggested that azidothymidine, because of the demonstrated short-term survival benefit, should be given in divided doses of 600 mg daily to all persons living with HIV infection who had CD4 counts $<500/mm^3$. The recommendation of a CD4 count of 500 as the threshold for initiation of treatment was made on an arbitrary basis (7).

In 1992, second (didanosine, or ddI) and third (dideoxycitidine, or ddC) antiretroviral drugs were approved by the FDA for administration to persons with CD4 counts <500. Each of these agents was approved for use as a single agent against HIV infection, on the basis of short-term benefit in clinical trials. Both didanosine and dideoxycitidine proved to have serious toxicities, of which the most frequent was severe, sometimes crippling, peripheral neuropathy.

In 1992, an NIH Advisory Panel recommended that the three available agents, AZT, ddI, and ddC be used in sequence, with discontinuation of an initial agent when either major toxicity occurred, or when CD4 count began to fall after an initial rise (8). The panel recommended that all HIV-infected individuals with CD4 T-cell counts below 500 be treated with such sequential monotherapy.

In 1992, trials of combination therapy with two of the above agents were initiated both in the United States and Western Europe. By 1995, two major clinical trials, the Delta trial in Europe (9) and an ACTG trial in the United States (10), indicated that combined use of AZT and ddI was more effective than AZT monotherapy in preventing the progression of immunodeficiency and death in persons living with HIV infection. The toxicities of any two-drug combination of the three available drugs, however, proved to be major limiting factors. It became clear that the use of ddI and ddC together was prohibitive because of frequent neurotoxicity and occasional lactic acidosis.

Each of the initial three antiretroviral agents acted by the same mechanism, inhibition of reverse transcriptase, an enzyme essential to the replication of retroviruses.

While the early evaluations of HIV therapy were based on clinical endpoints (i.e., progression to clinical AIDS or death), extensive immunological and virological studies defined two precise laboratory determinations, the CD4 T-cell count (CD4) and the plasma HIV-RNA level (the plasma viral load, PVL), which, in concert, proved to be effective gauges of the rate of progression of HIV disease, and of the response to antiretroviral therapy. Most helpful were longitudinal studies obtained from the Multicenter AIDS Cohort Study, which was initiated in 1985, and included men either infected by, or at high risk for, HIV infection (11). The studies,

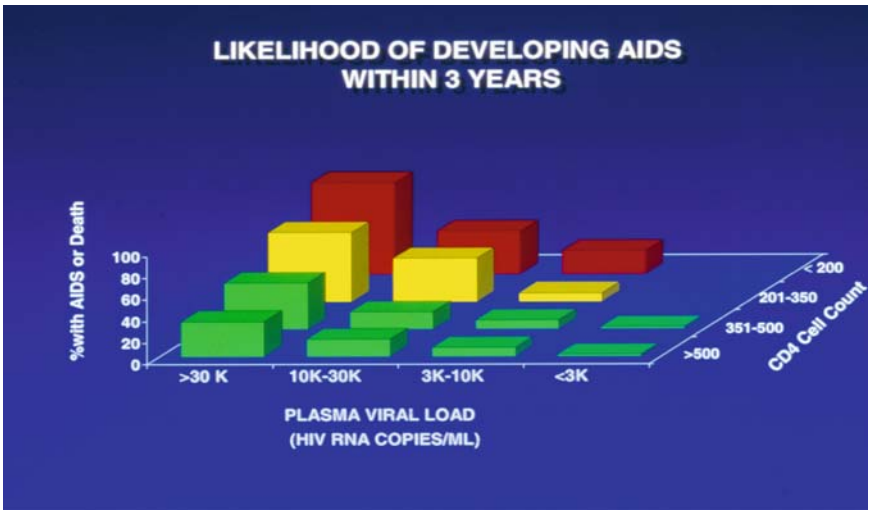

Fig. 1 The relationship of CD4 T-cell count and plasma HIV-1 RNA level to the 3-year probability of progression of persons living with HIV to clinical AIDS or death, in the preHAART era (10) (*See Color Plates*)

partially summarized in Fig. 1, provided the basis for more effective evaluation of the effectiveness of antiretroviral therapy and for earlier predication of failure of ART months or years before detectable change in clinical status (12).

Intensive further investigations by the NIH, several pharmaceutical companies, and many academic medical centers, especially in Europe and North America, have been initiated in late 1980s to develop an inhibitor of HIV protease, as protease activity is also essential for the replication of the HIV virus in human cells. In 1995, controlled clinical trials demonstrated that a protease inhibitor (saquinavir) was markedly effective in rapidly decreasing the level of HIV-RNA in persons living with HIV. The decrease in plasma viral load (PVL) was followed by a more gradual increase in the CD4 cell count. In rapidsuccession, two additional protease inhibitors, indinavir and ritonavir, were also shown to delay disease progression and death in persons living with HIV infection. All three protease inhibitors were approved by the FDA by early 1996. Studies indicated that resistance to each of the protease inhibitors also developed, although at a slower pace, than resistance to the reverse transcriptase inhibitors, over a period of months after initiation of monotherapy with each of the three protease inhibitors. These observations led to trials of three-drug combination therapy, including a protease inhibitor and two reverse transcriptase inhibitors. These highly active antiretroviral therapy (HAART) regimens caused significant and prolonged decreases in PVL, associated with progressive increases in CD4 count (13). These responses were accompanied by marked reductions in progression of HIV infection and death in persons living with HIV/AIDS.

By early 1998, both the International AIDS Society , USA, and the Department of Health and Human Services (DHHS) recommended that all persons li ving with HIV infection with CD4 counts <500, recei ve three-drug therapy, including a protease inhibitor and two reverse transcriptase inhibitors (14).

In 1998, a third cate gory of antiretro viral agent, the nonnucleoside re verse transcriptase inhibitor (NNRTI), was also shown to be effective, when given with two nucleoside re verse transcriptase inhibitors, in rapidly decreasing viral load with a subsequent progressi ve increase in CD4 count in persons li ving with HIV infection. It became clear that a three-drug re gimen containing either efavirenz or nevirapine combined with tw o nucleosides w as likewise markedly effective in decreasing disease progression and death related to HIV infection. Antiretro viral therapy, widely known as HAART, was universally recommended throughout the industrialized world by the end of the decade (15). HAART was rapidly adopted for treatment of HIV infection throughout the industrialized w orld, with mark ed clinical results in clinical progression and death. Figure2, presenting data from the CDC, demonstrates a fourfold decrease in age-adjusted death rates in USA due to HIV infections within 3 years after widespread application of HAAR T to treat HIV infection (16). Subsequent results have been most marked in Western Europe, where antiretroviral medications are generally pro vided, when indicated, to all persons who require therap y. Figure 3, based on reports from a multicenter European collaboration, demonstrates that in a 12,574 patient longitudinal cohort study, there w as little AIDS-related mortality in persons with CD4 counts >200 who initiated triple-drug treatment o ver a 3-year period. Indi viduals who be gan therapy at CD4 counts <200 also e xperienced a highly signif icant decrease in likelihood of progression to AIDS or death(17). Results from the British Columbia

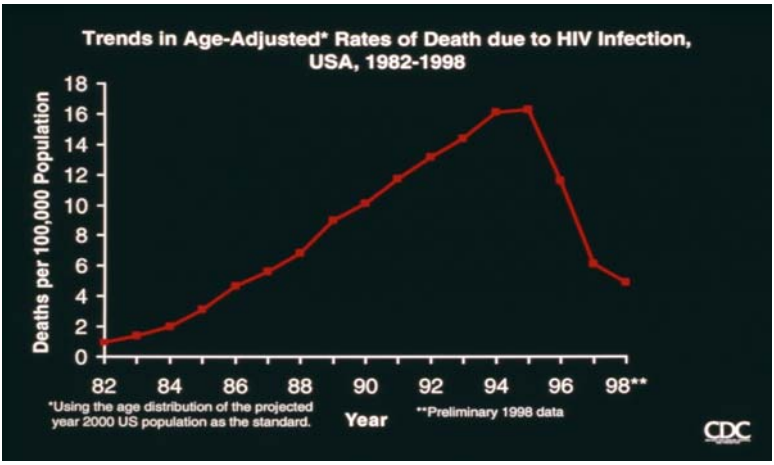

Fig. 2 This figure demonstrates the rapid reduction in age-related mortality rate due to HIV infection within 3 years follo wing widespread adoption of HAAR T therapy. Data from Centers for Disease Control and Prevention (http://wwwcdc.gov/HIV/graphics)*See Color Plates*)

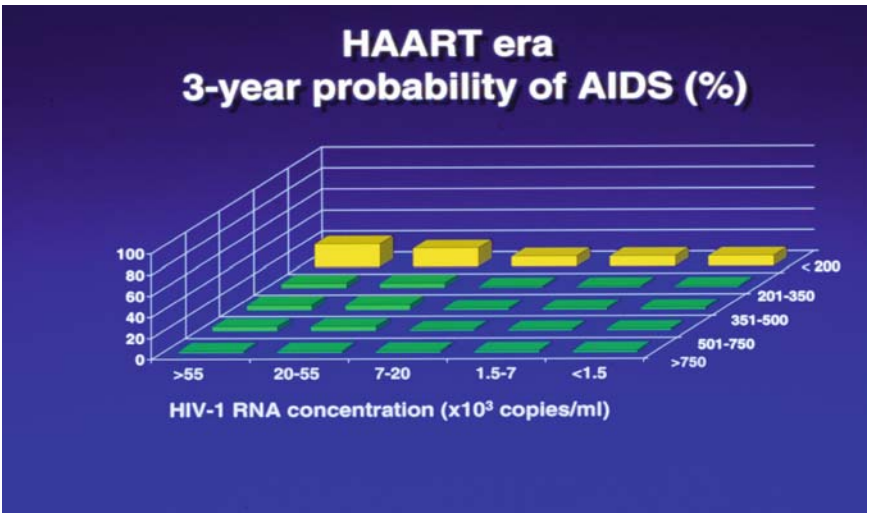

Fig. 3 Three-year probability of progression to AIDS in the HAART era, 1998–2002, in the ART Cohort Collaboration (17) (*See Color Plates*)

cohort were equally striking during that time period, as were smaller controlled clinical trials in the United States. Thus the widespread utilization of HAART ensured that the great majority of persons living with HIV in Western Europe and North America could be restored to good functional health by effective antiretroviral therapy.

In 2005, enfurvitide, the first of an additional class of antiretroviral agents, entry inhibitors, was approved for use by the FDA. Although more difficult to use than the earlier commonly utilized antiretroviral agent, as it required subcutaneous injection twice daily, enfurvitide in combination with two other antiretroviral agents to which the patient's virus was partially susceptible has proved to be life-saving in the small subset of patients with extensive resistance to other classes of retroviral agents.

In 2007, raltegravir, the first inhibitor of integrase, another enzyme essential to the replication of HIV, was shown to be highly effective when used with two other antiretroviral agents, and received FDA approval. This agent acts by preventing the integration of the single-stranded HIV-RNA into the DNA of the host cell, and provides a powerful additional approach to the treatment of persons with antecedent resistance to other classes of antiretroviral agents.

Also approved by the FDA in 2007 was a second class of entry inhibitor, maraviroc, which prevents binding of the HIV virus to the CCR5 receptor molecule of the CD4 T-cell, the primary target of HIV. This agent provides another effective agent for use in persons who have developed extensive resistance to previous antiretroviral agents, but its use is limited to the 75–85% of individuals infected by HIV strains which must utilize the CCR5 receptor.

Thus, it is now possible to provide effective therapy to all individuals newly infected with the HIV virus. In majority of the cases, the initial therapy can remain effective for periods of at least a decade. If adherence to the antiretroviral therapy regimen is excellent, there is little opportunity for the infecting virus to develop resistance to an effective HAART regimen.

Alterations in Neurocognition in HIV Infection

Neurocognitive deterioration has been recognized in HIV-infected individuals since the year in which AIDS was first recognized as a clinical entity. Prior to the development of effective antiretroviral therapy, the AIDS dementia complex (ADC), in which impaired intellectual function, often associated with progressive vacuolar myelopathy, was a common finding. The ADC, characterized by poor concentration, diminished memory, motor dysfunction, and often social withdrawal and apathy, seldom if ever occurs in persons who begin antiretroviral therapy prior to developing moderately severe immunodeficiency (e.g., before the CD4 count falls below 350 cells/mm^3). It has rarely been recognized in patients in whom the CD4 count has never fallen below 200 cells/mm^3.

There are at least two major issues that have not been adequately resolved in regard to neurocognitive changes related to HIV infection. The first is whether HIV infection may impair intellectual function in the early stages of immunodeficiency, i.e., when the CD4 count remains at a level above 350 cells/mm^3, the time at which initiation of antiretroviral therapy is currently recommended throughout the industrialized world. If indeed, intellectual deterioration related to the HIV infection can be demonstrated to occur, even in a small subset of patients with CD4 counts above this threshold, this finding would provide a sound basis for recommending initiation of antiretroviral therapy in all patients at an earlier stage in the progression of HIV disease.

A second unresolved issue is whether or not HIV-related cognitive dysfunction, once established in persons with more advanced HIV infection, will predictably improve following months or years of effective antiretroviral therapy.

Both these questions are of major importance in this phase of the HIV/AIDS pandemic, as the answers may prove critical to the timing of initiation of antiretroviral therapy. If HIV-related neurocognitive changes developed in some individuals at higher CD4 cell counts and neurocognitive dysfunction, once established, failed predictably to improve with effective antiretroviral therapy, a major worldwide effort would have to be initiated to identify and treat HIV infection at earlier stages of immunodeficiency. Although this would initially impose a large worldwide financial burden (especially in developing countries where the current WHO guidelines recommend initiation of therapy at a CD4 count threshold of 200 cells/mm^3), earlier initiation of HAART should become the international standard. This text explores the current understanding of the neurocognitive changes that occur in the course of HIV infection, describes the structural

neuroimaging correlates of these changes, and discusses current approaches to the prevention, evaluation, and approaches to treatment of altered cognition in persons living with HIV infection.

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Global Incidence and Epidemiology of the AIDS Pandemic, Distribution of HIV Subtypes, and Epidemiology of Hepatitis C Infection Among HIV-Positive Individuals

Karen T. Tashima and Aadia I. Rana

Introduction

It has been more than 25 years since the Centers for Disease Control and Prevention published a report in 1981 of *Pneumocystis* pneumonia in five previously healthy young men in Los Angeles, CA (1). These cases were later recognized as the first reported cases of acquired immunodeficiency syndrome (AIDS) in the United States (2). By the 1990s, an estimated 1 million people were infected with HIV globally. Since that time, the disease has become one of the greatest global public health challenges of our time, resulting in an estimated 65 million infections and claiming the lives of more than 25 million people (UN AIDS). The proportion of individuals worldwide infected with HIV is just under 1% and has been stable since 2001; however, population growth and longer survival of infected persons have resulted in the continuous rise of the number of people living with HIV. A reduction in the number of annual new HIV infections globally is a positive trend noted in 2007.

The HIV pandemic is believed to have started with a cross-species transmission from primates to humans in Central Africa. Three strains of HIV have been described based on the differences in their encoding proteins: M, N, and O. Group M strain is the most prevalent and is divided into subtypes (or clades), based on the whole genome, which are geographically distinct. HIV-1 group M strain is responsible for the vast majority of infections (see Chapter 15 for a comprehensive review of clade subtypes). HIV-1 subtype B is the predominant subtype in North America, Western Europe, and Australia but represents only about 12% of the global HIV pandemic. A complete understanding of global epidemiologic trends and the distribution of HIV subtypes is needed for future prevention and treatment efforts (3–9). An overview of the findings of the 2007 global UNAIDS HIV report, global distribution of

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HIV subtypes, and recent epidemiologic trends highlighting populations at risk of acquiring HIV infection is presented in this chapter. Because hepatitis C infection among HIV-infected individuals may pose an additional risk to neurocognitive health, current estimates and epidemiologic trends of dually infected persons has also been reviewed.

Global Epidemiology

In 2007, an estimated 33.2 million people were living with HIV infection; approximately 2.5 million people were newly infected, and 2.1 million lost their lives to AIDS (10). The number of children under 15 years living with HIV in 2007 is estimated to be 2.5 million. 420,000 children were newly infected with HIV and 330,000 children died of AIDS in 2007. 90% of all HIV-infected children live in sub-Saharan Africa. The UN AIDS/WHO 2007 report noted two patterns to the epidemic; first, the generalized epidemics continue in the general populations in many sub-Saharan African countries; and second, epidemics in the rest of the world are primarily concentrated among populations most at risk, such as men who have sex with men, injection drug users, sex workers, and sexual partners of these populations at risk. The most prevalent viral strains globally are HIV-1 group M subtypes A, B, C, D, CRF01_AE, and CRF02_AG (figure from (11)). Subtype A is found primarily in East Africa and in former Soviet Republics. Subtype B predominates in infections found in the Americas, Western Europe, and Australia. Infections in Southern and East Africa, and in India are subtype C and account for 50% of all the HIV infections worldwide. Subtype D is mainly found in East Africa and in West Africa. CRF01_AE and subtype B are the two subtypes found in southeast Asia, and CRF02_AG is found in West and West Central Africa. In South America, subtype B and BF recombinants, and subtype C are found (11).

Africa

The greatest HIV burden is in sub-Saharan Africa. 22.5 million people are living with HIV in this region, 1.7 million were newly infected in 2007, and more than three quarters of AIDS deaths in 2007 occurred here. In most other regions of Africa, HIV infections have been concentrated in various high-risk populations, but the HIV epidemic has become more widespread, and is termed as *generalized epidemic* in sub-Saharan Africa. Only about 10% of the world population lives in sub-Saharan Africa, but this region is home to approximately 68% of the adults living with HIV and 90% of children living with HIV. In sub-Saharan Africa, transmission is primarily through heterosexual contact, with more women infected with HIV than men. About 61% of adults living with HIV in 2007 were women. On average, three women in sub-Saharan Africa are infected for every two men. Among young people

aged 15–24, the gap increases even more to three young women infected for every young man. Three-quarters of all women aged 15 and older living with HIV globally are in sub-Saharan Africa (10).

The subregion of southern Africa is the epicenter of the AIDS epidemic; eight countries in this region have an estimated adult HIV prevalence exceeding 15%, while in Botswana, Lesotho, Swaziland, and Zimbabwe the prevalence exceeds 20%. Zimbabwe showed significant declines in HIV prevalence, while the prevalence is stable in the other countries in the region. South Africa, with an HIV prevalence of 18.8%, has the highest burden of HIV infections with 5.5 million persons living with HIV. In Southern Africa, 98% of HIV infections are caused by subtype C (11, 12).

There have been recent declines in HIV incidence rates in Kenya, Zimbabwe, Cote d'Ivoire, Mali, and urban areas of Burkina Faso (10). This is likely related to a combination of behavioral changes (increased condom use, delayed sexual debut, increasing avoidance of casual sexual relations) and high mortality rates from AIDS. Some African countries report a decline in HIV prevalence among women attending antenatal clinics, notably in Zimbabwe, Botswana, and in urban areas of Zambia and Kenya.

Overall in the region of West Africa, 21% of infections are caused by subtype A, 35% by subtype G, and 28% by subtype CRF02_AG, and other recombinants account for 14% (12). In Nigeria, which has the largest number of infections in West Africa, subtypes A (29%) and G (54%) predominate. In east Africa, subtypes A, C, D, and unique recombinant forms are found. In Kenya and Rwanda, the majority of infections are caused by subtype A (57%, 79%, respectively); in the United Republic of Tanzania subtype C accounts for 44% and in Uganda subtype D for 46% of infections.

In Central Africa, subtype A is found in 38% of infections; otherwise, the greatest diversity of subtypes and recombinants are represented in this region.

There have been significant improvements in access to antiretroviral therapy in sub-Saharan Africa in the past several years. From 2003 to 2005, there was an eightfold increase in the number of HIV-positive individuals receiving antiretroviral therapy, who were in need of it. However, that still represents less than 20% of the population in sub-Saharan Africa with indications for treatment.

Asia

The HIV epidemic in most Asian countries is attributable primarily to various high-risk behaviors, including unprotected intercourse with sex workers, injection drug use, and men who have sex with men. 29% of adults living with HIV in Asia are women. Of the approximately 4.9 million HIV-infected persons in Asia, 2.5 million of those live in India. New infections in 2007 are estimated at 340,000 adults and children, a decrease from 2001 when 450,000 new infections occurred in this region. While HIV prevalence has been declining in pregnant women in antenatal

clinics across Asia, HIV prevalence among men who have sex with men is increasing in countries such as Thailand. Declines in HIV prevalence were seen in Cambodia, Thailand, and Myanmar, whereas increases are noted in Viet Nam and Indonesia. 97% of HIV infections in India are subtype C, and in south and south-east Asia (Cambodia, Thailand, Viet Nam), subtype CRF01_AE accounts for 84% of infections and other recombinants 4%. The recombinant subtypes are somewhat less predominant in Myanmar, where subtypes B and C account for 24 and 12% of infections, respectively. In China, clades B', B, BC, and AE were found (13).

Recently updated reports from 2007 estimate that national adult HIV prevalence in India is approximately 0.36%, which corresponds to an estimated 2–3.1 million people living with HIV in the country. This is a reduction in previous estimates using better sampling methods across the country. These numbers show an epidemic that is stable over time with marginal decline in 2006 especially noted in the antenatal clinics in the southern states of Andhra Pradesh, Tamil Nadu, Maharashtra, and Karnataka, which have been the hardest hit by the epidemic. More than 80% of reported AIDS cases in India are due to unprotected heterosexual intercourse, and a significant portion of the new cases are in women. However, the 2006 surveillance figures showed an increase in HIV infection among several groups at higher risk of HIV infection, among people who inject drugs, and men who have sex with men. Injection drug use is the primary mode of transmission in the northeastern states of Manipur, Mizoram, and Nagaland as well as in major cities throughout India. There is a substantial overlap between those who inject drugs and those who engage in commercial sex.

In China, injection drug users account for almost one-half of the 650,000 people living with HIV. In certain areas of some provinces, owing to sharing needles and syringes, as well as high-risk sexual behavior among the drug users, HIV prevalence exceeds 50% among injection drug users. In China, subtype B is found in 38% of people living with HIV, CRF01_AE in 15%, and other recombinants account for 45% of infections. In Japan, subtype B causes 81% of infections (12).

In Thailand and Cambodia, the epidemics have been largely driven by commercial sex. In other countries in Asia, the overlapping risks of injection drug use and unprotected sex feature in several epidemics, including in Viet Nam. There have also been indications of epidemics among injection drug users in the past several years in Asian countries. There is a general decline in HIV prevalence in Asia in antenatal clinics, but along with other regions of the Asia and the world, there are increases in prevalence among men who have sex with men and injection drug users. HIV prevalence is increasing in China, Indonesia, and Viet Nam, with high rates in Pakistan and Bangladesh in the injection drug use population.

In Asia, like Africa, the number of people receiving antiretroviral therapy has increased significantly in the past several years. Nonetheless, only 16% of persons in need of treatment in Asia received it in 2005, with coverage in India still remaining below 10%. With the continuing expansion of the availability of generic antiretrovirals through manufacturers in India and government support of first-line therapy, these numbers are expected to increase significantly with continued global support.

Eastern Europe and Central Asia

The HIV epidemic in Eastern Europe accounts for approximately twice the number of newly diagnosed HIV cases as in Western Europe, and is primarily driven by injection drug use (IDU) (two-thirds) and secondarily through the heterosexual partners of these drug users (one-third of new infections). Approximately 1.6 million people are living with HIV in Eastern Europe and Central Asia and 150,000 people were newly infected in 2007. The majority of people living with HIV in this region live in the Russian Federation and in Ukraine. This is likely the result of the many political and social changes confronting eastern Europe, including changes in drug trafficking routes and drug prices, leading to an increase in the size of the population using drugs and HIV transmission within drug-sharing and sexual networks. (14)

New diagnoses among injection drug users, female sex workers, and men who have sex with men are reported from testing in other Central Asian countries, including Republic of Moldova, Georgia, Armenia, Azerbaijan, Uzbekisan, Kazakhstan, Tajikistan, and Kyrgyzstan. 79% of infections in the region are caused by subtype A and 15% by subtype B. CRF03_AB is found only in this region (12).

Latin America and the Caribbean

HIV infections in Latin America are reported mostly among men who have sex with men, injection drug users, and sex workers, but has also increased among the women in the general population of Brazil and Uruguay. Brazil, the most populous country in Latin America, has an adult HIV prevalence of 0.5% and comprises almost 30% of the population living with HIV in South and Central America and the Caribbean. High-risk behavior is still widely reported among young Brazilians with almost one-third reporting sexual debut prior to age 15, and 20% of young Brazilians aged 15–24 reporting greater than ten sexual partners. Approximately 73% of the estimated 400,000 people in need of antiretroviral therapy in Latin America received it in 2005. Brazil provides free antiretroviral therapy to those in need of treatment, and approximately 83% of HIV-infected persons receive therapy. Subtype B infections predominate in Latin America, with a smaller representation of subtypes C and F and recombinants totaling about a quarter of infections overall (12, 15). Clade B/F recombinants were common (48%) in a survey of treatment failure patients in Buenos Aires, Argentina (16). Populations at highest risk for HIV infection in Latin American countries are men who have sex with men and female sex workers (17).

The Caribbean is the second most HIV-affected region of the world. About three quarters of the 230,000 people living with HIV infection in the region live in Haiti or the Dominican Republic. 43% of adults living with HIV in 2007 are women. Transmission is largely through heterosexual intercourse; injection drug use (except in the countries of Bermuda and Puerto Rico) plays a minor role in the Caribbean's epidemic. Sex between men is estimated to be responsible for 12% of infection in

the Caribbean. Haiti is the most burdened Caribbean country with a recent prevalence near 4%. HIV prevalence has declined in urban areas of Haiti by 2005 estimates, but remained constant in other areas of the Caribbean. Subtype B is responsible for 94% of infections in Haiti, Dominican Republic, and Trinidad and Tobago. In Cuba, 48% were caused by subtype B and 41% caused by recombinant forms (11, 12). With the exception of Cuba, antiretroviral treatment access is highly uneven. In Haiti and the Dominican Republic, for example, fewer than 20% of people needing antiretroviral treatment were receiving it in 2005.

North America and Western Europe

In the developed world, including the United States and Europe, the HIV incidence rate dropped every year until the late 1990s when it stabilized translating into about 65,000 new infections in North America and Western and Central Europe. A total of approximately 2.1 million people are living with HIV infection in these regions. The rate has not continued to decline largely in part to a rising prevalence rate among immigrants, migrants, ethnic minority groups, and men who have sex with men. Men account for 74% of HIV infections in the United States. Half of new infections in the United States in 2005 were among men who have sex with men, 32% among women, and 18% among injection drug users (17). Racial and ethnic minorities, particularly African Americans and Latinos, represent 48 and 18% of new infections, respectively. There is a particular need for improved prevention, diagnosis, and treatment services in these populations. In the United States, there has been reported evidence of resurgent risk behavior among men who have sex with men (18). In Canada and Western Europe, new infections are significantly represented by immigrants who acquire the disease heterosexually. Spain, Italy, France, and the United Kingdom continue to have the largest HIV epidemics in the region. Fewer cases of new infections are attributed to injection drug users. Subtype B viruses predominate in North America and Western Europe, but immigration of people from other parts of the world have increased representation of other subtypes (19).

Co-Infection with Hepatitis C

Hepatitis C is a blood-borne infection, transmitted through contaminated blood, injection drug use equipment, and, less efficiently, through sexual intercourse. Prevalence of hepatitis C among the HIV-infected population is about 30% worldwide, but can vary from 10.4% in an Asian Pacific cohort (TREAT Asia HIV Observational Database) (20) to 51% in a largely injection drug use population in Columbia, Canada (21). In the United States and Europe, estimates are that 25% of HIV-positive individuals have hepatitis C infection as well. More recently, acute hepatitis C

outbreaks are being reported among men who have sex with men (21, 22) .Hepatitis C infection has emerged as an important cause of morbidity and mortality concomitant with the decline in HIV -related morbidity and mortality associated with ef fective antiretroviral treatment.

Conclusion

The advances in antiretro viral therapy in the last decade ha ve reduced morbidity and mortality in the de veloped world, including neurocogniti ve impairment and AIDS dementia. Antiretroviral medications have variable penetration into the central nervous system, and adequate levels may be important in preventing or reversing the neurocognitive deficits related to HIV infection for some patients. Access to these life-saving medications has improved globally, although only to a fraction of those in need, but appears to have similar beneficial effects. Expansion of antiretroviral coverage will also lead to increased HIV drug resistance and antiretro viral toxicities globally. These issues will continue to require signif icant resources and research in order to improve the lives of everyone living with HIV infection.

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New Insights into HIV Neuropathogenesis

Tory P. Johnson and Avindra Nath

Introduction

Over the last two decades, substantial progress has been made to understand the pathophysiology of dementia due to HIV infection; yet neuroprotective drugs have shown little or no effect on the syndrome. Although there may be multiple reasons for these failures, it also begs another look at our approach toward studying HIV neuropathogenesis. Importantly, it is being recognized that innate immune responses that have been often targeted by therapeutic approaches may have important antiviral effects. Further, the effects of the virus on neurogenesis may be critically important, and in patients treated with antiretroviral therapy, T-cell infiltration within the brain may be an important mediator of neuronal injury. This chapter brings to light these newer developments in the pathophysiology of HIV infection and highlights these areas requiring closer attention and further investigation.

Early in the epidemic, once it was discovered that HIV was a retrovirus and that it could be found in macrophages, many in the field thought that the pathophysiology of neurological complications due to HIV infection was obvious. As in other retroviruses that had been studied prior to HIV, such as visna virus that infects sheep causing an encephalopathy, it was thought that the infection of macrophages would be sufficient to drive all the glial and neuronal changes in the brain. However, the years since have proven that the neuropathogenesis of HIV infection is a tangled web. Over 20 years have passed since HIV dementia was first described, and even though we have learned a lot about some of the key elements of how HIV causes neuroglial dysfunction, there are other key questions that remain unanswered.

It is abundantly clear that the brain is an important reservoir for the virus and the viruses may reside in several cell types besides the macrophages. The mechanisms of viral persistence and latency, however, remain unknown. As a result there are currently no drugs available that may impact these reservoirs. Despite all the studies in

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pathophysiology of this disease, currently there are no clinically available surrogate markers for HIV-associated cognitive impairment. Further, to date all clinical trials with neuroprotective agents in HIV dementia have failed to show any significant clinical benefit. Although there may be multiple reasons for such failures, it also means that we need to reevaluate the pathophysiology of HIV-associated cognitive impairment to help identify novel targets and approaches for therapeutic development. In this chapter, we have focused the discussion of some of these newer emerging concepts.

Innate Immune Responses: Friend or Foe

Most studies consider the induction of innate immune responses such as cytokines, chemokines, oxidative stress, and proteases to be detrimental to the neuron. This concept has been applied to most neurodegenerative diseases, including HIV-associated cognitive impairment (Fig. 1). However there are reasons to believe that in the setting of viral infections, such responses may not always be hostile to the host. Organisms that lack a cellular immune response often use such innate immune responses to protect themselves from invading pathogens. For example, plants, without a specific adaptive immune system, may use metalloproteinases, along with other innate defense mechanisms, to combat infection. For example, the metalloproteinases-2 gene of the soybean, *Glycine max*, is upregulated in response to a variety of infections (1). Thus in circumstances where the cellular immune responses fail to control the pathogen such as persistent HIV infection of the CNS, the innate immune responses get activated. For example, it has been shown that matrix matalloproteinases (MMP), which are a family of structurally similar, zinc-containing endopeptidases, that are known to be increased in patients with HIV dementia can cleave the Tat protein of HIV and thus inactivate it and prevent the protein from causing neurotoxicity or from transactivating the HIV genome (2). Similarly, oxidative stress may be an attempt by the host to cause inactivation of viral proteins by modification by free radicals, nitric oxide, or reactive aldehydes released by lipid peroxidation. However, these types of offensive mechanisms are nonspecific and can result in damage to the host cells (Fig. 1). This is particularly true when there is a chronic activation of the innate immune responses. Considering the same example of MMPs, it has been shown that these molecules can enzymatically degrade the extracellular matrix proteins and can thus disrupt the blood–brain barrier and neuronal synapses (3–6)MMPs can also cleave other host proteins, such as chemokines (7), and these cleavage products can cause neurotoxicity. Further, MMPs may directly interact with integrin receptors on neurons, and initiate a cascade of events leading to neuronal cell death (8).

Further, innate immune responses may interact with one another. MMPs can become nitrosylated and persist in a hyperactive state, perhaps contributing to neurotoxicity under conditions of oxidative stress (9). Autopsy studies also confirm elevated levels of inducible nitric oxide synthase (iNOS) in patients with HIV dementia (10–11). iNOS is present in macrophages and microglia and its levels

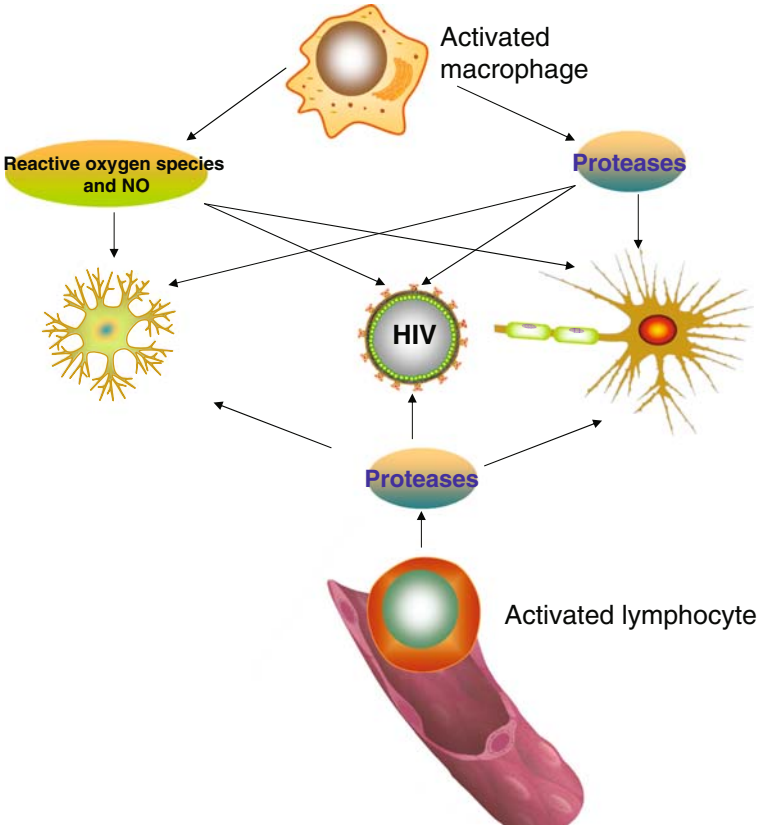

Fig. 1 Nonspecific antiviral effects of the immune system leads to CNS damage. Activated macrophages release free radicals and induce oxidative and nitrosative stress, which may directly interact with viral proteins and cause functional impairment. These cells also release proteases such as matrix metalloproteinases that may cleave viral proteins. However, these responses may also damage neurons and glial cells. Similarly, activated T cells may enter the brain in patients treated with antiretroviral drugs, leading to an immune reconstitution syndrome. These cells are unable to clear the virus from the brain, but in the process may release proteases such as granzyme, perforin, and granulolysin. These substances may also be toxic to other brain cells (*See Color Plates*)

correlate with the severity of HIV dementia (12–16). In a simian immunodeficiency virus model of HIV dementia, iNOS expression was found to correlate with dendritic injury (17). Nitric oxide and peroxynitrite are potently toxic to neurons and may mediate toxicity through the formation of iron–nitric oxide complexes of iron-containing enzyme systems, oxidation of protein sulfhydryl groups, nitration of proteins, nitrosylation of nucleic acids, and DNA strand breaks (reviewed in (18)). In the presence of both free oxygen species and nitric oxide, peroxynitrite may be formed. Peroxynitrite is highly reactive and modifies tyrosine residues in proteins to form 3-nitro-tyrosine, although it may modify cysteine and histidine residues as well. We found elevated levels of 3-nitro-tyrosine-modified proteins in

the CSF of individuals with progressive deterioration of neurocognitive dysfunction over several months, also termed *active HIV dementia*. 3-nitro-tyrosine levels are a much more sensitive indicator of nitrosative stress than nitrate and nitrite levels in CSF (Li et al., 2008).

Other forms of oxidative stress such as protein carbonyls, a measure of protein oxidation, and hydroxynonenol ester (HNE) levels, a measure of lipid peroxidation, are also elevated in the CSF and brain of individuals with HIV dementia (20). Measurement of ceramide and sphingomyelin levels in CSF may also have a predictive value in identifying individuals at risk of HIV dementia, as these lipid products are also altered by oxidative stress (22). Studies in vitro also demonstrated that HIV proteins gp120 and Tat may induce neuronal death through induction of oxidative stress (23). Future studies need to address the precise proteins that are functionally altered as a consequence of oxidative stress and if production of new proteins by the cells can overcome the posttranslational modifications by oxidative stress of these proteins. Importantly, it needs to be determined if there is accompanying alterations in chromosomal DNA or DNA repair enzymes by these processes, for it may have far-reaching consequences on cellular function.

Immune Reconstitution Syndrome: An Unrecognized Consequence of Antiretroviral Therapy

It has only recently been recognized that some patients may develop a devastating neurological syndrome following the initiation of combined antiretroviral therapy. This occurs despite a drop in viral load and improvement in CD4 cell counts. Although this syndrome may involve other organ systems, when it involves the CNS it may be fatal. The syndrome has been termed *immune reconstitution inflammatory syndrome* (IRIS) and is defined as a continual clinical deterioration of a patient successfully treated with combined antiretroviral therapy (24). The lower the CD4 cell count at the time of initiation of antiretroviral therapy, the greater seems to be the risk of development of IRIS, as well as increased risk of failure to completely reconstitute the immune responses (24, 25). The reconstitution of the immune system after the initiation of combined antiretroviral therapy follows a predictable pattern of an initial increase in memory T cells, followed by an increase in thymic production of naive T cells, with an increase in the overall quantity of CD4+ T cells (25, 26). Other risk factors for development of IRIS include a high viral load at the onset of antiretroviral therapy, a prompt reconstitution of the immune system after initiation of therapy, and infection with an opportunistic pathogen prior to combined antiretroviral therapy (27).

Complications arising from reconstitution of the immune system are discernible in the CNS as well as in other regions, and can lead to a rapid neurological deterioration of the patient over days (28). This process is mediated by a robust immune response targeted at either an opportunistic infection present prior to the initiation of combined antiretroviral therapy, or to unknown antigens, possibly even self-antigens

(24). IRIS occurs in approximately 15–35% of HIV patients initiating combined antiretroviral therapy, with similar percentages occurring in children (27, 29, 30). Some patients develop fulminant encephalitis once combined antiretroviral therapy is begun. Although the fulminant forms of CNS-IRIS have received attention, it is quite likely that, in the era of combined antiretroviral therapy, other milder forms of IRIS also exist.

Histology shows massive infiltration of T cells in the brain in patients with CNS-IRIS, which leads to an increase in neuronal death, and breakdown of the blood–brain barrier (31–33). This impairment of the BBB can then in turn permit greater immune cell access to the brain. Importantly, studies have emerged that identify increased T cells in the brain of patients who came to autopsy or underwent a brain biopsy in the postcombined antiretroviral therapy era (33, 34). HIV dementia is largely driven by macrophage activation and HIV-infected macrophages, whereas T cells appear to mediate the detrimental effects of IRIS (34, 35) (Fig. 1).

The clinical manifestations of CNS-IRIS are diverse and depend on the presence or absence of, as well as the type of, opportunistic infections present. Several opportunistic infections play an established role in the development of CNS-IRIS, such as *Mycobacterium* species, *Cryptococcus*, JC virus, and Cytomegalovirus, each with diverse clinical symptoms and outcomes (28). Once CNS-IRIS is identified, treatments include the use of corticosteroids to suppress the immune system (24, 28). Preventive measures include careful screening for opportunistic infections prior to the onset of combined antiretroviral therapy and appropriate intervening therapy if necessary to reduce antigen presentation.

The pathophysiology of IRIS is poorly understood, however, the production of both the antibody response and the CTL response depends on the effective stimulation by CD4+ helper T cells (37, 38). Apart from indirect control of antiviral immune responses, CD4+ cells are capable of effector functions via the release of cytokines and induction of cell lysis. A robust CD4+ cellular response is correlated with a lower persisting viral load, as compared with patients with a reduced CD4+ T-cell response (37), highlighting the importance of CD4+ T cells in controlling HIV infection. Additionally, CD4+ T cells may play important roles in controlling pathogens in the CNS (39, 40), as indicated by both functional studies and by CD4+ T cells comprising a higher percentage of the total T-cell population in the CNS (41, 42). However, HIV preferentially infects HIV-specific CD4+ T cells, leading to a depletion of this subset of T cells (43), in conjunction with other mechanisms (44). The loss of IL-2-producing CD4+ T cells causes an overall diminished immune response to HIV, as central memory T-cell (CCR7+, CD45RA-, IL-2-producing) numbers decrease compared with effector memory T-cell numbers (CCR7-, CD45RA-, low proliferation) (45). The adaptive immune response to HIV is important in controlling viral replication; however, the same response in the context of the CNS can be detrimental to a patient, as the neurons are not equipped to handle sustained and aggressive inflammation.

Much research is urgently needed to improve our overall understanding of the mechanisms that contribute to CNS-IRIS disease processes, especially in investigating the activation of T cells in the absence of opportunistic infections and in characterizing

the immune cells involved in IRIS. The recent development of a non-CNS-IRIS model in rabbits (46) should be a useful tool in dissecting, in part, the underlying mechanisms of aberrant T-cell activation, and should provide an insight into other nontuberculosis antigens the immune cells recognize. Development of an SIV model of CNS-IRIS would be advantageous, as this model could be used to test potential therapeutics. Until all factors contributing to IRIS are fully understood, the contradictions to combined antiretroviral therapy will remain unpredictable, and potential interventions to prevent IRIS will remain elusive.

Modulation of Neurogenesis in HIV infection: A New Target for Neuroregenerative Therapies

Much attention has been focused on trying to protect the injured or dying neuron. Several detailed studies have clearly shown evidence of neuronal apoptosis and dendritic loss in the brain of HIV-infected patients, and experimental studies have implicated HIV proteins and substances released from activated glial cells in causing the damage. Despite this overwhelming evidence, to date all clinical trials with neuroprotective therapies have shown little or no improvement in cognitive function in patients with HIV infection (47). These observations are not unique to HIV dementia but in most neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, stroke, and amyotrophic lateral sclerosis, neuroprotective therapies have been dismal failures. This has made us and others reevaluate the therapeutic targets. It is becoming abundantly clear that there is continuous replacement and regeneration of neurons during adulthood; hence, any impairment of neurogenesis may have far-reaching consequences on the brain. HIV has been shown to infect neural progenitor cells in vitro and in vivo. These cells express CXCR4, a coreceptor for HIV, and promote the differentiation of these cells into astrocytes instead of neurons (48, 49). Exposure of neural progenitor cells also results in decreased proliferation of these cells (50), causing an arrest in the G1 phase of the cell cycle via a cascade that consists of p38 mitogen-activated protein kinase (51). Thus therapeutic strategies that are able to overcome this block and promote neurore generation may be a new approach for treatment of HIV dementia and other neurodegenerative disorders. Renewed attention has thus been diverted toward growth factors such as erythropoietin and brain-derived growth factor as well as antidepressant drugs that promote growth factor production (52).

Regulation of HIV Reservoirs in Brain: Need for New Therapeutic Targets

HIV predominantly infects two cells types, the macrophages/microglia and perivascular astrocytes. The virus can reside in these cell types for extended periods of time. It leads to a productive or persistent infection in the macrophages; however, in astrocytes

it forms a latent infection, whereby the early viral proteins are formed but infectious virus is not produced. In this state, transient viral replication maybe stimulated by exposure to cytokines (53, 54). Astrocytes also have a very low turnover rate and hence these cells are perfect reservoirs for the virus. Some groups have shown that neurons, endothelial cells, and neural progenitor cells are also capable of getting infected and, similar to astrocytes, form a nonproductive infection. That the virus is able to infect multiple cells types comes as no surprise; however, eliminating these reservoirs is a formidable challenge. Mechanisms that regulate viral replication in these cell types or maintain them in this latent state are poorly understood. One study implicated the 68-kDa Src-associated protein that binds to Rev and is involved in its transport to the nucleus and is poorly expressed in astrocytes (55). Unpublished observations from our laboratory have shown that the promyelocytic leukemia protein is expressed at high levels in astrocytes compared with lymphocytes and macrophages and can bind to Tat proteins and thus prevent HIV replication (Galey and Nath, unpublished).

Role of Viral Strains and Clades in HIV Neuropathogenesis

The spectrum of viral genotypes or quasispecies are generated throughout the course of disease because of the low fidelity of reverse transcriptase, a lack of proofreading by the viral polymerase, high rates of viral production, and in vivo selection pressures (56). Hence once the virus enters the brain, it may evolve acquiring sequence heterogeneity different from that in lymphoid organs due to the different selective pressures in the brain. Thus far, only a limited number of studies have looked at viral sequences from brain tissue and a fewer have tried to make any functional correlation of the viral sequences. However, available evidence suggests that the brain-derived viral sequences tend to favor its establishment as a reservoir, e.g., brain-derived *tat* sequences from HIV-demented patients are poor transactivators of the HIV-LTR, which permits the virus to stay latent and thus escape the immune system (57). At the same time, they acquire more neurotoxic properties and both Tat and gp120 sequences from HIV-demented patients show increased neurotoxic potential (57, 58).

As the virus has evolved and spread to different regions of the world, it has become apparent that there are clear geographical differences in the neurological manifestations of HIV infection. In regions of the world infected with HIV clade C, only milder forms of cognitive impairment have been recognized even in patients with advanced immunosuppression in the absence of antiretroviral therapy (28, 59). While it is possible that patient selection bias may in part be responsible for these differences, there is also evidence to suggest that genetic differences in the *tat* gene of the HIV clades may also alter the pathogenicity of the virus. For example, the cysteine in position 31 of clade B virus is mutated to a serine in clade C virus. This mutation results in decreased chemotactic properties of clade C virus and decreased neurotoxicity (60, 61). Studies from Uganda suggest that individuals infected with clade D virus are more likely to develop dementia compared with those infected with clade A virus (62). The molecular determinants of these differences are unknown.

In summary, recent studies indicate that the pathophysiology of neurological complications are much more complex than that previously thought. They likely occur in genetically susceptible populations and may be impacted by the strain and clade of the virus. The role of T cells and innate responses in mediating the syndromes have become increasingly important in the era of antiretroviral therapy. These insights will dictate new therapeutic approaches for this population.

Role of Host Genetic Factors in HIV Neuropathogenesis

The epidemiology of HIV dementia suggests that host genetic factors must contribute to the pathophysiology of HIV dementia. Some patients despite high viral loads and profound immunosuppression remain cognitively intact, while a smaller percentage of such patients develop a dementing illness. Despite this overwhelming evidence, only a handful of genes have been studied as a potential factor in HIV neuropathogenesis. One reason is that such studies require large sample sizes. The *Apo E* genes have been best studied in this regard. Both population-based and experimental studies in vitro and in vivo suggest that individuals with *ApoE4* gene are more likely to develop HIV dementia (63) in particular among older HIV+ individuals (64). Individuals with HIV infection and ApoE4 allele have increased oxidative stress in the brain and CSF (65, 66) and human neuronal cultures with the ApoE4 allele are more vulnerable to toxicity by HIV proteins (66). Further, human lipidated apoE3 greatly protects neurons from HIV Tat protein-induced toxicity, whereas human lipidated apoE4 shows no protection (67). Other epidemiological studies suggest that macrophage chemoattractant factor-1 or CCL-2 mutations (68) and mutations in its receptor CCR2 (64-I allele) (69) correlate with the presence of dementia likely by influencing macrophage infiltration. Tumor necrosis factor-α promoter polymorphisms also correlate with the presence of dementia likely by influencing levels of tumor necrosis factor-α production, which may induce neurotoxicity (70). Polymorphisms in the iNOS gene have been found in humans. A functional CCTTT-repeat polymorphism in the promoter region of the gene was not found to affect HIV viral load or CD4 cell counts in HIV-infected individuals (71); however, its role in inducing nitrosative stress in the brain of HIV-infected individuals has not yet been studied.

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Neuropathological Findings Associated with Long-Term HAART

Iain C. Anthony and Jeanne E. Bell

Introduction

The introduction of highly active anti-retroviral therapy (HAART) in 1996/1997 had a profound impact on the course of HIV infection. The use of HAART results in a significant decrease in viral load, often below the limits of detection in serum. This, coupled with increased CD4 T lymphocyte counts and at least partial restoration of the immune system, provides protection for infected subjects from opportunistic infections, which were previously the major cause of morbidity and mortality in HIV. HAART is not a cure for HIV and the virus is never fully eradicated, but for those subjects able to tolerate its toxic side effects, HAART has converted HIV infection into a long-term chronic disease with reasonable life expectancy.

Since the first reports of AIDS in the early 1980s, it has been clear that the central nervous system (CNS) is frequently a direct target of the disease. The disease manifestations that point to brain involvement include neurological dysfunction as well as neurocognitive deficits, which may progress to dementia. HIV-related dementia (HAD) was typically sub-cortical in that psychomotor slowing and executive dysfunction in addition to memory loss were prominent features. HAD was common in the pre-HAART era, occurring in 10–20% of AIDS subjects. However the exact pathological basis of this dementia has proved difficult to elucidate. Although HIV can infect the brain directly by invading microglial cells, the ensuing encephalitis (HIV encephalitis, HIVE) was not found to be present in all individuals who had developed HAD. To further complicate matters, some of the opportunistic conditions that affect the brain in untreated AIDS can also cause dementia and at autopsy nearly all AIDS cases proved to have some form of pathology in the CNS. Unfortunately, the problem of HAD has not been eclipsed since HAART became available. Although the prognosis for HIV-infected individuals treated with HAART has changed immeasurably for the better, with a decline in the incidence of the more

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severe forms of HAD, neurocognitive disability in the form of mild neurocognitive disorder (MND) is still detectable in a significant proportion. The challenge remains to determine the cause of MND while accepting that HAD remains incompletely understood. Neuropathological investigation of the brain in HAART-treated individuals, including those with cognitive impairment, is likely to contribute in solving this problem so that preventive or protective strategies may be devised for long-term HIV-infected survivors. To assess the pathological findings in the brains of HAART-treated individuals, it is helpful to first consider the effects of HIV in the brain before HAART was introduced.

Neuropathology of HIV-Infected Subjects in the Pre-HAART Era

The mortality of untreated HIV infection is most often associated with symptomatic AIDS, resulting in many published studies relating to the neuropathology of this novel condition. There are far fewer studies of the autopsy brain in the pre-symptomatic stages of HIV infection, but these should not be neglected since there is evidence that HIV enters the brain compartment quite soon after initial infection and before the onset of AIDS.

Neuropathology in Untreated Pre-Symptomatic HIV-Infected Individuals

HIV-infected pre-symptomatic subjects rarely die before the onset of AIDS, since they generally have CD4 lymphocyte counts above 400 cells/μl and are not then vulnerable to the range of infections seen in the end stages. Drug abuse and overdoses, accidental or otherwise, are the usual reason for death in pre-AIDS and have provided opportunities to investigate CNS involvement in the pre-symptomatic phase of HIV infection (1, 2). Studies of a unique cohort of HIV-infected intravenous drug abusers in Edinburgh (UK), who were known to have acquired their infection in late 1983/early 1984, showed relatively minor changes in comparison with those seen in AIDS (1). Characteristic AIDS-related conditions, including HIVE and CNS opportunistic infections, such as toxoplasmosis, cytomegalovirus (CMV), varcella zoster virus (VZV) or Cryptococcus neoformans were found to be absent in pre-AIDS brains. Despite this, there is evidence of inflammation in the CNS of many of these subjects, in the form of a low grade lymphocytic leptomeningitis and perivascular lymphocytic cuffing, particularly in the central white matter (1, 2). The perivascular cuffs are composed predominantly of CD8 positive lymphocytes, although significant numbers of CD20 positive B lymphocytes are also present (3) .There is little evidence of CD4 T-lymphocytes within the infiltrates. In addition to lymphocyte responses in the pre-symptomatic brain, microglial activation has also been demonstrated,

together with subtle gliosis (4, 5). Mild axonal damage can sometimes be observed in the brains of pre-symptomatic subjects (6). This is demonstrated by the accumulation of molecules such as β amyloid precursor protein (βAPP), as a result of disrupted transport within affected axons. Axonal damage can be caused by a number of insults, including trauma, inflammation, and hypoxia, all of which may be operational in pre-symptomatic HIV-infected individuals.

These appearances are suggestive of a CNS response to viral infection, and there is evidence that HIV does enter the nervous system before the onset of AIDS (7). There is some evidence that the CD8 lymphocytic responses contribute to the control of viral infection in the early stages of the disease (8). It is unclear whether the activation of microglia and astrocytes is a direct result of virus penetration of the CNS compartment or whether it is simply an indirect effect of a vigorous systemic response to infection, driven by aberrant release of cytokines in the systemic compartment. In pre-symptomatic subjects, there is no evidence of productive HIV infection in any cell type. However, PCR studies have confirmed low levels of HIV in the brains of some pre-symptomatic subjects (2). There is still no conclusive evidence as to which brain cells are harbouring the virus in the early stages of infection. Analysis of the virus recovered from the brains of pre-symptomatic subjects reveals a genotype consistent with a normally macrophage (CCR5) tropic HIV variant, suggesting that microglia are the source (9).

Neuropathology of AIDS in the Pre-HAART Era

As HIV-infected subjects progressed into symptomatic AIDS before HAART became available, CD4 lymphocyte counts drop, leaving subjects vulnerable to opportunistic pathogens and tumour formation. Common opportunistic conditions observed in the CNS are shown in Table 1. The prevalence of opportunistic conditions varies somewhat depending on the geographic location of the cohort studied and the risk group for HIV exposure. These opportunistic conditions may be found in isolation or together, but there is no convincing evidence to date of synergy between them. HIVE itself may be found in isolation or together with one or more opportunistic conditions in the brain.

Table 1 Common opportunistic CNS conditions encountered during HIV/AIDS in the Edinburgh Cohort

Opportunistic condition	Pre-HAART (n=228)	Post HAART (n=42)
Cytomegalovirus (CMV) encephalitis	9%	5%
Primary Central Nervous System Lymphomas (PCNSL) driven by Epstein Barr virus (EBV)	6%	7%
Toxoplasmosis	5%	0%
Herpes simplex virus encephalitis	>1%	>1%
Progressive Multifocal Leukoencephalopathy (PML) (associated with JC virus infection of oligodendrocytes)	3%	3%
Varicella Zoster Virus encephalitis	>1%	>1%

CMV is promiscuous in its cellular targets and viral particles may be identified in endothelial cells, neurons and glial cells. Typically, the infected cell shows enlargement of the nucleus and/or the cytoplasm and viral inclusions may be identified in both. Two major forms of CMV encephalitis are described. The first of these is a microglial nodular encephalitis in which CMV inclusions may be quite hard to find. The other form displays more florid inflammation and CMV inclusion-bearing cells are relatively frequent in association with polymorphonuclear leucocytic infiltration and foci of necrosis.

Toxoplasma gondii is a protozoan that can exist in the brain parenchyma as free organisms or in the form of characteristic cysts. It can give rise to a necrotising encephalitis, particularly in the periventricular tissues, and the associated acute inflammatory exudate may spread to involve the ventricular cavities.

Cryptococcus is a fungus that, if it involves the CNS, causes a meningitis with a characteristic gelatinous exudate. If the infection spreads to the brain there is a predilection for the basal ganglia where small punctate cavities may become visible to the naked eye. The inflammatory reaction is usually quite sparse.

Progressive multifocal leucoencephalopathy (PML) results from the reactivation of a persistent papovavirus infection in the brain. This infection manifests itself as demyelinating lesions that are often periventricular or at the gray–white matter junction. The lesions may be necrotic and are associated with inclusion-bearing oligodendrocytes and enlarged, often bizarre astrocytes.

A few cases of herpes virus infections of the CNS other than CMV have been reported in AIDS. Herpes simplex virus (HSV) encephalitis is caused by infection with HSV1 or HSV2, initially latent within sensory ganglia and reactivated to target the limbic system causing a necrotising inflammation primarily in the temporal lobes. Inflammatory infiltrate may be diffuse in the meninges, and viral proteins and inclusion bodies can be identified in the affected areas. In a similar way, varicella zoster virus may spread from latently infected sensory ganglia to cause myelitis or encephalitis. However, these were rare complications of AIDS.

Primary central nervous system lymphomas (PCNSLs) are high-grade lymphomas of B-lymphocytic origin and are usually monoclonal. Epstein-Barr virus (EBV) is the aetiological agent that drives B-cell proliferation and eventual neoplastic transformation. EBV is present in almost 100% of AIDS-related PCNSLs (10–12). In nearly all instances, there is expression of two key EBV oncogenes LMP-1 and EBNA-2. Expression of LMP-1 leads to upregulation of anti-apoptotic genes such as BCL-2 in the infected B lymphocyte, while EBNA-2 is responsible for driving the infected cell into S-phase of the cell cycle (13, 14). The expression of these two proteins plays a key role in the immortalisation of B lymphocytes. PCNSLs are often diffuse and multifocal, with tumour cells forming concentric layers around blood vessels (Fig. 1). The tumours can be found in almost any location in the CNS, including the brain stem and spinal cord.

The immune dysfunction that results from HIV infection permits the development of the opportunistic conditions described earlier. However, HIV itself can also establish a primary infection within the brain. The predominant CNS target cells are microglia. These cells express low levels of CD4 antigen in addition to the

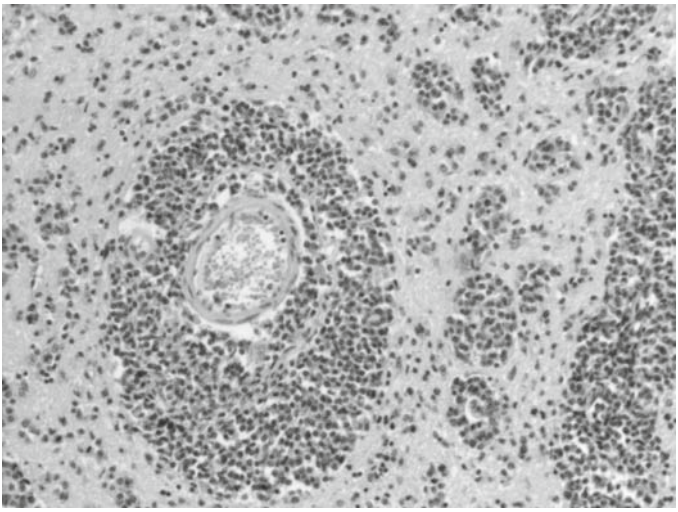

Fig. 1 Primary Central Nervous System Lymphoma in the brain of an AIDS patient. The Epstein-Barr Virus positive cells are of B lymphocyte origin and form in concentric rings around blood vessels

chemokine receptor CCR5 (15). Both perivascular and parenchymal microglia are capable of supporting productive HIV infection, giving rise to HIVE (16). The prevalence of HIVE in the pre-HAART era varied greatly between cohorts, ranging from 5 to 30% of cases (17–19).

During productive infection of the CNS a number HIV proteins may be detected immunohistochemically in microglia, including p24, gp41, gp120 and Nef(20–26). HIV-infected microglia may fuse to give rise to multinucleated giant cells (Fig. 2), which together with microglial nodules form the pathological hallmarks of HIVE (27, 28). A variable degree of macrophage infiltration and microglial activation is also present in HIVE, together with evidence of astrocytosis and myelin pallor or white-matter damage (29). Foci of HIVE may be present in any area of the brain, but the basal ganglia and central white matter are particularly affected, while the neocortical grey matter and brainstem are sometimes involved. The severity of HIVE also varies from mildly affected cases in which only a few productively infected microglia and/or giant cells are seen, to florid cases with numerous giant cells, widespread inflammation and extensive tissue damage. The variations in severity of HIVE are likely to contribute to the range of cognitive symptoms in untreated AIDS. Neuroimaging of patients with HAD reveals generalized white-matter reduction, with additional grey-matter loss, particularly in the basal ganglia and posterior cortex (30, 31). These findings fit with the general neuropathological findings in these cases. Neuronal loss has been described in HAD, and apoptotic cells are commonly found in the basal ganglia and to a lesser extent in other regions of the brain, including the hippocampus and frontal cortex (32, 33). Particular subsets of

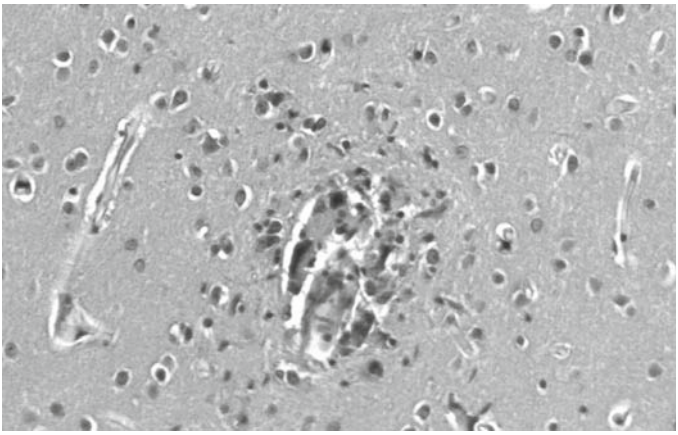

Fig. 2 HIV infected microglia may fuse to give rise to multinucleated giant cells, which together with microglial nodules form the pathological hallmarks of HIVE

neurons may be particularly vulnerable in HIV-related CNS damage. Axonal damage is also evident, with myelin pallor and accumulation of β amyloid precursor protein (βAPP) in axons, which displays focal axonal swellings and disruption of axonal transport. At a more subtle level, evidence of synaptic and dendritic damage has been reported in AIDS (34, 35). Animal models and in vitro systems have been used extensively to study the pathogenesis of HAD (36, 37).

There has been significant interest in the evidence of activated microglia and macrophages in the brain since the discovery that this was the feature that correlated most closely with the onset of HAD (38), irrespective of whether activated cells were actually HIV infected. Activation of microglia, particularly in the basal ganglia, and influx of macrophage/monocytes are prominent features in the brains of subjects with HAD and have been suggested by a number of authors to be the pathogenetic basis for the observed clinical symptoms (38–41). Although it is likely that neuronal loss and damage form the proximal substrate for cognitive impairment, the fact that microglial activation also correlates well with cognitive status engenders suspicion that these cells are the major source of neurotoxic molecules, such as pro-inflammatory cytokines, nitric oxide, free radicals and others, which lead to neuronal damage (42, 43). These microglia/macrophages display upregulation of a variety of cellular markers, including CD14, CD16, CD45, CD68 and MHC class II (17, 38, 43–47). The degree of activation and upregulation is also related to the type of infection present, whether it be opportunistic or HIV itself. Thus CMV encephalitis induces upregulation of CD68 on microglia. In contrast, toxoplasmosis preferentially upregulates MHC class II, while HIVE provokes upregulation of both markers (48). In addition to changes in the phenotype of resident microglial cells, increased influx of monocytes and macrophages from the blood has been reported (39, 40), possibly facilitated by changes in the blood–brain barrier (49).

In most subjects with CNS opportunistic infections or HIVE focal infiltrates of CD8 lymphocytes are present. However, it is unclear how effective these cytotoxic T cells are in late-stage AIDS when the systemic immune system is in a state of terminal dysfunction. The astrogliosis observed in AIDS may be more significant than just a reaction to neuronal and other damage in the CNS, since these cells are believed to be capable of supporting a restricted form of HIV infection (50, 51), which may cripple their neuronal glutamate buffering functions. However the extent of astrocyte infection in vivo remains unknown since the evidence of productive infection is not detected in these cells.

In occasional AIDS patients, even at advanced stages of immunosuppression, there is little evidence of significant CNS disease, and HIV-related disorders may not be evident in the brain at autopsy. However, the brain is rarely entirely normal even if the changes are minor and non-specific.

Some Effects of Drug Abuse in the Brain Mimic Those of HIV

Drug abuse is clearly a confounding factor in assessing the effects of HIV in the brains of pre-symptomatic and some AIDS subjects, and the influence of drug abuse on the CNS must be considered together with HIV in this context. The problem of drugs as possible co-factors for AIDS progression has been explored in animal models and in vitro (52). Drug abuse is known to cause mild activation of microglia, possibly adding to the neuroinflammatory response observed in pre-symptomatic subjects (5). Axonal injury as shown by expression of βAPP is also evident in the brains of HIV-negative drug abusers (53, 54) A number of studies have demonstrated other neuronal and dendritic damage in HIV-negative drug abusers (53–56). Some of this CNS damage is undoubtedly hypoxic/ischaemic in origin. Intravenous drug abusers are at risk of co-infection with hepatitis B or C. Liver dysfunction, particularly cirrhosis, can cause hepatic encephalopathy, contributing to cognitive problems in this group of subjects. Recently there has been growing interest in the possibility that hepatitis C can enter the CNS and infect the brain directly thus leading to signs and symptoms of brain dysfunction (57–59).

Neuropathological Findings in the Post-HAART Era

The introduction of HAART has resulted in a marked improvement in the prognosis for HIV-infected subjects, with HIV becoming a chronic disease in those who are compliant with long–term HAART. AIDS defining illnesses are no longer the major cause of death in HIV. Instead other factors such as hepatitis C infection are becoming important in HIV-related mortality. Drug abuse continues to contribute to mortality in these circumstances. The benefits of HAART are apparent not just in the systemic organ systems, but also in terms of CNS disorders despite the poor penetration of

the brain by some of the drugs used in HAART (60). Since the effect of HAART is to limit disease progression and maintain treated subjects in a state of partial immune competence, it would seem logical to predict that post-HAART neuropathology would closely resemble that observed in pre-symptomatic subjects in the pre-HAART era. However, the evidence accumulated to date suggests that this is not the case. There is a continued concern that the CNS acts as a sanctuary site for viral persistence and for the emergence of drug resistant HIV and that HAART is not successful in eradicating HIV from the brain compartment (16, 61, 62).

Although the incidence of HAD has decreased since the introduction of HAART, there has been a rise in reports of more minor cognitive dysfunctions (63, 64). In addition clinical reports suggest that the regions of the brain maximally affected in HIV have altered (65). In the pre-HAART era subjects with HAD displayed primarily sub-cortical symptoms that correlated well with pathological findings of damage and inflammation in the basal ganglia. Post-HAART, clinical symptomatology in some studies points towards damage in the hippocampus and temporal lobe, although sub-cortical neurodegeneration characteristic of the pre-HAART era is still noted in some studies (66, 67). Dementia is reported as more common in older HIV-positive individuals, suggesting they are more at risk of this complication (68).

The success of HAART in reducing mortality rates has meant that opportunities for autopsy-related study of the effects of HIV on the brain have become much less common. Nevertheless small cohorts of clinically well characterised, HAART-treated subjects have been examined at post-mortem by a number of groups in the US and Europe. It is important to note that the cause of death in these cases may not be directly attributable to HIV or to a failure of HAART to control the virus. As noted above, both drug abuse and hepatitis may influence the neuropathological outcomes in these subjects. Others who have been treated with HAART may indeed die after failure of therapy, either because of viral resistance or more likely intolerance of the drug regime. If the period between withdrawal of therapy and death is relatively long, then any changes observed in the brain may not be representative of those to be found in well-treated subjects. These considerations underline the importance of pursuing studies in clearly defined groups of patients with well-documented clinical details.

The incidence of most of the major CNS complications that were observed prior to the introduction of HAART has fallen. Table 1 shows the changes in the Edinburgh cohort since the introduction of HAART. There has been a marked decline in the incidence of CMV and of toxoplasmosis. The US Multicenter AIDS Cohort Study (MACS) has also shown a significant decrease in the incidence of cryptococcal meningitis and CNS lymphoma, with a non-significant decrease in toxoplasmosis. The incidence of PML dropped only marginally (69). Some studies have reported an actual increase in HIVE or more severe forms of HIV-related brain disease in HAART-treated individuals (70–73). Gray et al. have shown that in the French cohort there is a decreased incidence of cerebral toxoplasmosis and CMV encephalitis, with the incidence of PML and PCNSL unchanged (72). Gray et al. also report an increase in varicella zoster encephalitis and herpes simplex encephalitis, both previously rare neurological complications of HIV. The decline in opportunistic conditions is undoubtedly due to the HAART-induced recovery of the systemic

immune system, providing greater protection against common pathogens. Those opportunistic conditions that continue to pose problems may be due to the reactivation of persistent infections as in PML. Reports of HIV resistance to many of the drugs used in the HAART combination are becoming increasingly common, causing concern about the return of rising opportunistic infections. Data from the Centers for Disease Control (USA) suggest that approximately 15.2% of new HIV diagnoses possess strains resistant to at least one antiretroviral drug, with 3.2% being resistant to two or more drugs (74).

One HAART-related effect that has attracted much comment is the emergence of a new condition termed the *immune reconstitution syndrome* (IRIS). In IRIS cases a sudden and usually fatal episode of encephalopathy follows the commencement of HAART and is associated with extensive demyelination and white-matter damage (75, 76). The myelin damage is accompanied by marked CD8 lymphocytic infiltrate of the brain parenchyma, suggesting that an immunological pathogenesis (75). In most subjects HAART has a positive effect on the systemic immune system, resulting in increased CD4 counts and restoration of immune function. The subsequent upturn in the numbers of circulating CD4 and CD8 lymphocytes may result in sudden massive influx of these cells into the brain (75). No information is available with regard to the viral load in brain tissue in these cases. Although there is an assumption that the observed demyelination is caused by the influx of auto-immune lymphocytes into the brain, it should be noted that CD8 lymphocytic infiltrate of the brain is also prominent in some pre-symptomatic individuals without obvious myelin damage. Equally, the majority of patients started on HAART do not display the signs and symptoms of IRIS, suggesting that those individuals who do develop this condition have additional factors that drive their recovering immune system in the direction of autoimmunity. The factors involved in this process are unclear, but given the role of the thymus in the elimination of auto-immune cells during development it seems possible that this organ may play a role in IRIS.

Even in the absence of overt HIV-related pathology, significant changes have been observed in the brains of HAART-treated subjects, including neuroinflammation in the form of significant microglial upregulation of MHC class II and CD68 (17). This is particularly prominent in the hippocampus and temporal cortex. In contrast, the basal ganglia are relatively quiescent in this respect. This finding highlights the shifting pathology in the HIV-infected brain since the introduction of HAART and correlates well with the clinical findings. Kusdra et al. showed a significant rise in CD14/CD69 cells in the blood of HAART-treated individuals with HAD as compared with non-demented HAART subjects (77).

It has been postulated for some time that those who survive long term with HIV in the HAART era will be predisposed to the early onset of neurodegenerative conditions, principally Alzheimer's disease (78). In part this relates to the view held by some that neuroinflammation may make a significant contribution to the early stages of Alzheimer's disease (79, 80). There is pathological evidence to support this hypothesis. Gelman and Schuenke (81) showed increased levels of ubiquitin–protein complexes and decreased synaptophysin in AIDS subjects compared with controls (81). Green et al. have shown elevated levels of β-amyloid in the brains of

HAART-treated subjects (82). However, this finding has not been replicated in other studies (83) although in vitro studies suggest that HIV proteins elevate amyloid levels by inhibiting neprilysin(84). β-amyloid is one of the two key pathological proteins found in Alzheimer's disease, the second key protein is an aberrant version of the neuronal protein Tau.

Hyperphosphorylated Tau has been shown to accumulate at an accelerated rate in HIV-infected subjects treated with HAART (83). Tau is a microtubule associated protein mainly expressed in neurons of the CNS. It has a central role in the formation and stabilisation of microtubules, which are essential structural components of the cell and which also facilitate the traffic of organelles along axons and dendrites. Tau is phosphorylated and de-phosphorylated as part of the normal biology of the cell; the protein has multiple phosphorylation sites, which are utilised in this normal process (Fig. 3). Tau binding and the stabilisation of microtubules is controlled by the phosphorylation state of the Tau protein. Phosphorylation of Tau leads to dissociation of Tau from microtubules, which promotes microtubule instability. This is part of normal cell functioning for remodelling and growth. However, hyperphosphorylation of Tau is abnormal and can lead to the formation and deposition of paired helical filament (PHF) Tau in the form of insoluble neuritic threads, neurofibrillary pre-tangles and tangles.

In the adult human brain, six isoforms of Tau are expressed by alternative mRNA splicing from a single gene. Abnormalities in Tau mRNA splicing are linked with frontotemporal dementia and parkinsonism linked to chromosome 17, and similar alterations are suggested in sporadic tauopathies, such as progressive supranuclear palsy or corticobasal degeneration (85). Alterations in Tau mRNA have also been linked with alterations in neurofilament gene expression, suggesting that these structural support proteins of the neuron are intrinsically linked to the degenerative process (85). In vitro studies have shown altered neurofilament gene expression in neuronal co-cultures exposed to supernatant from HAART-treated macrophages (77). Changes in neural cell signalling proteins as well as structural and functional proteins may represent subtle forms of cellular dysfunction rather than frank cell death (77).

Hyperphosphorylated versions of the Tau protein accumulate in the brain with increasing age at low to moderate levels. Higher (pathological) levels of Tau are observed in the tauopathies (86–88). Neurofibrillary tangles (NFTs) are one of two diagnostic pathological observations in Alzheimer's disease. NFTs fill the neuronal soma, leading to loss of structural integrity in the affected neurons and eventually to cell death, while the presence of hyperphosphorylated PHF Tau in neurites may interfere with structural integrity of the axon or dendrite in addition to disrupting axonal or dendritic transport.

The phosphorylation state of Tau is controlled by a series of kinases and phosphatases, several of which can potentially be influenced by both direct and indirect effects of HIV and/or HAART. Enzymes that play a part in controlling Tau phosphorylation includes glycogen synthase kinase 3β (GSK-3β), cyclin dependant kinase 5 (CDK-5) protein phosphatase 1 (PP-1) and PP2b.

The predominant regions of the HAART-treated brain in which Tau accumulations occur are the hippocampus, temporal cortex and frontal cortex. The thalamus is also

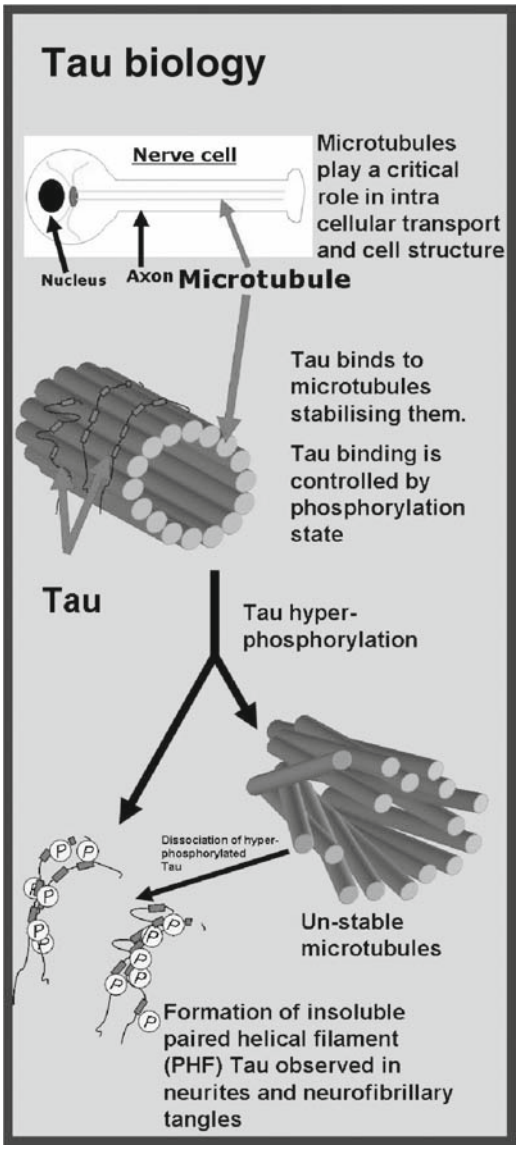

Fig. 3 The Biology of Tau Protein

affected though to a lesser degree. Interestingly there is little evidence of Tau deposition in the basal ganglia or in the brain stem. Evidence of T au pathology includes the presence of neurof ibrillary tangles and pre-tangles (Fig. 4). Ho wever, the most prominent feature is the accumulation of hyperphosphorylated T au in neuritis (Fig. 5 and 6). These Tau-related changes show a strong correlation with the expression of the enzymes GSK-3ß and CDK-5. The HIV protein T at has the potential to upregulate GSK-3ß activity in vitro (89). Tau-related changes are not observ ed in

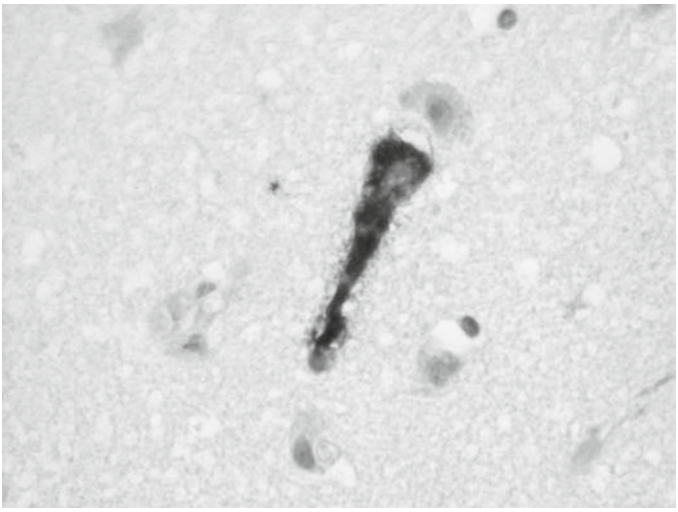

Fig. 4 Hyperphosphorylated Tau in the Neuronal Cell Body

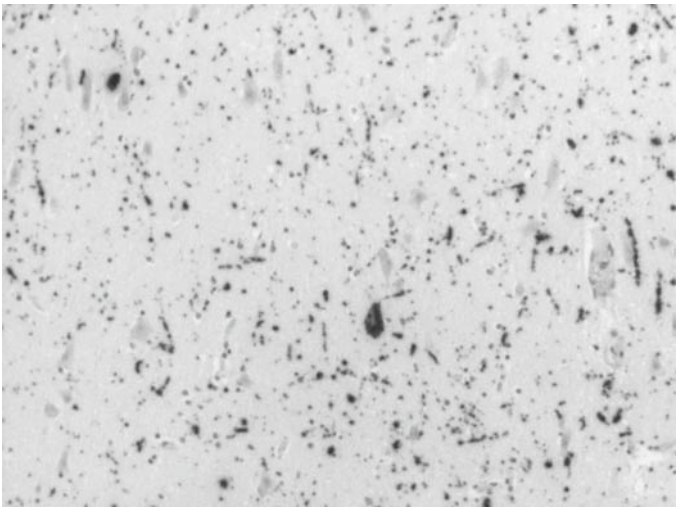

Fig. 5 Hyperphosphorylated Tau Accumulating in Distal Neurites

pre-HAART subjects, thus raising the question of whether HAART itself is inducing this pathology. Other potential confounding factors include drug abuse and hepatitis C as before. However, while drug abuse alone has been shown to induce similar Tau-related changes (53), elevated levels of hyperphosphorylated Tau are found in HIV-infected HAART-treated subjects in both drug abusers and non-drug abusers.

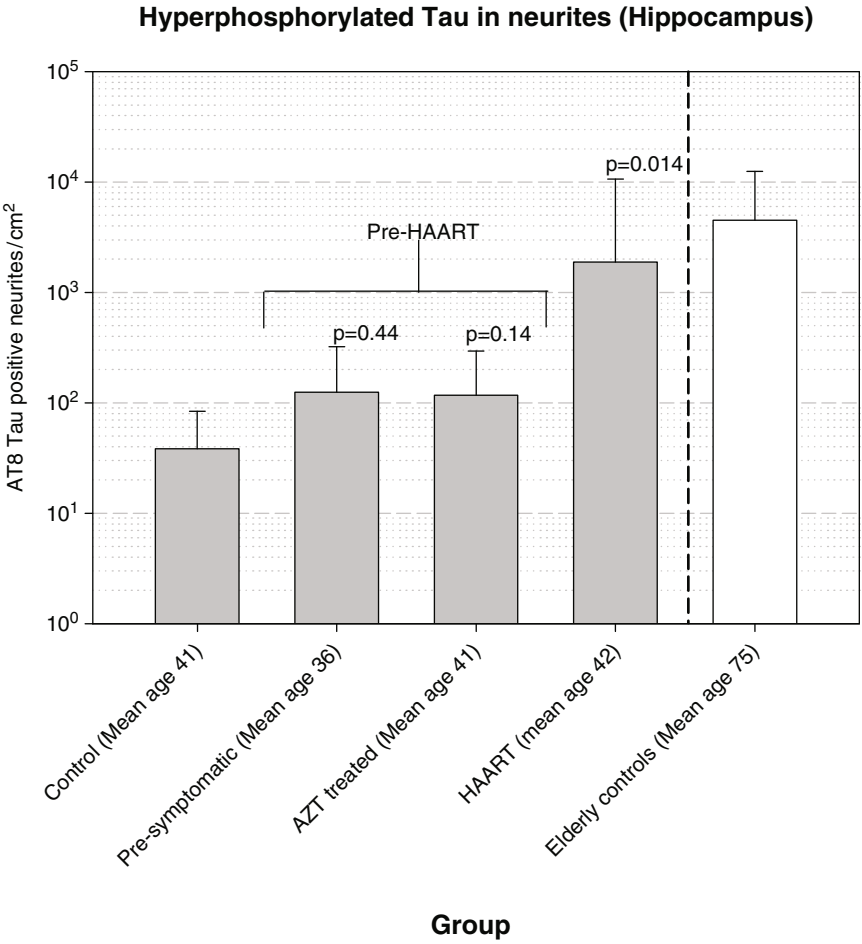

Fig. 6 Quantitation of Hyperphosphorylated Tau in Neurites

Equally, while hepatitis C is highly prevalent in HIV-infected subjects, co-infection does not correlate well with the presence of hyperphosphorylated T au. HAART is well recognised for its toxicity , particularly to mitochondria, and it may be that mitochondrial damage plays a k ey role in the upre gulation of GSK-3ß, which in turn promotes Tau phosphorylation (Fig. 7). It is of interest that sodium v alproate, which inhibits GSK-3ß, is under investigation as a therapeutic agent to achieve this in the clinical setting (90).

A recent study has sho wn that levels of Tau are increased in the cerebrospinal fluid (CSF) in HIV-infected individuals while the levels of β amyloid were reduced, showing similarity to the CSF findings in Alzheimer's disease (91).

In addition to the accumulation of neurode generative proteins, other mechanisms may be contrib uting to cumulati ve brain damage. Although there is little understanding at present of ho w neural progenitor cells contrib ute to the normal

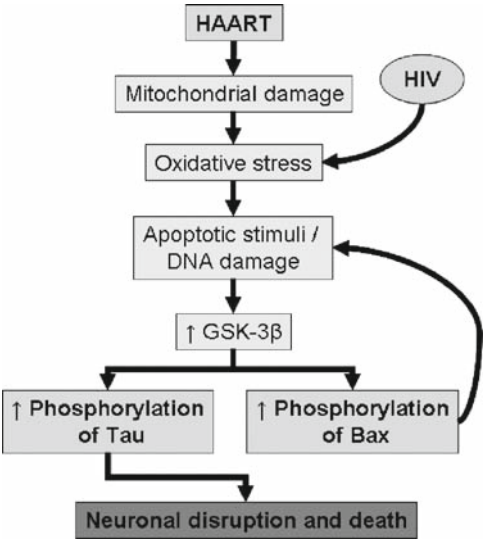

Fig. 7 Potential Mechanisms for T au De-regulation and Dysfunction during HIV infection

maintenance of the human brain if at all, it is noted that these cells e xpress high levels of chemokine receptors, are vulnerable to neuroinflammatory c ytokines, undergo apoptosis, and are capable of being infected with HIV (92–94).

Conclusions

The brain represents a viral sanctuary in HAART-treated individuals, and developing an understanding of how the virus persists and evolves at this site is critical to further improving the treatment for infected subjects.

The incidence of common CNS complications such as HIV-associated dementia, HIVE and many CNS opportunistic infections has declined since the introduction of HAART, but none have been completely eliminated. As the number of HIV-infected subjects rises year on year, the prevalence of many of these conditions is actually increasing despite the fall in incidence rates.

New forms of cogniti ve deficits have been identif ied in the HAAR T era and these are undoubtedly the result of new forms of pathology, which were not previously observed in HIV. Cognitive impairment is often more cortical than sub-cortical and this is reflected in a shift in pathology to neocortex rather than the basal ganglia. The major pathological changes are persistent and elevated levels of neuroinflammation coupled with the presence of neurodegenerative proteins such as hyperphosphorylated Tau. All of the current data point to progressi ve neurodegeneration in subjects maintained long term on HAART.

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Biomarkers of HIV-Related Central Nervous System Disease

Bruce James Brew and Scott Letendre

Introduction

Biomarkers are important, some would say essential, for the management of patients with HIV-related central nervous system (CNS) disease. However, at present there is much that still needs to be done. It would be premature to say that they have reached the point in their development at which they could, or even should, be used routinely. That said though, it should be stressed that an appreciation of the field is important: there are some areas that can be used in day to day clinical practice. In this review, we have focused on HIV-related brain disease (HBD) in the form of dementia (HIV-associated dementia – HAD) as well as its less-severe manifestations namely Minor neurocognitive disorder (MND) and asymptomatic neurocognitive impairment. Biomarkers of opportunistic HIV-related brain complications are largely available, for example cryptococcal antigen. This review will be confined to biomarkers of HBD and will focus on those measured in the blood or cerebrospinal fluid (CSF). In addition, this chapter will focus on the older nomenclature for HIV-related cognitive disorders.

There are several reasons for the importance and need for biomarkers in HIV-CNS disease. First, an objective marker(s) that could diagnose or predict the presence and severity of HBD has been a critically important and largely unmet clinical need since the advent of the epidemic. Several markers have been evaluated to date, but they have been largely nonspecific for HAD or MND. The acuity of this need is linked to the logistical challenges of diagnosing these conditions in resource-limited settings and to selection of the antiretroviral drugs that are most effective in the CNS. The specificity of a diagnostic marker is essential in clinical situations that are increasingly complex and diverse. For example, affected patients often have confounding conditions. In the pre-HAART era, these were opportunistic infections or tumors.

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In the era of highly active antiretroviral therapy (HAART), increasing numbers of patients are developing more chronic conditions, such as hypertension, vascular disease, and viral hepatitis, that can potentially confound attribution of cognitive impairment to HIV. A marker of the severity of HBD could provide an objective measure of the quantum of the deficit that was related to HIV, as opposed to the confounding condition. This would inform the aggressiveness of the clinical intervention, obviating the need for a wait and see approach, which was used previously.

Second, recent data support the existence of different clinical phenotypes of HBD, including an inactive form, in which there is no ongoing brain damage, both at clinical and subclinical levels. The ability to identify inactive disease *in real time* using a marker, as opposed to serial testing over weeks, is clearly desirable. Indeed, the identification of disease activity is clinically important for two reasons. Unrecognized inactive disease may mean that the patient is given new antiretroviral drugs needlessly with the consequent increased risk of toxicity. Further, the lack of recognition of disease activity in clinical trials could lead to the inclusion of a sizeable number of patients with inactive disease leading to the premature conclusion of a trial of a novel agent because of the misperception of the agent's inefficacy, when in fact the trial patients did not have active disease that would allow the agent to work.

Third, a marker(s) that can diagnose the presence and activity of HBD would be invaluable in clinical trials. It is becoming increasingly apparent that the trials of investigational drugs must be on a background of optimal HAART. In such a situation, the degree and rapidity of clinical improvement is likely to be small and slow. A sensitive surrogate marker could mean faster delivery of effective new agents to the pharmaceutical armamentarium.

Fourth, a reliable marker would be helpful at the level of the individual patient in assisting the assessment of response to antiretroviral drugs. While it is clear that such response can be assessed clinically, it is equally clear that clinical response can take weeks or even months. A marker that can predict clinical response would be valuable.

The approach taken in this review will deliberately be synthetic with a clear clinical practical orientation. We have not detailed every study of every biomarker that has been explored. Rather we have attempted to integrate the data into a cohesive whole that will either have direct clinical practicality or will at the very least provide the clinician with an appreciation of the area that will facilitate understanding of future markers.

Many biomarkers have been described; broadly these can be divided into those related to pathogenesis and those related to the relevant cells. For example, monocyte chemotactic protein (MCP)-1 induces migration of replication-competent monocytes across the blood–brain barrier, which may increase the production of neurotoxic HIV-encoded proteins in the CNS. The second category contains markers reflecting the state of cells (for example, activation or injury) that play roles in these processes but not thought to be involved in pathogenesis: neurofilament-light reflects injury of neurons, but is not thought to reflect a mechanism of injury. We have chosen to meld the two categories using a pathogenetic framework. Although it is true that the pathogenesis of HBD is not completely understood, the general features are

reasonably appreciated. In broad terms, the disorder can be divided into effectors (host cells or HIV), modulators, toxins, and target(s), and within these there are the mononuclear cells, microglia, astrocytes, neurons, endothelial cells, and the blood–brain barrier. In addition to this unidirectional schema of disease causation, there is also the reverse component, namely repair.

Principles

Several principles are critical to appreciate not only for the understanding of the potential for a marker to be valuable in management but also in relation to the interpretation of existing tests, especially those in the CSF.

The first is that HIV disease is heterogeneous. This may seem self-evident but the concept extends beyond the issue of opportunistic conditions. HIV-infected individuals differ in their likelihood of having brain disease according to several fundamental factors – the most important being CD4 cell count and HIV replication, at least in untreated patients. Disease duration may also be a factor, although the evidence is less clear at present. Thus, studies must use appropriately matched controls to validate the efficacy of a particular marker.

Second, brain injury is not a universal complication of HIV infection even if patients have lived with HIV infection for an extended period. Consequently, studies must include sufficient subjects who have or who are likely to have HIV-related brain disease. In the pre-HAART era, approximately 20% of patients with advanced HIV disease would be expected to develop HIV-associated dementia. The proportion of subjects who will develop HAD, at least of moderate-to-severe intensity, in the HAART era is much smaller.

Third, it is important to appreciate that antiretroviral drugs differ in their distribution characteristics and neurologic effectiveness. Evidence is accumulating that at least three such neurologically effective drugs provide better treatment for HBD (1). Thus, accounting for interindividual differences in antiretroviral distribution characteristics, as well as the duration of therapy, may bias the results of marker studies involving subjects on HAART.

Fourth, the blood–brain barrier can be injured during HIV infection and as such may not competently exclude markers at the endothelial lumen from the CNS. Thus, accounting for interindividual differences in blood–brain barrier injury is probably important when interpreting the analyses of markers in the CSF, particularly if appropriate controls are not studied.

At the level of individual patient assessment, clinicians should be aware of several concepts, each of which may potentially interfere with interpretation of the significance of a particular marker (2). The first concept is that of "layering," that is to say, several abnormalities are frequently layered one upon another in HIV disease. This is especially true of CSF analyses and brain imaging. For example, a mild mononuclear pleocytosis is often found in HIV disease and may be attributable to the disease itself without any clear clinical significance. Furthermore, there is the concept of parallel tracking – several conditions occur in different parts of the

neuroaxis at the same time, sometimes leading to difficulties in clinical assessment as well as interpretation of test results. For example, vacuolar myelopathy often occurs with HAD at least in the pre-HAART era, thereby making the diagnostic interpretation of biomarkers associated with white-matter damage potentially difficult. Finally, clinicians should be aware of the increasingly important issue of confounding conditions, especially as patients live longer. Such conditions may be difficult to diagnose and may compound existing predispositions to brain injury. New biomarkers should be cautiously applied in such patients – they may have limited utility because of the confounding conditions.

Overview

Biomarkers associated with HBD should confirm the diagnosis and, when possible, exclude other disorders that may be playing a contributory role. This review first discusses markers from a pathogenic perspective – categorizing markers as reflecting effector cells, modulators of pathogenesis, toxins, or target cells – and then discusses markers that are practical for confirmation of HBD followed by those that are exclusionary. Finally, there is a brief discussion of the probable future for biomarkers.

Effector Cells

Lymphocytes

CD4Cell Count

While the CD4 cell count per se is not a direct marker of the effector cells or toxins associated with HBD, it is a useful indirect marker. At least in the pre-HAART era and in untreated patients, HAD occurred most often in patients with advanced HIV disease – usually at the time of vulnerability to opportunistic conditions, namely CD4 counts below 200/μL (3). Indeed, the lower the CD4 count the greater the risk of development of HAD (3). This probably reflected impaired immune control with increased viral replication and compensatory but ineffective immune activation.

In HAART-treated patients the association has changed. The CD4 count in treated patients now is much higher and indeed in some cases it is normal (4, 5). There are several potential explanations for this change, including a greater number of survivors due to the effects of HAART, as well as the presence of inactive disease in some. Increasing evidence now points to the value of the nadir, rather than the current, CD4 cell count (5–7).

β-2-Microglobulin

β-2 microglobulin (β_2M) is the invariant light chain of the major histocompatibility complex class I. It is constitutively expressed on the surface of all nucleated cells with the exception of neurons and is particularly highly expressed on lymphocytes, thus serving as a marker of such cells. In the case of HIV disease, it seems that CSF β_2M dominantly reflects cytotoxic T cells. Again it is not surprising that elevated concentrations are nonspecific, with raised concentrations being found in both inflammatory and lymphoproliferative conditions (8). CSF β_2M correlates well with the severity of HAD (8). A cutoff value for CSF β_2M at 3.8 mg/L had a sensitivity for HAD diagnosis of 44%, specificity of 90%, and a positive predictive value of 88% in the pre-HAART era (9). CSF β_2M levels also fall with successful treatment of HIV (8, 10), including in HAD patients. Raised CSF β_2M concentrations confer an increased risk of HAD in patients with advanced HIV disease (11).

Monocytes

CD14+/CD69+Monocytes

Most investigators consider the monocyte/macrophage to be important in HBD pathogenesis. Increased numbers of the subset CD14lo/CD69hi in the peripheral blood appear to be important (12), but they are nonspecific as they can be elevated in the presence of coexisting infection. Pulliam et al. were the first to describe increased numbers of the subset and their correlation with HAD (12). The prognostic significance of an elevation of this subset in asymptomatic patients is presently unknown. HAART reduced this subset in one study (13).

One group (14) measured this subset in a large number of patients, although none was demented. Patients who were on a HAART regimen containing a protease inhibitor were most likely to have significant elevations in this monocyte subset in the CSF. Both the reason for this and its prognostic significance are unknown.

SolubleCD14 (sCD14)

Soluble CD14 is found principally on human monocytes, exists in both membrane and soluble forms (15), and is released by stimulated monocytes in vitro. Elevations in serum are associated with HIV disease progression in vivo (16, 17). Ryan reported that sCD14 concentrations were higher in plasma in cognitively impaired compared with those from unimpaired subjects taking combination antiretroviral therapies (18). An important distinction from other markers of macrophage activation may be that in the CNS; sCD14 may derive primarily from trafficking monocytes and perivascular macrophages, rather than native microglia (19). As such, sCD14 may indicate interindividual differences in infiltration of immune cells into the CNS. If levels of sCD14 correlate with those of CD14+/CD69+, they may be a more clinically accessible

indicator of CD14+/CD69+ cell numbers, since they can be measured by simple ELISA rather than specialized flow cytometry. Although HAART can decrease sCD14 levels (13), detection of high levels may identify those at risk for subsequent neurological injury, although no validation of this concept yet exists.

Neopterin

Neopterin is a product of guanosine triphosphate metabolism (20). It is mainly produced by activated monocytes, macrophages, and microglia (21), and as such serves as a marker for such cells. Consequently, it is not surprising that high CSF concentrations are found in patients with opportunistic CNS infections as well as HAD. Furthermore, the CSF concentrations correlate with HAD severity (21). Elevated CSF concentrations increase the risk of HAD at least in patients with advanced HIV disease (11). The CSF neopterin levels decrease with antiretroviral therapy (21). However, after 2 years of virologic suppression, only 55% had normal CSF neopterin levels (22). What this means in terms of the risk of later development of HAD is unknown.

Quinolinic Acid

Quinolinic acid (QUIN) is a product of the kynurenine pathway, the principal degradative pathway for tryptophan metabolism (23). It is produced by monocytes after stimulation by a number of agents, especially by interferon-γ (IFN-γ) and HIV proteins. It is important as it not only reflects monocyte activation but is a toxin in itself: QUIN is an agonist of *N*-methyl-D-aspartate receptors and so can lead to excitotoxic cell death. Furthermore, it can cause cell death through lipid peroxidation and the generation of free radicals (24). At present, QUIN can be measured only by gas chromatography/mass spectrometry.

Increased CSF QUIN concentrations may be seen in opportunistic conditions as well as HAD (25). CSF QUIN levels are correlated with the severity of HAD (23). There is only one small study showing that elevated CSF concentrations confer an increased risk of HAD through increased psychomotor slowing (25). CSF QUIN is also relatively unique in that it reflects disease activity within the brain – QUIN cannot cross an intact blood–brain barrier at least in the short term, so elevated CSF concentrations usually indicate an intrathecal process (26). Only CSF S100b, neurofilament-light (NFL), and tau have such brain specificity. CSF QUIN levels fall rapidly with antiretroviral treatment (23, 26).

Microglia

At present there is no specific marker of microglia. The development of such a marker would be of considerable benefit given the fact that the degree of activation of microglia is the best correlate of the presence and severity of HAD in neuropathological

terms (27). Thus, for the moment, CSF markers of microglia are inferred from those previously discussed in relation to monocytes.

Astrocytes

S-100β

S-100 is an acidic calcium-binding protein that exists in dimer forms of α and β subunits. S100β is virtually exclusively found in astrocytes (28). As such it is one of the few biomarkers that reflects brain damage with astrocytosis. S100β may be more than just a marker of astrocytosis as high concentrations may lead to neuronal apoptosis (29). Elevated CSF S100β concentrations occur in any condition that causes astrocytosis. Raised levels occur in patients with either moderate or severe HAD and predict rapid progression to death (28). There are no published data on response to HAART.

Glial Fibrillary Acid Protein (GFAP)

GFAP is another protein produced by astrocytes, but its levels in CSF do not appear to have a role in HBD or at least HAD (30).

Modulators

HIV primarily targets cells of the immune system, and so measuring modulators of immune activation or suppression are rational foci for biomarker investigations. Many critical interactions among cells of the immune system are controlled by soluble mediators called cytokines, a diverse group of intercellular signaling peptides and glycoproteins. Each is produced by particular cell types in response to a variety of stimuli and produces characteristic effects on the growth, mobility, differentiation, or function of target cells. Collectively, they regulate immune and inflammatory responses as well as healing, hematopoiesis, angiogenesis, and many other biologic processes (31).

Interleukins

The most studied interleukins are produced by two types of cells, helper T lymphocytes, the primary targets of HIV, and macrophages, the cells that play a central role in HIV neuropathogenesis. The interleukins produced by helper T lymphocytes are typically categorized as being produced by Th1 cells (for example, IL-2), which generally activate macrophages, or Th2 cells (for example, IL-6, IL-10), which

generally activate B lymphocytes. Others, such as IL-1, are not produced by Th1 or Th2 lymphocytes but instead are produced by macrophages and other antigen presenting cells and can promote inflammation.

The interleukin family is large and diverse but most interleukin studies in neuroAIDS focused on just three members, IL-1, IL-2, or IL-6. Among six studies that measured IL-1, four identified a relationship with HBD, either in adults (32, 33) or in children (34, 35). Most of the nine studies that measured IL-6 also identified associations with brain injury, in either adults (32, 33, 36, 37) or children (34, 35). In contrast, none of the studies of IL-2 identified associations with neurologic disease. In fact, only three studies even compared IL-2 or its soluble receptor to a measure of brain injury (32, 38, 39). Of the interleukins measured in other studies (40–42), only IL-10 was associated with HBD, which was identified by one of the two largest studies in this series (43).

As IL-1β, IL-6, and IL-10, but not IL-2, are produced by antigen presenting cells, such as macrophages, these findings are consistent with the central role of macrophages, but not Th1 lymphocytes, in HIV neuropathogenesis. Th2 lymphocytes can also produce IL-6 and IL-10, and so the findings may also implicate these cells in HIV neuropathogenesis.

TNF Superfamily Proteins

Tumor necrosis factor (TNF) is the prototype of a family of molecules that are involved with immune regulation and inflammation (44, 45). Receptors for TNF and other proteins, such as soluble Fas and CD30, constitute a superfamily of related proteins (46–50). The prototypical member of the superfamily, TNF-α, is produced by activated macrophages and microglia and plays a central role in several pathologic processes. In HIV disease, TNF-α can upregulate HIV replication (51). Indeed, mRNA expression of TNF-α is elevated in the brain tissue of individuals with HAD (52–54).

Most studies that measured TNF-α in CSF identified associations with measures of brain injury, including clinical staging, HIV RNA levels in CSF, and focal CNS damage (33, 36, 53, 55–60). Most of the studies that reported no association with brain injury were unable to detect TNF-α in most or all of the specimens.

Among studies of other TNF superfamily proteins, five reported that levels of soluble TNF receptors (sTNFRs) were elevated in CSF in HIV-infected individuals and both studies that compared these levels to a neurological outcome identified an association (61, 62). Of interest, one study identified persistently elevated levels of sTNFR-II in CSF despite effective antiretroviral therapy, supporting persistent neuroinflammation in these individuals (63).

Three studies measured levels of the apoptosis-associated proteins, soluble Fas (sFas)/TNFRSF6, and Fas ligand (FasL)/TNFSF6, and identified associations between higher levels of sFas and HAD (64–66). In a recent analysis, the HNRC GROUP measured ten biomarkers, including sFas, in 29 HIV-infected, cognitively impaired subjects before and 12 weeks after a change in antiretroviral therapy (67).

In multivariate analyses, cognitive improvements were associated with reductions in sFas, even after adjusting for multiple, potentially confounding conditions.

Thus, a preponderance of the studies that have reported on TNF superfamily proteins in CSF to date have identified links with HBD. These findings are most consistent for proteins other than TNF-α, though, perhaps because endogenous regulation of this potent proinflammatory cytokine makes it difficult to measure in body fluids. Strong evidence exists that sTNFRs (63) and sFas (67) can be detected in body fluids despite antiretroviral therapy, supporting that these proteins might be useful biomarkers of ongoing neuroinflammation in treated individuals.

Interferons and Interferon-Inducible Proteins

The interferons (IFNs) are a family of cytokines that can be categorized into two major subgroups, type I (IFN-α, β, ω, and κ) and type II (IFN-γ), based on their properties and cellular receptors. In the brain, astrocytes and microglia in particular can produce IFN-α. This endogenous IFN-α may help to protect the brain from viral infections, but with prolonged exposure and/or high concentrations, may injure the brain. For example, transgenic mice that overproduce IFN-α in astrocytes have a high incidence of severe neuropathology, manifesting as intractable seizures and early death (68). The expression of IFN-α is also elevated in the brains of patients with HIV encephalitis and correlates with the severity of antemortem cognitive impairment. IFNs can induce the expression of over 300 different genes, some of which may be the actual mediators of the antiviral and antitumor effects of IFNs (69). Some, however, may also promote pro-apoptotic actions (70) that could lead to neurodegeneration.

Three studies have measured IFN-α and three others have measured IFN-γ in CSF. All three studies of IFN-α in CSF identified that higher levels were associated with HAD (71–73). Two of these also linked higher IFN-α levels to higher HIV RNA levels in CSF (71, 72), indicating ineffectual antiviral activity. Two of the three studies of IFN-γ identified higher levels in HIV-infected individuals (74, 75), although a third was unable to detect IFN-γ in CSF (76) and none of the studies identified links to HBD.

Four studies reported levels of the interferon-inducible protein, IP-10. Two compared IP-10 levels to HIV RNA levels in CSF and identified statistically significant correlations (63, 77). Gisolf et al. identified that IP-10 was elevated in some subjects despite apparent control of HIV replication in CSF, similar to their findings with sTNFR-II (63). The two studies that compared IP-10 to brain injury both identifed links between higher levels and adverse neurologic outcomes (41, 78).

These studies implicate IFN-α and IP-10 more than IFN-γ in HIV neuropathogenesis. Notably, all three studies that measured IFN-γ were published prior to 1992, whereas nearly all of the studies on IFN-α and IP-10 were performed after 1996. Thus, the advent of HAART in 1996 and its resulting impact on the neurologic complications of HIV could account for important differences in the findings of these studies.

Chemokines

Multiple lines of evidence support the role of chemokine receptors and chemokines in HIV neuropathogenesis. For example, in vitro studies first recognized that HIV could induce expression of MCP-1/CCL2 from astrocytes (79) and that MCP-1 can potently induce chemotaxis of monocytes across endothelial barriers (80). Human studies corroborated these observations, identifying MCP-1 on brain macrophages of subjects dying with HIV encephalitis (81) and genetic associations with HAD (82). Fifteen published studies have reported levels of MCP-1 in CSF in HIV-infected individuals, making it one of the most studied biomarkers of the HAART era. Of the nine studies that compared levels to a neurologic outcome, eight identified associations between higher MCP-1 levels and worse outcomes (40, 60, 79, 83–87).

A smaller number of studies compared the levels of CC chemokines, MIP-1 α, MIP-1β, and RANTES to neurologic outcomes. These chemokines bind to CCR-5, the most commonly used receptor by HIV for entry into lymphocytes and microglia (88). These chemokines have been implicated in HIV neuropathogenesis by the identification that their mRNA levels are high in brain tissue from subjects with HIV or SIV-encephalitis (89–92). The findings of the four published CSF studies, however, are inconsistent, identifying only that levels of RANTES/CCL5 (40) and perhaps MIP-1 α/CCL3 (93) were elevated in subjects with ADC, although others have had difficulty detecting these three chemokines in CSF (41), particularly in treated individuals.

Fractalkine, a chemokine that binds to CX3CR1, appears to be important in reducing the neurotoxicity associated with activated microglia (93). Two published studies measured fractalkine in CSF in HIV-infected individuals, demonstrating nonspecific elevations in those with neurologic complications, including HAD (95, 96). These findings seem contrary to the in vitro data, as a neuroprotective chemokine would be expected to be lower in HBD, not higher. Perhaps the elevated levels reflect the host's attempt at neuroprotection, but the levels are not high enough. Indeed, the MRS Consortium Group demonstrated that lower fractalkine levels in CSF were associated with lower neuronal pattern scores on proton magnetic resonance spectroscopy, arguing for a loss of neuroprotection in subjects with evidence of neurodegeneration (97).

Other Modulators

Transforming Growth Factor (TGF)-β

TGF-β is involved in down regulation of T-cell and macrophage activation, modulation of proinflammatory cytokines, and protection against HIV-mediated excitotoxicity (98). As such it may not only set the stage for reparative processes to begin, but also participate in such processes. In HIV disease, TGF-β is produced by CD8 cells, microglia, and astrocytes. CSF TGF-β concentrations are elevated in mild

HAD and undetectable in more severe disease (72, 99). The effect of HAART and the prognostic significance are not known.

Urokinase Plasminogen Activator Receptor (uPAR)

Soluble urokinase plasminogen activator receptor (suPAR) is the receptor for the urokinase plasminogen activator (uPA), or urokinase. These two molecules are the main components of the uPA system, which regulates extracellular proteolysis and intracellular signaling for chemotaxis. Raised CSF suPAR levels are seen in HAD (100) and decline significantly with HAART. The prognostic significance is unknown.

Toxins

Viral Toxins

HIV RNA

Quantitative measurement of HIV RNA reflects productive viral replication. Plasma HIV RNA levels are generally of limited use as a biomarker for HBD. Plasma HIV RNA levels are not specific or sensitive to HBD. That said, there is some clinical utility in the significance of a plasma HIV RNA, which is below detection – HAD is unlikely to be present at least as an active process in HAART naive patients. However, in HAART-treated patients, an undetectable plasma RNA level seems to occur more often in HAD for reasons that are unclear (101).

CSF HIV RNA is also nonspecific, with elevated levels in asymptomatic patients and those with opportunistic infections as well as HAD (102, 103). But CSF HIV RNA levels do correlate well with the severity of HAD in HAART naive patients (101, 102) and fall with HAART (104). HAD developing in the context of HAART is not related to CSF HIV RNA (60). Also, elevated CSF viral loads (≥200 copies/mL) in HAART-treated patients may predict progression to neuropsychological impairment after a median follow-up of approximately 1 year (105).

HAD can occur in the absence of an elevated HIV RNA in CSF (6, 60, 106), but it is uncommon. One explanation for this is the occurrence of HAD that has not fully responded to HAART, so that there is a residual deficit that reflects permanently damaged tissue (inactive HAD) (6). A second explanation is that the clinical expression of the deficit may be driven not by HIV but by a confounding condition, such as hepatitis C disease (107, 108). Third, the disorder may have been initiated by HIV, but have subsequently become independent – autonomous unchecked immune activation (60). Fourth, the virologic response in the CSF may occur sooner than the neurologic response in some patients, although there is little evidence at present to support this. Finally, some patients may experience an immune

restoration disorder after the initiation of HAART (109), which may mitigate the beneficial effects of treatment.

HIV DNA

HIV DNA levels can be measured and reflect latent infection. Not unexpectedly, plasma HIV DNA is nonspecific, but it does appear to have some sensitivity to the presence of HAD. Interestingly, HIV DNA levels are still elevated significantly in HAD patients (110). Thus far, there are no published data on CSF HIV DNA.

HIV-Encoded Proteins

The HIV-encoded proteins gp120, nef, tat, gp41, and vpr are all neurotoxic in vitro. Their measurement in blood or CSF has been problematic because of the very low concentrations that appear to be present. Vpr has been assayed in the CSF, but it is not clear whether the results reflected cell-free or cell-associated vpr (111). More sensitive techniques are in development that will hopefully allow more accurate measurement of vpr as well as the other HIV neurotoxins.

Host Toxins

Host toxins include arachidonic acid metabolites/prostaglandins, nitric oxide, and platelet activating factor (PAF). Other host neurotoxins, including QUIN, S100-β, interferons, interleukins, and TNF-α, have been discussed in previous sections.

Arachidonic Acid Metabolites and Prostaglandins

The lipids in macrophages are highly enriched in arachnidonic acid, which can be metabolized to prostaglandin products (prostaglandin E2, F2 α, and thromboxane B2) by the cyclooxygenase pathway. These are highly correlated with the presence and severity of HAD, as well as with β2M and neopterin. Studies were performed before the introduction of HAART but nonetheless, there was no appreciable decrease in patients treated with antiretroviral drugs. The prognostic significance of elevated concentrations is unknown (112).

Nitric Oxide

Nitric oxide is considered to be an important neurotoxin in HBD, where it is dominantly produced by macrophages and microglia. CSF levels of nitric oxide and its

metabolites are, however, not raised in HAD despite the presence of increased activity of its associated enzyme in HAD brain tissue(113). CSF concentrations are raised in opportunistic complications of HIV disease that affect the CNS (114), and indeed there is some evidence that they reflect damage to the blood–brain barrier (115). Its role as a CSF biomarker of HAD therefore seems doubtful.

Platelet Activating Factor

PAF is a product of infected or activated monocytes. While it is pleiotropic in its actions, there is convincing evidence of its neurotoxicty, which at least in part is mediated by *N*-methyl D-aspartate receptor activation (116–119). PAF levels are elevated in HAD, but they do not appear to correlate with severity. The prognostic significance and the response to HAART are unknown (120).

Target Cell

Neuron

Neurofilament-Light (NFL)

The neurofilament is a major structural element of neurons, mainly found in large myelinated neurons. It is composed of a triplet protein, of which the light subunit (NFL) is the essential component of the neurofilament core (121). Its main function is to maintain the axonal caliber. CSF NFL levels are significantly but nonspecifically raised in HAD and rise with HAART interruption (122, 123). Recent data also show that levels fall to normal in the majority of patients commenced on HAART (124). CSF neurofilament heavy chain concentrations may be elevated in the context of significant neuropathies such as Guillain-Barré syndrome (125), but thus far this does not seem to be the case for NFL in HIV neuropathy. Some asymptomatic patients with advanced HIV disease have raised CSF NFL concentrations; this seems to carry a significant risk of HAD over the next 2 years (126).

Tau

Tau is a structural neuronal protein. There are two dominant forms that can be measured: total tau (t-tau) and phosphorylated tau (p-tau). Both reflect neuronal damage nonspecifically, though p-tau is more often elevated in patients with Alzheimer's disease (127). In HIV disease, however, both are elevated in the CSF even in a proportion of otherwise normal patients (128). There is no relationship to HAD severity. Other studies have found varied results, possibly because of the

effect of age. The precise relationship between tau and NFL in HBD is yet to be determined, but broadly the two neuronal markers reflect damage to different types of neurons, with NFL dominantly indicating damage to large myelinated axons.

Endothelial Cells/Blood–Brain Barrier

Albumin, Immunoglobulin G, and Total Protein

Albumin, immunoglobulin G (IgG), and other large proteins are normally excluded from the CNS by an intact blood–brain barrier. When the BBB is injured, however, its permeability to large molecules may increase. Thus, levels of these proteins in CSF may reflect the severity of BBB injury and exposure of normally protected brain tissues to extraneural toxins. Elovaara et al., for example, reported that the albumin ratio was increased in patients with neurological "deficits" (129), although Marshall et al. reported that the albumin ratio increased over time even in neuroasymptomatic individuals (130). Hall et al. reported that "disturbances" in the albumin ratio in 30% of 59 subjects were greater in those with more advanced HIV disease (131) and Singer et al. confirmed this finding in 139 subjects (132). In 2001, Andersson et al. reported increased albumin ratios in only 15% of 110 neuroasymptomatic, HIV-infected subjects (133). More recently, elevations were identified in just 5% of asymptomatic individuals, although 56% still had an abnormal IgG index that persisted in 41% even after antiretroviral treatment (134). Few, if any, studies have identified correlations between total protein levels and HBD. Somewhat unexpectedly then, the HNRC Group identified strong associations between changes in total protein levels in CSF and cognitive improvements before and 12 weeks after changes in antiretroviral therapy (67). Until others confirm this finding, however, total protein levels in CSF should not be considered a reliable marker of HBD.

Serum Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor (VEGF) is a potent angiogenic and mitogenic peptide. Thus far, there is one report of CSF and serum levels in HIV disease. Serum but not CSF levels were nonspecifically, significantly increased in HIV infection especially in HAD and decreased with HAART, although the numbers were small. Interestingly, even with effective viral suppression, serum VEGF levels were increased (135).

Intercellular Adhesion Molecules

HIV gp120 and pro-inflammatory cytokines can upregulate adhesion molecules, including intercellular adhesion molecule (ICAM)-1, on the luminal surface of brain microvascular endothelial cells (136). Rieckmann et al. measured a soluble

form of ICAM-1 (sICAM-1) in CSF, finding that levels were higher in individuals with meningeal inflammation than in HIV-seropositive subjects and were associated with BBB damage (137). Heidenreich et al. compared sICAM-1 levels in HIV-seropositive patients with a different group (HIV-seronegative patients without neuroinflammatory disorders) and found that CSF levels were, in fact, higher among HIV-seropositive patients. The highest levels were found in individuals who had "HIV encephalopathy" (138).

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) are a family of neutral proteases that are important in normal development and have been implicated in many pathological processes, including neuroinflammation. In the CNS, MMPs can degrade components of the basal lamina, leading to disruption of the BBB (139). Sporer et al. (140) found that active MMP-9 was detected more frequently in HIV-infected subjects with neurological deficits or CNS opportunistic infections and was associated with higher CSF-to-serum albumin ratios. Conant et al. (141) confirmed that MMP-9 (along with MMP-2) activity was more frequently detectable in the CSF of subjects with HIV dementia (9/16), compared with nondemented seropositive (2/11) or seronegative (0/11) controls. Liuzzi et al. (142) reconfirmed this finding more recently in 138 HIV-infected individuals.

Biomarkers of Repair

At present almost no studies have addressed this area, yet it is important and clinically relevant. As discussed earlier, clinical evidence of improvement can take weeks or even months. A biomarker that predicts improvement would be valuable. Unfortunately, imaging does not appear to be particularly helpful in this regard at least in relation to magnetic resonance spectroscopy.

The study by Albrecht et al. (143) is interesting. It did show that CSF levels of nerve growth factor were raised in HAD patients, while brain-derived nerve growth factor levels were low. However, more data are needed on the relationship to HAD severity, prognostic significance, and the effect of HAART.

What Biomarkers Should Be Measured to Confirm HBD?

The diagnosis of HAD and its less-severe forms is still primarily a clinical diagnosis. Nonetheless, there are three biomarkers in current clinical practice that can be of supportive value: CD4 cell count, CSF HIV RNA, and CSF protein.

In untreated patients, the CD4 cell count can be helpful in determining the likelihood of HAD. If the CD4 cell count is above 200 cells/μL, a diagnosis of HAD is

unlikely. In resource limited countries, the lymphocyte count derived from the full blood count may be used – a normal lymphocyte count is unusual for HAD. On the other hand if the patient is on HAART or has failed therapy, the nadir CD4 cell count is probably more useful than the current value, which may be near-normal in a substantial proportion of patients. The same can be said for the lymphocyte count in resource-limited settings.

The second biomarker that is potentially helpful is the CSF HIV RNA level. Again its utility is chiefly in those with untreated HIV disease or in those who have failed HAART. In such patients, the CSF HIV RNA is almost always elevated above 50 copies/mL. In HAART-treated patients, the CSF HIV RNA load is much less reliable and just as is the case with CD4 cell count, a sizeable proportion of patients may have undetectable or minimally raised concentrations.

The third biomarker that can be clinically helpful is the CSF protein. Almost all HAD patients have a raised CSF protein.

Is There a Biomarker to Indicate Inactive HAD?

Intuitively, one would consider that HAD was inactive if markers of activity were absent. However, given that there are so many markers, it is not clear at present which is most sensitive. Furthermore, it is unknown whether there may be an effect that we have termed *stunning*. A biomarker such as NFL or t-tau may reflect neuronal damage, the cause of which is no longer operative – a "hit and run" phenomenon. If this is the case, then therapy directed at the presumed inciting agent would be inappropriate.

Recent data from Sacktor et al. (144) have raised the possibility that raised CSF concentrations of sphingomyelin may serve as markers of inactive HAD. However, it is not clear yet how long sphingomyelin concentrations remain elevated.

What Biomarkers Should Be Measured to Exclude HBD?

There are several simple biomarkers in the blood and CSF should be measured to exclude other diseases that may mimic HAD and its more minor forms.

B12, Red-Cell Folate, and Thyroid Function

These are commonly used tests in the screening of patients with dementia. They are also entirely appropriate for HAD. Some of the symptoms associated with B12 and red-cell folate deficiency can mimic those associated with HAD, especially the combined involvement of cognitive deficit and myelopathy, sometimes with neuropathy. Similarly, hypothyroidism on occasion can have symptoms and signs not dissimilar from those of HAD, especially the psychomotor slowing.

CSFLeukocyte Count

This simple biomarker has considerable utility in an exclusionary sense. A CSF white-cell count in excess of 50 cells/μL is unlikely to be due to HIV alone, especially when the CD4 count declines below 200/μL (145) and suggests another disease process, for example cryptococcal meningitis. In addition to the total count being helpful, the differential is also useful. For example, a polymorphonuclear pleocytosis is unlikely with HAD and raises the possibility of cytomegalovirus encephalitis.

What Biomarkers are Likely in the Near Future?

There are two clear developments in the field of biomarkers. First, since HBD is multifaceted and unlikely to be diagnosed by a single biomarker, a combination of markers will likely be required to address specific questions. Such a combination would ideally incorporate representative biomarkers of the pathogenic schema presented in this review. One such combination that has been forwarded is CSF HIV RNA, CSF neopterin, and NFL (146). This combination, however, is not readily available in the clinic and its utility is yet to be tested. Furthermore, this combination does not assess an important arm of pathogenesis, namely regenerative/reparative markers.

Second, the application of proteomics to the CSF is an important development. This is a powerful tool to uncover a more specific marker or combination of markers of HBD (147–149). However, it must be judiciously applied. Approximately 50% of patients with minor and mild cognitive deficits remain unchanged over the subsequent months (6). Studying large numbers of patients with HAD and HBD to ensure that there are sufficient numbers with active disease may, however, be practically difficult. Despite this challenge, the development of a biomarker of inactive disease is critical for the advancement of the field.

Conclusions

The field of biomarkers is rapidly maturing, especially in relation to HBD. However, the process of validating the clinical utility of pathogenesis-focused biomarkers has been complicated by the multitude of biomarkers implicated in HIV neuropathogenesis and the marked shifts in disease that followed the introduction of HAART. Despite this, we consider it best to continue to approach this challenge from a pathogenic perspective, as this ultimately facilitates the clinical application of these markers. Furthermore, this approach fosters the development of new markers and encourages the use of combinations of markers appropriate to the diagnosis of current HBD and the prediction of the risk for its development in the future.

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Neuroimaging Among HIV-Infected Patients: Current Knowledge and Future Directions

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Early in the human immunodeficiency virus (HIV) pandemic, in vivo medical imaging methods (computed tomography (CT) and magnetic resonance imaging (MRI)) were used to examine the impact of HIV on the central nervous system (CNS), including HIV-associated opportunistic infections (OIs). Over the years, additional studies have led to many key findings that have furthered our understanding of HIV's effect on the brain, as well as provided better clinical prognosis. It is expected that future studies will continue to add to our growing understanding of the evolution and progression of HIV-associated CNS injury, such that surrogate imaging markers of treatment efficacy can be established and routinely implemented in the care of HIV-infected patients. In this chapter, we highlight much of the current literature in an attempt to provide the reader with a summary of HIV neuroimaging studies conducted within the past decade, as well as identify future directions that we believe will provide valuable insights into HIV-associated neurological injury.

Examining the CNS for injury in HIV-infected patients is important for several reasons (see Table 1). More generally, there is significant neuropathological evidence of CNS injury associated with HIV infection. For example, common pathological findings in HIV-infected patients include microglial nodules containing multinucleated giant cells, myelin vacuolation, astrocyte proliferation, cortical neuronal loss, and reduction in synaptic density (1–3). The potential of neuroimaging to provide proxy markers of common pathological processes in HIV infection is particularly relevant because HIV activity and its translation to CNS involvement can differ greatly among individuals. Clinical markers of disease evolution and progression are therefore essential for examining host and viral variables that might affect disease progression and/or treatment efficacy. Though not always

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Table 1 Summary of the current clinical and research objecti ves of MRI e xamination in HIV+ patients

Screen or rule out the possibility of neurologic opportunistic infections
Understand disease etiology/pathogenesis
Assess disease severity (a single MRI exam allows to assess the amount of CNS in volvement)
Monitor progression (serial MRI pro vides markers of progression–translation of HIV acti vity into neurodegeneration)
Evaluate treatment effect (both CNS-specific treatment as well as generic treatment to the extent that neurodegeneration is a co variate of general progression)

etiologically specific in isolation, multiple imaging modalities used in combination demonstrate improved ability to discern specif ic processes of HIV -associated pathological injury.

Additionally, since the be ginning of the pandemic, there has been a subset of patients who developed significant cognitive symptoms consistent with a diagnosis of dementia (4). Though the number of patients e xperiencing frank dementia has declined in the era of highly acti ve antiretroviral therapies (HAARTs), there is evidence that the number of mild cogniti ve symptoms has increased (5, 6). These findings continue to suggest the CNS in volvement. These CNS findings combined with neuroimaging surrogate studies will greatly improve our ability to predict clinical and cognitive progression over time as well as impro ving treatment decisions.

Another general reason for examining HIV-associated CNS injury is that despite the improvements in HIV medication re gimens, there continues to be pathological evidence of CNS involvement. In fact, when examining the postmortem samples (7, 8), the incidence of HIV encephalitis continues to gro w regardless of treatment improvements. This finding is perhaps the most important reason for conducting imaging studies, as it will be imperative to understand why these symptoms persist and what effects treatment does or does not ha ve on CNS preservation.

By way of organizing the direction of the chapter, we have discussed the following topics. First, we be gin by briefly discuss the quantitati ve clinical and research neuroimaging findings. This section of the chapter is di vided into specific imaging modalities (e.g., structural MRI, magnetic resonance spectroscop y, diffusion imaging, etc.) for easy na vigation. Our discussion of these v arious modalities is limited to findings primarily from the last decade (though we ha ve included earlier study findings in some places to provide relevant contextual information). This was done in order to limit studies to patient populations that were more lik ely to be on HAART regimens, as treatments of this type are thought to alter the natural progression of HIV and, therefore, could present differently in the CNS. Finally, we have concluded the chapter by summarizing the literature and suggesting future directions for HIV neuroimaging research, including longitudinal/prospecti ve methods as well as multimodal imaging methods that ha ve been used successfully to examine other CNS diseases.

Qualitative and Quantitative Structural Neuroimaging

CT and MRI have been used since the beginning of the HIV pandemic to examine a host of clinical and structural complications associated with HIV infection. Early imaging was often used to identify common comorbid opportunistic infections (OIs) and/or tumors (e.g., lymphoma, meningitis, toxoplasmosis, progressive multifocal leukoenchephalopathy). Generally these neurologic OIs present with well-defined space occupying lesions and/or have readily recognizable imaging findings (9–11).

This early literature is still very useful in more immunologically compromised and/or treatment-resistant patient populations where the prevalence of these comorbid disorders is much higher. Additionally, the gross structural changes as observed in Fig. 1 and the clinical ramifications of these changes underscore the importance of monitoring HIV disease progression and the prevention of neurologic OIs through early diagnosis and thorough treatment.

Clinical research of OIs was followed by examination of the direct effects of HIV on the CNS. Initial studies have shown general atrophy in both cortical (See Fig. 2) and subcortical regions of the brain (12), often related to the regional concentrations of HIV (13). More specifically, these regions include frontal white matter and basal ganglia (14, 15), with alterations in these areas becoming more prominent in later stages of HIV infection.

In particular, tissue volume reduction in the caudate nucleus is repeatedly cited as a common HIV quantitative imaging finding (15–17). These findings are clinically important, as they are often associated with measures of cognitive function and/or disease burden. For example, reduction of various brain volume measures has been significantly associated with measures of cognitive function (18), including global measures of cognition (19–22), cognitive speed (23, 24), executive function (25), fine motor tests (26, 27), verbal fluency (25), and memory (28), with the most consistent findings associated with measures of cognitive speed and executive function.

The relationship between quantitative MRI findings and HIV disease burden has not been consistent across studies, making it difficult to understand the true nature of the relationship between these variables. For example, there are several studies demonstrating significant associations between CD4 cell-count decline, global atrophy (22, 29), caudate atrophy (29, 30), putamen atrophy (31), and cortical thickness (22). Yet other researchers do not find associations with CD4 or viral load (20) or they simply do not report associations (32, 33). Importantly, there are several methodological and sampling-related issues that may provide an explanation for these equivocal findings. One important caveat to these results is the lack of longitudinal studies that could be used to model the potentially dynamic nature of HIV infection (see discussion at the end of this chapter). An exception to this criticism is the longitudinal imaging study conducted by Stout et al. (30), where they examined the prospective imaging data for 86 HIV+ men and 23 seronegative controls. Measures for total CSF, total brain volume, white-matter volume, gray-matter cortical volume, and subcortical gray-matter nuclei volumes were examined separately for symptomatic and asymptomatic HIV+ patients (30). Though all the HIV+

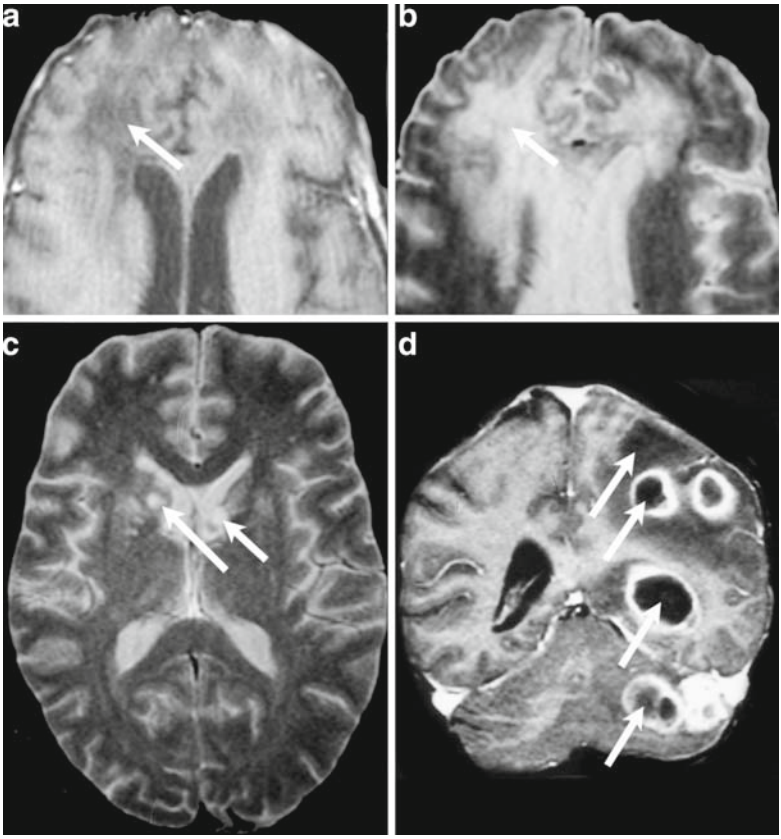

Fig. 1 Composite image of common opportunistic infections (OIs) MRI findings. (**a**) and (**b**) are T1 and T2 axial images of the anterior half of the brain from a patients with progressi ve multifocal leukoencephalopathy (PML). The T2 image (**b**) demonstrates the diffuse, asymmetrical white-matter injury commonly observed in PML (see *white arrow*) while the T1 image (**a**) demonstrates the hypointense area (see *arrow*) within lesion. The combination of these two findings together is diagnostic of PML. (**c**) is a T2 image of a patient with cryptococcal meningitis with bilateral infarctions in the caudate nuclei. (**d**) is a T1 image of a patient with toxoplasmosis. *Arrows* illustrate the frank lesions as well as edema (dark hypointense area surrounding the bright ringed lesion) resulting from injury. Images courtesy of Peter Hildenbrand, MD

patients were free of CNS OIs, the symptomatic patients demonstrated increases in CSF volume that was significantly different from HIV+ asymptomatic patients and controls. Significant reductions in white-matter volume were also noted in symptomatic HIV+ patients. Of the subcortical gray matter nuclei e xamined, only the caudate demonstrated accelerated atrophy , though this atrophy w as only signif icant for patients at the most adv anced CDC stage. Furthermore, though the size of the caudate and CSF v olume were unrelated to CD4 counts at either time point individually, patients experiencing the most decline in CD4 cells demonstrated the most change in quantitati ve MRI measures. This f inding is signif icant in that it

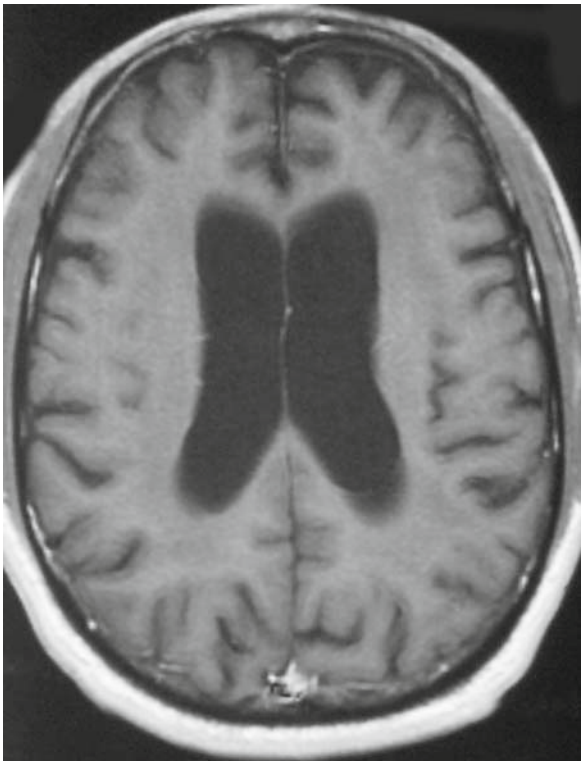

Fig. 2 T1-weighted image of an HIV patient with enlarged lateral ventricles (general a non-specific sign of atrophy). Images courtesy of Peter Hildenbrand, MD

provides evidence that the association between immunological function and MRI measures may be more evident in prospective studies and can be effectively modeled to examine the progression of CNS injury relative to clinical measures of immunological function.

Another important caveat to these early MRI research findings is that many were conducted in the early/middle 1990s before the introduction of HAART. Since the introduction of HAART, there has been an alteration in the natural progression of HIV as well as marked improvement in the life expectancy of patients (34, 35). With these improvements in immunological function and life expectancy, renewed interest in examining the structural neuroimaging findings associated with HIV infection has been generated (32, 36) with similar findings of global atrophy (32, 36), ventricular enlargement (29, 36), reduction in caudate volume (29, 36), corpus callosum (22), and even cerebellar atrophy (37, 38).

Additionally, recent modifications of MRI sequences and postprocessing methods have improved the clinical utility of imaging as well as improved the cost effectiveness of large-scale MRI studies of HIV-associated CNS injury. Advances in digital image processing and increased automation have not only enabled researchers to effectively

and efficiently query vast amounts of MRI data, but also have opened up new avenues for studying neurodegeneration (i.e., data-driven approaches to test for structural changes without an a priori hypothesis). For example, Thompson et al. (39) have used the T1-weighted MRI sequence, along with 3D cortical surfacing software, to determine the areas and amount of thinning in the cerebral cortex of HIV/AIDS patients. Their analysis of the cortical maps of 26 AIDS subjects and 14 controls generated results of significant cortical thinning in primary sensorimotor, premotor, and visual areas of AIDS patients (39). These regions of cortical thinning are in stark contrast to those areas affected by other common noninfectious dementias, such as Alzheimer's disease where it is the medial temporal, limbic, and association cortices that are affected first (40). They also found that atrophy levels in the prefrontal and parietal cortices predicted cognitive impairment, and that cortical thinning of the language areas and frontal poles of both hemispheres was an accurate predictor of CD4 cell counts. In addition, this group assessed the role of HAART, comparing AIDS patients on and off treatment, and discovered evidence that suggested limited utility of HAART in mediating the severe pattern of cortical thinning.

A year later, Thompson et al. published another study, which evaluated corpus callosum atrophy and ventricular expansion in an HIV/AIDS cohort, and utilized similar 3D statistical anatomic maps methods (22). Fifty-one patients were selected, including 30 AIDS patients and 21 seronegative controls. The T1 sequence scans were used to create 3D surface mesh reconstructions of the CC and lateral ventricles, with structural alterations then being correlated with viral load, T-cell counts, and cognitive impairment. Their results showed thinning throughout the CC, with the frontal three-fifths having the greatest sustained atrophy (25% reduction), which correlates well with the caudate nucleus volume reductions and increased viral load seen in other studies (30). This CC thinning was strongly linked to CD4 counts in both traditional volumetric measurements and mapping, suggesting that CC thickness can potentially be applied as an MRI-based marker of white-matter integrity in AIDS patient populations. Additionally, the study established a 3D pattern for ventricular expansion in AIDS patients, with the frontal horn maps providing the greatest distinction between AIDS subjects and controls. These 3D ventricular changes were again significantly linked with CD4 counts, as well as cognitive impairment.

In another very sophisticated analysis of HIV-associated structural imaging abnormalities in HIV+ patients, Lepore et al. (41) examined 26 AIDS patients and 14 seronegative controls using a tensor-based morphometry approach (TBM). Using this method, very precise volumetric differences can be mapped and correlated to clinical and/or cognitive measures. Significant reduction in volume was noted bilaterally in the primary and sensory association areas and subcortical areas of the brain for HIV+ patients. The volumetric reduction (especially reduction in white matter) significantly correlated with cognition and declines in CD4 cell counts(41). This method appeared to improve the sensitivity of volumetric findings capturing significant amounts of atrophy that have not been observed utilizing less sophisticated methods. The findings from this study emphasize the importance of frontal–subcortical areas in the development of cognitive dysfunction observed in more immunosuppressed HIV+ patients.

Although not a signif icant defining MRI feature of HIV+ encephalopathy , another common imaging finding worth mentioning is the presence of T2-weighted hyperintensities or signal abnormalities (see Fig 3.) in and about the white matter of the CNS (white-matter signal abnormalities, WMSAs) (12, 42, 43).

In the HIV Neuroimaging Consortium multisite imaging study , we found that 25% of the HIV+ patients had a measurable degree of WMSAs, which is similar to other studies (36, 42, 44). These findings may be important in HIV patient populations due to the association they have with pathological findings in HIV encephalopathy

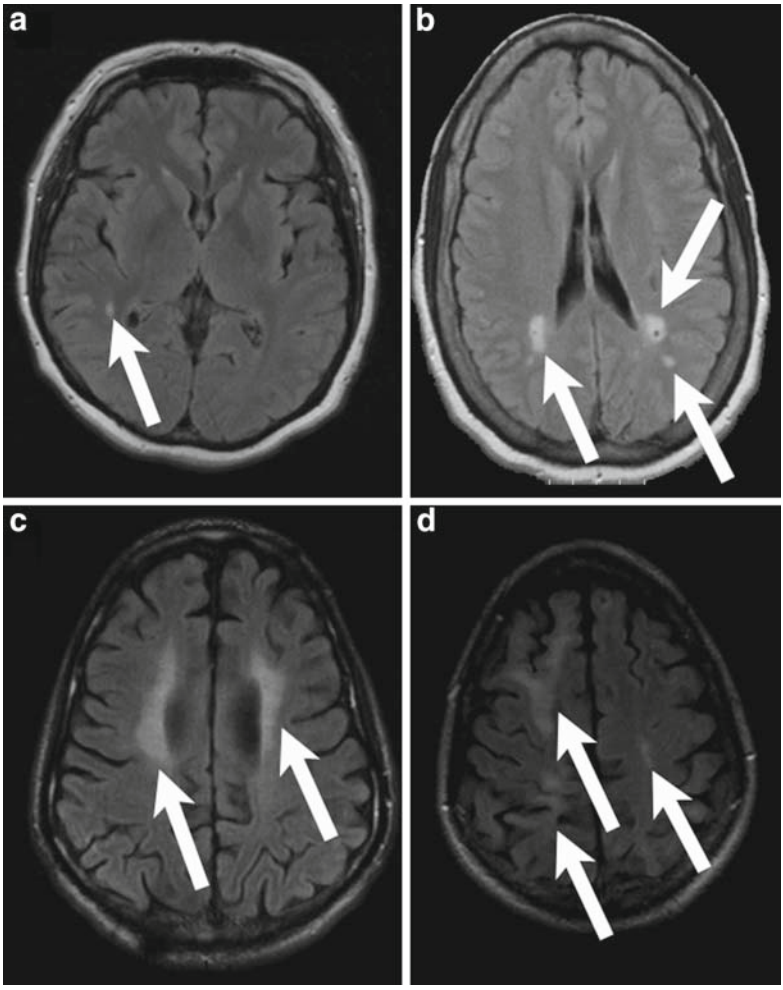

Fig. 3 Set of T2-weighted images illustrating the range of WMSAs seen among HIV patients. *White arrows* point to areas of WMSAs. P atient (**a**) has a single small circumscribed WMSA. Patient (**b**) has several areas of WMSAs with necrotic centers. Patients (**c**) and (**d**) have more diffuse WMSAs with less def ined boundaries (often called dirty white matter) . Images courtesy of NIH funded (RO1NS03624) HIV Neuroimaging Consortium

(1, 3). For example, increasing WMSA load or volume was shown to be related to a pathological diagnosis of HIV encephalitis, including dendritic pruning (45). However, in a recent study by Valcour et al. (46), WMSAs were also shown to be related to vascular risk factors among an older aging HIV cohort, emphasizing the need to examine in additional detail the role and pathological correlates of these signal abnormalities (46). With regard to cognition, there does not appear to be any relationship between WMSA and cognition among HIV-infected patients (44). However, to date, this relationship has not been examined thoroughly and as such may provide a unique line of investigation.

In summary, structural imaging findings appear to be more sensitive to changes at later stages of HIV infection, with the most common findings being global atrophy and caudate volume atrophy. These MRI findings are often (though not always) associated with performance on cognitive tests and, as such, are thought to be useful in examining the brain–behavior relationships among HIV patients. Associations with immunological function (CD4) or disease severity (viral load) are not always found, though longitudinal prospective imaging studies may improve our understanding of progressive CNS involvement among HIV+ cohorts.

Proton Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) has been proven to be particularly useful in examining HIV-associated CNS abnormalities. This MRI method allows researchers to measure chemicals/metabolite concentrations in the brain noninvasively, without removing any tissue or using radioactive tracers. It is based on the principle that different chemicals resonate at different frequencies when stimulated by a static magnetic field. In this manner, MRS is capable of identifying and quantifying a specific set of various neurochemicals.

As illustrated in Fig. 4, different chemical metabolites appear at various points along the *x*-axes (termed the chemical shift), with the shift being measured in parts per million (ppm). MRS signal intensity (*y*-axes) or height of the peak is related to the concentration of the metabolite. By examining the area under the chemical shift peak for each metabolite, the amount of metabolite can be estimated for analysis. This method has been used extensively to evaluate disorders of the CNS with a high degree of success.

Though MRS is capable of quantifying many chemical compounds (see Table 2 for a list of common metabolites captured by MRS), the most commonly reported chemical spectra in the assessment of HIV+ patients include *N*-acetylaspartate (NAA), myo-inositol (mI), Choline (Cho), and creatine (Cr). Next to water, NAA represents the largest peak of proton signal in the CNS. It has been found almost exclusively in neurons and is considered a measure of neuronal integrity (47–49). NAA is reduced in tissue where neurons are being destroyed in a disease process and, as might be expected, exists in higher concentrations in the gray matter (48). In contrast to NAA, mI is found almost exclusively in glial-cell populations. It is

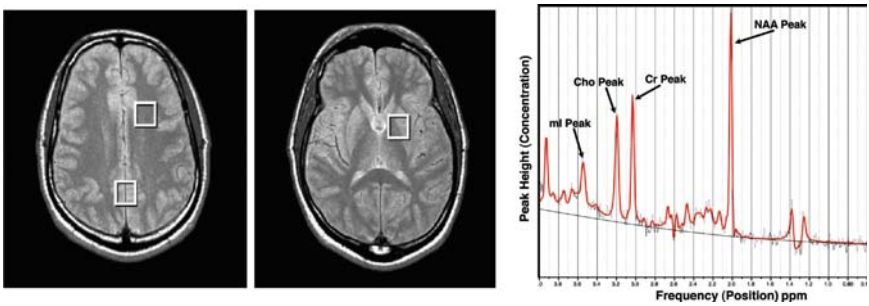

Fig. 4 Typical placement of regions of interest and a common spectra output from an HIVinfected patient. Images courtesy of NIH funded (R O1NS03624) HIV Neuroimaging Consortium (*See Color Plates*)

Table 2 Common metabolites measured with MRS and their ppm peak location

ppm	Metabolite	Properties
1.3	Lactate	Marker of cell death and necrosis
2.0	NAA	Neuronal integrity
2.1–2.4	Glutamine/GABA	Neurotransmitters
3.0	Creatine	Energy metabolism
3.2	Choline	Cell-membrane turnover
3.5	Myo-inositol	Glial-cell marker

often found in higher concentrations in the gray matter and is considered a mark er of glial-cell proliferation. Cho is associated with cell-membrane synthesis, since phosphocholines are released during myelin breakdown (48). Thus, Cho is particularly useful in examining the white mater of HIV+ patients where pathology evidence is suggestive of myelin abnormalities. The Cr signal in the MRS spectra is often used as a reference peak against which to normalize metabolite concentrations. This is generally an accepted method because the Cr signal is relati vely constant across subjects, though this method is not without contro versy.

There are a couple of technological caveats worth mentioning. Technical challenges in MRS arise from spatial resolution limits because of rapid loss of signal with smaller field of vie w. A reliable signal requires f airly large quantities of tissue, which limit studies to the most abundant metabolites and relatively large anatomical regions of interest, though as higher field strength magnets become more mainstream, there will be some improvements. Higher field strength will also enable additional metabolites to be studied because of the impro ved separation of chemical shift peaks. Another qualif ication is that the determination of absolute concentration measures from the observed spectra requires careful calibration and complex spectral fitting algorithms. Self-normalizing ratios, such as N AA/Cr, have often been used

as surrogates of absolute NAA concentrations. The rationale is that Cr is a principal energy metabolite, and therefore assumed to be evenly and constantly distributed throughout the brain. There are concerns, however, that naturally occurring fluctuations of Cr would render it unfit as a variable for normalization. Astrocytes also have higher Cr levels than neurons, which could explain Cr rises in areas of gliosis (50, 51). Since glial-cell proliferation is a possible pathological factor in HIV, the use of Cr as a variable for normalization may be questionable. Additionally, Cr and Cho levels appear to correlate with age (52), requiring proper normalization and control in longitudinal and cross-sectional studies, especially in aging HIV+ populations.

Despite these limitations, MRS has generally been more sensitive to changes in the brain at earlier stages of HIV infection when compared with other imaging modalities and as such may represent an important method in understanding early neurochemical mechanisms of HIV-associated CNS injury. Findings using MRS have been generally consistent, with the pattern of metabolites demonstrating elevations in Cho, mI, and occasionally Cr in frontal areas and in the basal ganglia (53–57). Elevations in these metabolites are often interpreted to be a sign of increased glial activation, astrocytosis, and/or inflammation, all of which are readily observed in postmortem neuropathology studies (1). Additionally, decreases in NAA have also been observed in advanced disease (49, 54, 58), signaling the loss of neurons.

Given the significant effects of HAART on the progression of clinical symptoms and HIV viremia, investigators have sought to examine the effects of these medications on common MRS spectra. Unfortunatlely, the research is mixed with some studies demonstrating improved metabolite function in HIV+ patients (59, 60) while others have only demonstrated partial or no recovery of metabolite ratios (56, 61). For example, the Chang et al. (61) study of 33 HIV+ patients and 26 seronegative controls demonstrated no significant improvement in the metabolite function of the HIV+ cohort, despite improvements in CD4 cell counts and viral loads (measured in the plasma and CSF) after 3 months of treatment (61). The persistent abnormalities were interpreted to represent mechanisms of ongoing repair of reactive inflammatory processes in the areas sampled. Tarasow et al. (56) noted modest improvements in NAA/Cho ratios approximately 6 months into treatment suggesting improved neuronal integrity in the frontal/subcortical areas of the brain (56). Similarly, Stankoff et al. (60) examined the effect of HAART on 22 AIDS patients, half of whom exhibited cognitive impairment. At baseline, AIDS patients with cognitive impairment exhibited reduced NAA levels in the frontal white matter. After 9 months of therapy with HAART, the severity of cognitive difficulties and the magnitude of NAA abnormalities improved among patients with cognitive impairments at baseline (60). Taken together, these findings have led many to postulate that MRS might be an important method for examining treatment efficacy, albeit the small cohort sizes (with potential selection bias from subgroups of patients who might be nested within larger samples who experience improvement), short follow-up intervals, and various methodological differences (i.e., different ROIs, different metabolite ratios reported, etc.) should be considered when interpreting results.

MRS findings associated with cognitive function have also been a topic of interest among HIV-infected patient populations. Worsening metabolite ratios are generally

associated with cognitive decline across studies, especially when there are NAA reductions in the basal ganglia or cerebral white matter (62, 63). For example, in the recent paper by Paul et al. (64) associations between NAA/Cr and mI/Cr ratios in the frontal white matter and basal ganglia and cognitive performance were particularly robust, especially with measures of motor function and processing speed. In contrast, metabolite ratios in the parietal cortex were not associated with any cognitive measure suggesting regional significance of metabolites in these areas of the brain and their specific impact on commonly observed cognitive abnormalities in HIV-infected patients (64).

Similar to structural imaging findings, MRS investigators have also examined several potential confounds known to confer additional neurological risks, including alcohol abuse, drug abuse, and aging. In the Pfefferbaum et al. (49) study, the authors compared the metabolite findings of four experimental groups: HIV+ plus alcoholism (n = 15), HIV+ only (n = 9), alcoholism only (n = 8), and 23 controls. Importantly, HIV+ groups were matched for CD4 cell counts and alcoholic patients were matched for self-reported lifetime alcohol consumption. Metabolites measured in the parietal–occipital region of the brain demonstrated significant findings for the HIV+ alcoholic group only with nearly a full standard deviation reduction in NAA and Cr regardless of HAART status (49). Though there was no significant alteration of these metabolites for the HIV+ or alcoholic only groups, this may be the result of sampling the parietal–occipital region only rather than areas known to be affected in both excessive alcohol use and HIV infection.

In the Chang et al. (65) study, the effects of methamphetamine (meth) drug abuse on MRS measured metabolite ratios were examined. The results of this study demonstrated significant additive effects of chronic meth use by examining four experimental groups: HIV+ meth user (n = 24), HIV+ only (n = 44), meth users only (n = 36), and controls (n = 39). Importantly, Chang et al. attempted to quantify the actual amount of meth used during their lifetime with a meth use history questionnaire which was used in the analyses as a covariate. Regions of interest placed in the frontal gray matter, frontal white matter, and basal ganglia demonstrated several significant differences in metabolites between the groups. Specifically, NAA was reduced in the frontal regions of the brain for chronic meth users, HIV+ only, and HIV+/meth user groups compared with controls with the HIV+/meth user group having the most decline. In fact, the HIV+/meth users group demonstrated significant declines in NAA for all three regions compared to the other groups with an average 7.2% decline for the three ROIs demonstrating a significant additive effect of comorbid methamphetamine use among HIV+ patients (65).

Aging is another potential confounding factor in HIV+ research settings. We know that in normal aging, there are observable metabolite changes, including slow but steady increases in the glial marker mI (66). Some studies have demonstrated increases in Cho and Cr as well (66–68) though others have not (69, 70). Age is becoming an increasingly important topic of research among HIV+ cohorts as the introduction of HAART has vastly improved the life expectancy of HIV+ patients. In the multicenter HIV MRS Consortium study by Chang et al. (71), 100 HIV+ patients underwent assessment of metabolites in the frontal white matter, basal

ganglia, and parietal cortex. These patients were stratified into three groups according to disease-associated cognitive performance (61 AIDS Dementia Complex (ADC), 39 neuroasymptomatic (NAS), and 37 seronegative controls(SN)). Results demonstrated worse metabolite ratios, particularly for Cho/Cr and mI/Cr ratios, for the ADC group with aging interacting with group status (71). In another study by Ernst and Chang (72), 46 HIV+ patients and 58 seronegative controls were examined using MRS. Measurements of metabolites in the frontal white matter and basal ganglia were shown to be worse in older HIV+ patients (72). When examining this cross-sectional data by decade, there were notable increases in glial markers, Cho, and mI such that the percentage of increase in these metabolites was approximately >10% per decade for HIV+ patients compared with <3% for seronegative controls. NAA also showed decreases in the basal ganglia across decades though the decline was not as significant as the increases in other metabolites (<4% per decade). One important caveat was that this finding was in HAART naïve patients, which might have resulted in worse findings.

There have also been attempts to look at different combinations of MRS metabolites that have proven useful. For example, Yiannoutsos et al. (73) examined factor groupings of metabolite ratios using a statistical factor analysis approach. The results from this study of 100 HIV+ participants identified three coherent factors (inflammatory, basal ganglia, and neuronal) that were associated with unique patterns or combinations of metabolite ratios (73). Specifically, the inflammatory factor was associated mainly with elevations of mI/Cr in all three regions (frontal, parietal, and basal ganglia) and Cho/Cr increases in the frontal and parietal white matter. The basal ganglia factor was associated with NAA/Cr decreases and Cho/Cr increases in the basal ganglia ROI. The neuronal factor was associated with reductions in the NAA/Cr ratio in the frontal and parietal white matter. These factors were found to be useful in discriminating between the groups of cognitively impaired and unimpaired participants, with the neuronal pattern being strongly associated with ADC staging. Such a statistical approach could greatly improve our understanding of the combination of these factors.

In summary, there is significant evidence of altered metabolic function in HIV-infected patients, early in the course of disease progression. This is especially true for metabolic markers of glial proliferation (mI) and membrane turnover (Cho) suggesting a clear metabolic reaction to HIV infection. Over time, neuronal integrity is compromised, signaled by a reduction in NAA especially in frontal and subcortical areas of the brain. There is equivocal evidence of metabolite improvement with the introduction of HAART, though this important issue requires further examination. Importantly, there are clear associations between cognitive performance and abnormal metabolite function with more robust associations being observed when NAA is reduced in frontal and subcortical ROIs. This finding emphasizes the known pathological spatial distribution of HIV throughout the CNS and the subcortical cognitive presentation so often observed in HIV infection. For these reasons, researchers have emphasized the utility of MRS in examining the temporal evolution and progression of HIV-associated CNS injury.

Diffusion Magnetic Resonance Imaging (DTI)

Diffusion MRI sequences are relatively new developments in the MR arsenal of imaging tools. Diffusion imaging examines the rate and direction of gross thermal molecular water movement (Brownian motion) at each imaging voxel. As water molecules move about in the tissue of interest, they encounter the physical barriers of cell membranes, myelin sheaths, and other tissues that restrict the otherwise random nature of their movement. This anisotropic movement may be quantified providing both vector and velocity information at each imaging voxel. Thus, the amount of movement and the direction of the movement can provide unique information regarding structural tissue organization and coherence at a microscopic scale well beyond typical imaging resolution (74).

Though there are a variety of ways for quantifying diffusion data, researchers have focused on two primary metrics (or some derivation of these two indices). These two metrics include the mean diffusivity (75) and fractional anisotropy (FA). MD is a measure of the magnitude of water diffusion at a particular imaging voxel and produces values that range from 0 to 1 (values closer to 0 representing reduced water movement and values closer to 1 indicating unrestricted water movement). FA as a metric includes information about diffusion directionality and reflects a difference between isotropic diffusion and linear diffusion. Values for FA range from 0 to 1 with 0 reflecting more random diffusion and 1 indicating more directional linear diffusion.

Examination of HIV-associated CNS injury using DTI began shortly after 2000 as researchers realized its clinical utility in the field. Though axonal membranes are generally sufficient to cause anisotropy (76–78), there is evidence that changes in myelin density (79, 80) and/or axonal degradation (81) can also alter FA values such that a reduction reflects altered myelin and/or reduction in white-matter volume. This ability to examine subtle changes in white-matter micro-architecture makes diffusion imaging particularly attractive when examining white matter integrity among HIV-infected patients. Despite this ability, there are a limited number of studies in the general HIV literature to date. Below, we provide a short review of the DTI studies and then finish with a summary of our own developing research in this field.

General DTI findings demonstrate consistent reductions in FA measures and intermittent increases in MD. These altered scalar metrics are interpreted as an indication of white-matter damage. For instance, a study in 2001 conducted by Pomara et al. evaluated DTI metrics among a cohort of six HIV+ patients and nine controls utilizing a regions of interest (ROIs) approach in the several white-matter areas of the CNS. The analyses of ROIs indicated a statistically significant decrease in FA for the frontal lobes of HIV patients, but no significant group differences for the parietal lobes, temporal lobes, or the two corpus callosum ROIs. At the same time, FA was significantly increased in the internal capsule of the HIV cohort, while MD values were not significantly different among the groups, regardless of the ROI. In 2004, Ragin et al. studied the whole-brain fractional anisotropy differences amongst a small HIV cohort (six) and healthy controls (nine). The results demonstrated

whole-brain FA measures that were significantly reduced in the patients with HIV (82). Yet, whole-brain ADC (a variant of MD) values indicated no significant differences between the two groups.

Beyond these general findings, some researchers have sought to assess the impact of clinical measure of disease severity (i.e., viral load and CD4) in the context of DTI metrics. In 2002, Filippi et al. related diffusion tensor metrics to viral load in the white matter of a small HIV+ cohort. In this small study, the results of ten HIV patients showed significantly lower FA values in HIV patients with higher viral loads (44,000–200,000), particularly in the splenium and genu of the corpus callosum (CC) (83).

In addition to these viral load associations, several groups began assessing DTI measures with respect to cognitive variables. For instance, the Ragin et al. (82) study not only demonstrated that FA was reduced in the whole brain of HIV+ patients, but that it was also significantly associated with the degree of dementia of these patients (84). In 2005, Ragin et al. again showed that DTI metrics were significantly related with loss of function in specific cognitive domains (85). Significant relationships were identified between measures for putamen and verbal memory (75), visual memory (FA), working memory (FA), and overall cognitive impairment (75). The caudate only demonstrated a significant correlation between FA and visual memory, whereas metrics for the centrum semiovale showed significant correlation with visual memory deficits (75) and visuoconstruction (FA). In 2006, Wu et al. evaluated diffusion alterations in the CC and associations with cognitive performance and motor skills. Utilizing the same cohort as Ragin et al. (85), they found a significant reduction of FA in the splenium of HIV patients, which correlated with dementia severity and deficits in motor speed (86). Likewise, there were also increases in MD measures that correlated with deficits in motor speed. FA values in the genu were also significantly correlated with performance on measures of visual memory.

Throughout all the previous DTI-HIV studies, the issue of small sample size (generally approximately ten patients and ten controls) presents itself, demanding a more thorough review. One interesting exception to this criticism is the 2005 Thurnher et al. study of 60 HIV patients and 30 healthy controls (87). In this study, the results indicated a significant difference in DTI measures (FA and MD) only in the genu of the corpus callosum. No statistically significant differences were found in the splenium, but an *increase* in FA was noted among the controls compared to HIV+ patients. In addition, there was no correlation found between plasma viral load and FA/MD values, nor between CD4 counts and FA/MD.

Modest discrepancies in these studies may in part reflect differences in design and/or the effects of possible confounds. While differences in technical design are sometimes difficult to assess, revealing potential confounds amongst these various studies has proven to be somewhat easier. The largest confound has been elucidated by the research of Pfefferbaum and Sullivan, who have shown the importance of controlling for patient comorbid neurologic injury risks such as alcohol consumption. For example, in their recent study (2007), they assessed four patients groups: alcoholism alone ($n = 87$), HIV infection alone ($n = 42$), alcoholism and HIV infection comorbidity ($n = 52$), and non-affected controls ($n = 88$) matched for lifetime alcohol consumption histories and CD4+ counts and viral loads. Results showed that, compared to controls, each group had lower FA and higher MD in the genu and splenium, but the effects were

only significant in the two groups with alcoholism (with the genu more affected than the splenium). Evidence also demonstrated a compounded alcoholism-HIV effect – when the HIV+ groups were separated by disease severity (an AIDS-defining event or CD4+ counts < 200), the HIV/alcoholism comorbid group exhibited an increased significance in FA and MD abnormalities compared to more immunologically intact patients (88). In this study, the associations between motor deficits and low FA and high MD supported the functional relevance of the microstructural abnormalities. The study concluded that the strong DTI findings in HIV-alcoholism comorbidity underscore the role of white-matter abnormalities as HIV infection progress to AIDS, and that DTI's sensitivity to such white-matter disruption may provide an early diagnosis of HIV-associated dementia. Most importantly, this study clarified the need to control for potential neurologic risk factors often present in HIV-infected cohorts.

Recently, our group (Tate et al. submitted) (89) sought to further clarify white-matter abnormalities in the CC of HIV+ subjects utilizing DTI-MRI. Twenty HIV+ subjects on HAART and 20 seronegative controls were selected and matched in alcohol consumption histories using a brief questionnaire that quantifies frequency, quantity, and duration of alcohol use (Kreek-McHugh-Schlesinger-Kellogg (KMSK)).

The results demonstrated gross CC FA values that were reduced for HIV-infected patients when comparing the two groups (see Fig. 5). In addition to gross difference, FA values were significantly different for all regions of the CC examined, even when considering corrections for multiple comparisons. The average percent reductions in FA values were highest for the genu and the splenium (27 and 32% reduction respectively), similar to other studies. These reductions in FA were observed despite relatively intact immune functioning (average CD4 of 461.3) and reduced plasma viral loads (80% of patients with less than 10,000 copies per ml) suggesting CNS injury despite improved immunological function.

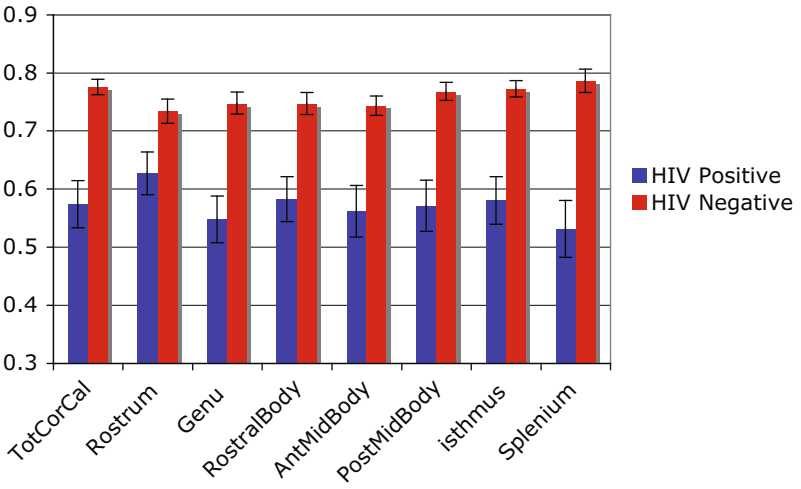

Fig. 5 This figure depicts the divisions of the corpus callosum with bars demonstrating the difference between HIV+ participants and controls. Colored bars represent mean values with standard error (*See Color Plates*)

We also investigated unique global quantitative tractography methods to examine the difference between 22 HIV-infected patients and 6 seronegative controls. Each participant underwent 12-direction diffusion imaging with sufficient resolution for deriving global tractography maps utilizing methods described elsewhere (90). When deriving tractography maps for other analyses, it became apparent that there were consistent qualitative differences between HIV-infected patients and the seronegative controls. For example, as seen in Fig. 6 there is a clear reduction

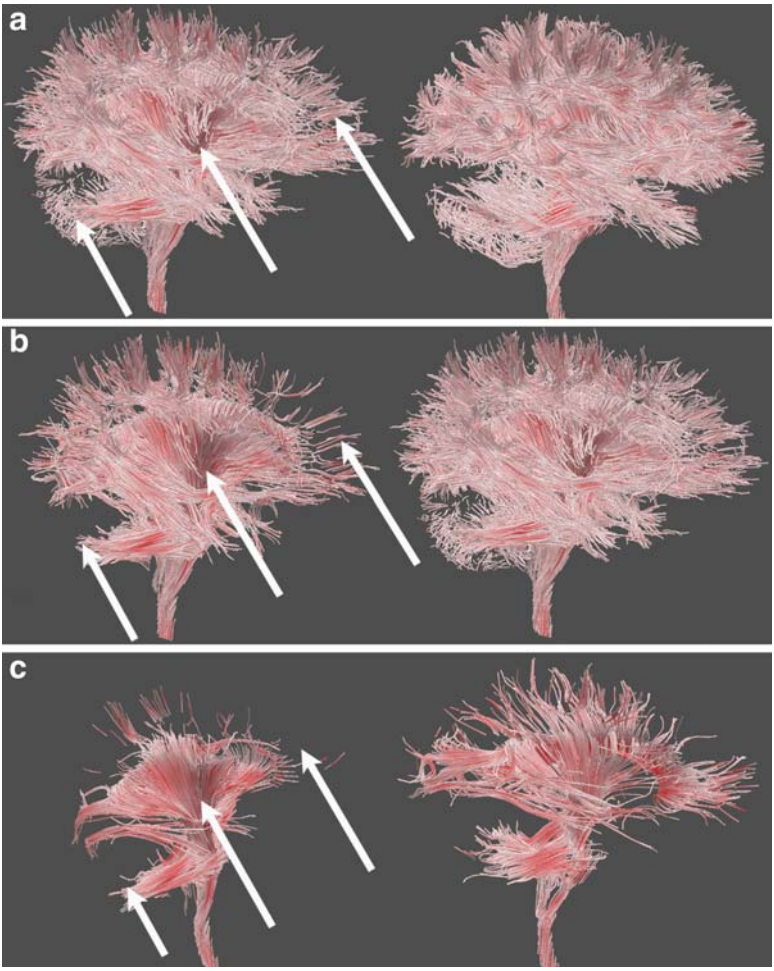

Fig. 6 This illustrates the gross qualitative differences between an HIV+ participant and control using more stringent FA criterion ((**a**) *lowest* FA value, (**b**) *middle* FA value, (**c**) *highest* FA value) in the generation of the tractography models. This clearly illustrates the reduction of tract generation in the frontal, subcortical, and cerebellar regions (*white arrows*) when higher FA constraints are used to generate tracts. This may be an indication of increased disorganization and/or diffusion coherence in these areas (*See Color Plates*)

in the number of tracts generated by the tractography algorithm in the frontal, subcortical, and cerebellum, though the same parameter constraints (namely FA) were used to generate each model.

With such unique qualitative observations, we sought to develop unique tractography metrics that might capture relevant information about the coherent organization of the white matter among HIV-infected patients (i.e., number of tracts, length of tracts, average FA along the tracts, etc; for a full description see the Correia, et al. (2008) paper) (91).

In preliminary analyses of these two experimental groups, we examined several metrics including number of tracts generated, total length of tracts, and average linear FA along the length of the tracts. Results demonstrated no significant differences for number of tracts generated or the total length of tracts (though both were reduced in HIV-infected patients). There was a significant difference for the average linear FA along the length of the tracts with lower FA found for HIV-infected patients. The total length of the tracts and the average FA values for the HIV+ patients were significantly associated with the plasma viral load, but not CD4 cell counts. Furthermore, there were several significant associations between the tractography metrics and cognitive tests (e.g., estimate of IQ, short-term memory, speed of processing, and mental flexibility). We interpreted these findings to indicate the usefulness of tractography in examining HIV-associated CNS injury, as there was a trend to significant differences between the groups for the measures as well as many significant associations with measures of disease severity and cognitive performance.

In conclusion, as the literature suggests, there is a significant amount of evidence that DTI is sensitive in revealing subtle white-matter abnormalities in the HIV+ cohort. General reductions in FA and increases in MD are apparent in multiple white-matter regions, especially in the frontal white matter and the CC, as compared to healthy controls. Continued research in this field must be done to further elucidate the role of HIV in disrupting white-matter integrity. Particularly, it will be imperative for researchers to control for the confounding influence of alcoholism, as well as increase the number of patients in future DTI-HIV studies. One additional current limitation in the HIV+ literature is the lack of specific pathological correlates with diffusion metrics. This limitation is being examined in several other disease modalities in postmortem studies though no specific studies have been conducted in HIV+ patients. Until such time, such results should be interpreted cautiously until we can fully clarify the specific etiological pathologies that are associated with each of the specific diffusion metrics. Nonetheless, it is important to push forward with these DTI methods, as there appears to be both clinical and cognitive utility being established in the CNS of HIV+ patients.

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI (fMRI) aims to observe neural activity during predefined tasks conducted while in the scanner. Contrast for this imaging method is based on the differences between the magnetic susceptibility of oxygenated and nonoxygenated

blood (termed the blood oxygen-level dependent or BOLD response). This BOLD signal reflects increases blood oxygenation associated with a particular task conducted while in the scanner, locating individual or functionally-related brain areas participating in the given task.

Research using fMRI in HIV-infected patients is limited though there have been a few studies examining attention, working memory, and/or motor function in HIV patients. The Chang et al. (90) study of 11 HIV-infected patients and 11 seronegative controls demonstrated an increase parietal activation for subjects participating in a simpler task of attention, a simple reaction time task (92). As the task demands were increased, additional activation of frontal lobes was required to accomplish the task with the HIV-infected patients exhibiting significantly more activation in these areas compared to controls. Ernst et al. (2002) demonstrated a similar finding among asymptomatic HIV-infected patients (93). These results extend the Chang et al (92) findings by demonstrating abnormal activation pattern earlier in the disease process (92). However, the additional activation differences were only noted in the lateral prefrontal cortex during the more complex attention task, while the simpler attention task did not demonstrate any differences in this cohort of patients.

Studies of working memory also suggest an overall increase in cerebral blood volume (CBV) in several of the deep gray matter structures of HIV-infected patients when compared to seronegative controls (94) despite the lack of evidence for cognitive function deficits as measured by neuropsychological testing. More recent studies of working memory have also demonstrated similar findings among HIV+ patients. The Chang et al (92) and the Ernst et al (93) studies also examined working memory (92, 93). Both of these studies found additional areas of activation for HIV+ symptomatic and asymptomatic patients when participating in the working memory tasks (n-back task paradigm). Specifically, additional areas of activation were observed in the lateral prefrontal and supplementary motor areas of the brain. Interestingly, the Ernst et al. (93) examined the relationship between MRS and fMRI findings without finding a significant association between measures of *N*-acetylaspartate (NAA) (a marker of neuronal integrity) and increased activation. However, other glial metabolites, especially frontal metabolites, were associated with increased recruitment for working memory tasks. These findings were interpreted to mean that inflammatory factors associated with glial activation were decreasing the efficiency of cortical connections, and thereby requiring the recruitment of additional neural networks (93). These additional areas of activation regardless of the task (attention or working memory) are interpreted as abnormal and as a sign of reduced cortical efficiency (HIV+ patients require additional areas of brain activation in order to complete the task).

It is important to realize that fMRI relies on several assumptions about the shape and duration of the BOLD response or the basic hemodynamic response function (HRF) and there may be reason for proceeding cautiously with future studies. Juengst et al. (95) examined the HRF of HIV+ patients for differences that might be associated with age, brain hemisphere, or even disease status (95). fMRI data

from 16 seronegative controls and 30 HIV+ patients were examined. There were no significant findings associated with age, hemisphere, or HIV status, though there was a notable delay in the time it took the HRF to return to normal in patients with more severe cognitive difficulties. So, the basic shape of the HRF for HIV+ patients is not different from controls and studies examining the fMRI results among HIV+ patients can move forward. However, there will be need for future studies to examine the HRF in more advanced disease stages to completely understand the reason for the delay in returning to normal. Thus, fMRI studies relying on longer event-related paradigms may be affected by this slow HRF return and studies using fMRI in more advanced disease should still consider the potential difference in HRF shape as a possible confounder of group comparison.

Positron Emission Tomography (PET) Imaging and Single Positron Emissions Computed Tomography Imaging (37)

PET and single positron emissions computed tomography (23) are similar in that they depend on intravenous injection of the specific radioisotopes used to tag specific chemicals in the brain. They differ in their complexity of use, the amount of specialized equipment required to acquire images, and the types of brain processes they are capable of capturing. SPECT is a relatively simpler (i.e., often at lower resolution) technique that provides general information regarding cerebral blood flow (CBF). PET requires the use of a cyclotron thereby increasing its cost, but through a set of specific radioactive tracers is capable of capturing more specific brain functions (e.g., CBF and glucose metabolism).

SPECT imaging: From the very beginning of the pandemic, SPECT has been useful in detecting global alterations in CBF (96–98). It was demonstrated through these studies that CBF changes were often observable before any measurable structural changes). Consistently, these studies demonstrated reductions in CBF in the frontal, temporal, and parietal areas of the brain, the severity of which was shown to be associated with severity of cognitive symptoms. Importantly, however, reductions in CBF were shown to be improved through treatment, with CBF reductions returning to near normal levels (99).

More recently, there have been additional studies using SPECT imaging. For example, Ernst et al. (100) examined the SPECT measured CBF and metabolite measure for a cohort of 24 HIV+ patients and 34 HIV– controls(100). SPECT CBF was shown to be significantly reduced in the temporoparietal white matter for the HIV+ cohort. These findings were interpreted in the context of abnormal metabolite measures using MRS, where the abnormal MRS findings appeared to precede abnormal SPECT findings. This suggested that MRS, as a measure of HIV-associated CNS involvement, is more sensitive than SPECT. In a similar study, Chang et al. (101) compared the findings from SPECT and perfusion MRI in a small cohort of patients with HIV-cognitive motor complex (101). Nineteen patients

with HIV and 15 healthy seronegative controls were examined. HIV-infected patients demonstrated reduced CBF bilaterally in the inferior lateral frontal lobes and the inferior medial parietal lobes. These reductions correlated significantly with measures of disease severity including CD4 count, plasma viral load, Karnosfsky score, and HIV–dementia scale measures. There were no significant differences between the perfusion MRI and SPECT measures of CBF.

Among HIV-infected patients, SPECT abnormalities have also been shown to generally worsen over time. A 46-month prospective/longitudinal study by Christensson et al. (102) found a reduction of SPECT perfusion and cognitive performance in HIV+ subjects (102). Results of the repeated SPECT scanning demonstrated a group reduction of CBF over time. At the same time, cognitive testing was also shown to progressively worsen, though none of the patients developed dementia. However, patients with the worst cognitive functioning showed increased tracer uptake indicating hyperperfusion in several regions of the brain including several cortical and subcortical regions, which was interpreted to be an indication of a specific HIV-induced inflammatory response and that this increase in a subset of patients may obscure reductions in HIV-infected patients.

PET imaging: In the early years of the HIV pandemic, PET work primarily focused on cerebral glucose metabolism. These studies often demonstrated hypermetabolism in the basal ganglia (103, 104) or thalamus (105), as well as in the temporal and parietal lobes (103, 106). These changes were often observed early in the disease with changes in metabolism demonstrated well before the onset of any cognitive dysfunction (104). Though the reasons are still relatively obscure, the pattern of hypermetabolism early in the disease process appears to evolve into hypometabolism for cortical and subcortical gray matter (107) in more advanced disease. For example, the van Giesen et al. (57) cross-sectional study of 19 HIV-infected patients demonstrated hypermetabolism in the basal ganglia that was associated with intact motor performance. In the patients who demonstrated moderate motor slowing, the metabolism levels began to diminish toward hypometabolism. Patients who had the most severe motor slowing had the most widespread hypometabolism throughout the basal ganglia. This study, regardless of the small sample size, provides evidence for the evolution and progression of metabolism abnormalities beginning with early hypermetabolism that progressively worsens into hypometabolism in more advanced disease stages.

PET imaging may still prove useful in future HIV studies. There are many new and novel tracers developed over the past several years that have the potential to examine very specific metabolites and/or neurotransmitters. For example, the use of the PET ligand [11C]-PK11195 might provide a window into active areas of inflammatory processes in HIV infection. Examination of multiple sclerosis (MS) patients using this ligand has demonstrated increased sensitivity of MS activity, often extending into normal appearing white matter, especially during active clinical phases of the MS activity (Vowinckel, Banati, Debruyne). Thus, there may be additional opportunities to examine the effects of HIV-associated CNS injury using PET technology.

Other Neuroimaging Modalities (e.g., Perfusion MRI, MTR)

There are several other MRI imaging modalities that have been used to examine HIV-associated CNS effects though these studies are limited. In this section, we have discussed a couple of methods that have demonstrated interesting results including, perfusion MRI, magnetization transfer imaging, and postcontrast enhancement imaging.

Perfusion MRI (pMRI) is an MRI imaging method capable of measuring the rate of arterial blood flow. One of the major advantages of pMRI is the fact that it uses no radioactive tracers to capture this information. It captures cerebral blood flow (CBF), cerebral blood volume (CBV), and the mean transit time it takes blood to flow from one part of the brain to another. Complex mathematical algorithms and corrections schemes are used to quantify pMRI metrics and it has been used successfully in a couple of studies to examine the effects of HIV infection on pMRI metrics.

One study by Chang et al. (101), demonstrated significant decreases in CBF in a group of HIV+ patients with early cognitive and motor complex problems (101). These decreases in CBF appeared predominately in the lateral frontal lobes and medial parietal lobes. There were also notable increases in CBF in the posterior parietal white matter when compared to age match controls. The alterations in CBF were also found to be associated with CD4 cell counts, HIV disease scale, and other measures of disease severity. In a study by Wenserski et al. (108), 32 HIV+ patients with varying degrees of minor motor deficits were examined using pMRI and MRS (reviewed above). Patients were divided into three groups based on motor exam with one group having normal function ($n = 10$), eight patients with their first altered motor slowing in a series of the tests, and 14 patients who had been experiencing motor slowing on objective testing for at least 6 months (108). There were increased CBF findings that were primarily relegated to the basal ganglia of the eight patients with initial motor findings. This is similar once again to the recent findings of the Ances et al. (109) study of 42 HIV+ patients and 17 seronegative controls using continuous arterial spin labeled (CASL) MRI. There was a stepwise reduction in caudate blood flow for HIV+ patients with increasing worse neurocognitve function, with the most cognitive impaired patients having the most reduced caudate blood flow (109). Blood flow in the caudate and caudate volume were poorly correlated though there were general decreases in volume related to cognitive severity. So, measures of CBF as captured with various pMRI methods has the ability to discriminate between HIV+ patients and seronegative controls. It is also noteworthy that the basal ganglia is the area where the most change is observed and may provide another unique surragate marker of HIV-associated CNS involvement.

Magnetization transfer (MT) attempts to obtain a signal from macromolecules, which are otherwise invisible to MRI, because the T2 relaxation times of their protons (less than 200 μs) are orders of magnitude below that of free water. MTI applies an extra off-resonance saturation pulse intended to resonate with the bound protons in macromolecules, yielding a signal once the magnetization is transferred to the surrounding free water. Hence MTI is considered to have partial sensitivity

towards macromolecules of cell membranes, such as the cholesterol and galactocerebroside found in myelin (110). MTI has been successfully applied for clinical assessment in several neurodegenerative diseases, such as MS (111–113) and other conditions (114, 115).

As with MRS or DTI, a potential confound to MTI is the dilutive effect of edema, where the additional water also causes a reduction in MT. Longitudinal changes of MT have also been proffered as complements to help distinguishing edema and different forms of pathology in MS (112), suggesting that MTI may indeed be sensitive to tissue destruction (116). A principal contribution of MTI lies with its potential specificity to demyelination and its alleged sensitivity to detect diffuse disease. In MS, several findings point toward MT sensitivity regarding damage of normal appearing white matter (NAWM) (117, 118). A technical confounder in MTI is the off-resonance pulse, which varies between scanners and is difficult to calibrate well, possibly biasing comparisons and multicenter trials.

Despite these limitations, the Ragin et al. (2004) examined nine HIV+ patients and nine healthy controls using whole-brain MTR (82). Additionally, the MTR results were compared to DTI metrics. Results from this study demonstrated reductions in MTR for HIV+ patients that were related to measures of psychomotor speed. MTR was also found to be related to the apparent diffusion coefficient (ADC) by measures of fractional anisotropy (FA). Though accomplished in a small cohort of patients, this study demonstrated the utility of MTR in distinguishing between experimental groups. This finding was essentially equivalent to an earlier MTR study of HIV patients. In the Ge et al. (119) study of 15 HIV+ symptomatic patients, eight HIV+ asymptomatic patients, and ten seronegative controls, both HIV+ groups demonstrated significant reductions in the mean and median values for whole-brain MTR (119). Differences for the two HIV+ patient groups included a downward shift in the mean when compared to the control group as well as a significant reduction in the height of the histogram peak for the symptomatic patients. Furthermore, this study also demonstrated that MTR was modestly related ($r > 0.50$) to a measure of brain atrophy (BPF) such that when MTR was reduced there was a reduction in BPF. So, global and regional MTR measures have the ability to discriminate between HIV+ patients and healthy controls early in the disease suggesting possible pathological changes in axonal membranes.

Another interesting line of research in HIV neuroimaging studies is the use of contrast agents to examine blood–brain barrier (BBB) permeability. Given the many significant volumetric, metabolite, and perfusion abnormalities in the basal ganglia a few researchers have focused MRI methods at understanding the mechanism of injury in this area associated with HIV+ infection. Of note in particular is the study by Avison et al. (2004), where they examined gadolinium (gd) enhanced imaging findings (120). In this study, HIV-infected patients were injected with gd and examined for areas of enhancement. In this cohort of HIV+ patients, there were several areas of enhancement in and about the basal ganglia indicating increased permeability of the BBB in these areas. This finding is particularly interesting as there is evidence that infection with HIV leads to BBB permeability. This study provides direct evidence of permeability in the case of HIV infection.

Summary and Future Research

Despite the advances in MRI and the many important findings in HIV-infected patients to date, improvements can be made in several key areas. One significant improvement in future research studies might be in participant selection. Generally, HIV-infected patients present with additional neurological risks that might be better controlled through patient selection and/or the addition of supplementary control groups with different conditions. As already illustrated, Pfefferbaum/Sullivan have demonstrated the significant contribution of alcohol abuse among commonly presenting HIV-infected populations. Much has also been written about other subpopulations within HIV-infected cohorts such as drug abuse (71, 121, 122), hepatitis C (HCV) coinfection (75, 123, 124), etc. The use of more controlled research designs will not only broaden our understanding of the neurological effects of these additional factors, but will improve our understanding of the specific mechanisms of HIV-associated CNS injury.

Another significant improvement that will advance the HIV infection literature will be larger, prospective studies. To date, the vast majority of imaging studies are cross-sectional in design. There are a few notable exceptions, though these studies are often limited to smaller cohorts and limited time points (not more than two time points). One major advantage of prospective studies is the improved statistical power when using participants as their own controls. There has been much work recently reported in the literature, regarding time series analyses of prospective imaging data among several different patient populations (125, 126). The interest in this type of imaging data has resulted in a growing set of methods for dealing with longitudinal data, including subtraction imaging (see Fig. 7), our own time series analysis (see Fig. 8), etc. For example, in a study of multiple sclerosis patients (an interesting possible archetype for HIV-associated neurodegeneration) the level of disease activity varies greatly among individuals, as does the severity

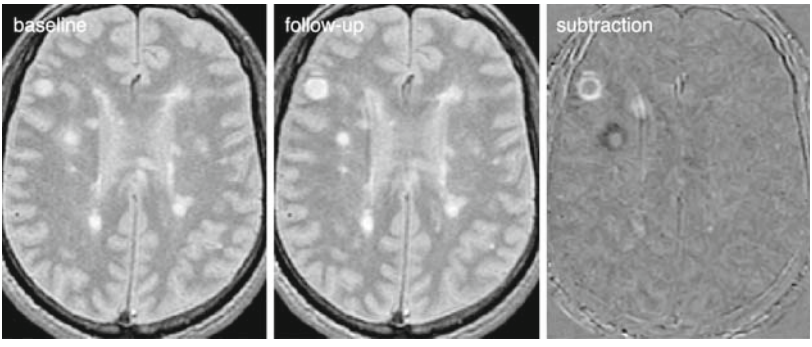

Fig. 7 Example of structural change detected by serial MRI. A subtraction of co-registered and intensity-normalized baseline and follow-up exam reveals both new and resolving pathology, visible as hyper- and hypointensity, respectively, relative to the neutral gray. Changes are highlighted as all stable anatomy cancels in the subtraction

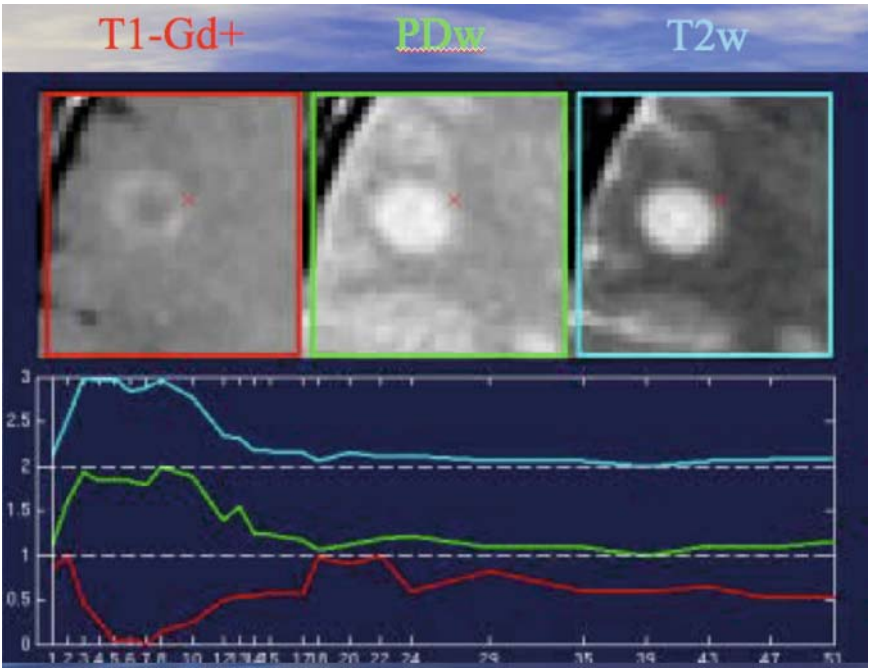

Fig. 8 Example of time series analysis examination of a MS lesion in a single patient. The three images represent three types of MRI sequences (gadalinium enhanced (*red*), proton density (*green*), and T2 weighted (*blue*)). The graph below represents the intensity of the voxel marked by the *red* x over the time course of the study. In this manner the variability and magnitude of the lesion can be examined (*See Color Plates*)

and rate of progression. Morphological change is reflected in focal lesions as well as global and regional atrophy, with both brain and spinal cord afected. Occurrence, duration and residual of individual MS lesions are often stochastic in nature (see Fig. 9) potentially confounding associations with clinical outcomes. Additionally, emerging longitudinal studies of Alzheimer's disease have revealed significant variability in the rate and progression of neuroimaging abnormalities. Morphological alteration in AD is reflected in global and regional atrophy as well as specific anatomical abnormalities such as hippocampal atrophy. Despite the complexity, there has been encouraging success in modeling lesion variability in MS patients (126) and global/regional atrophy rates in AD patients (127, 128) that might also be applied to HIV-infected patients. Monitoring the literature for advances in longitudinal methods among other patient populations will most certainly reveal additional ways of examining HIV-associated CNS injury and/or treatment efficacy.

What should be clear from the current neuroimaging research literature is the fact that MRI variables in isolation provide limited pathological specificity. Future studies of HIV-associated CNS injury would benefit from the use of multimodal imaging methods that exploit the complimentary and unique sensitivities of different imaging modalities (see Fig. 10). For example, the combination of MRS and structural

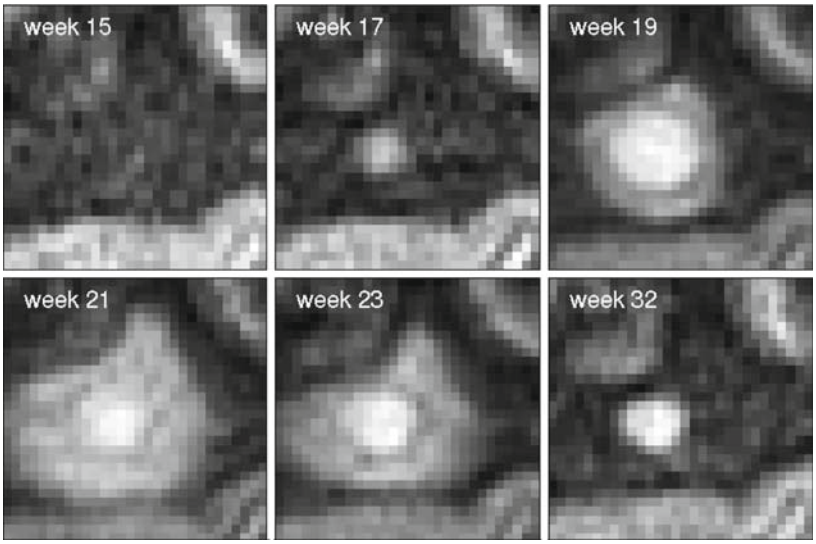

Fig. 9 Example of the dynamics of an MS lesion captured in serial T2-weighted MRI. A new lesion appeared in week 17, undergoing rapid edematous changes over the next 5 weeks

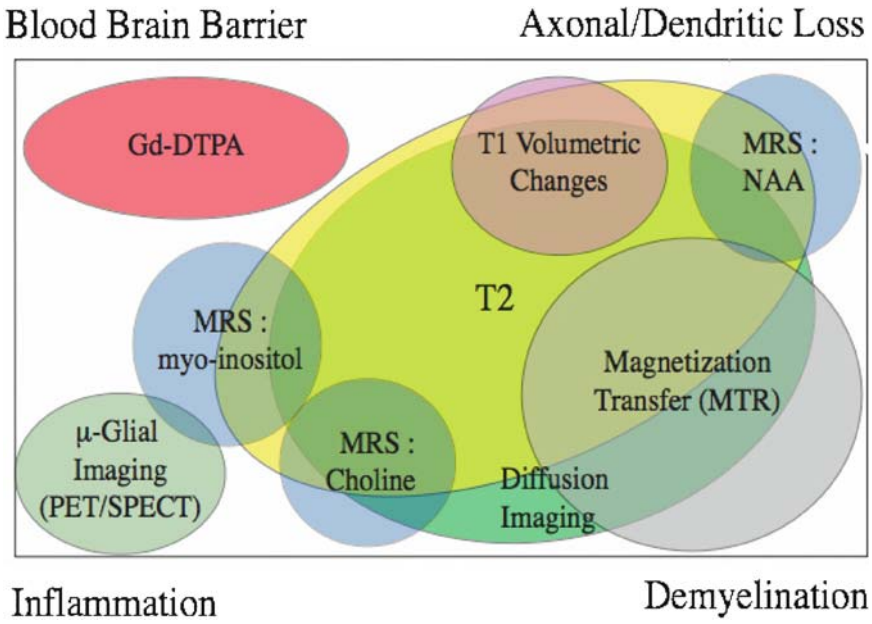

Fig. 10 MRI specificity matrix illustrating the complimentary and unique pathological correlates of different MRI sequences described in the te xt for four common pathological f indings in HIV encephalitis. *Gd-DTPA* gadolinium enhanced; *MRS:NAA* *N*-acetylaspartate; *T2* T2-weighted sequences (*See Color Plates*)

MRI has the potential to distinguish between two different pathways of injury among HIV-infected patients – inflammatory and noninflammatory (129). Studies designed to maximize the dissociative qualities of different imaging modalities have the best potential of establishing pathological specificity not afforded by clinical and/or cognitive variables. Though there is still much to be learned about HIV-associated CNS injury (see Table 1), it is obvious that MRI and other associated imaging modalities hold significant promise for evaluating the evolution, progression, and treatment effects among HIV-infected patients.

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The Assessment of HIV-Associated Neurocognitive Disorders: New Challenges in the HAART Era

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Introduction

The introduction of highly active antiretroviral therapy (HAART) in the mid-nineties has changed the global picture of HIV infection. From a life threatening illness, HIV/AIDS has become a chronic disease with a much-prolonged life expectancy. These marked changes have been also observed in the context of HIV-related neurological diseases with a decrease in the incidence of HIV-associated dementia (HAD) since 2001. The HAART era is now characterized by a higher prevalence of HIV-associated neurocognitive disorders (HAND) with predominantly a milder form of the disease. This higher prevalence was interpreted as reflecting at least in part an increased survival rate in individuals with HIV infection.

Associated with the increased survival are potentially new characteristics of the recently infected population and comorbidities in the longer-term infected population that may complicate both the assessment of HAND and its nature. In Western countries, the epidemiological figures of HIV infection have changed from a mainly Caucasian gay male population to a more diverse population where women of ethnic minority and of low socio-economic background are overrepresented and there are a significant number of individuals with a history of substance use disorder. This shift could also be interpreted as the old- and newly-infected population in the Western countries. Importantly, the individuals who have been infected between 20 and 10 years ago are now aging and contribute to the global aging of the HIV population. It is currently unclear whether aging will be associated with a more severe or different form of HAND.

The newly-infected population in the eastern countries of Europe, for example, is overrepresented by intravenous drug users. In North America, a large proportion of drug users are often coinfected with Hepatitis C virus. Recent work has reported

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a higher proportion of neurocognitive impairment in coinfected individuals in comparison with mono-infected individuals. Hepatitis C virus is therefore one of the most important comorbidities that HIV-infected population are facing.

Another complexity of chronic HIV-related neurological disease is the long-term therapeutic management involving optimization of HAART to counter side-effects, lower the pill burden to potentially improve adherence, and to minimize the resistance that most patients eventually develop. Moreover, while more definite evidence remains to be collected, there is the potential for neurotoxicity-related to some or all of the component drugs when patients are on long-term HAART. Lastly, there are controversial results regarding whether immune reconstitution syndrome may lead to the expression of HAND in what was previously subclinical disease.

In the last several years, research into HIV-related neurological diseases has extended from a mainly Western population to an international one especially in developing countries, where the HIV epidemic is increasing such as in Asia and Sub-Saharan Africa. Importantly, in these developing countries, the HIV-infected population usually differs in terms of socio-economic status, gender, and sexual orientation compared with the original population in Western countries. More specifically, very large regional differences are possible within one country, for example, between the urban and the rural population. As in the newly-infected population in the Western countries, women of lower socio-economic background are often over-represented as well as drug users and sex workers. Related to this population is often a low level of education and sometimes illiteracy that challenges the conventional neuropsychological method which is often based on the assessment of some academic skills. In addition, extreme poverty or survival conditions affect all aspects of medical and neurological health. Furthermore, there are issues of cultural differences and the frequent lack of local normative data again hindering the use of standard neuropsychological tests.

Moreover, some work suggests that regional differences in HIV clades may lead to variation in the expression and severity of HAND. However, more recent and more rigorous studies have tended not to support such clade related effects. Nonetheless, more work is needed. Lastly, HIV-related opportunistic infection remains common in some countries where ART access is still limited. In resource-limited settings, the cause of HAND may be multiple and sometimes compounded by high rate of malaria or tuberculosis.

In light of these new findings and challenges, it appears important to be able to reevaluate the state of our knowledge regarding HAND. The complexities of the disease itself with a relapsing and remitting course, the complexities of HAART itself with its direct and indirect effect on the progression of the disease, and the complexities of the social characteristics of the population studies render the HAART era particularly challenging. Because HAND has become a chronic disease, when treatment is available, part of the focus of the research and the clinical evaluation need to be redirected to the long-term follow-up of the HIV-infected individuals. Moreover, because HIV/AIDS is a global disease, it is particularly important to try to understand whether the manifestations of HAND are similar across the world as well as developing pragmatic strategies to assess HAND in developing countries.

In this chapter, we have summarized the current knowledge regarding the use of neuropsychological method in HAND to detect cogniti ve impairment and change in cognitive functioning, emphasizing indi vidual case methods. W e have also described what may be the new risk factors for HAND and how this may affect the pattern of neuropsychological dysfunctions usually observ ed in HAND. The discussion regarding the assessment of neuropsychological dysfunction in the de veloping countries is part of the chapter entitled "Impact of Clade Di versity of Neuropsychological outcomes".

The Assessment of Cognitive Functions in the HAART Era

The Typical Neuropsychological Assessment

The diagnosis HAND or HAD remains the decision of a neurologist because other neurological disorders need to be e xcluded as the cause of the cogniti ve impairment by neurological and neuroimaging e valuations. The assessment of neuropsychological functions is required to delineate whether the prof ile of impairment thought to be typical of the ef fect of HIV on the brain is present. Moreo ver, this assessment allows classifying the se verity of the deficits in addition to the assessment of e veryday life functioning.

Three main nomenclatures hav e been produced in the pre-HAART era to classify the cognitive, motor and neuropsychiatric manifestations of HAND. First, Price & Brew (1) established a framework of five stages for *AIDS–Dementia Complex* severity including a preclinical phase. Then, in 1991 (2) and 1996 (3), the American Academy of Neurology proposed a modif ied nomenclature to better delineate the mild and more se vere forms of the disease because the mild neurocogniti ve deficits, observed commonly in advanced HIV infection, were not severe enough to be termed as dementia. The y defined two stages: *HIV-1-Associated Minor Cognitive/Motor Disorder (MCMD) and HAD Complex* respectively with the main difference between the two stages residing in the severity of cognitive symptoms impacting significantly on activities of daily living. Finally, Grant & Atkinson in 1999 (4), defined a partially revised nomenclature consisting of *HIV-1-Associated Dementia-HAD and HIV-1-Associated Mild Neurocognitive Disorder (MND*). The main distinction between the AAN criteria and the Grant & Atkinson' s criteria for the diagnosis of HAD, resides in not requiring a disturbance in either motor functioning or moti vation, emotional control, or social behavior in addition to the cogniti ve deficit.

Recently, all these nomenclatures were updated and merged into a common one. This updated nomenclature (5, 6) defined an additional stage in HAND as "asymptomatic neurocognitive impairment" (ANI) which recognized the possibility of subclinical cognitive impairment. This updated nomenclature otherwise k eeps the Grant and Atkinson (4) definitional criteria which gives a greater priority to cognitive impairment as compared to motor and emotional dif ficulties. Central to these definitional criteria is the assessment of cognitive functions that is to be documented

by a formal neuropsychological examination. Global impairment is defined by a deficit of at least one standard deviation below the normative mean in a minimum of two cognitive domains. This cut-off is relatively strict and may be more relevant to the research context as there is a 15% false-positive classification rate for the ANI category. The assessment needs to be comprehensive enough to assess abilities of attention/working memory, speed of information processing, learning, delayed recall, verbal functioning, abstraction/problem solving and motor functions. While a step-down battery exists (7) as well as brief cognitive scales such as the HIV-dementia scale (8, 9), it is recommended to use these instruments either as screening tools or as part of a more comprehensive assessment. It is also important to use demographically-corrected norms even for these screening tools (10). However, it should be said that these brief instruments maybe of practical importance in limited-resource settings.

Because HAND is thought to mainly represent HIV brain injury to the striato-frontal neuronal networks (11), the neuropsychologist expects that areas of speed of information processing, attention/working memory, learning and active retrieval (as opposed to recognition in memory tests) will be primarily affected (for a recent review of the neuropsychological profile in HIV-infection, see (12)). Any focal deficits such as agnosia, apraxia or aphasia would be indicative of another diagnosis depending on neurological and neuroimaging results. The presence of focal neurological and neuropsychological findings may indicate that an HIV-related brain opportunistic infection is present. Although this is less frequent in the HAART era, the neurological and the neuroimaging investigation should be able to provide this differential diagnosis. In addition, any rapid forgetfulness in memory tests, anomia, and semantic paraphasia in language tests as seen in Alzheimer's disease would signal the need for further investigation. Gross visuo-spatial deficits as seen in Alzheimer's disease, Parkinson's disease, and Huntington's disease are also unlikely, but may not exclude a diagnosis of HAND in the absence of identification of other pathology by neuromedical examination. Overt dysexecutive functioning especially when accompanied by gross frontal type of behavior is unusual except in the advanced stage of HAD. However, milder forms of abstraction and problem solving disturbances are often observable on neuropsychological tests.

The exact composition of the neuropsychological battery for the assessment of HIV-infected individuals suspected or at risk for cognitive impairment may vary, but the clinical neuropsychologist can find some guidance from several sources. Currently, neuropsychological test compendia such as Lezak et al. (13) provide recommendations for selecting a number of neuropsychological test measures. There is also the Halstead-Reitan battery (14) for which, some of the tests have been recommended in the use of HIV-infection (15, 16). International experts during a National Institute of Mental Health (NIMH) workshop have also outlined recommendations for what is named the NIMH battery (17, 18). Lastly, Maj et al. (19) have provided recommendations for a testing battery in international settings.

Theoretically, the neuropsychologist should have the same number of tests in each cognitive domain to make a statistically sound decision regarding domain-specific level of cognitive impairment (20). It is often the case that research

over-represents tests of processing speed and attention (see 21, 22 for reviews). Nevertheless, the aim of the clinical assessment is to represent as comprehensively as possible the current neurocognitive abilities of one individual.

In addition to the neuropsychological tests, it is also recommended to briefly assess the level of depressive complaints using a validated psychiatric scale as well as anxiety and cognitive complaints (for more information see 23, 24). Importantly, the assessment should be complemented by an examination of activities of daily living (25) as this assessment serves to ascertain the presence of dementia vs. milder stages of HAND (5, 6). In the context of HIV/AIDS, a caregiver is not often available to provide a more objective assessment of everyday life functioning. Self-reported everyday functioning is used on scales such as the Instrumental Activities of Daily Living Scale (IADL, 26), the direct assessment of functional status instrument (DAFS, 27). The current research in this area shows that the reports of cognitive complaints, depressive complaints and IADL should be interpreted together, as the different types of complaints may be inter-related while they do remain for the most part independent of the neuropsychological level of impairment at least in mildly impaired individuals (24, 25, 28).

Because of the increasing overlap between HIV-infection and substance use disorders, assessment of substance use history is of particular importance (see also 12 for recent review). Preferably validated psychiatric structured interviews or scales should be used, rather than open questions to the examinee (for an extended and recent review of psychiatric disorders in HIV-infection, see 23). The type of drugs, length of use, mode of use, and dosage should be recorded as they help to interpret the current level of neurocognitive abilities. Lastly, medication adherence should always be monitored as it has been shown to be associated with severity of cognitive impairment in HIV-infection (29). A recent article provides an overview of the instruments that are available (30). They conclude that even a brief assessment of medication adherence is recommended.

It is common that a comprehensive assessment will require at least 2 h of testing and 1 h to collect other information. Depending on the instruments used, the assessment will vary in length. It is likely that the clinician will be aware of the current HIV diagnosis of the examinee. More importantly, the clinician will pay attention to the degree of fatigue that may interfere with the test results. Patients at the AIDS stage are more likely to demonstrate fatigue-related cognitive deficits often observable by a decrease level of sustained attention. This is why most clinicians opt for a focused battery of tests likely to detect HAND which will likely be applicable to most of the patients in an HIV clinic. Nevertheless, the neuropsychologist should remain open to test additional cognitive domains when an atypical pattern is detected. Fortunately, a lot of the tests used in HAND are also used in degenerative diseases allowing the clinician to detect atypical deficits that would be indicative of a differential diagnosis. However, focal deficits such as agnosia, or hemi-neglect will need the addition of specific tests. Psychiatric features other than mild depressive and anxiety complaints should be thoroughly investigated by a psychiatrist. Finally sensory deficits whether related to HIV/AIDS should temper the interpretation of the results. The most common in the context of HIV/AIDS is severe peripheral

neuropathy in the upper limbs, which can sometimes significantly reduce motor-coordination abilities. Lastly, effort, cooperation, and motivation ought to be constantly monitored during the testing session. Instruments aimed at detecting lack of effort and or motivation will help the interpretation (12, 31).

The Importance of Appropriate Norms for a Given Population (Effect of Age, Education, Ethnicity, and Gender)

The effect of age and education and gender to a lesser extent has been long recognized in neuropsychological testing (32). The proper use of neuropsychological instruments demands the corrections of at least these two factors on the raw results obtained by an individual. Unsurprisingly, the most commonly used tests and the most trusted by the neuropsychologists are also tests that have been amply validated and that have also normative data based on large samples. Some of these tests have already a large pool of cross-cultural data and the best examples are the Wechsler adult intelligence scale (WAIS-III, 33) and Wechsler memory scale (WMS-III, 34) already translated in many languages. However, their application in developing countries is till sparse – this has been addressed in the chapter entitled "Impact of Clade Diversity of Neuropsychological Outcomes" Importantly, the data from the cross-cultural validation within Western countries of the well-known batteries tend to demonstrate a "universal" effect of age and education on the neuropsychological abilities (35). When gender norms are available, the clinician is encouraged to use them. The same logic applied to ethnicity where it has been shown in some countries to affect the neuropsychological performance (36). Some neuropsychologists also recommend the use of reading levels to account for quality of education differences between ethnic groups within the same country (37). However, the clinician should remain aware that these corrections are probably the proxies of complex and multifactorial effects on the brain. Therefore it is the current socio-cultural and socio-economic as well as historical context that will render these variables and their interactions (e.g., gender and ethnicity) more or less pertinent (38). Some authors also recommend the assessment of levels of acculturation by taking into account specifically designed measures of acculturation (39) as well as verbal fluency in the nonnative language, length of residence in the adoptive country, socio-economic status, and persistence of poverty (40, 41). As explained in more detail in "Impact of Clade Diversity of Neuropsychological Outcomes" one aspect that is less likely to affect testing performance in Western countries is the effect of rural or urban division although this may not have been true in the past. In developing countries, this distinction is of particular importance and may be complicated by its interaction with gender (42).

Altogether, clinicians should avoid using tests with poor normative standards. Despite the fact that the procedure for developing neuropsychological norms corrected for demographic factors is a demanding and arduous process in a globalizing world, this method still represent the most validated approach to determine level of cognitive impairment. The difficulties of neuropsychological norms development

are that they need to be redeveloped approximately every decade (i.e., "Flinn effect"). This process is costly and needs to be done on a large scale. More fundamentally, the relevant demographic factors between one population and another may differ and change overtime in different ways (43). This inherently hampers the development of "universal" normative data, and implies that local normative data are by definition relative and transient.

The application to the developing countries is even more challenging because some of the factors impacting on neuropsychological function need to be ingenuously investigated. The effect of age, education, and gender may be different from the developed countries because of unexpected interactions between these factors especially, in poorer settings. Lastly, the comparison of one individual to a group encompasses some theoretical limitations as well as statistical limitations due to the Gaussian assumptions that the reference population has to respect (44). Here, the rapid progression of the research in statistical psychology is hoped to develop complementary mathematical tools to address the inherent complexity of this type of behavioral data. One way to partially overcome this problem is to focus on the longitudinal assessment of cognitive functions, when one individual becomes his/her own normative standard. However, repeated assessments of cognitive functions also need normative standards in order to correct for practice effect and define what may be significant change.

The Importance of Long-Term Follow-Up

The course of HIV-associated neurocognitive impairment is variable and almost any pattern of progression can be seen with phases of relapse and remission of unknown duration (45). In addition to this, the natural course of HIV-associated neurocognitive impairment has potentially been altered by the widespread use of HAART. There has been an increase in patients' survival (46) leading to the emergence of the concept of inactive disease (47). Brew (48) and McArthur et al. (49) have proposed that HAND may be now subdivided in four categories depending on the disease evolution and the response to treatment: active HAND happens with no antiretroviral treatment, inactive HAND happens with successful treatment but is a "burnt out" form of the disease where some irreversible brain injury remains stable, chronic HAND where slow brain HIV replication provokes a low level of neuroinflammation and a transformed HAND where age, Hepatitis C virus in the brain, direct and indirect toxicity of antiretroviral drugs, increased cerebrovascular risks in long-term HIV-infection, and immune reconstitution syndrome may change the clinical profile of HAND. The ultimate complexity comes also from the fact that these different types of HAND may happen at different times in the life of a single HIV-infected individual and may even overlap to a certain extent.

Because these new definitions of illness are based on the evolution of HAND and the recovery, partial recovery, progression, or stabilization of cognitive deficits, it is clear that a strategy for repeated assessments is becoming crucial. As in other

slowly progressing diseases, a yearly evaluation appears to be suitable. However when HAD has occurred before or in between antiretroviral therapy, a follow-up assessment should be given 6 months after treatment initiation as this has been shown to be the probable time window for HAART benefit (50).

The follow-up neuropsychological assessment should comprise the same tests as the baseline assessment and include alternate versions of test measures when these have been shown to provide equivalent results. The neuropsychologist should be aware of the reliability data on the NP test measures used to facilitate the interpretation of change. Information regarding disease evolution, change in any comorbid factors, drug use should be recorded. Evaluation of depressive, anxiety and cognitive complaints as well as activities of daily living should be also reassessed.

It should be noted now that no systematic criteria have been published for what may be normal and abnormal cognitive change. Therefore, in most published works, the cross-sectional criteria have been applied to data collected on each follow-up session and abnormality is defined when these are outside normal ranges. However, this method does not take deterioration in cognitive function overtime as the core definition for HAND, but instead requires that the patient's neuropsychological performance be compared to the performance of the normative sample. There are at least two main problems with this approach. First, practice effects are well-known to occur with repeated administration of neuropsychological tests (51). Therefore, normative data should contain modifications for this practice effect, or better still, also provide data from normal individuals or clinically stable individuals who have been assessed repeatedly. Second, the requirement that abnormality be defined when performance data fall outside some normal range means that patients who show significant deterioration in cognitive function, but whose performance is still normal, will not be classified as abnormal, or worse still, not considered for special CNS related therapy.

There have been few studies that have evaluated the long-term outcome of HAART on cognitive function have been conducted in patients who met the criteria for neurocognitive impairment at their initial visit (before HAART initiation) and were then reassessed up to 2.½ (52), and 4 years (50) later. These studies observed improvement in complex attention/psychomotor speed (52) and in motor-coordination (50) and interpreted such improvement to reflect a HAART-related CNS benefit. Tozzi et al. (50) showed that 57.3% of their 16 patients had varied neurocognitive improvement after a median time of 45 months of HAART (range 36–52), although sustained improvement was found only for the Stroop interference subtest and for the grooved pegboard dominant hand task. None was found for attention, simple processing speed, verbal memory, or visuo-construction functions. However, neither of these prospective studies compared the cognitive change observed in the advanced HIV group to any control group. Thus it is possible to conclude that the performance change observed in either study reflected in part a practice effect: the HIV-infected individuals became more practiced at performing the tests and the magnitude of such an effect was unknown. Another limitation is that while Tozzi et al. (50) used a relatively comprehensive range of neuropsychological tests, Sacktor et al. (52) included only the Trail Making and Symbol Digit Modalities tests in their battery.

In addition to these studies, our longitudinal observational study conducted in 2006 (53) in Australia tended to address some of the limitations of these previous studies. We used a comprehensive neuropsychological assessment over a 4-year period. We developed norms for change in an HIV-sample and used the reliable change index (RCI) method to determine cognitive change in each individual. In this study we found that a majority of HIV+ participants stabilize their performance (between 76 and 66% from first to last visit, while 7.5–29% improved), independent of the attrition rate. However, neuropsychological decline does occur in a minority (between 16.5 and 5% from first to last visit): it is not linear in that several years may pass between symptoms of progressive neurocognitive impairment.

Several studies have been published in normal controls and clinical groups other than HIV/AIDS to address cognitive change. We have summarized below the most important guidelines that come out of these studies.

Practice Effect and Regression Toward the Mean

Repeated neuropsychological assessment is subject to a learning effect that differs depending on the test measure used and on the initial level of impairment of the individual. The psychometric property of the tests will interfere with the ability to observe change. Indeed, tests that have a skewed distribution of measures and a restricted range of responses will not perform as well as measures that have an infinite number of potential measures and/or with a normal distribution. This is one of the reasons why time-based tests perform better than measures of verbal learning for example. Moreover, by nature, some cognitive abilities will remain more stable than others and this is why language tests, in healthy population, are usually less subject to improvement compared to executive function based tests (54) and memory measures (55). Keeping this in mind, the clinical neuropsychologist is encouraged to evaluate potential cognitive change in a comprehensive number of cognitive abilities and use tests on which test retest reliability and practice effect data have been published. When data are skewed, the normalization of the data distribution may be approximated using appropriate statistical transformation (see 56). Moreover, one strategy has been to use a battery approach in the evaluation of cognitive change (57). This method has several advantages in HIV infection: the use of a composite score on which to base change computations improves the reliability of the observed change and it appears to be clinically relevant in the diffuse type of neurocognitive disorders where the decline or improvement is likely to affect a range of cognitive functions. However, when decline is expected in specific areas of cognitive functioning, individual measures need to be explored.

The interval between assessments has not been shown to be a major factor on the magnitude of the practice effect in some studies (58, 59), but not in others (60–62); while others have found that it does not affect all tests to the same extent (63). It is often that the largest practice effect is observable at the second assessment (64) although this may depend on the age, the education, and the initial level of

impairment of a given individual (65, 66). To circumvent this effect, some authors have proposed the use of a dual baseline assessment (67). Although this method may correct for part of the larger effect of practice, it appears to be more easily applicable when using brief screening battery (58, 59). The current pragmatic attitude in research is to include a statistical correction for the number of assessments given (53). Some have also suggested to monitor change in cognitive functions using practice effect itself (68). More work is currently made which hopefully will provide clearer guidelines for clinicians.

To account for practice effect, it is required to include a correction of the test retest difference that can be derived from a normative or reference sample. Several computational methods to derive change scores which take into account practice effect have been developed and we have outlined them below. These methods also allow correcting for regression towards the mean. Regression towards the mean results in an increment for lower average baseline score or decrement for higher average baseline score of the retest score toward the group mean due to the least square method of the regression prediction (69).

We chose to present only the most contemporary methods because the theoretical detail of longitudinal statistics is beyond the scope of this chapter. However, we provide ample citations to which a more interested reader can refer. In addition, we will not discuss research statistical methods that have been developed to look at cognitive change overtime in groups because we are interested in change at the level of the individual in the clinical setting. However, the reader can find examples of these methods in NeuroAIDS research in Sacktor et al. (70) using the generalized estimating equations (GEE – 71). There is also the possibility of using the mixed effect regression models (72), which has been also used in NeuroAIDS research (e.g., Ferrando 73). This last method can provide both group and individual analyses as well as the modelized the drop out effect, which is common in this type of studies.

Defining What is Significant Change

Below, we present three statistical methods that have been validated for interpreting change overtime in individuals. The reader is encouraged also to refer to the original publications for any application of these statistical procedures that have been briefly described here. These three methods have been outlined in Temkin et al. (63) and Heaton et al. (65). The first method was originally described by Jacobson and Truax (73) and is the RCI method. Since then modified RCIs have been produced to better account for practice effect, and variability of performance overtime. (see 74, 75 for reviews). This has been developed further below.

The second method is based on the use of linear regression of the retest scores on the baseline scores in a control or reference sample to develop a formula for predicting a follow-up score from any baseline score (63, 76). The third method is the use of a stepwise linear regression in which factors such as demographic and

overall baseline level of cognitive performance are accounted for in a stepwise fashion according to the prediction formula (63).

A crucial process in the determination of norms for change is the use of an index to standardize the performance overtime which is ideally derived from an appropriate normative sample. In the case of the Temkin's RCI (63), this is the standard deviation of the difference; others have used the within standard deviation (53, 75, 77). In the simple linear regression model, the residual standard deviation is used (63), while the corrected residual standard deviation is used in the multiple linear regression model (63, see also formulas 1 & 2). Importantly, Heaton et al. (65) have found that the RCI corrected for practice effect provided similar results to the more complex regression models mentioned in a mixed clinical sample. Authors have traditionally used the 90% confidence interval which indicates that in the reference or control sample, it is expected that 5% of the individuals will significantly improve and 5% will significantly decline. Additional research is needed in this area to be able to define systematic criteria for change that will help clinical neuropsychologists. It should be noted that most of the well-known standard neuropsychological batteries such as the WAIS, WMS, and HRB have published test retest reliability data, nevertheless these data are unequal in quality and authors are still debating on what are the best indices for standardization (55).

Formula 1: *Reliable change index (RCI) with practice effect correction*

$$\text{RCI} = (X_2 - X_1) - (U_2 - U_1)/\text{SD diff}$$

where X_2 = individual time 2 performance (or any follow-up); X_1 = individual time 1 performance; U_2 = reference or control mean time 2 performance (or any relevant follow-up); U_1 = reference or control mean time 1 performance; and SD diff = standard deviation of the difference (other have used the within standard deviation; see (74, 75)for reviews).

Significant change can be defined using a 90% confidence interval. This corresponds to 5% of a normative sample improving (i.e., RCI $\geq$ 1.64) and 5% of a normative sample declining (i.e., RCI ≥ -1.64).

Formula 2: Regression-based change score (RCS)

$$\text{RCS} = (\textit{actual } X_2 - \textit{Predicted } X_2)/\text{SD residual}$$

where actual X_2 = actual individual performance at time 2 (or any follow-up); predicted X_2 = predicted individual at time 2 (or any follow-up); and SD residual = residual standard deviation of the control or reference sample (or corrected residual standard deviation in the stepwise regression model).

Significant change can be defined using a 90% confidence interval. This corresponds to 5% of a normative sample improving (i.e., RCI or RCS $\geq$ 1.64) and 5% of a normative sample declining (i.e., RCI or RCS ≥ -1.64).

Lastly and very importantly, Heaton et al. (65) noted that the initial level of impairment or performance is crucial to understand the expected change (i.e., change is expected to be larger in low performing individuals). They recommend that the reference group used to develop norms for change have the same baseline performance level as the clinical groups that are tested. In the clinical context, this

often represents groups with a specific disease that remain stable (i.e., with no significant clinical or treatment changes) rather than "only" healthy controls. Another method is to use multiple reference groups as suggested by McCaffrey & Westervelt (69). This method may be particularly useful in the clinical setting, while in the research setting the choice of the type of reference group should be guided by the scientific questions that the study is investigating. Besides the clinical similarity between the sample used to develop norms for change and the sample on which the norms will be applied, factors such as age, education, gender, and other demographic variables should also be considered. Indeed, recent work suggests that these factors may affect the methods used to detect change in a complex manner (see (78) for further details).

Again this area of research is in constant evolution and it is anticipated that the criteria and guidelines for cognitive change will be formalized in the future. A multidisciplinary effort is currently underway in NeuroAIDS research and other clinical areas where change contributes to the definition of the disease (e.g., postoperative cognitive related deficits, (75)).

Is the Neurocognitive Profile of HAND Changing, and What Are the Effects of Age, HCV, and Gender?

Evidence for neuropsychological changes in the pattern of HAND with HAART introduction came from studies demonstrating that HAART was associated with significant improvement in neuropsychological functioning and in particular psychomotor slowing (50, 52, 70, 79–83). Historically, the extent of improvement in neurocognitive functioning had no parallel, with some patients fully recovering from mild to moderate degrees of dementia.

Most of the neuropsychological investigations conducted in the HAART era assessed a relatively comprehensive range of neuropsychological functions and most have demonstrated a positive significant impact associated with HAART on psychomotor speed tests and/or motor tests. However, not all demonstrated sustained effects on learning, memory, visuo-spatial functions, and verbal fluency (50, 80). This may indicate that improvement on HAART is not equal for all cognitive domains. Alternatively or additionally, the extent of improvement may be dependent on the initial severity of cognitive impairment. It is now recognized that the overall effect of HAART is that the severity of the cognitive disturbances has decreased (49). Cysique et al. (84) have attempted to address whether the detailed pattern of cognitive performance has changed by comparing cohorts of advanced HIV-infected individuals in the post-HAART and pre-HAART era who were comparable in terms of demographics, socio-economic background, HIV risk factors, and disease severity. They found a similar prevalence of cognitive impairment before and after HAART supporting previous results from the MACS and NEAD cohorts in the U.S. (85). However, a potential change in the neuropsychological profile was not explored between the two American cohorts because of the substantial difference in

demographic and HIV risk factors. Because this was not the case in the Australian cohorts, Cysique et al. (84) compared their two cohorts on nine cognitive domains and noted that the pattern of neuropsychological impairment had changed across pre-HAART and HAART eras with a reduction in attention, visuo-spatial, and psychomotor speed deficits but with a trend toward greater memory impairment and a progression of executive deficits. This change remained even in patients with an undetectable plasma viral load, although the severity was partially diminished. This study and our longitudinal results (53) implied first that patients still had deficits either because of "carry over" of pre-HAART residual deficits, that is an inactive disease component, and/or new deficits from "grumbling" chronic disease. The prospective study however, showed that approximately 50% were stable on HAART implying that inactive disease can only account for some of the lack of change between pre- and post-HAART cohorts. It also implies that there must be a dynamic flux between no deficit and deficit in HAART-treated patients.

However, direct cohort comparison is potentially fraught with difficulty in interpretation. Some authors argue that the interpretation of a difference may be due to unknown factors. Nevertheless, because of the intrinsic complexity of the disease, historical cohort comparisons should remain a potential strategy coupled with prospective studies in the HAART era. Factors, such as rapidly evolving treatment, significant changes in demographic characteristics of the HIV epidemic including more women and more minorities, aging, and HCV coinfection render the interpretation of HAND profile change in longitudinal data in the HAART era very complex as well.

Is the Pattern of HAND Changing with Aging?

There have been several publications demonstrating an increase in cognitive impairment in older HIV-infected individuals compared to younger HIV-infected individuals (86–88). Interestingly, a relatively old publication by Hinkin et al. (89) demonstrated a similar level and pattern of deficit between young individuals with HAD and older healthy individuals as compared with healthy young individuals. This pattern was characterized by a predominance of psychomotor slowing, working memory, and complex attention deficits. The authors hypothesized that HAD was a form of premature aging and this hypothesis rebounded in the HAART era with the increasing aging of the HIV-infected individuals (90). Some authors have suggested that an additive or interactive effect of age on HIV may amplify some minor neurocognitive disturbances (91). However, the exact neuropsychological consequences remain to be thoroughly explored. Normal aging is mainly associated with decreased cognitive speed (92) and this is thought to be related to striato-frontal dysfunction. HAND has also been interpreted as resulting from striato-frontal injury, although other parts of the brain are also affected (93). Aged HIV+ individuals could potentially show an overall worsening of their cognitive ability driven by decreased psychomotor speed. However, comorbid factors associated with aging may complicate this picture.

Indeed, aging itself is the primary risk factor for neurodegenerative diseases (94) of which the most frequent is Alzheimer's disease (95). Therefore a logical axis of research is now to find potential corroboration of the possibility for neurodegenerative pathological development in HIV-infected individuals (48). There have been now several reports demonstrating the existence of neuropathological mechanisms pertaining to Alzheimer's disease in HIV-infection, such as increased β-amyloid brain deposits (96, 97); CSF amyloid β42 and tau levels paralleling those in Alzheimer's disease (98) and complex neuro-inflammatory pathways (99). As mentioned earlier, the neuropsychologist is advised to use a comprehensive assessment of cognitive abilities. If so, unusual features such as rapid forgetting on memory tests, gross verbal disturbances in naming tests could alert that a patient who is HIV+ is also developing Alzheimer's disease. Some have also suggested that the progression of HAND may be more rapid with the copresence of a neurodegenerative disease (90), but more research will be needed in this area. If this happens it will be important to discover which pattern of neuropsychological deficits is predictive of disease progression. Other neurodegenerative disorders that are less common than Alzheimer's disease could also be more prevalent in long-term HIV-infected individuals, such as Parkinson's disease which shares a common dopaminergic neuropathogenesis with HAD affecting mainly the basal ganglia (100). Here, gross visuospatial and motor deficits should alert the clinician that a differential diagnosis may be needed.

Older HIV-infected individuals may be also at higher risk for cerebrovascular insults due to a combination of aging factors (increased incidence of cardiovascular, cerebrovascular, metabolic diseases such as diabetes and hypercholerostemia), HIV disease factors (decreased immune competence that is accelerated with aging) and HAART-related toxicity (lipodysytophy, immune reconstitution syndrome) (90). From a neuropsychological perspective, focal cerebrovascular events of subcortical areas in older individuals with HAND may precipitate dementia with additional psychomotor slowing as a predominant feature. It may also translate into increased deficits in learning and memory as well as executive functions. More work is also needed in this area to understand whether some white matter diseases commonly seen in HIV-infected individuals (101) and vascular cognitive impairment (102) are the result of low-grade cerebrovascular injury and how they may affect the pattern of cognitive deficits in older HIV+ individuals.

Lastly, it has been shown that psychiatric disorders have a greater prevalence in older HIV-infected individuals as compared to younger HIV-infected individuals. This is the case not only for depressive symptoms, but also alcohol abuse and dependence as well as drug abuse and dependence. While depressive disorders have been demonstrated to be independent from HAND (28, 103), this was shown in relatively young individuals and needs to be fully explored in older individuals. Contemporary nonacute drug use in HIV-infection is known to worsen the overall cognitive deficits (104), but the chronic effects of such drugs are less clear (105). It has been shown that lower socio-economic status in HIV+ drug users had more influence on neuropsychological performance than the drug use status per se (106).

Therefore, these characteristics should be kept in mind when investigating how age may affect cognitive performance in HIV-infection.

The Potential Additive Effect of HCV and HIV on the Brains

There is evidence that approximately 30% of HCV+ individuals with mild liver disease present at least mild neuropsychological dysfunction that is independent of substance use and other comorbid factors such as depression and fatigue (107). From a series of six studies (104, 108–112), it appears that the most robust cognitive dysfunction was found in domains of sustained attention and complex attention as well as motor functions compatible with fronto-striatal models of neurocognitive impairment (113). An additive or synergistic effect of HCV in HIV-infected individuals has been hypothesized and there is an emerging evidence that coinfected subjects are more likely to be neuropsychologically impaired, (104, 114)particularly in tests of executive functions (111, 115) and psychomotor speed (114).

Are Female Gender and Sex Hormones Associated with a Higher Prevalence of HAND?

There are currently no data in the HAART era to support that women are more at risk for HAND or at more at risk for more rapid progression (116), but studies addressing this question have been rare. A European epidemiological study from the pre-HAART era noted that women were more likely to be diagnosed with HAD as compared with men (117). However, as with drug users, the effect of basic demographics should be carefully reviewed to evaluate such data. Because the gender distribution is changing in the developed countries and now includes more women especially from minority backgrounds, and that women represent the largest pool of individuals in developing countries (118), studies addressing a potential difference in HAND between genders are needed. Cohen et al. (81) noted that in the HIV epidemiological research study (HERS) cohort, HIV+ women receiving HAART also showed neurocognitive improvement in domains of verbal fluency, psychomotor speed, and executive functions especially after 18 months, while untreated women worsened in the same cognitive abilities areas. Nonetheless, more specific studies are needed. Indeed, such studies should be coupled with other factors such as hormonal status and corrected for other potential discrepant factors such as economic status.

The influence of sex hormones particularly testosterone on cognition is complex. Endocrine abnormalities are common in HIV-1 infected patients (119) and testosterone deficiency has been reported as the most common one (120–122). Usually, testosterone level is investigated in HIV-infected men, but recent data, using a more sensitive measure have shown that HIV-infected women also had lower free testosterone than seronegative women (123). Symptoms include depressed mood, decrease libido

and energy, loss of weight, and muscle mass (124). Testosterone deficiency has been associated with higher occurrence of opportunistic infections, a CD4 cell count below 200 cells/mm^3 and treatment with megestrol acetate (125). However, other studies did not replicate these results and could not find any relation with HIV illness markers (126). Testosterone supplementation in HIV-1 infected individuals induces a positive effect on depression (127), libido, energy and weight, and muscle mass (124, 127–129) as well as improved quality of life (130). So far, no studies have addressed whether testosterone deficiency could lead to cognitive deficits in HIV-infected subjects. However, recent data suggest that testosterone deficiency contributes to the occurrence of Alzheimer's disease (131, 132) and that testosterone supplementation may have a neuro-protective effect (133). The question remains also open for the female hormone estrogen, which has been shown in some studies to have a beneficial effect on cognitive functions in women with Alzheimer's disease (134). Although, recent advances demonstrate that it is a combination of select neuro-protective estrogens that could provide an increased and clinically meaningful efficacy (135). Promising results come from recent studies showing a protective effect of estradiol on neurotoxins that have been implicated in HIV neuropathogenesis (136).

New Risk Factors for HAND?

Nadir CD4

There are now several reports that have shown that the nadir CD4 cell count may be a new risk factor for HAND in the HAART era (53, 137, 138). The fact that the worst historical impairment of immune function accounts for the current neurocognitive status, while current traditional markers of HAND such as plasma viral load and CSF viral load are less effective as markers of the disease (139), confirm that the neuropathogensis of HAND has shifted from an acute process to a more chronic process (48). It should be noted that there is some evidence that the combination of low nadir CD4 and previous HAD is a risk factor for further neurocognitive decline, even if years had passed between episodes of HAND (53). Potential new markers of this chronic neuro-inflammation have been investigated in several studies. MCP-1 which was a potential candidate (140) appears to be now less likely to be associated with HAND in long-term treated patients. Indeed, recent investigations showed that increased levels of the vitamin E and triglyceride C52 predicted the onset or worsening of HAD (141). Moreover the authors showed that elevated levels of sphingomyelin were associated with inactive HAD and that elevated levels of ceramide and the accumulation of 4-hydroxynonenals were associated with active HAD. But, it is perplexing that inactive HAD should be associated with active process that elevates sphingomyelin. In this regard, it should be noted that approximately half of these patients were intravenous drug users, raising the possibility that this elevation may be related to drug use. Others have found that HIV proviral DNA was

associated with baseline neuropsychological performance, but was not predictive of HAND decline (142) .

Duration of HIV

There are no clear data showing that the duration of HIV affects the occurrence and progression of HAND. However, this may need to be reconsidered for two reasons. First, it is possible that an effect of HIV disease duration will only show after the second decade and the oldest surviving patients are now for the most part in their first decade with the disease. Secondly, the current tools to capture the duration of the disease are poor. What may be necessary is the development of an algorithm that takes into account the nadir CD4, the response to treatment and resistance, and comorbidities. Therefore additional work is needed in this area.

Is Neuro HAART Important?

There have been several reports demonstrating that HAART composed of agents able to cross the blood–brain barrier (BBB) is more effective at improving neurocognitive deficits in HIV-infected individuals with HAND (143, 144). In a longitudinal study of 15 months in average, and using the RCI method, Cysique et al.(53) reproduced their initial findings (143) of better neurocognitive performance in HIV+ individuals receiving at least three antiretroviral drugs with good CNS-penetrance. More longitudinal studies are necessary in a wide range of HIV+ infected individuals who differ in terms of their HAND severity at baseline. Correction for previous antiretroviral history is ideally needed. Moreover, as we outlined in the previous paragraph, robust longitudinal design taking into account practice effect, baseline performance, and a reference range of cognitive fluctuation is needed to correctly infer cognitive change in long-term treated individuals. Lastly, it should be noted that a detailed scoring system for CNS-penetrance has been proposed by Letendre et al. (145) .

Immune Reconstitution Inflammatory Syndrome (IRIS)

Following HAART initiation some HIV+ individuals can develop a paradoxical neurological deterioration, despite improvements in HIV viral load and CD4+ T-cell counts (146). This IRIS has been reported in several case studies which observed severe worsening of brain opportunistic infections as well as the occurrence of a severe dementing illness (147, 148). Although these studies suggest that IRIS may be responsible for HAND worsening in some cases, a recent longitudinal study

demonstrated that long-term immune reconstituted HIV+ individuals had improved neuropsychological functioning over a 96 weeks period (149). The authors also showed that improved cognitive functioning corrected for practice effect was not associated with higher CD4 cell count, but was associated with plasma viral suppression. Finally, as mentioned earlier, the role of IRIS in aging patients may differ from the role of IRIS in younger HIV+ individuals. More longitudinal studies will be necessary to thoroughly address these questions, but it appears that IRIS is a very uncommon cause of HAND expression or deterioration.

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The Changing Face of HIV-Associated Cognitive and Neuropsychiatric Disturbance

Ron Cohen

Over 25 years have passed since the first descriptions in the weekly report of Centers for Disease Control and Prevention of five homosexual men in Los Angeles, California, with a rare pneumonia seen only in conjunction with weakened immune systems (1). They turned out to be the first recognized cases of acquired immune deficiency syndrome (AIDS (2, 3)). In addition to opportunistic infections and physical wasting observed in these early cases (4, 5), mental status changes were evident, with some patients showing severe functional impairments indicative of dementia (6–8). Since then, a remarkable number of scientific advances have occurred with respect to the viral mechanisms underlying AIDS, its clinical expression, and available treatment approaches (9, 10). Despite these advances, the possibility of developing brain dysfunction remains a major concern for people infected with HIV.

In this chapter, I have considered the neuropsychology of HIV from a historical perspective, reviewing the cognitive and neuropsychiatric disturbances that were first described prior to the availability of antiretroviral treatments through some of the major developments in the field to the present. This will be followed by discussion of some of the major factors that influence the neuropsychological symptoms of HIV, as well as how the cognitive and behavioral effects of the illness relate to associated brain changes. The chapter concludes with discussion of some potentially important considerations for the future.

Clinical Cases

Three cases are presented below from the author's clinical experience. These cases illustrate the transformation in the neuropsychological manifestations of HIV that have occurred over the past 25 years.

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Case 1 (1982): As a neuropsychology intern on the psychiatry consultation service at UCLA in 1981, I assessed my first patient with AIDS. At that time, HIV had not been recognized as the cause for AIDS, and in fact there was considerable disagreement over the very nature of the disease. The patient, a 36-year-old homosexual male was quite ill, with severe pneumonia, from which he was slowly resolving. He also had an unusual skin disorder that was being worked up for possible cancer. The nursing staff was quite concerned about his mental status and behavior. He was poorly oriented and had great difficulty maintaining his attention. He waxed and waned between periods of relative clarity and other periods in which he was extremely disinhibited and emotionally labile. On several occasions, he undressed and was found wandering in the halls. An assessment was conducted at bedside with great difficulty, in part because of the patient's circumstantial and tangential thinking and poor attentional capacity.

An evaluation was completed over the course of three separate days with results suggesting severe and global cognitive dysfunction (Modified Mini Mental Examination, MMSE = 15). However, his presentation was also remarkable in several ways. Although he had difficulty staying on task and expressing his thoughts in a coherent and fluent manner, his comprehension and verbal reasoning abilities appear relatively intact. His performance on a test of confrontation naming was also only very slightly below expectancy, and he showed the ability to hold information in memory on recognition testing, though this was not consistent over time. In contrast, the patient showed severe impairments of learning and memory recall, along with severe impairments on almost every measure of executive functioning, including the Wisconsin card sorting test, Porteus mazes, trail making, the stroop interference test, and verbal fluency (controlled oral word association test, COWAT). His dementia is quite evident from his performance on clock drawing, and his copy and recall of a complex figure (see Fig. 1). He had difficulty in maintaining set on even the trail making A test. Performance was even severely impaired on simple behavioral inhibition tests, such as the Go-No-Go. Basic ADLs were impaired. Approximately 1 month after this evaluation was completed, the patient died of complications associated with a recurrence of pneumonia. At the time of his death, he showed severe wasting, with a body weight that was below 90 lbs.

Case 2 (1993): The patient, a 28-year-old woman with a history of injection drug use (heroin and cocaine), was referred for outpatient neuropsychological assessment. She was asymptomatic without any prior AIDS-associated infection, but with impaired immune function (CD4 < 200). She was examined prior to the availability of combined highly active antiretroviral therapy (HAART), but was being treated with an early reverse transcriptase inhibitor (zidovudine). She had stopped using injection drugs 2 years earlier and was trying to return to employment. However, she was experiencing great difficulty learning new information in the classes she was taking. She also reported problems with focusing on tasks and sustaining attention with considerable distractibility. Her family described her as being very apathetic. There was some concern about depression, though she denied sadness and most other depressive symptoms. The evaluation revealed that she was not demented on the MMSE (MMSE = 27), but was having mild problems with learning and recall,

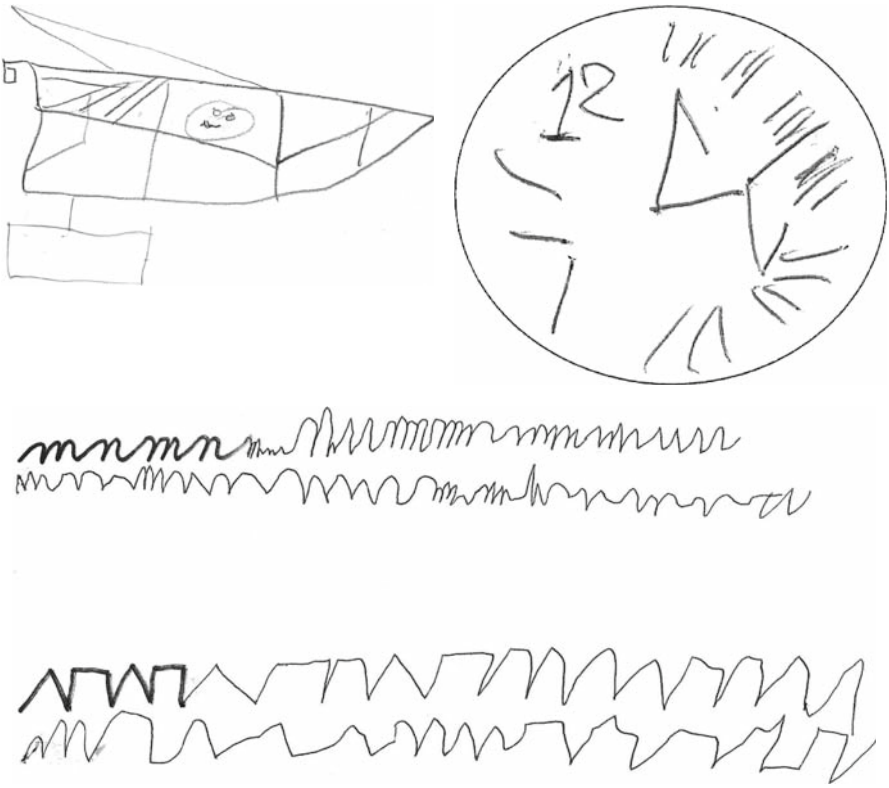

Fig. 1 (**a–c**) are the drawings of Case 1; a patient with AIDS–dementia. The drawing depict a level of performance commonly seen in patients with middle-stage dementia (e.g., Alzheimer's disease) with strong evidence of frontal lobe dysfunction. (**a**) Copy of a complex figure was poorly organized with lack of attention to detail and spatial distortion; (**b**) clock drawing within a presented circle; performance is severely impaired; (**c**) rampart figures are impaired with evidence of both perseveration and breaks in response set

along with mild impairments on executive measures (Stroop and Trail Making). The most notable finding was extreme slowing on motor tasks and also on cognitive tasks requiring information processing speed.

Case 3 (2005): The patient, a 49-year-old college educated homosexual male, underwent neuropsychological evaluation 2 years ago on the request of his physician who had noticed forgetfulness and the patient's inability to recall certain current information and details of recent events in his life. The patient had been symptomatic with pneumonia secondary to AIDS 8 years before. His CD4 nadir had been below 100, and he had experienced a viral load of greater than 20,000 copies at the time. However, he was treated successfully with HAART and has consistently had CD4 levels of greater than 400 over the past 5 years as well as viral loads that were almost undetectable. He was admitted for increased forgetfulness that was affecting his work as an accountant. The examination revealed an MMSE = 27. He only recalled one of three words on short delay and no words on longer delay. He

showed impaired recall and recognition performance on the California Verbal Learning Test (CVLT). Motor slowing was evident, along with below average performance on attention and executive measures.

The Transformation of HIV-Associated Brain Dysfunction

The three cases described earlier assessed at different time points over the course of 25 years demonstrates the evolution of HIV-associated neuropsychological disturbance in the United States. It is somewhat ironic that as better treatments for AIDS became available, concern about the cognitive sequelae of HIV have increased. Treatments were not available in early years of AIDS, and so mortality was very high, with most patients dying within a few years of diagnosis. Dementia was quite common among patients who were symptomatic, though it usually was not the primary concern, as the critical issue was to simply keep patients alive. By the mid to late 1980s a number of drugs became available, and patients were beginning to survive longer with AIDS. Consequently, AIDS-associated dementia became increasingly prevalent. As treatments became more effective in the 1990s, a decline in cases of AIDS–dementia was seen, particularly following the advent of HAART in the late 1990s. Increasingly, patients were not developing the opportunistic infections associated with AIDS and were remaining largely asymptomatic. As it is discussed in greater detail subsequently, patients were presenting with less severe cognitive problems, though continued reports of cognitive difficulties have remained. One key feature of the illness remains unchanged. Despite all of the available treatments and advances in the field, to date the infection is not curable. Once infected, people must live with the virus in their body, with a possibility of AIDS occurring at some later point. Consequently, people infected with HIV experience all of the psychological, social, and economic problems that go along with other chronic diseases. In sum, there has been a marked increase in the number of people infected with HIV reaching advanced age, who have lived with the infection for many years. The effects of chronic HIV in the aging brain are yet to be fully understood, though there is reason to believe that these effects are continuing to evolve. In the following sections, factors that influence HIV-associated neuropsychological disturbances are discussed.

Mechanisms Underlying Brain Dysfunction

The neuropathology and mechanisms underlying brain dysfunction of HIV is reviewed in "Co-occurrence of HIV, hepatitis C, and substance use disorders: effects on brain functioning." A few key points have been highlighted that provides insights into its neurocognitive manifestations. Neuropathological studies have consistently demonstrated that HIV has a particular predilection for the basal ganglia and white-matter pathways (11–18). Why these selective regional neuropathological effects occur is

not fully understood, though the virus seems to cross the blood–brain barrier most effectively in the parenchyma surrounding the basal ganglia. There is some evidence that gp120 associated with HIV alters the blood–brain barrier , which facilitates the central nervous system (CNS) penetration (19). The virus directly infects supportive cells of the brain, including mononuclear phagocytes such as microglial cells, astrocytes, and macrophages (20– 22)Strong evidence for viral replication within neurons does not exist, but markers of HIV have been found in neurons, microvascular endothelial cells, cells of the choroid plexus, and oligodendrocytes (21) .Once cerebral mononuclear phagocytes are infected, a paracrine-amplified inflammation occurs, which seems to persist throughout the infection (23). Cellular disturbances result, which appear to be associated with proinflammatory cytokines, (e.g., interleukin-8), nitric oxide, quinolinic acid, progeny virions, and regulatory proteins (24). With ongoing viral replication in the brain, greater neuropathology develops.

HIV infection affects the brain both directly and indirectly (25, 26). Brain abnormalities are considered to be directly caused by HIV if they can be due to neuropathological factors attributable directly to the effects of virus in the brain. Alternatively, secondary brain abnormalities occur because of opportunistic infections, and other diseases develop as HIV infection progresses to AIDS. Evidence of direct CNS effects comes from cases in which there has been no opportunistic infection of the brain; yet there is significant neurocognitive impairment, not attributable to other neurological brain diseases. In such cases, there are often brain neuroimaging abnormalities evident by neuroimaging on MRI, as well as evidence of HIV-RNA in the cerebral spinal fluid (CSF), and in brain tissue (27–29). Human and animal studies have both demonstrated that the virus can be detected in the brain within 2 weeks of initial infection, where it remains presumably until death (27, 29, 30). Elevated free calcium is thought to occur directly from HIV effects, such as the enveloping of proteins (e.g., gpl20), with calcium influx via ionic channels causing neuronal damage (26). Excitatory amino acids and receptor antagonists, such as quinolinic acid, also seem to play a direct role. Although all of the direct mechanisms underlying HIV neuropathology have not been resolved, there is compelling evidence that HIV infection directly disrupts normal brain functioning.

HIV infection also indirectly causes opportunistic infections, tumors, and cerebrovascular disturbances, which can produce dramatic brain dysfunction(25, 26). Both viral (e.g., JC virus (progressive multifocal leukoencephalopathy, PML), cytomegalovirus, herpes simplex) and nonviral infections (e.g., toxoplasmosis, cryptococcus) may occur (31–44). For example JC virus is associated with PML, a rapidly progressive and fatal disease that is characterized by the development of multiple subcortical white-matter lesions (43, 45). PML causes severe cognitive impairment associated with the extensive white-matter pathology, and the prognosis of these patients is very poor. It is important to note that the overall impact of opportunistic infections is relatively minimal compared with the direct effects of the virus. The impact of HIV-1 on cognitive and behavioral functions cannot be fully accounted for by the secondary effects of opportunistic infections that affect the brain. In the era of new treatments for HIV, only a small percentage of HIV -infected individuals have secondary brain infections; yet neurocogniti ve dysfunction occurs in 30–87% of

infected individuals (46). They are less common now, though they still occur. For the most part, these infections are treatable and a majority of patients are now able to recover (36). Yet, there continues to be reason for some concern as infections such as cytomegalovirus may induce T-cell-independent apoptosis in brain (47).

A retrospective autopsy study of HIV between 1988 and 1996 revealed brain lesions in 79% of patients (48). Both focal and diffuse brain lesions were evident, with various types of pathology present, including multifocal myelin loss (21%), microglial nodules (18%), infarcts–hemorrhage (15%), angiocentric pallor (6%), and calcification (5%). At a cellular level, multinucleated giant cells, macrophagic subcortical infiltration, myelin pallor, and gliosis may occur. Leukoencephalopathy (myelin loss, nucleated macrophages/microglia, reactive astrogliosis) is very common. Vacuolar leukoencephalopathy is associated with deep white-matter swelling. Damage to axons, myelin, and large astrocytes may occur as either a direct effect of HIV and due to encephalitis or othersecondary infections. Vasculitis may develop in patients, and this is associated with increased risk of infarctions secondary to hemorrhage in subcortical regions of the brain.

To summarize the above literature, brain function is compromised early in the course of the disease both directly through infection of macrophages and in some cases indirectly through opportunistic infections (49–54). HIV encephalitis occurs following the accumulation of perivascular accumulations of microglia cells, monohistocytes, and macrophages. Leukoencephalopathy often occurs following diffuse myelin loss, proliferation of astroglial cells, and infiltration by mono- and multinucleated macrophages (25–47).

HIV-Associated Neurocognitive Dysfunction

As discussed earlier, the prevalence and to some extent the nature of HIV-associated neurocognitive dysfunction has changed since AIDS was first recognized approximately 25 years ago and HIV was identified. It is likely that in the early days of the epidemic, a majority of patients may have eventually developed dementia if they lived long enough, though most patients died prior to showing this degree of functional impairment. As treatments became available, the prevalence of severe cognitive dysfunction declined, such that by the mid-1990s approximately 15% of patients with AIDS were diagnosed with dementia, though many more seemed to have milder forms of cognitive dysfunction (55, 56). In the past, the prevalence of neurocognitive impairments was less in asymptomatic patients, though impairments occurred among patients with very impaired immune functions and sustained elevations of viral load (57). Currently, estimates of the prevalence of dementia and neurocognitive impairment vary depending on the criteria that are used for defining impairment. In the current NIH supported studies being conducted by my group in the Brown University Center for AIDS Research (CFAR), approximately 30% of HIV-infected patients have some cognitive impairments, though somewhat less than 5% have severe impairments that meet dementia criteria. These findings are

consistent with rates described in multicenter studies of HIV-associated brain disease, suggesting that the incidence of AIDS–dementia in this country has declined from what was observed in the early years of the disease (7, 11, 58, 59).

HIV-associated dementia is diagnosed when there is evidence of marked declines in function across more than one cognitive domain, along with evidence of functional deterioration affecting activities of daily living (ADLS) and self care. By definition, there must be evidence of significant declines from premorbid abilities. When first recognized among early cases, HIV-associated dementia differed substantially from the dementia associated with Alzheimer's disease (AD) and other cortical degenerative diseases (60). The neuropsychological profile associated with AIDS–dementia involved impairments on measures of complex attention, information processing speed, and verbal memory, and presented clinically as distinct from classic neurodegenerative dementias, such as Alzheimer's disease. As was evident in Case 1, patients with dementia secondary to HIV tend to experience their dementia in the context of other AIDS symptoms. Many are physically ill and most have very compromised immune systems.

A large number of studies conducted over the past 20 years have supported the conclusion that the cognitive, behavioral, and functional presentation of AIDS–dementia differs from that of Alzheimer's disease and related neuronal dementias (56, 61–68). Tests sensitive to mental flexibility, motor and information processing speed, verbal fluency, and learning and memory recall tend to be affected (69, 70). This pattern is typical of "subcortical dementia," in which the neurocognitive presentation suggests functional disruption of subcortical–frontal brain systems (71–73). This differs from the severe primary amnesic disorder evident in AD, in which there are usually also impairments across core cognitive functions (language, visual–spatial, conceptual abilities). The cognitive deficits found among patients with HIV-associated dementia tend to be greatest in the areas of information-processing speed and efficiency, attention-executive control, and psychomotor functions. The dominant finding is usually marked slowing on a variety of tasks that require rapid processing speed. With respect to learning and memory, impairments also differ from those seen in Alzheimer's and related cortical dementias. HIV-infected patients tend to have greatest problems with their efficiency for new learning and with retrieval of information from memory that has been learned. Yet, most patients continue to show the ability to store new memory, and often their recognition memory performance is stronger than recall, pointing to the fact that their primary memory systems (e.g., hippocampus) are more spared than is the case in Alzheimer's disease. In sum, most patients with dementia secondary to HIV do not exhibit primary amnestic disturbances.

While this "frontal–subcortical" pattern of impairment is most typical of AIDS–dementia, considerable heterogeneity in symptom presentation exists, reflecting the variety of underlying neuropathology. Among some patients, severe memory impairments affecting memory encoding and storage may exist that are virtually impossible to distinguish from AD. In general, HIV-associated dementia differs from degenerative dementias such as AD with respect to temporal consistency. Patients with HIV are more likely to show significant variations in functional abilities

in association with their disease status. Yet, the functional impact of HIV-dementia is devastating, as patients experience major cognitive and behavioral problems that affect daily living.

Patients with dementia who have opportunistic brain infections are particularly variable in their cognitive presentation. Furthermore, their dementia severity often fluctuates with changes in their infection. Many patients show marked improvements as their brain infection resolves.

HIV-associated cognitive-motor disorder (CMD) is the diagnosis given to HIV-infected patients with milder functional impairments not meeting the criteria for diagnosis of dementia (53). The prevalence of AIDS–dementia complex (ADC) has declined since the introduction of effective antiretroviral therapies (50, 74, 75). Though less severe than dementia, CMD still often affects daily functioning and quality of life (49–54, 65, 66, 76–87). Mirroring AIDS–dementia, HIV-associated CMD tends to have greatest impact on attention, executive, and psychomotor functions (88–112). The most commonly observed finding involves slowing on tasks requiring rapid information processing and on tasks requiring motor or sensory-motor response. Such slowing is rather ubiquitous in HIV and can be observed on a wide range of neuropsychological tests, including simple motor tasks (e.g., Finger Tapping, Grooved Pegboard), simple and choice reaction time, and more complex cognitive tasks that require information processing (e.g., digit symbol, trail making). I have briefly discussed past findings regarding impairments of specific cognitive processes and domains.

Reaction Time and Information Processing Speed

Although there continues to be a debate about the extent to which slowing of cognitive processes secondary to HIV accounts for the variety of impairments associated with HIV, there can be little doubt that it is among the most common impairments among HIV-infected patients (53, 88, 90, 93, 99–101, 103, 107, 113–116). Furthermore, impaired reaction time and reduced information processing speed likely account for many of the impairments of attention and executive function (117–120). Cognitive slowing presumably reflects the effects of HIV on subcortical white and the basal ganglia, most notably the caudate nucleus. The caudate has been shown to be particularly vulnerable to HIV (95, 113, 121–139).

Executive Functioning and Attention

When neuropsychological functioning is impaired, the cognitive domains most commonly affected are those of attention and executive functioning (6, 53, 65, 66, 78, 80, 84, 140–142). Impairments of executive functioning and attention in HIV must be considered in the context of the psychomotor and information processing

speed deficits, as impairments in these domains in past studies often occur against the backdrop of cognitive slowing (116). Two primary factors account for the effects of diminished speed of information processing on attention and executive control: (1) performance on attention and executive measures is often time dependent so that a person's scores on tests will be negatively affected by generalized slowing; and (2) slowed processing speed reduces the amount of information that can be handled at any given time resulting in diminished processing capacity and increased effortful demands on tasks requiring controlled focused attention (95, 114–116). In effect, reducing processing speed capacity tends to also reduce information processing efficiency, a necessary element of effective attention and executive control. The first factor can be partially controlled for by selecting tasks to assess these functions that do not require rapid processing and responding. However, the second factor is more critical as reduced processing capacity associated with cognitive slowing may affect performance on any attention and executive control task that is demanding enough to be sensitive to impairments in these domains.

Slowed cognitive processing does not account for all of the attention and executive impairments that occur among people infected with HIV. Symptomatic patients who have not progressed to the point of AIDS–dementia may have problems with response initiation, inhibition, alternation, and control that extend beyond what can be explained by cognitive slowing. Furthermore, impairments of higher-order executive processes that involve problem solving, abstraction, and planning may also occur, and are difficult to explain solely on the basis of slowing. Several studies have demonstrated attention and executive impairments in humans and other HIV-infected primates that are not attributable to generalized slowing (89, 107, 116). Although severe impairments of executive functioning and attention that extend beyond the effects of slowing are not universal among all HIV-infected patients with CMD, they represent an important basis for functional impairments among some patients. Beyond the general effects of slowing, these attention and executive impairments are most likely attributable to disrupted frontal–subcortical pathways (65, 143–150).

Psychomotor Functioning

It has long been recognized that many HIV-infected patients show impaired performance on motor tasks when other cognitive functions are relatively intact (141). Typically this involves slowing on reaction time measures and tasks requiring fine motor speed and dexterity (e.g., Grooved Pegboard), though among some people impairments may involve more substantial problems with motor control (58, 151). The presence of motor problems along with other cognitive problems is one of the key factors that distinguished AIDS–dementia from Alzheimer's disease and related dementias (53). Clinically, psychomotor slowing makes interpretation of more generalized cognitive slowing somewhat difficult, as it is difficult to disentangle slowing solely attributable to motor dysfunction from more pervasive slowing affecting information processing. Impaired psychomotor functioning is thought

to reflect the proclivity of the HIV to affect basal ganglia systems, including the caudate and putamen.

Learning and Memory

Historically, primary amnesic disorders have been uncommon among HIV-infected patients. Even patients with AIDS–dementia do not show a failure to store new information similar to that seen in Alzheimer's disease. For example, the patient with AIDS–dementia who was described earlier (Case 1) had major impairments of new learning and encoding and poor recall of material that he had tried to learn. Yet, he had the ability to retain information once learned, and showed relatively intact recognition memory performance. Learning and memory performance were not significantly impaired among women in our CDC-HERS cohort, whereas performance on the tests of attention-executive functioning and psychomotor function (Grooved Pegboard) was reduced in HIV-infected patients, and worsened in those not treated with HAART (69, 152). This pattern of results corresponds with past evidence that at least in the past, HIV did not affect hippocampal and related temporal lobe systems involved in primary memory. Instead learning and memory difficulties seemed to reflect dysfunction resulting from subcortical–cortical interactions (79, 121, 139, 153–156).

When learning and memory problems occur among patients with CMD, they tend to involve learning efficiency and retrieval, particularly on tasks requiring the processing of large quantities of new or complex information that is difficult to organize (e.g., California Verbal Learning Test, Complex Figure Test). However, other problems with specific processes associated with learning and memory have also been described. For example, working memory is often affected in patients with CMD (137, 157, 158). Difficulties with semantic processes and priming associated with learning and memory have also been described (159). Yet, problems with semantic memory are not always evident (137, 157, 160) and relate more to executive dysfunction than to memory encoding or storage per se when they occur (161). It should be noted however that there is recent evidence that in the current era of HAART, HIV may be causing greater hippocampal damage and hippocampal-associated memory impairments. Moore et al. found that hippocampal and putamen microtubule-associated protein and synaptophysin in the hippocampus and putamen, reflecting neuronal cell body, dendritic, and presynaptic terminal health, were independently associated with overall HIV-associated neurocognitive impairment (87, 162–164).

Language

Primary language functions tend not to be greatly affected in HIV (53, 165–168), except in some cases of advanced ADC. It is rare to encounter a patient with severe aphasia. Yet, problems with verbal fluency are common, often evidenced by

reduced performance on the COWAT, with deficits on this test typically associated with executive dysfunction involving impaired response generation and persistence (168). Performance on verbal fluency for "action" words has even been shown to predict dependence of instrumental ADLs (159). Language-related problems involving semantic processing (e.g., semantic priming) also seem to often relate to executive dysfunction (158, 160, 167, 169). Yet, some studies have shown semantic impairments attributable to reduced activation of automatic semantic networks, particularly in children (170). The more marked impairments of psychomotor, attention, and executive functioning may mask more subtle effects of HIV on language functioning in the developing brain (87, 162–164).

Visual Functions

Primary visual perception and visual–spatial functioning are usually not severely impaired by HIV (66, 171–176). Yet, past studies have shown abnormalities of certain visual functions (173, 175–177). Abnormal visual contrast sensitivity and color detection may occur (173, 175–177). Visual abnormalities have tended to involve ocular abnormalities, as well as problems associated with ocular movement (66, 172, 174). However, problems with visual selective attention under dual-task or other demanding conditions also occur, and may account for some of the observed problems with primary visual perception (110).

The Importance of Preserved Neurocognitive Function

Besides the fact that cognition is a core element of the human experience, there is now considerable evidence that preserving cognitive integrity is important for health, functional status, and overall quality of life. HIV-infected patients without dementia who have milder cognitive impairments usually continue to function independently in their community, though often with much greater difficulty. Even mild neurocognitive effects have health ramifications. Clinical evidence suggests that patients with even mild neurocognitive impairment have an increased risk of mortality, and identification of mild neurocognitive disturbances may also be important in predicting disease course. Early HIV-associated cognitive impairments, specifically psychomotor slowing, is associated with an increased risk of mortality at a 3.5-year follow-up (110, 142, 178, 179). Patients with only a 25% reduction in processing speed have been found to be at 6.4 times the risk of mortality compared with those at the 75%. Psychomotor slowing in HIV infection has also been found to be a particularly strong predictor of subsequent dementia and death (180). Therefore, treating these neurocognitive impairments may have critical ramifications for overall health outcome. Patients with CMD are more likely to benefit from behavioral interventions to improve their functional capacity, and early detection of such impairments might ultimately enable interventions to prevent dementia.

Neurocognitive impairments have adverse effect not only on health status (181), but also on quality of life (QOL) and functional capacity (182). Support for this comes from a large number of studies involving a wide range of different medical disorders, such as heart disease (74). We have found that among HIV-infected women, neurocognitive performance was a strong correlate of QOL (50, 75). In this study of 44 HIV-infected women enrolled in psychosocial support groups, we examined neurocognitive functioning, along with depression severity, quality of life (MQOL-HIV), and immune function status (CD4). We found that neurocognitive status was strongly associated with QOL, measured by the MQOL-HIV ($R = 0.60$, $p < 0.01$) and perceived health status as measured by the SF-36 ($R = 0.56$), accounting for more variance than CD4 and depression severity, though depression severity contributed additional variance. The results reinforced the functional significance of neurocognitive impairments in HIV. Other studies have found a similar relationship between neurocognitive status, QOL, and health status among HIV-infected patients (50, 74, 183–185). HIV-associated neurocognitive impairments are associated with the need for independent living capacity, occupational performance, and ability to engage in ADLs (186). Recent findings suggest that in the current era of HAART, memory function may be an increasingly important predictor of ADLs, such as return to employment, with youth also being an important factor (187–195). Depression improved after return to work.

The Influence of Viral and Host Factors

Immunological Compromise

Efforts to characterize HIV-associated factors that contribute to the development of neurocognitive dysfunction initially led to the examination of markers of immune system disturbance. This was a logical starting point as HIV infection impairs the immune system, resulting in reduced CD4 cell count, and historically clinical outcome in HIV has been found to be associated with the integrity of immune system function (50, 61, 67, 134, 196–206).

Past studies have also shown a relationship between CD4 cell and neurocognitive functioning, as well as increased risk for dementia and cognitive abnormalities on EEG, MRI, and other indices of brain dysfunction (207, 208). This relationship was most obvious prior to the development of HAART. The risk of cognitive impairment associated with HIV is clearly greatest among symptomatic patients with AIDS who have CD4 cell counts below 200 (209). In one study, the risk of cognitive dysfunction was found to increase threefold in patients with CD4 counts below 200 mm^3, and sevenfold among patients with CD4 counts below 100 mm^3 (55). We have observed the strongest association between neurocognitive performance and CD4 count among patients with CD4 levels below 100; with marked increases in impairment

the farther below this level, CD4 falls (53). There was also early evidence that rate of decline in CD4 was an important determinant of cognitive status (77, 204, 210–212).

Today a much more complex relationship exists between CD4 and neurocognitive functioning. Some studies continue to find reduced CD4 levels to be associated with cognitive dysfunction, but others do not (213). There are several reasons for differences across studies: (1) the range of CD4 among patients in particular cohorts varies quite markedly; (2) the CD4 levels used to group patients is often quite different; (3) CD4 nadir (i.e., lowest level of immune function during disease course), duration of CD4 suppression, and duration of infection vary across studies; (4) whether symptomatic patients are considered in a study; and (5) when treatments available at the time a particular study was conducted. In the post-HAART era, the relationship between CD4 cell count and cognitive impairment has become less clear cut. It is possible that plasma levels of HIV-RNA and CD4 cell count may or may not fully reflect the degree of viral suppression in the CSF, because of differential penetration of drugs across the blood–brain barrier.

While neurocognitive studies of impaired immune function have primarily focused on the CD4, other lymphocytes have also been implicated in HIV infection, including CD8, CD14, CD16, and CD57. CD8 has been linked to age-associated changes in T-cells (214), and both CD4 and CD8 appear to aggregate in the brains of people with AIDS (215). Subsets of lymphocytes (e.g., CD8+CD57+) also occur in the context of viral infections, such as measles, which seem to be augmented in interaction with HIV (216). The significance of these lymphocytes with respect to HIV-associated neurocognitive function is still not fully understood, though.

Immune response genes (e.g., CCL5) have been identified, including CCL5, which remain upregulated throughout the course of HIV infection and over time can be found in infiltrating lymphocytes (217). These genes seem to affect multiple phenotypic responses and affect the brain during critical periods of viral and host interaction, likely damaging both immune cells and neurons in chronic infection. They also may play a role in linking Tau protein, which has long been implicated in Alzheimer's disease to neuropathological brain changes in HIV (218). Accordingly, CD4 levels likely are only part of the story in accounting for brain changes secondary to HIV.

Although various issues remain unresolved regarding neurocognitive dysfunction in the context of immune system suppression, several conclusions can be reached:

1. Asymptomatic patients with CD4 levels greater than 400 or 500 cells/ml typically have little cognitive impairment that can be attributed to HIV after other factors are accounted for.
2. Patients with CD4 levels below 100 are much more likely to have impairments.
3. When CD4 drops below 200 cells, a curvilinear relationship seems to exist; as levels approach 0 cells, there is a marked increase in impairments. Greatest impairments occur among patients whose CD4 levels have fallen below 50.
4. (4) Both CD4 nadir and the duration of immunological suppression may be important factors that influence the likelihood that cognitive impairment will occur.

Viral Load and Neurocognitive Functioning

While CD4 cell count provides an index of immunological health, the burden of HIV is ultimately a function of viral load, measured by the number of copies of virus detected in the blood plasma or cerebral spinal fluid (209, 219) Historically, plasma viral load was shown to be associated with the development of symptoms and HIV prognosis. Patients with plasma HIV-RNA > 50,000 copies/ml have 12–18 times the risk for developing and dying from AIDS than do patients with reduced viral load. Relative risk markedly increases between 500 and 50,000 copies/ml, doubling between 500 and 3,000, with 6–10-fold increases at a viral load of 50,000 (220, 221).

Plasma viral load prior to the initiation of antiretroviral therapy is associated with subsequent neurocognitive decline and the development of AIDS–dementia (222). McArthur et al. examined over 1,600 patients from the MACS cohort with baseline serum viral load collected over a decade ago (223). Plasma viral loads of greater than 50,000 copies/ml were predictive of subsequent dementia, with a relative hazard of 9.1 compared with those patients with viral loads of less than 500. Patients with lower CD4 cell counts at baseline also had increased risk for developing dementia. Similar findings have been reported by other groups (211). In sum, past studies suggested that sustained elevated viral load and chronically suppressed CD4 levels predict subsequent functional status (224). However, there is evidence that this association may have changed in large part because of sustained viral suppression secondary to HAART.

HIV infection of the brain is characterized by replication of viral RNA in the CSF, as well as rapid turnover, suggesting that the CNS effects are caused by rapidly proliferating cells (67, 126, 221, 225–234). Viral load measures taken from the CSF of HIV-infected patients provides one of the few ways of assessing HIV infection in the CNS, as direct brain biopsy is not generally feasible. The relationship between systemic CD4 cell count and plasma viral load and CSF viral load is complex, though, as one might expect, CSF viral load has tended to relate more strongly than plasma viral load with neurocognitive performance and the occurrence of AIDS–dementia (67, 234). The strength of relationship that is observed depends on (1) whether symptomatic or asymptomatic patients are examined, (2) the range of CD4 levels that are considered, and (3) the confounding variables that are controlled in a particular study. The CD4 threshold used to group patients appears particularly important. Also, results differ depending on whether plasma or CSF viral loads are analyzed. Strongest relationships between systemic and CNS viral load seem to exist among patients with the greatest systemic viral load and impaired immune functions.

A relatively strong relationship exists for patients with CD4 less than 200, whereas the relationship is weak for those with CD4 > 500. For example, when the relationship between cognitive performance and disease status as measured by CD4 cell counts, plasma, and CSF viral load was examined in a study that grouped patients based on CD4 levels (<200, 200–500, >500 cells/mm^3), CSF viral load, but not plasma viral load was found to be a significant predictor of neurocognitive impairment. This relationship was particularly strong for patients with CD4 < 200 (235). Other studies have shown a significant relationship between HIV-RNA in the

CSF and severity of HIV-associated dementia and neurocognitive impairments in both adults and children (43, 48– 49,101– 106)McArthur et al. (58) found that HIV-RNA levels in CSF in the pre-HAART era were significantly higher in patients with dementia after adjusting for CD4 count ($p < 0.01$), whereas plasma levels did not correlate with the presence of dementia among these patients. There are some data suggesting that viral replication may occur in the brain even when it is suppressed systemically, as measured in the plasma viral load, as well as data suggesting that HIV in the CSF may be virologically different from HIV found in plasma, though these issues remain unresolved. Perhaps, a more critical issue stems from the fact that both cell-free plasma and CSF RNA levels are now typically well suppressed by HAART. This has led to the need to examine cell-associated viral burden. Recent studies in HAART-experienced HIV-positive patients suggest no relationship between either plasma or CSF HIV-RNA levels and neurocognitive performance suggesting that HAART may attenuate HIV replication within the CNS (236).

Proviral DNA

In most patients, several months of HAART usually suppresses HIV-RNA to less than 50 copies/ml (237). Yet, there is considerable evidence that HIV continues to replicate within cells, despite suppression of free virus, and that this may create a substantial burden on the system over time (238, 239). Accordingly, quantitative methods were developed for measuring cell-associated "proviral" DNA among patients with HIV (240).

Against this backdrop, it is important that while incidence has declined, people continue to develop HIV-associated dementia despite HAART (241, 242). A significant relationship has been shown between levels of circulating provirus and HIV-associated dementia, not only in this country but in other parts of the world, where AIDS is less well-controlled (243). Recently, Shiramizu et al. demonstrated that circulating HIV proviral DNA is significantly associated with neurocognitive function as well (215). In fact, HIV-DNA levels correlated with performance across many different cognitive domains, including learning and memory, motor function, attention and working memory, executive functioning and language, independent of age, ethnicity, intellectual level, and plasma viral load. Yet, baseline HIV-DNA levels did not predict change in these cognitive functions over time. Therefore, it is likely that cognitive function varies in its relationship to changes in HIV proviral DNA over time.

Other Medical and Viral Conditions Exacerbate Brain Dysfunction

HIV infection almost always occurs against the backdrop of other medical conditions and preexisting exposure to other viruses. For example, the CD8+CD57+ interactions (244) that exist among patients with previous exposure to measles points to viral

synergistic effects that may influence the effects of HIV on the brain. Hepatitis C virus (HCV) is a common coinfection occurring with HIV that affects many infected patients, particularly those with history of intravenous drug use (IDU). HCV infection is characterized by chronic inflammation of the liver and development of hepatic cancer in many cases (245, 246). HCV has been associated with cognitive impairments and cognitive decline in its own right, with impairments extending beyond effects that can be attributed to comorbid medical and psychiatric conditions, adverse effects of treatment effects, or hepatic cirrhosis by itself (247). Cortical electrophysiological changes have also been reported in this population, with HCV patients exhibiting delayed P300 latencies, which correlated with the severity of cognitive impairment (248, 249). Importantly, these cognitive changes were unrelated to treatment of HCV with interferon, a medication known to result in fatigue and cognitive compromise (53, 77, 134, 170, 185, 250–253). It is beyond the scope of this chapter to review the important interactions that may occur among HCV, HIV, and other viruses (see "Co-occurrence of HIV, hepatitis C, and substance use disorders: effects on brain functioning"), though it seems clear that such conditions contribute to HIV-associated neurocognitive dysfunction, and likely augment the effects of HIV in the brain.

Symptomatic or Not?

One factor that consistently emerges as an important determinant of cognitive dysfunction among HIV-infected patients is whether they have been symptomatic with AIDS. There is little doubt that neurocognitive dysfunction is most common among patients who have been symptomatic and had CD4 levels drop below 200 cells and been diagnosed with AIDS (66, 78, 212, 254), as discussed earlier. There are a number of reasons why cognitive dysfunction is more common among symptomatic patients. Opportunistic brain infections are more common among symptomatic patients. In fact, by definition such infections could not have occurred in a patient considered to be asymptomatic. Furthermore, symptomatic patients are usually sicker and may experience functional problems as a result of systemic illnesses. Perhaps most importantly, symptomatic patients are likely to have experienced prolonged elevated viral loads with CNS penetration and severely impaired immune function, exposing them to the direct effects of HIV on brain structural and functional integrity.

The neuropsychological literature has been more ambiguous with respect to neurocognitive function among asymptomatic patients. In some studies conducted in the pre-HAART era, asymptomatic HIV-infected patients with CD4 cell counts above 200 were found to have impairments compared with seronegative controls (255). Yet, other studies have provided more mixed results. For example, in an initial well-controlled study of asymptomatic HIV-infected gay men, which controlled for various comorbid and demographic factors, Stern et al. found mild motor slowing in the asymptomatic patients. Yet, in a subsequent study, Stern et al. again employed rigorous experimental control for age, education, and other clinical factors, and failed to show differences in sensitive information processing measures between asymptomatic HIV-infected

women compared with controls (77, 251). Similar findings of limited or no impairments have been reported in other studies of asymptomatic patients (256). In a recent study comparing a large sample from the MACS cohort, there was no evidence of cognitive decline among the asymptomatic patients (257–259). Performance on two cognitive tests with known sensitivity to brain functioning in HIV (Symbol Digit Modality Test, Trail Making Test) did not decline over an extended time period in three groups of asymptomatic HIV-infected homosexual men compared with seronegative controls. The results provide strong evidence that asymptomatic HIV-infected people can live for a relatively long time of period with low levels of HIV, without experiencing significant cognitive declines. By comparing three asymptomatic HIV patient subgroups, evidence is provided that etiological factors, including the absence of recurring elevated HIV-RNA levels, lack of progression to AIDS, and preservation of CD4 above 200 cells/μl, are important for preserving cognitive function. Whether these results hold for patients who have had more variable patterns of CD4 and viral load over time are still an open question, as well as the outcome for these patients as they reach more advanced age.

Chemokines and Inflammatory Processes

One of the presumed mechanisms by which HIV results in brain dysfunction is through the triggering of inflammatory processes in immunological response to the virus. Inflammatory processes are mediated by a variety of biochemical events in response to viral infiltration, including the release of chemokines, which mediate white-blood-cell activity (260). Chemokines such as CCRC5, CCR3, and CXCR4 serve as important cofactors, which in association with CD4 cells control the entry of HIV into target cells (211, 261–265). Cytokines, which are present in cerebral microglia and astrocytes, are believed to be important in the development of neuropathological brain changes, neuronal dysfunction, including apoptosis and HIV-associated cognitive decline (266, 267). Cytokines generated in response to virus in the brain(21) are thought be an important factor underlying HIV-neurocognitive dysfunction (268). Various cytokines have been implicated, though MCP-1, MIP-1β, and TNF-α appear particularly important, as these cytokines correlated strongly with cognitive function in a large cohort of HIV patients (269). Further, a recent study conducted by the ACTG demonstrated subtle improvement in grooved pegboard function among HIV patients treated with CP1189, a compound that inhibits TNF-α, though no other cognitive benefits were observed (269, 270, 271). Strong relationships between elevated TNF levels and severity of cognitive function, and brain atrophy and brain metabolite abnormalities have been described in other studies as well in the pre-HAART era (272), providing further evidence for the role of cytokines in HIV-associated brain dysfunction. However, a recent study in HAART-experienced patients found no relationship between either CSF or plasma immune activation markers and HIV-dementia, again suggesting an attenuated CNS inflammatory response in HAART-experienced HIV-positive patients (236).

Cognitive Reserve May Provide Some Functional Protection

The construct of cognitive reserve was developed to explain the clinical observation that people with strong premorbid cognitive abilities seemed to have greater preservation of neuropsychological functioning following brain injury (273, 274). Evidence for this phenomenon came from studies of Alzheimer's disease (275). Both educational and occupational attainment reduced AD risk. Both environmental and innate factors seem to contribute to cognitive reserve. Cognitive reserve also seems to influence neuropsychological status in HIV (272). Stern et al. found that well-educated people (>12 years) have less HIV-associated neurocognitive impairment (15.8%) than less well-educated people (38.1%). When a cognitive reserve score was derived based on demographic and clinical factors, patients with the lowest scores had the greatest functional impairment.

Cognitive reserve implies that people have different capacities to withstand functional decline in the context of the amount of brain injury, and there may be a number of reasons for this. Cognitive reserve presumably reflects cognitive and/or brain capacity, which in turn sets the threshold for neurocognitive dysfunction after brain injury (276, 277). The fact that cognitive reserve is associated with educational and occupational attainment may either point to the benefits of environmental enrichment. Alternatively, greater educational and occupational accomplishment reflects stronger premorbid cognitive abilities and greater intrinsic functional brain capacity. This second possibility is supported by the evidence that cognitive reserve is associated with increased brain size and weight, increased dendritic arborization and length, and improved neuronal efficiency. Genetic predisposition also influences neuronal development and ultimately the amount of brain reserve that exists. Prior brain injuries or disease, and developmental brain disorders that affect brain functioning, may also reduce this reserve. For example, prior stroke and head injury have been shown to be risk factors for the development of AD. Also psychiatric problems such as chronic substance abuse, affective disorder, or schizophrenia may reduce reserve. Clinically, it may be extremely difficult to disentangle the exact basis for reduced cognitive reserve among HIV-infected patients with multiple comorbidities, which may include psychopathology, substance abuse problems such as chronic injection drug use, prior head trauma, and neurological conditions, together with effects of limited education and environmental impoverishment.

Psychiatric Comorbidity in HIV

It is well recognized that certain comorbidities common among people infected with HIV affect neurocognitive and functional status in their own right, perhaps in part by reducing cognitive reserve. That HIV and psychiatric comorbidity often interact to affect behavior has made this an important area of investigation (278). Among the most significant psychiatric comorbidities among HIV-infected patients are substance abuse and major depression.

When considering psychiatric comorbidity among patients with HIV, it is important to distinguish between long-standing psychopathology predating the HIV infection vs. conditions that have developed after infection. Furthermore, psychiatric and behavioral problems that have developed following infection with HIV or the occurrence of AIDS may either represent a response to associated stress, uncertainty, and emotional pain, or may represent a direct neuropsychiatric manifestation of HIV in the brain. I have briefly discussed some of these distinctions in relationship to particular types of psychopathology in the sections that follow.

The Significance of Substance Abuse

One of the most common comorbid conditions associated with HIV is substance abuse, in particular IDU of opiates, cocaine, and methamphetamine. This is due in large part to the fact that IDU is the major mode of HIV transmission besides sexual activity. The proportion of patients having current or past substance abuse histories varies across clinics, though typically they represent a sizeable number of the patients in most centers. The proportion of cases of HIV-infected people with IDU histories has increased in recent years largely due to greater success in prevention of HIV through sexual activities. In our clinical setting, approximately 50% of cases have a history of IDU. Of this group, about 80% had heroin IDU, though the drug of choice varies greatly across the country.

The effects of substance abuse in the context of HIV are complex and difficult to disentangle fully, in part because effects differ depending on the drug of abuse. There is a little doubt that during acute periods of intoxication, people using opiates, alcohol, and other drugs of abuse experience diminished cognitive performance. For example, chronic cocaine use has been associated with brain dysfunction (279). However, the effects of chronic use are less clear cut and vary depending on drug type. It is beyond the scope of this chapter to review the research literature on this question, though there is strong evidence that certain forms of long-term drug abuse are associated with chronic brain dysfunction, and chronic drug use can not be assumed as the basis of cognitive dysfunction among all past substance abusers (280).

Beyond the direct effects of drug of abuse on brain function, substance abuse tends to be associated with other behaviors that increase the risk of brain injury, including head trauma, poor health care utilization, and nutritional problems. Among patients enrolled in the Brown CFAR and HERS projects, we have found that those with current IDU had poorer adherence to HAART than those without current or past IDU. Furthermore, those with daily IDU had poorer adherence than those using less than four times a week, and patients with poly-substance abuse had the poorest adherence. This observation is consistent with reports from other groups. Woods et al. found that while rates of viral suppression were similar among IDU and non-IDU patients after correcting for rates of HAART adherence, patients with current IDU had worse outcome, attributable to poorer adherence (163).

There is growing evidence that patients with severe poly-substance abuse problems fare the worse with respect to neurocognitive outcome. Our analysis of the Brown CFAR cohort has revealed that patients with active IDU (primarily heroin addiction) had weaker cognitive function than patients without substance abuse history. This finding is consistent with results from studies comparing HIV patients who are gay vs. injection drug users, with the IDU showing greater cognitive impairment prior to being symptomatic with AIDS (281, 282). In contrast, patients with former IDU involving a single drug did not differ greatly from those without IDU after controlling for age, education, and level of depression in our CFAR cohort. This observation is consistent with results from other studies that have found limited cognitive impairment among heroin addicts after detoxification (283–285).

The effects of chronic substance abuse on brain function appear to be more pronounced among HIV patients who have been poly-substance abusers. In our CFAR cohort, this subgroup showed poor neurocognitive outcome than did the others. Grant et al. have reported similar findings for people who abused multiple drugs. In a national collaborative study, greater cognitive impairments were observed on the Halstead Reitan battery among patients with poly-substance abuse problems immediately following treatment and after 3-month follow-up. This study suggested that while some long-term improvement occurred following successful abstinence, persisting impairments existed.

Major Depression

Problems with depression and emotional distress are extremely common among HIV-infected patients (283, 286–288), with the prevalence of concurrent major depressive diagnosis between 4 and 10% among patients diagnosed with HIV(289) The lifetime prevalence is estimated to be 22–45% (288, 290–292). A much larger proportion of infected patients have significant depressive symptoms, but have not been formally diagnosed with major depression, with estimates approaching 50% in our clinic. The risk of depression is elevated even among patients at risk for contracting HIV and also among people prior to being diagnosed first (290) ,and in the early stages of the disease, the prevalence of major depression in HIV-positive patients is similar to that of demographically similar HIV-negative individuals (288, 290, 293). It should be emphasized that people with HIV report a history of depressive symptoms prior to seroconversion (283). This suggests that many people who develop depression after diagnosis with HIV may be neurobiologically vulnerable to affective disturbance.

The likelihood of depression increases as the severity of HIV illness increases (67, 294, 295), with a majority of patients (60–70%) reporting significant depressive symptoms over a 7-year period. As much as 20–30% of HIV -infected people with advanced disease experience severe depression (296–302). This is important given that patients with advanced HIV are 30 times more likely to commit suicide than are healthy controls, and depression has been implicated in as many as 50% of suicides among HIV-infected people (276, 277).

Interactions of HIV and Depression

HIV and major depressive disorder (MDD) may interact in important ways to affect disease progression (303–306). At a behavioral level, depressed patients have greater problems adhering to treatments (307–315). Poor treatment adherence has important implications, as beneficial effects from HAART appear dependent on sustained viral suppression and good clinical outcome (316–321). Failure to maintain adherence increases the possibility of treatment resistance and increased disease burden.

Depression and psychosocial stress has been associated with greater disease progression independent of adherence (322–338). While the extent to which the psychological state affects the viral replication in HIV is not resolved, there is a large body of research that demonstrates that it does have an adverse impact on immune system health (339–345). The mechanisms underlying this association are not fully understood, and considerable research effort has been focused on examining specific neurobiological factors. For example, studies have shown that cortisol may reduce immune system function by directly affecting the CD4 cell or other lymphocytes (322). Antoni et al. (306, 346–353) demonstrated that immune reconstitution is preceded by a reduction in cortisol following psychotherapy and psychosocial intervention.

Overall, there is considerable evidence that depression and psychosocial stress affect HIV-associated mortality and morbidity (354). There is evidence that this association continues even in the HAART era (355), particularly with advanced age (356–358). On the other hand there is also evidence that the rates of depression are declining as a function of the availability of more effective treatments (358). Findings are mixed with respect to the association between depression and neurocognitive function in the HAART era. Some studies have suggested that these factors continue to be linked, and that improved neurocognitive function corresponds with decreases in depressive symptoms (359, 360), while others have found either a weaker relationship between depression and neurocognitive function, or that they are independent factors (361).

Neuropsychiatric Manifestations of HIV-Associated Brain Effects

The relationship between psychiatric comorbidity and HIV-associated brain dysfunction is made complicated by the fact that neuropsychiatric symptoms may occur as a direct result of the effect of HIV infection in the brain. These symptoms may occur early in the course of infection before overt cognitive dysfunction or brain abnormalities are evident, and may mimic psychiatric symptoms that have a more "functional" origin (283, 362–366). Because neuropsychiatric and behavioral problems may either reflect emotional and behavioral response and adaptation to having a severe and stigmatizing disease or underlying brain disturbance, a careful assessment of the evolution of the psychiatric symptoms within the individual patient is essential with an emphasis on determining prior history of depression or

other psychiatric conditions, as well as the immediate antecedents and psychosocial factors contributing to current symptoms.

Neuropsychiatric symptoms were relatively common among many of the patients with AIDS–dementia assessed in the early years of the epidemic (6, 364, 367). For example, the patient described earlier (Case 1) was extremely disinhibited in his behavior. He would consistently try to remove his clothes while walking in the hospital corridors and would make inappropriate remarks to nurses and other patients on his unit. Furthermore, he showed evidence of pseudobulbar affect, characterized by rapid fluctuations in his expressed affect, and incongruence between his affective behavior and his described mood. This type of behavioral presentation was not uncommon among many people with AIDS–dementia before treatments were available, and still occurs in a small subset of patients. Increased irritability and even agitation may also be observed. Apathy is among the most common neuropsychiatric manifestation of HIV, and was described in early studies of AIDS–dementia (91, 129).

Apathy

Symptoms of apathy, characterized by indifference, reduced motivation, and a lack of behavioral initiative continue to be common among HIV-infected patients (363, 368–370), and may be attributable to several different factors in HIV (367, 369). Given that these symptoms also occur as a direct result of mood disturbance, the possibility of MDD needs to be given first consideration. However, patients without MDD may also describe apathy or exhibit related behaviors. In such cases, the possibility of apathy as a neuropsychiatric manifestation of HIV in the brain should be considered.

That apathy should occur among HIV-infected patients is not altogether surprising considering the typical neurocognitive dysfunction associated with HIV, and the functional neuroanatomic systems known to be most vulnerable to the virus, most notably the basal ganglia (11, 371). The nucleus accumbens (NA) of the basal ganglia is of particular interest in this regard, as it is involved in the limbic regulation of mood, reward, and behavior. The NA is located adjacent to the head of the caudate and has consistently been tied to the development of HIV-associated neurocognitive dysfunction. Neuropathology studies of the basal ganglia of patients who had HIV have indicated elevated viral load, along with the presence of gliosis and multinucleated giant cells (369). While caudate nucleus volume has received the most attention, HIV aggregates in other regions of the basal ganglia, potentially affecting limbic structures, such as the NA.

Brain morphometric studies conducted by our group have indicated the NA volume in HIV-infected patients; smaller NA volumes are associated with increased apathy (368). In contrast, caudate volume was not significantly associated with apathy measured psychometrically. Apathy also was associated with cognitive performance (69, 91, 129, 152, 367). Although apathy tends to be a symptom that affects work performance and other aspects of daily living, there is at least some

evidence that it may be less important than the broader constellation of MDD in accounting for quality of life among people infected with HIVHowever, NA volume is also significantly associated with clinical severity of MDD. Our findings regarding the NA are consistent with models of its role in emotional re gulation, as part of a broader frontal–striatal–limbic network (6, 372– 374) .

Psychosis and Delirium

Severe psychopathology, such as psychosis and delirium, also occur among patients with HIV (372, 375–380). These symptoms are most common among patients with advanced disease who are symptomatic with AIDS (381–385) or as an adv erse reaction to pharmacotherapy (386) .

Neurobiological Bases of Neuropsychiatric Symptoms

Apathy, depression, and other neuropsychiatric symptoms that occur secondary to HIV share much of the same pathophysiology that underlies HIV -associated neurocognitive impairments and brain dysfunction. As discussed earlier , limbic and mesolimbic areas are affected, including frontal–striatal systems, which raises the specter of dopamine dysregulation. Dopamine postsynaptic receptors are present in the basal ganglia, including NA. Laboratory animal studies ha ve shown effects on dopamine regulation in both symptomatic and asymptomatic SIV-infected monkeys, with reductions in the dopamine metabolites homo vanillic acid and 3, 4-dihydroxy-phenylacetic acid in the NA and other nuclei.

Various HIV-associated neuropathological processes may affect dopamine metabolism. For example, brain-derived neurotropic factor (BDNF) may play an important role. BDNF, a neurotrophin that appears to mediate CNS function and dysfunction (387) , is widely distributed throughout the brain (388, 389) .BDNF has a number of important roles related to brain function as it influencesneurogenesis and neuronal survival and growth (390), and serves to both strengthen excitatory synapses and weaken inhibitory synapses (391–393). BDNF also enhances neuro genesis. Intraventricular infusion of BDNF results in an increase in neurons in the thalamus, septum, and basal ganglia. Notably, BDNF also regulates the release of dopamine in mesolimbic systems, and down-regulation of dopamine receptors occurs when BDNFis infused into NA (394) , and BDNF levels are reduced by HIV (395). The fact that BDNF pro vides a link between dopamine regulation in the NA and basal ganglia and neuropathological effects of HIV in the brain makes it a factor for explaining how HIV may trigger neurobiological changes underlying neuropsychiatric symptoms such as depression and apathy.

Besides playing a significant role in neuronal function, BDNF levels also change in response to stress. Behavioral and physical stressors, such as immobilization and physical stress reduce BDNF le vels in the brain (396), whereas antidepressants

increase BDNF indices (397), and BDNF delivery to the brain results in sprouting of serotonergic neurons in rats (398). It would be an oversimplication to focus entirely on BDNF, as disorders such as MDD are affected by complex interactions involving the limbic hypothalamic pituitary adrenocortical axis in response to stress. These findings highlight the important role that BDNF plays in the regulation of mood and the symptoms associated with dysregulation of this system. Such findings illustrate how BDNF and other factors of this type may become dysregulated in response to the psychosocial stress associated with living with HIV, and at the same time contribute to the neuropsychiatric presentation. In light of the complex interrelationship between HIV-associated neuronal changes and the functional neuroanatomic impact of HIV on brain systems involved in emotional and behavioral control, along with the fact that living with HIV is associated with tremendous psychosocial stress and emotional challenge, it clear that careful assessment of neuropsychiatric status is essential for patients infected with HIV, and much more research is needed to fully understand these associations.

HIV in the Era of HAART

Effective treatment of HIV with combined therapy involving HAART was first reported in 1998 (9, 399–401). An essential feature of these treatments is the combined use of medications. HAART has proven to be remarkably effective in reducing plasma viral load to undetectable limits, increasing CD4 levels, preventing opportunistic infections from developing and greatly reducing AIDS-related morbidity and mortality (402–409). Until 1996, only a small percentage of infected patients were treated with combined therapy consisting of drugs that constitute HAART. For example, no participants of the CDC-HERS study were HAART-treated, and about half of the cohort was HAART naïve by the final follow-up evaluation. In our Center for AIDS Research at Brown University, about 15% of newly referred patients are on HAART prior to their first clinic visit, but among patients followed in the clinic the percentage approaches 85%.

It is now well established that at least over the short-term HAART markedly reduces systemic viral load and that with sustained viral suppression, immune functionsrecover as well (410–415). However, there was initially greater concern over whether HAART would produce CNS benefits, in part because early studies suggested that nucleoside analogs crossed the blood–brain barrier to only a limited extent (224). Furthermore, there is evidence of rapid turnover of the virus in the brain (221, 228, 236, 416–418). Fortunately, subsequent studies found that CSF viral load is reduced in patientstreated with HAART (419). Overall, recent studies have shown a reduction in CSF HIV-1 RNA levels, often to below detectable limits, with combinations of antiretroviral medications. In this context, there is also growing evidence that HAART improves survival associated with CNS opportunistic infections and diseases (221, 225, 230, 416, 420). These findings are encouraging, though it is possible that HIV-1 RNA in the CSF does not fully

reflect levels in actual brain tissue. Some patients seem to show persistent virus in the CNS and brain disturbances even with sustained treatment (53, 421–423).

HAART Improves Cognitive Function

Studies have also shown that HAART improves cognitive function (53). Our group examined a large cohort of women enrolled in the CDC-HERS study (423). Women who received HAART exhibited no decline in cognitive function. By contrast, women who did not receive HAART exhibited significant declines on tests of psychomotor speed and memory. Other groups have reported similar findings. Ferrando et al. examined 130 men with HIV on measures of attention, concentration, psychomotor speed, learning, and executive function (422). Individuals taking HAART exhibited lower viral loads, higher CD4 cell counts, and they performed better on most cognitive tests. Tozzi et al. prospectively examined 116 patients with advanced HIV (57, 122, 424–427). In this study, the prevalence of neurocognitive impairment decreased from 81 to 50% in the first 6 months of taking HAART, and then declined further to 22% after 15 months. Improvements were greatest for information processing speed and verbal learning. Similar findings have been found in other recent studies of the neurocognitive effects of HAART (428), providing strong evidence that HAART has been effective in reducing neurocognitive dysfunction in HIV.

Given these neurocognitive benefits of HAART, what are the costs of not being treated? It is somewhat difficult to do studies at this point in time to answer this question, given that most patients are treated with HAART when they have certain clinical criteria. However, data exist from the time period immediately following the advent of HAART. For example, in our analysis of the CDC-HERS cohort described earlier, women who were not treated with HAART showed a sharp divergence over time from those treated with HAART, with untreated patients worsening over time.

Even now, not all patients are treated with HAART, either because of problems tolerating the drugs or lack of adherence to treatment recommendations. Studies show that successful viral load reductions depend on adequate HAART adherence (429), and that when HAART is discontinued for 12 months, viral load returns to levels similar to those seen in HAART-native patients (430, 431). Yet, heterogeneity in treatment response exists, and longer-term HAART-effects are still not well understood (432–434). Whether continuous HAART is required to prevent brain dysfunction is also unresolved; short-term treatment interruptions have produced accelerated CD4 declines and viral load increases in some studies (203). Postponing the initiation of HAART until CD4 drops to low levels may increase the likelihood of patients developing neurocognitive impairments, though conversely there is also some evidence that HAART use in patients with elevated CD4 levels may actually have detrimental effects on cognitive function (435, 436). Therefore, achieving optimal treatment outcome may be more complicated than that originally thought, although the bulk of evidence to date suggests that failure to treat patients with compromised immune function and elevated viral loads tends to result in poor neurocognitive outcome.

Nosology of HIV-Associated Neurocognitive Disorders: 2007

In response to the changes that have occurred in the prevalence and manifestations of HIV-associated neurocognitive dysfunction since the advent of HAART, the National Institutes of Health created a working group to critically review the adequacy and utility of current definitions and diagnostic criteria and to identify the aspects in need of updating (437). The report provides a major view of the collective experience of the workgroup members with HIV-associated neurocognitive disorders (HAND). This nosology discusses the impact of comorbidities, and suggests inclusion of the term asymptomatic neurocognitive impairment to categorize

Table 1 Nosology of HIV-associated neurocognitive impairment (437)

HIV-associated asymptomatic neurocognitive impairment (ANI)
Acquired impairment in two or more cognitive domains, with evidence of performance >1.0 SD below the mean for age- and education-appropriate norms on standardized neuropsychological tests
Cognitive impairment does not interfere with everyday functioning
Cognitive impairment does not meet the criteria for delirium or dementia
No evidence of another preexisting cause for the AHI
If prior ANI existed, but no longer does, a diagnosis of ANI in remission is made
Diagnosis deferred for patients with major depression or substance abuse on examination
HIV-associated mild neurocognitive disorder (MND)
Acquired impairment in two or more cognitive domains, with evidence of performance >1.0 SD below the mean for age- and education-appropriate norms on standardized neuropsychological tests
Typically, impairment staging corresponds to an MSK scale stage of 0.5 to 1
The cognitive impairment produces at least mild interference in daily functioning (at least one of the following): (a) self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning; (b) observation by knowledgeable others that the individual had undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning
The cognitive impairment does not meet the criteria for delirium or dementia
No evidence of another preexisting cause for the MND
Remission and comorbid psychiatric disturbance criteria similar to that for ABI
HIV-associated dementia (HAD)
Marked acquired impairment in at least two cognitive domains. Typically impairments involve multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration
The impairments must be >2 SD below average on neuropsychological testing
Correspond to an MSK scale stage of 2.0 or greater
The cognitive impairment markedly interferes with daily functioning
The impairments do not meet the criteria for delirium
No evidence of another preexisting cause for dementia, such as CNS infection, neoplasm, etc., or severe substance abuse compatible with CNS disorder
Remission and comorbid psychiatric disturbance criteria similar to that for ABI and HAND. However, if dementia persists after one month on remission of major depression, a reassessment should be conducted to reassess for dementia

individuals with subclinical impairment. An algorithm is proposed to assist in standardized diagnostic classification of HAND. The resulting nosology differs from earlier classification systems in that a category is now included for mild cognitive problems that are largely asymptomatic. The nosology also recognizes the significance of comorbid factors and builds this into an algorithm for clinical decision making.

As shown in Table 1, this nosology distinguishes among (1) mild asymptomatic neurocognitive impairments (ANI), (2) HAND, in which greater cognitive impairments are evident that have mildly adverse effects on daily living, and (3) HIV-associated dementia (HAD), in which significant functional impairments are evident. Patients who had experienced HAD at some point in the past, but are no longer demented, are classified as "in remission." The clinical algorithms provided with this updated nosology give guidelines for decision making regarding (1) cognitive impairment, (2) functional decline, (3) factoring in comorbidities, and (4) alternative approaches when full neurodiagnostic assessment capabilities are not available (437). This nosology has considerable potential clinical value for the post-HAART era.

HIV and the Aging Brain

The prevalence of older HIV-infected patients is increasing (9, 438–440), as treatment advances have led to major reduction in the progression of HIV infection and significantly improved survival (441–444). Patients over 50 years of age account for an increasing percentage of cases, as the lifespan of HIV-infected people is approaching that of the general population (424, 445–449). Mounting clinical and laboratory evidence suggest a significant relationship between aging and HIV infection (450, 451). Senescence of the immune system occurs with advanced age, affecting T-lymphocytes and blood monocyte-derived macrophages (452). In T-cells infected with HIV (both CD4 and CD8), shortened telomeres occur with advanced age (193, 453–460), and T-cells show reduced proliferation and interleukin-2 production in both HIV-infected and elderly people. Thymus production also decreases with both age and in HIV-associated immunological impairment, which likely contributes to age–HIV interactions. Opportunistic infections have age-related response in older patients as well (461). Another important issue is that reconstitution of the immune system after treatment also appears diminished with advanced age (441, 443, 449, 462). Age-related immunological changes likely affect functional outcome for older HIV-infected patients (455, 458, 459). Furthermore, risk for comorbidity also increases with age (463). Neuropathological changes secondary to HIV may induce oxidative and inflammatory processes in the brain endothelium, factors that may contribute to interactions between age-associated vascular changes and HIV effects in the brain (62, 464).

Advanced Age Appears to Aggravate Neurocognitive Symptoms of HIV

Although some evidence for age-associated differences in neurocognitive impairment in HIV has existed from the pre-HAART era (134, 355, 421, 441, 445–447, 449, 465–484), research on the effects of HIV on brain function as infected people reach advanced age has just recently begun to emerge over the past several years (445). HIV affects the brains of young and old people differently. Older patients (>50 years.) are more likely to be demented than are younger patients (446) (Table 2). Cherner et al. (468, 485) found age-related trends; older HIV-infected patients were more likely to have cognitive impairments than do younger patients, with greatest effects when CSF viral load was in the detectable range. Valcour et al. found that older HIV-infected patients had greater impairments than younger patients on the Memorial Sloan-Kettering scale (355, 476, 486, 487). Others have reported similar age-associated findings, with interactions between age, HIV, and various clinical factors, including comorbid psychiatric status (478).

Our findings to date suggest that patients over age 45 have greater impairments and declines over time. In a pilot study of patients in the Brown CFAR, we com-

Table 2 Comparison of neurocognitive performance between young (<45 years) and older (>45 years) HIV-infected patients and seronegative controls

Cognitive task (baseline)	HIV-infected (age <45)	Controls (age <45 years)	HIV-infected (age >45 years)	Controls (age >45 years)
Trails A	23. 5 (7.2)	19.4 (6.6)	37.1 (12.4)	29.5. (9.2)
Trails B	62.2 (12.3)	40.33 (10.9)	124.7 (12.1)	86.2 (7.6)
COWAT	45.3 (8.8)	41.8 (7.6)	29.5 (10.4)	40.2 (8.6)
GPB-D	73.5 (12.5)	68.4 (10.3)	114.2 (18.6)	86.1 (16.3)
Stroop	38.7 (7.4)	42.2 (8.6)	25.5 (8.3)	38.4 (7.6)
HVLT-total	25.7 (4.4)	28.2 (5.5)	17.6 (7.0)	24.5 (5.7)
HVLT-delay	9.4 (2.2)	10.3 (2.5)	6.8 (3.3)	8.3 (2.7)
24 months	Performance change	Performance change	Performance change	Performance change
Trails A	**2.6 (2.3)**	**−4.3 (3.6)**	**10.2 (7.5)**	**3.3 (6.2)**
Trails B	2.4 (5.5)	0.6 (5.5)	**12.8 (9.6)**	**4.7 (8.5)**
COWAT	0.2 (2.1)	0.4 (2.1)	−1.5 (4.0)	3.3 (4.5)
GPB-D	−3.2 (4.1)	−6.3 (4.7)	**14.0 (5.3)**	**2.3 (4.4)**
Stroop	3.8 (8.5)	5.2 (7.5)	**−3.3 (6.9)**	**4.0 (5.7)**
HVLT-total	−0.3 (2.8)	1.3 (2.5)	**−3.4 (2.1)**	**1.8 (2.4)**
HVLT-delay	0.5 (1.3)	1.3 (1.5)	**−1.1 (2.0)**	**0.6 (1.2)**

Baseline raw score performance is given in the top half of the table; change scores between the baseline and 24-month assessment is given in the lower half of the table. All HIV patients included in this analysis had a CD4 nadir < 400 cells. **Bold:** p **<0.05**

Trails A trail making test (s); *Trails B* trail making test (s); *COWAT* controlled oral word association test (number of words); *GPB-D* grooved pegboard-dominant hand (s); *Stroop* stroop color word interference test – interference trial (number of words); *HVLT* hopkins verbal learning test (words recalled)

pared the change in performance across these same measures between baseline and 24-month follow-up in 40 HIV-infected patients (young = 16, older = 24) and 20 seronegative controls (young = 10, older = 10). The mean age of the older group was 53.3 ± 5.4 years; the mean age of the younger group was 34.6 ± 7.3 years. All the HIV-infected patients had exhibited a past decline in CD4 to below 200 cells. At baseline, the older patients showed weaker cognitive performance compared with older seronegative controls than did younger HIV-infected patients relative to the younger controls. Change scores were computed to compare performance at 24-month follow-up to baseline (see Table 1).

As is evident from these data, older HIV patients showed greater decrements in performance over 24 months compared with younger patients. It is noteworthy that older HIV-infected patients showed some decline in memory performance over 24 months, whereas the younger patients showed little change. This finding suggests that the cognitive change occurring with HIV in the context of aging may differ from that historically found with HIV-CMD, an intriguing finding given the reports of cortical thinning in patients with chronic infection (476). However, it is important to note that not all studies have shown interactions of age by HIV status with respect to cognitive function. For example, Kissel et al. (447) reported independent effects for age and HIV on cognitive function, but not a significant interaction age by HIV status after controlling for education, concluding that people are not at an increased risk for HIV-related cognitive impairment when normal age-related cognitive changes are taken into account. Clearly the question of HIV-associated neurocognitive effects in the context of the aging brain remains an unresolved issue.

Aging in the Context of Chronic Infection

HIV effects on the aging brain are potentially amplified by a variety of host and viral factors. Perhaps, the most obvious and important factor is that as HIV-infected patients age, they experience chronic infection of increasing duration. Even among patients whose infection is well managed with HAART, there is the potential for periods of increased viral activity, thereby increasing the risk of brain dysfunction. While these conclusions are intuitive, there is still relatively little data directly addressing the interaction between advanced age and chronic infection, though research supporting this conclusion is emerging. Goodkin (446) provided data supporting this assumption, suggesting that older patients had a longer duration of known infection. Cherner et al. (421, 466) found that older HIV patients (>50) had duration of infection 4 years greater than younger patients. Our data support this relationship as well, as infection duration accounted for some but not all age-related effects (421). This has clinical implications, as improved cognitive function secondary to HAART may not persist, as there is some data suggesting that within 2 years of achieving undetectable viral levels, 40–50% of previously treated patients develop increased viral load (424, 468, 485, 488, 489) Despite declines in rates of ADC (56),

chronic HIV infection in the context of an aging brain remain an important question (478). Whether the prevalence of dementia will increase as HIV-infected patients live longer remains an open question.

The Changing Face of HIV-Associated Brain Dysfunction

There is a little doubt that the nature of HIV-associated brain dysfunction has changed markedly over the past decade since the advent of HAART, particularly in the United States. AIDS–dementia is less common, and fewer patients are experiencing encephalopathy due to opportunistic infections, such as PML and toxoplasmosis. Yet, the possibility of developing severe cognitive impairment continues to be a significant concern for many people infected with HIV, particularly given the prospect of growing old with chronic viral infection of the brain.

The third case vignette discussed earlier provides an illustration of this change. This patient who was almost 50-years old exhibited what appeared to be a more primary amnestic disorder. He also had greater cortical atrophy than would be expected at his age. In many ways he presented like that of much older people who are commonly seen in memory disorder clinics with mild cognitive impairment, suggesting prodromal AD. Of course, it would be impossible to draw conclusions from a single patient (Case 3); it is possible that this patient was actually experiencing early AD, completely independent of their HIV status. Yet, HIV may eventually contribute to cortical atrophy, even though the subcortical pathology once seen is less striking. In the past, cortical atrophy occurred in many patients with advanced HIV, and some degree of global cognitive decline would likely to have occurred if patients lived long enough. Now people are living many years with a lower grade of infection.

As HIV has changed from a subacute often fatal illness to one that is more indolent, though still disruptive to the quality of life of HIV-infected persons, there has been a corresponding increase in the complexity of factors that determine whether a particular patient will develop neurocognitive dysfunction. As illustrated in Fig. 2, viral factors likely interact with an aging brain to influence the extent to which neuropathological processes occur. While HAART is effective in reducing cognitive impairment and improving functional status over the short term, and perhaps even over the long term when viral control is maintained (490), there is also mounting evidence from studies of proviral DNA that HIV may continue to have detrimental neuronal influences, even when plasma viral load has been reduced to almost undetectable levels. Furthermore, there is emerging evidence that the nature of cognitive impairments in older patients with chronic HIV may differ from that observed in the early years of the AIDS epidemic, with greater involvement of the hippocampus and mesial temporal systems, as well as the possibility of cortical thinning (491–493). This raises the specter of older HIV-infected patients developing memory problems beyond the psychomotor and information processing slowing that has been characteristic of HIV-CMD in the past. Furthermore, data from recent

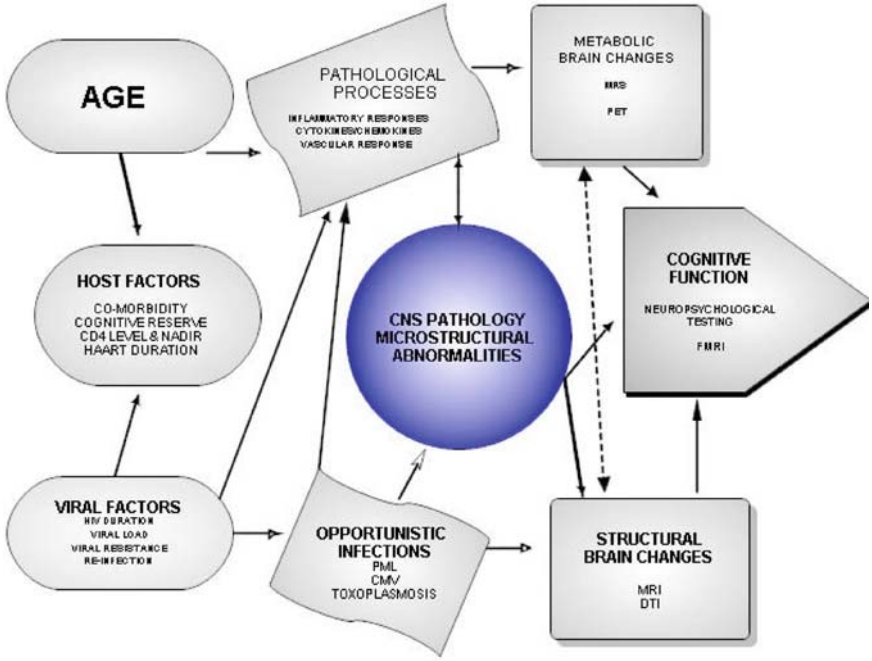

Fig. 2 Factors implicated in HIV-associated neurocognitive dysfunction

neuroimaging studies employing proton magnetic resonance spectroscopy (MRS) and other highly sensitive brain imaging methods demonstrate that brain metabolic abnormalities may have developed prior to the time that neurocognitive impairments becomes evident, even in the setting of stable disease.

Many questions remain. Are cortical changes in fact occurring in the context of chronic HIV that cannot be explained by normal aging or an independent neurodegenerative process such as? Do basal ganglia effects of HIV evident in past studies evolve into a more cortical presentation over time? Is there a diaschesis at work such that abnormal subcortical white-matter projections to cortical areas lead to associated cortical changes? Alternatively, are cortical changes occurring that are largely independent of basal ganglia abnormalities previously observed? Undoubtedly, answering these questions will require longitudinal studies in which infected patients are followed over an extended time period to examine the interactive effects of the various host and viral factors that influence chronic HIV infection as patients reach more advanced age. Recent advances in structural and functional brain neuroimaging (e.g., diffusion tensor imaging, functional MRI), as well in vivo measurement of brain metabolic function (MRS) should greatly facilitate these efforts.

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Youth with HIV/AIDS: Neurobehavioral Consequences

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Epidemiological Data on Children and Adolescents with HIV Globally and Within the US

While HIV/AIDS is primarily considered a disease that affects adults, there are a substantial number of children and adolescents living with the disease throughout the world. At the end of 2007, it was estimated that there were 2.5 million children (those less than 15 years) living with HIV around the world (1). An additional 10 million adolescents and young adults (2) (15–24-years old), also are living with HIV. Just under half a million children became newly infected with HIV in 2007 (1) and almost 6,000 young people become infected every day (3). The majority of children living with HIV reside in sub-Saharan Africa; however, large numbers of children with HIV also live in the Caribbean, Latin America, and South/South East Asia.

The numbers of infants becoming infected in the United States have decreased substantially over the past 15 years due to breakthroughs in the prevention of mother-to-child transmission using antiretroviral therapy and increased access to care (4). In 1991, the number of estimated perinatal HIV-infections reached a peak at 1,650 (5) and declined to an estimated range of 144–236 in 2002 (CDC, unpublished data, 2006). Among adolescents, very little change has occurred in new infections of HIV from 1994 through 2002 (6). An estimated 4,883 youth were diagnosed with HIV-infection or AIDS in 2004, representing about 13% of the persons given a diagnosis during that year (7). In developing countries where access to HIV testing and the prevention of mother-to-child transmission (PMTCT) prophylaxis therapy is not widely available and breast feeding is almost universal,

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rates of mother-to-child transmission remain high (4). PMTCT coverage remains low with less than 10% of pregnant women offered services worldwide, resulting in an increasing pediatric HIV epidemic (8).

The majority of children living with HIV (around 90%) acquired the virus via mother-to-child transmission (vertical transmission), either in utero, intrapartum, or through breastfeeding (9). Other routes of transmission during childhood and adolescence include exposure in a medical setting (the use of unsterilized needles or a blood transfusion), through risky sexual behavior, either voluntary or coerced, or from drug use. Lastly, some children are exposed through sexual abuse or rape.

Given the numbers of children and adolescents living with HIV in the world, and the fact that HIV is a neurovirulent virus, it is important to understand the impact that HIV/AIDS and its treatment have on the developing central nervous system (CNS).

Overview of Impact of HIV on the CNS in Children

Infants and children infected with human immunodeficiency virus-type 1 (HIV-1) are at increased risk for developing CNS disease, that may impact cognitive, language, motor, and behavioral functioning. The severity of HIV-related CNS manifestations in children range from subtle impairments in one or two specific domains to severe deterioration of global developmental skills.

Neuropathology

In high resource environments, severe CNS dysfunction in children with HIV disease is typically the result of HIV-1 infection in the brain (10, 11). HIV-1 has been isolated from the CNS tissue of fetuses (12) and the cerebral spinal fluid (CSF) of adults soon after infection (13–15) suggesting early CNS invasion. The timing of CNS infection for infants is variable and likely influences neuropathology and neurodevelopmental effects (12, 16–18). Astrocytes, macrophages, and microglia may be infected with HIV-1, while neurons seem to remain largely uninfected. Various neurotoxic factors released by the virus and host cells are postulated as the main cause of neurologic damage (11, 19, 20). Secondary CNS complications due to immune deficiency, such as brain tumors, other infections such as Cytomegalovirus (21), or cerebrovascular diseases, also may cause CNS manifestations but are less common in developed countries and usually occur in older children (22). Coinfections, however, are more common in infants in the developing world, even among those that are not yet immunocompromized (23, 24) and can result in significant CNS manifestations (25, 26).

Prevalence of HIV-Related CNS Disease

Prior to the introduction of antiretroviral therapy, approximately 50–90% of children with HIV-1 infection exhibited severe CNS manifestations (27, 28) termed HIV encephalopathy. Subsequent studies, when combination therapy was standard of care, have reported HIV encephalopathy prevalence rates of approximately 13–23% (29–32). The prevalence rates in the era of highly active antiretroviral therapy (HAART) have not yet been determined, but probably are even lower. Children exhibit CNS disease more frequently than adults (16 vs. 5%) (32) with new pediatric cases of encephalopathy occurring primarily during the first 2 years after birth (32) and often as the initial AIDS-defining symptom (32, 33). When adults as well as older children and adolescents develop CNS complications it tends to be more common during the advanced stages of the disease (33, 34). Some of the key similarities and differences in the impact of HIV-1 on the CNS between adults and children are listed in Table 1.

The decline in the prevalence of severe HIV-related CNS manifestations may be related in part to the earlier and more generalized use of combination antiretroviral treatment (ART), including HAART that combines various agents with at least one protease inhibitor (PI) or nonnucleoside reverse transcriptase inhibitor (35–38). HAART is effective in suppressing systemic viral replication (39), which in turn may reduce the number of HIV-infected cells entering the CNS (40). However, the CNS is a separate compartment from the rest of the body and it may serve as a reservoir for persistent HIV-1 infection (41). Many antiretroviral agents, including

Table 1 Key features of HIV-1 neuroAIDS in children and adults (42)

Adults	Children
CNS HIV-1 invasion during primary infection, often followed by compartmentalization	CNS HIV-1 invasion during primary infection, likely also often followed by compartmentalization
Target cells include macrophages, microglia, and to a lesser degree astrocytes	Same target cells, but astrocytes may play a more central role and neurons may also be actively infected
Long latent period between infection and neurological manifestations	Neurological disease more often the first AIDS-defining illness, even before important immunodeficiency
Deterioration of mature CNS with brain atrophy	Impairment of immature CNS and impaired brain growth
Both motor and cognitive functions deteriorate	Motor, cognitive, and language functions are impaired
CNS opportunistic infections and cerebrovascular disease are common	Cerebrovascular disease and CNS opportunistic infections are rare, but the latter may be more frequent in developing countries
ART reduces incidence and can reverse neurological manifestations present at the start of treatment	Similar preventive and therapeutic effects of antiretroviral treatment on CNS manifestations

PIs, do not penetrate well into the CNS (43, 44). Since HAART has become available, a proportional increase in AIDS dementia complex compared to other AIDS-defining illnesses has occurred in adults with HIV-1 disease (45). In a pediatric study of children being treated with HAART, IQ scores were significantly different between patients with encephalopathy, CNS compromise, and no apparent CNS disease; however, the absolute CD4 counts and viral loads of the three groups were not significantly different (46). These studies suggest that combination ART may provide systemic benefits, but not be as effective in treating the CNS (47) so that HIV-infected patients with well-controlled systemic disease may still be at risk for developing CNS manifestations.

In addition to the effects of HIV-1 on the developing brain, infected children also may have other medical and environmental risk factors that can contribute to neurobehavioral abnormalities. Thus, assessment of neurobehavioral functioning throughout childhood and adolescence is important for identifying and monitoring the effects of HIV-1 on the CNS over time, evaluating response to antiretroviral therapy, making treatment decisions, and planning educational and rehabilitative interventions. Neuropsychological test scores also can provide information, beyond that obtained from medical surrogate markers of HIV status that is predictive of later disease progression (48, 49).

Clinical Presentation of HIV-Related CNS Disease in Children

Pediatric HIV-related encephalopathy has characteristic features and distinct patterns, although the clinical presentation varies in onset, severity, and prevalence in different subgroups. Factors associated with variations in the presentation of HIV-related CNS manifestations include age of infection, route and timing of transmission, maternal and child disease status, genetic factors, treatment history, and other medical and environmental conditions.

Infants and young children tend to exhibit the highest rates of HIV-related CNS disease and the most severe neurodevelopmental impairments (50–52), while older children and adolescents tend to have the lowest rates and less severe manifestations of CNS disease (29, 52, 53). The greatest risk for encephalopathy occurs during the first year of life, when it is often the initial AIDS-defining symptom (30–33, 54). Children with early onset of HIV encephalopathy, before the age of 1 year, have smaller head circumference and lower body weight at birth, suggesting a different pathophysiology compared to later occurring encephalopathy (32).

Major factors determining the risk for the development of encephalopathy seem to be the timing of the infection as well as maternal and infant characteristics. Earlier infection seems to be associated with higher risk for CNS disease and more severe CNS manifestations. Vertically-infected children with apparent utero transmission (positive HIV-1 cultures or polymerase chain reaction positivity during the first week of life) more often display severe HIV disease (55) and poorer neurodevelopmental function (18) compared to children with

presumed intrapartum infection (negative cultures at birth), who in turn are more affected than children infected through blood or blood products in early childhood (33, 56). Adolescents infected with HIV, often through sexual transmission, also appear to have less CNS symptoms, with a clinical presentation resembling that seen in adults (34).

The in-utero environment also seems to moderate the risk of encephalopathy; it is highest in HIV-infected children born to mothers with more advanced disease as measured by CD4 cell count and viral load (57) and is lowest in children also infected in the perinatal period through blood or blood products but born to uninfected mothers (33, 56). Infant factors associated with a high risk for the development of CNS disease are high plasma viral loads (31, 32, 58, 59), more severe immunodeficiency early in life (30–32, 55), and host genetic factors in the child (60–62). ART may prevent the development of HIV-associated CNS manifestations as HIV-infected children who are naive to ART (52) or who are on monotherapy (53) appear to be at greater risk than children on combination ART, such as HAART (38, 63). Very early ART exposure, however, as in children with HIV-1 infection exposed to zidovudine in utero and for 6 weeks after birth, does not seem to prevent encephalopathy or cognitive deficits (32, 64).

Finally, other medical and environmental conditions, such as maternal substance abuse during pregnancy, low birthweight, preterm birth, exposure to toxic substances (i.e., lead), other CNS infections, impoverished socioeconomic and environmental background, and psychosocial difficulties, also may negatively influence the development of children with HIV-1 infection. As vertically-infected children live longer, such conditions may have a greater cumulative impact on neurobehavioral function and need to be considered when assessing the effects of HIV-1 on the developing CNS.

Patterns of HIV-Related CNS Disease in Children

Despite variations in the presentation of CNS disease among different subgroups of children with HIV-1 infection, three main patterns have been described: encephalopathy, CNS compromise, and apparently not affected (65, 66).

HIV-related encephalopathy is characterized by pervasive and severe CNS dysfunction. Children with HIV-related encephalopathy exhibit global impairments in cognitive, language, motor, and social skills as well as significant neurologic impairments that affect their day-to-day functioning. Although overall functioning tends to be globally impaired in encephalopathic children, differential deficits may be observed in selective functions. For example, expressive language is often more severely impaired or may deteriorate more quickly than receptive language. HIV-related encephalopathy can be progressive (subacute or plateau subtypes) or static (67–69). Subacute progressive encephalopathy, the most severe subtype, is characterized by progressive, global deterioration, and loss of previously-acquired abilities and skills. In the plateau course of progressive encephalopathy, the acquisition of new skills becomes slower compared to their previous rate of development or may

stop, but previously-acquired milestones are not lost. Both subacute and plateau subtypes result in a significant decline in standardized scores on repeated neurodevelopmental testing. Children with static encephalopathy continue to consistently gain new skills and abilities but at a slower rate than their normally developing peers. Thus, their scores on standardized tests are below average but remain stable over time. The prevalence of encephalopathy appears to be declining in pediatric HIV disease, most likely due to earlier treatment and improved therapeutic options. New cases of encephalopathy are seen most often in infants and young children (29, 30, 32), particularly those naive to ART (52), and older children in advanced stages of disease (34). Encephalopathy is listed as a Category C condition in the CDC classification system for HIV infection in children less than 13 years (70).

HIV-related CNS compromise is characterized by overall cognitive functioning that is within normal limits but with either significant decline in psychometric test scores in one or more areas of neurobehavioral functioning, which remains above the low average range, or significant impairments in selective neurodevelopmental functions (66). Patients who were functioning within normal limits but exhibited significant improvements after initiation or change in ART also are included in this category. Children with HIV-related CNS compromise continue to have adequate functioning in school and activities of daily living. With the widespread availability of HAART, children displaying CNS disease are more likely to exhibit this more subtle form of CNS compromise rather than the more severe and pervasive encephalopathy that was frequently seen during the first decade of the AIDS epidemic. CNS compromise is not a condition listed in the CDC classifcation system for HIV infection in children (70) but is comparable with the HIV-1-associated mild neurocognitive disorder (MND) in the new revised research criteria for HIV-associated neurocognitive disorders among adults published in 2007 (71).

The CNS of children is considered to be apparently not affected by HIV when their cognitive functioning is at least within the normal range and without evidence of HIV-associated significant deficits, decline in functioning, neurological abnormalities that affect day-to-day functioning, or therapy-related improvements.

Children infected with HIV-1 also may have non-HIV-related CNS impairments. Some HIV-1-infected children may be at greater risk for these non-HIV-related CNS impairments because of their complicated medical histories and/or difficult social situations. It is possible for children to exhibit both HIV- and non-HIV-related impairments. Determining whether developmental deficits are related to HIV-1 disease or other etiologies is complex but is important for making treatment decisions particularly in low-resource settings.

Effects of Antiretroviral Treatment on Cognitive Function

ART may be preventative and/or therapeutic for HIV-associated CNS disease. Since 1996, patients with HIV disease in developed countries have been offered HAART, which contains at least three different antiretroviral agents. With the availability of

effective HAART, the prevention of CNS disease appears to be related to the suppression of systemic viral replication, which reduces or eliminates the invasion of HIV-carrying cells into the CNS (40). However, the CNS is a separate compartment from the rest of the body and it may serve as a reservoir for persistent HIV-1 infection (41) and there is evidence that HIV may invade the CNS shortly after systemic infection, and in infants even in the early stages of gestation (12). Some antiretroviral agents have been found to penetrate the blood–brain barrier (44, 72, 73), inhibit viral replication in the CNS (74, 75), and reduce the neurotoxic effects of the virus on the brain (19, 76). In children with evidence of HIV-associated CNS manifestations, treatment studies have shown that some antiretroviral drugs, particularly used in combination (46), may improve neurobehavioral functioning (53, 77, 78) as well as reduce cortical atrophy (79). These improvements in CNS functioning are likely due to treatment-related decreases in viral replication in the brain (75, 80).

Findings regarding the impact of HAART on the neurodevelopmental functioning of children are somewhat mixed. Rates of progressive encephalopathy and static encephalopathy have declined since the advent of HAART, decreasing from 40.7 to 18.2% (81). Young children treated with HAART, including a protease inhibitor, exhibited limited improvements in neurodevelopmental functioning when compared with a group of HIV-exposed but HIV– infants (63), but at 3 years there were no significant differences between the two groups any longer. Another study failed to find overall improvements in neuropsychological functioning in a large group of HIV+ children following a change in treatment to a PI based regimen (82). The later study did not include a control group, but instead compared scores with established norms. In a study of twelve relatively immunocompetent children receiving their first HAART regimen, there were no significant changes in cognitive functioning over the course of the 96-week follow-up period (83). There were also no changes noted in the mean rating of CT brain scan abnormality at weeks 24 and 48. However, one child, also described in a case series (84), evidenced declines in her performance IQ score at week 24. The patient's regimen was changed to include zidovudine instead of stavudine and her IQ score improved back to baseline level. Within the French Perinatal Cohort (84), none of the infants born since 1996 and who initiated HAART before 6 months of age ($n = 40$) developed encephalopathy, whereas 3 of the 43 infants who started HAART after age 6 months developed encephalopathy during the first 2 years of life. In summary, findings indicate that children with HIV-related neurobehavioral deficits should be given ART that includes at least one agent that has adequate CNS penetration, such as zidovudine (ZDV) or stavudine, in order to reduce HIV replication in the CNS.

Neuroimaging Findings

Previous research and clinical observations have indicated a reasonable correspondence between the findings from brain imaging studies and current level of neurocognitive functioning in children with HIV CNS disease, particularly in children

prior to ART (17, 86) and increasingly in those receiving ART (87, 88). Cortical atrophy (seen either as ventricular dilatation and/or sulcal enlargement) is a good indicator of degree of compromise (86, 89) and has been correlated with CSF viral load (89). Moreover, significant changes in cortical atrophy are associated with comparable changes in neurocognitive functioning (17, 90). Intracerebral calcifications also indicate significant HIV-related CNS compromise. Such lesions are most frequently seen in young vertically-infected children and have been associated with poor prognosis and encephalopathy, particularly when moderate to severe cortical atrophy is also noted (91). Minor white matter abnormalities detected on MRI brain imaging are frequently transient and have not been associated with altered cognitive function (92, 93). However, more severe white matter lesions that are apparent on CT brain scans have been related to cognitive impairments (94). While more advanced brain imaging techniques, such as diffusion tensor imaging and multisectoral structural imaging, have been used in adults to evaluate the impact of HIV on white matter (95, 96), studies using these techniques in children have not yet been published.

Proton magnetic resonance spectroscopy (^{1}HMRS), which allows for noninvasive measurement of brain metabolites associated with different aspects of neural cell function (97), provides markers of the effects of HIV in the brain that are different from changes seen on structural neuroimaging (98, 99). In children with HIV-associated CNS disease, studies demonstrated a decrease in *N*-acetyl aspartate (NAA) signal or in the NAA/Cr (creatine) ratio suggesting a decrease in neuronal density. These studies also noted an increase in the lactate signal, which may indicate active inflammation or severe tissue damage causing impaired blood perfusion and resulting ischemia (100–102). Moreover, normalization was seen in these parameters with ART; an increase in the NAA/Cr ratio and a decrease in the lactate peak was evident after the initiation of therapy in two children with progressive encephalopathy (102). Another study of children with MRS abnormalities stable on HAART (103) failed to note changes in ^{1}HMRS metabolites over time. A decreased choline creatine ratio (CHO/Cr), which could be indicative of demyelination has also been found in pediatric patients without encephalopathy when compared with control children (100). Recent research also suggests that HIV-infected children do not demonstrate a normal age-associated increase in NAA in the frontal white matter and hippocampus (104). Children with more cell loss in the hippocampus and resultant lower choline concentrations appeared to have poorer spatial skills. ^{1}HMRS is not a standard component of the clinical evaluation of children with HIV but clearly offers possibilities to further monitor HIV-associated CNS disease, evaluate the effects of therapy, and investigate the neuropathogenesis of neurobehavioral manifestations. Future studies need to investigate whether ^{1}HMRS can be used in children with HIV-infection as early indicators of brain abnormalities or delays in normal development. In children who continue to have HIV-associated encephalopathy but who have shown a decrease in structural brain imaging ^{1}HMRS abnormalities, improvements may reflect incomplete functional recovery.

Neurodevelopmental Functioning in Specific Domains Among Children in Developed Countries

General Cognitive Function

As noted earlier, children with HIV CNS disease can present with a wide range of neurodevelopmental sequelae. In children with HIV encephalopathy, the effects of the disease on the CNS tend to be generalized with cogniti ve function and brain structures severely and globally affected (66, 90, 105) although some domains (i.e., receptive/expressive language, gross/f ine motor) may be dif ferentially impaired. Furthermore, measures of general cognitive functioning are sensitive to HIV-related changes in CNS function and correlate well with information obtained through other studies, such as brain imaging (86, 94) cerebrospinal fluid analysis (10, 91) and virological and immunological parameters (105). However, in children with less severe CNS manifestations, the abnormalities may be less generalized (17) and neurobehavioral functions may be differentially affected by HIV.

Infants infected with HIV generally score lo wer than serore verters on se veral measures of early development (106–109). Mean developmental test scores ranged from the borderline to low average range (107, 108). However, in a study, where the children diagnosed with an AIDS-def ining diagnosis (with the e xception of lymphoid interstitial pneumonia) were e xcluded (109), HIV-infected infants did not differ from the group of serore verters. More recent data suggest that inf ants with more severe HIV symptomatology may remain at risk for compromised neurodevelopmental outcomes (110), while infants who are treated ef fectively (62) or are considered long-term nonprogressors may evidence neurodevelopment comparable to uninfected children from similar backgrounds and f amilies.

During the past 10–15 years, research has increasingly focused on the neurodevelopmental functioning of HIV -infected school-aged children gi ven that lar ger numbers of children are survi ving into adolescence and adulthood (87, 88, 111–114). Earlier in the epidemic, children who survi ved to be over the age of 6 exhibited significantly less evidence of CNS disease when compared with children under the age of 3 (52, 115). Children who survi ved into childhood and adolescence tended to have slower disease progression and experience lower rates of opportunistic infections and encephalopathy early in life. Ov erall, performance on global cognitive measures of intelligence in school-aged HIV+ children ha ve been found to fall in the average to low average range (47, 87, 111, 114, 116–118) with some children presenting with se vere neurocognitive impairments as well as neurologic and neuroimaging abnormalities (52, 88, 114). See Fig. 1 for a graphical representation of the relationship between neuroimaging abnormalities and composite cognitive scores in children treated with HAAR T, based on data from Martin and colleagues (88). This figure illustrates that the group with CT scans that are within normal limits have IQ scores that follo w the normal curve, while the scores of the group with mild-moderate CT scan abnormalities are more positi vely skewed.

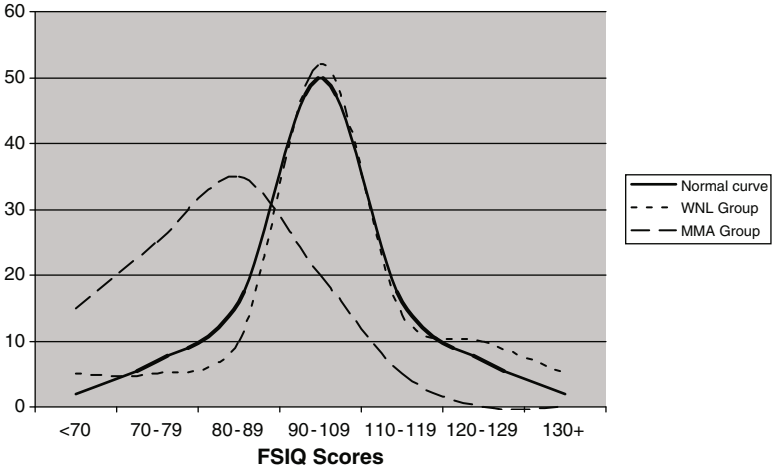

Fig. 1 Full scale IQ distributions for the within normal limits (WNL) computed tomography (CT) brain scan group, the minimal to moderate abnormalities (MMA) CT brain scan group, and the theoretical normal curve (87)

Children and adolescents infected as a result of hemoglobin treatment also e xhibit cognitive functioning that generally is within the normal range. Minimal differences in functioning were evident between HIV+ and HIV– hemophilia patients (119–121). The prevalence of neurological dysfunction w as low and generally limited to participants in adv anced stages of immunodef iciency (122) (CD4+ cell counts below 200). Given that there is now almost universal access to HAART for children living in developed countries, more children ha ve access to ef fective treatment from an early stage and therefore are less likely to experience severe immunosuppression and CNS disease. Dif ferences in neurocogniti ve functioning associated with immune dysfunction may become less pronounced while other relationships between CNS manifestations and f actors unrelated to prior disease or HAAR T exposure may become more important. Gi ven that global cogniti ve measures may not detect subtle def icits (123), it is important to e valuate specific areas of neuropsychological functioning for potential deficit areas as described below.

Language

Language deficits are a major characteristic of neurobehavioral dysfunction in pediatric HIV disease, which marks a signif icant difference with the impact of HIV on adults as language skills are generally left intact (124). Among children with symptomatic HIV-1 infection, speech and language abnormalities are frequently present (28, 125–127). These abnormalities may appear prior to declines in cogniti ve function (125, 128) and e ven when recei ving antiretroviral therapy (128). Expressive

language tends to be significantly more impaired than receptive language in pediatric HIV disease. Children with HIV-1 encephalopathy exhibit more deficient overall language skills than do nonencephalopathic children; however, the degree of discrepancy between receptive and expressive language is similar for both these groups (127). Furthermore, uninfected siblings score higher than their HIV-infected siblings on tests of both expressive and receptive language and do not show a discrepancy between these two language components (127) suggesting that the deficit is related to HIV disease and not environmental factors. In a study of children who were neurologically asymptomatic (CT or MRI were normal), there were no differences in language functioning between HIV+ children and a group of seroreverters (111). HIV-related language deficits may be due in part to an impoverished representation of words and objects likely related to reduced neural networks in the brain (129). The differential deficit in expressive language also may reflect a more general HIV-associated impairment of expressive behavior (130), including motor function and emotional language (131).

Executive Functioning

Executive functioning has been attracting more attention as an important domain to study among children and adolescents. In this section, only research that involves the direct assessment of executive functions will be reviewed. Research that focuses on caregiver and child self-reports of behavior and attentional deficits have been included in the section on behavioral, psychosocial, adaptive and family functioning. Executive functioning has many components, such as the ability to sustain or flexibly redirect attention, the inhibition of inappropriate behavioral or emotional responses, the planning of strategies for future behavior, the initiation and execution of these strategies, and the ability to flexibly switch among problem-solving strategies. These various abilities may be differentially affected in pediatric HIV disease. In one small study, both asymptomatic and symptomatic HIV+ children evidenced deficits on executive functioning measures when compared with a group of seroreverters (111). In a study of attention among children and adolescents with hemophilia (132), children and adolescents with HIV-1 and hemophilia exhibited greater difficulty sustaining attention over time on a continuous performance task when compared to the children with hemophilia who were HIV–. In another small study comparing school-aged children with HIV with age-appropriate norms, the only differences between groups were on neuropsychological tests assessing attentional flexibility, visuospatial working memory, and processing speed (113). Koekkoek and colleagues found significant relationships between working memory functioning and a higher percentage of CD4 cells at initiation of HAART as well as longer treatment duration and attentional control. Similarly, Martin and colleagues (88) found that higher CD4+ percentages were related to higher working memory and processing speed scores in children treated with HAART. Furthermore, scores on measures of global cognitive functioning and tasks involving executive functions (88) were

significantly lower in HIV-infected children with minimal to moderate brain scan abnormalities compared with children with normal CT brain scans. These studies suggest that relationships between immune functioning and subtle neuropsychological functions may exist.

Memory

In general, studies of children with vertically acquired HIV-1 infection have documented memory impairments (112, 133, 134) while studies of children with transfusion-acquired HIV infection, either for hemophilia or neonatal problems, have not found deficits in memory function (56, 120, 121, 135). More recently, however, declines in memory functioning over time were found in HIV-infected hemophiliacs with low CD4 counts (136). In addition, children with evidence of HIV CNS compromise exhibited significantly poorer performance on verbal learning and recall trials compared with children without CNS compromise, while these two groups performed similarly on a recognition task (137, 138). Such a pattern suggests a retrieval deficit, which is similar to findings from studies of memory in HIV-infected adults, and may indicate subcortical pathology (139–141). Given that children with neurologic abnormalities (134, 137, 138) and poorer immune function (111, 136) exhibit more frequent and severe memory deficits, the etiology is likely related to HIV infection rather than other factors.

Motor Functioning

Children with HIV-1 CNS disease frequently exhibit motor impairments, which often coexist with cognitive deficits (51, 107, 142)). In a large multicenter clinical trial, approximately 23% of symptomatic children who were naive to antiretroviral therapy exhibited some type of motor dysfunction (51). Infants less than 1 year of age developed motor impairments more frequently than school-age children (51) (45 vs. 9%, respectively). Children with encephalopathy and/or abnormal CT scans exhibit the most severe motor involvement and may lose previously attained motor milestones (67, 143). Gross motor function, particularly running speed and agility, tends to be more impaired than fine motor skills when compared with the normal reference population (144). In a small study comparing HIV+ children to a control group of siblings of children with HIV infection, subtle motor impairments were documented in the HIV+ group. Scores for both groups fell within the average range, however, children with HIV had lower performance on measures of fine motor skill and motor strength (87). Oral-motor functioning also may be affected resulting in articulation problems, expressive language deficits, and feeding and swallowing difficulties (126). Motor deficits may interfere with developmental progress and the performance of everyday living skills. Furthermore, motor dysfunction is highly predictive of later disease progression (48).

Behavioral, Psychosocial, Adaptive, and Family Functioning

In addition to cognitive deficits, children with HIV-1 infection may also present with behavioral and emotional difficulties. Psychosocial functioning may be negatively influenced by the effects of HIV disease on the CNS, prenatal insults, the psychological stresses of living with a chronic illness, exposure to additional stressors of living in a family exposed to HIV/AIDS (parental death, substance use, poverty), prolonged exposure to antiretroviral therapy, and other familial genetic factors. In some studies, certain behaviors have been linked to immune status and the presence of encephalopathy. As assessed by a standardized parent report scale, children with encephalopathy exhibited more severe impairments in everyday behaviors, such as daily living skills and socialization skills, compared with children without encephalopathy (144). Furthermore, deficits in adaptive behavior were associated with CT brain scan abnormalities (94) and immune status (144). Improvements in adaptive functioning were noted after the initiation of ART (145) suggesting that impairments in adaptive functioning are related to the effects of HIV-1 on the CNS.

Approximately two out of every five (40%) children with HIV disease meet the criteria for attention deficit/hyperactivity disorder (145–148, ADHD). This rate is higher than expected, given that the rate within the general population is thought to be between 3 and 7% (150). It is unclear, however, whether this increased prevalence of attention problems are directly attributable to HIV (121, 147, 148). Such attention deficits in children with HIV-1 may contribute to school and learning problems and may respond to stimulant medication.

In terms of behavioral and emotional problems, children and adolescents with HIV appear to have higher rates compared with established national norms (117, 151) but similar rates to those among HIV-exposed but uninfected children (147, 148, 152) and/or with a demographically-matched non-HIV-exposed control group (147, 153). Behavior in these studies was assessed on behavior checklists completed by the primary caregiver. Another study (46) found that rates of psychiatric diagnosis reported by parents were not significantly different between patients with or without CNS disease. Additionally among HIV+ adolescents, those who have lost a parent were more likely to report a history of depression (151). These findings suggest that some behavior problems are not related to the effects of HIV on the CNS but rather to other etiologies, such as environmental conditions, biological factors, or psychosocial difficulties.

Little has been published on the prevalence of more severe psychiatric illness among HIV-infected children. Gaughn and colleagues (146) documented higher rates of psychiatric admissions among perinatally-infected youth in the PACTG 219C cohort. Rates were compared to both the general pediatric population as well as a group of HIV– but HIV-exposed children. Out of 1,808 participants, 32 had been hospitalized at some point in their life for psychiatric manifestations. Fifteen of the 32 had been hospitalized more than once. Common reasons for admission included depression ($n = 16$) and behavioral disorders ($n = 8$).

Neurodevelopmental Outcomes Among Children in Developing Countries

The majority of research on the neurodevelopment of children living with HIV disease has been conducted in developed countries such as the US, France, Italy, and the UK; however, a small number of studies have been conducted in developing countries. This line of research is particularly important given that the majority of HIV+ children currently are being born and living in these settings. While there are many lessons to be learned from research within developed countries, there are a number of factors that distinguish these populations. Children growing up in developing countries face different challenges than children in developed countries that may impact their neurodevelopment, including the availability and quality of prenatal care, increased prevalence of coinfections (cerebral malaria, tuberculosis, and bacterial meningitis), access to medical treatment, and appropriate nutrition (zinc deficiency and protein malnutrition) and variability in the access to and quality of education. Malaria as well as other common comorbidities such as malnutrition or micronutrient deficiencies may interact with HIV and result in worse neurocognitive outcomes among children (25). Lastly, some of the children studied in the United States have also been exposed to drugs of abuse in utero, such as crack cocaine and heroin. Therefore, it is unclear if the findings from the US will generalize to populations of vertically-infected children that have not been exposed to the same types of drugs. While, studies have been conducted in a number of high prevalence countries including Uganda, Thailand, and Brazil, there are still many questions that remain to be answered about the neurodevelopment of children within these environments.

The majority of neurodevelopmental studies in developing countries have focused on early child development, predominantly within the first 2 years of life (133, 154–157). Two important domains of functioning during this time period are a child's cognitive and motor development. Significant differences begin to emerge between HIV– and HIV+ children in these domains during their first 2 years of life. Overall, cognitive development appears less affected than motor development among HIV+ infants (133, 155–158); however, HIV+ infants demonstrate earlier onset of cognitive impairment when compared with uninfected infants (154, 155). While the mean scores on a measure of cognitive ability for both HIV+ and HIV– but exposed children were found to fall in the average range, scores for the HIV+ children were significantly lower (154). Additionally, higher percentages of HIV+ children have been found to fall within the deficient range, when compared with children who seroreverted (159).

Even fewer studies have focused on the neurodevelopment of school-aged children in developing countries (160, 161). As a result of increased access to testing and antiretroviral therapy, more children in late childhood and adolescence are being identified with HIV (162) and greater numbers of HIV+ children will be surviving into late childhood and beyond. In a school-aged sample of HIV+, ART naïve children in Uganda, cognitive and academic functioning was in the normal range. No differences were noted between the HIV+ children and

two control groups (one of seroreverters and one group of age and gender matched HIV– children). This sample of HIV+ children is unique in that these children were most likely long-term nonprogressors. The majority of the studies described within developing countries have focused on children who were not taking ART due to a lack of access to medications. A recent study from Thailand highlights how access to ART for children is beginning to increase in various parts of the developing world (161). This small study of 34 HIV+ children compared three groups with different treatment histories: (1) those starting HAART, (2) those who had been treated with HAART for at least 1 year, and (3) those who remain untreated. The children were followed for a year and their psychomotor functioning was monitored during that time. Psychomotor performance deteriorated in all three groups over the course of the study, even in those treated with HAART. In another study (163), Thai children with HIV did not evidence higher rates of emotional or behavioral problems as assessed by the Thai version of the child behavioral checklist when compared with children with hematologic/oncologic diseases, or children from similar socioeconomic backgrounds. The authors report high levels of emotional and behavioral problems within these groups; half of the children in each group had significant problems, with adolescent females being the most at risk.

Some of the limitations that plague research on the neurodevelopmental functioning of children living with HIV disease in developed countries also apply to research in developing countries. Limitations include the lack of neurodevelopmental assessment instruments that are culturally appropriate and have local norms, small sample sizes, lack of an appropriate control group, use of screening measures instead of more comprehensive assessment tools, and studying only asymptomatic children thus limiting the generalizability of the findings.

The study of the neurodevelopment of children living with HIV in developing countries is in its infancy. More research needs to be undertaken to address a number of questions, including determining the best methods for assessing neurodevelopment in these varying contexts, the impact of other medical conditions on a child's neurodevelopment (e.g., malaria, malnutrition/diarrhea, TB, etc.) and whether these other conditions may actually compound the effects of HIV, and lastly the role of contextual variables in a child's neurodevelopment (e.g., maternal health, family functioning, stigma in the community).

Issues Regarding Neurodevelopmental Assessment of Children with HIV Disease

As the research reviewed in this chapter indicate the approach taken when evaluating a child's neurodevelopment is crucial. Within the developed world, children are experiencing lower rates of encephalopathy; however, more subtle, domain specific deficits are being identified. Detecting more subtle deficits requires the administration of a more comprehensive battery that includes many different domains of

functioning so that patterns of functions that are differentially affected can be determined in children and adolescents with HIV.

In resource poor settings, conducting comprehensive neurodevelopmental assessments can be almost impossible and even administration of screening batteries can be challenging. Barriers to an adequate assessment include lack of access to appropriate neurodevelopmental tests, due to lack of availability in the child's language or those that are culturally appropriate, scarcity of individuals trained to conduct neurodevelopmental assessments, and not enough resources to support the inclusion of neurodevelopmental testing within a clinic or hospital setting. More efforts are needed to develop valid and reliable assessment tools and approaches that can be used in these settings. Lastly, both within developed and developing countries, the use of appropriate norms and control groups for comparisons are essential. As has been demonstrated in multiple studies within the US, high prevalence rates of neurobehavioral abnormalities in HIV+ youth have been found to be similar to control groups when appropriate matched controls were used (e.g., HIV-exposed but not infected children; (147, 152). Studies making comparisons to general population norms or controls that are not matched on important factors such as socioeconomic status may lead to incorrect conclusions, specifically attributing differences to HIV status instead of other factors such as the environment.

Conclusions

Advances in ART has made a significant impact in reducing the prevalence and severity of CNS disease in children and adolescents in developed countries; however, much research remains to be done. In the next decade, pediatric research in HIV disease will likely focus on infants and children born in developing countries and adolescents with either perinatal or behaviorally-acquired HIV infection in higher resource environments. Studies conducted so far can provide guidance for addressing neurobehavioral issues in certain neurodevelopmental domains (general intellectual functioning, language functioning); however, data are lacking in other areas (executive functioning, memory). The numbers of youth with behaviorally-acquired HIV and adolescents and young adults with perinatally-acquired HIV are increasing and represent important groups to study. However, at this time, no studies of cognitive functioning specifically in behaviorally HIV-infected youth have been identified in the literature; in articles in which these groups were included, numbers were small and the subsample otherwise was not characterized. Finally, CNS disease continues to be evident in a subset of patients, even those treated with HAART. Thus, research investigating the neuropathogenesis of HIV CNS disease and specific treatments and interventions for those affected is still needed.

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Co-Occurrence of HIV, Hepatitis C, and Substance Use Disorders: Effects on Brain Functioning

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Detrimental effects of HIV on brain systems and neurobehavioral functions remain a primary focus of neuropsychological and biomedical research. The neuropathological changes and neuropsychological dysfunction that often accompanies HIV, as well as its detrimental effects on instrumental activities of daily living and quality of life have become increasingly well-characterized and have been discussed at length by other contributors in this volume. The neurocognitive consequences of HIV are particularly pressing for HIV-seropositive (HIV+) individuals who have co-occurring medical and psychiatric conditions that also are known to impinge upon neurocognitive functioning. Most notably, substance use disorders (SUDs) and Hepatitis C (HCV) are the two conditions that commonly co-occur with HIV and share in common a number of neuropathological and neurocognitive sequelae. In this chapter, we present and evaluate research that examines neurocognitive functioning among HIV-infected persons who are also infected with HCV and/or have a SUD. As we highlight throughout, the presence of an SUD and/or HCV in concert with HIV infection may increase the vulnerability to neurocognitive dysfunction. In the process, we also devote some attention to unique challenges in the study of these vulnerable populations and briefly touch upon some treatment-related issues.

Co-Occurrence of HIV, HCV, and SUDs

There are several factors that contribute to the common co-occurrence of HIV, HCV, and SUDs. For instance, risky injection drug use behaviors, such as sharing dirty needles or used syringes, are a prominent vector for blood-borne viruses, such

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as HCV and HIV. The World Health Organization estimated that approximately one-third of new HIV infections worldwide are transmitted through injection drug use, with sub-Saharan Africa excluded (1). In Central Asia and Eastern Europe, injection drug use was reported to account for approximately 80% of new HIV cases (1). Moreover, the occurrence of HIV among injection drug users has continued to increase in many developed countries (2).

HCV mono-infection (i.e., without comorbid HIV) is relatively common among injection drug users, with the estimated prevalence rates as high as 70% for acute cases (3) and as high as 60–90% for chronic infection (4). HCV infection among HIV+ injection drug users is also prevalent, with recent estimates indicating that approximately 25–30% of urban HIV+ injection drug users are co-infected with HCV (5, 6). However, rates of co-infection may vary depending on prevalence of various risky behaviors. For example, Sherman et al. (7) reported a 16.1% prevalence rate for HCV infection among HIV+ individuals in the United States, but rates varied drastically when groups were stratified as "high risk" and "low risk" based on the behaviors they endorsed. Rates of co-infection were roughly 72.6% among those who engaged in "high-risk" behaviors (e.g., unprotected sex and injection drug use), but only about 3.5% among those who did not. Rates of HCV infection among HIV+ persons has become an increasingly important issue, as end-stage liver disease has been identified as a leading cause of mortality among HIV-infected individuals in developed countries (8, 9).

Although rates of HCV and HIV co-infection appears to be more common among injection drug users, it is important to note that the co-occurrence of HIV and HCV is not limited to this population. Rates of HCV and HIV co-infection have ranged from 2 to 35.3% among noninjection drug users (10). The mechanisms for transmission of HIV and HCV among noninjection drug users are many, but may include higher prevalence of risky sexual practices (such as unprotected anal sex) during intoxication, sharing of some types of drug paraphernalia (e.g., cocaine "straws"), and sharing of tattoo needles (most commonly in prison settings) (11–13).

A recent study conducted by Danta et al. (14) underscores the importance of risky behaviors in the co-occurrence of HIV, HCV, and SUDs. They examined HCV infection among HIV+ men in London, England, who have sex with men (MSMs). Their findings pointed more directly to permucosal vs. percutaneous transmission of HCV infection, with a greater number of HCV-infected individuals reporting more frequent high-risk sexual behavior (e.g., "barebacking" and group sex participation) compared with HCV-seronegative (HCV−) individuals. Recreational drug use in this population, although a predictor of HCV-infected cases in univariate analyses, was no longer a significant predictor in more complex multivariate models. The authors concluded that drug use likely leads to HCV transmission indirectly through increased high-risk sexual behaviors. It is interesting to note that risky sexual practices among HIV-infected MSMs have increased since the advent of HAART (15, 16). The reasons for this increase are many, but often include the misguided belief that HIV is no longer a life-threatening illness, or, more pointedly, that HAART can "cure" HIV infection (17). Thus, high-risk sexual and drug use practices appear to be important vectors for both HIV and HCV.

There is substantial evidence for common neurobehavioral deficits among individuals with HIV, HCV, and SUDs, which we review in this chapter. The neuropathology and neurocognitive deficits associated with HIV alone are discussed in detail by others in this book. The specific effects of various classes of controlled substances and effects of HCV alone are well beyond the scope of this chapter, but we note that SUDs and HCV may exacerbate brain dysfunction through overlap in some of the neural pathways they disrupt, namely prefrontal–striatal systems. That said, each of these conditions is associated with damage and dysfunction that extend beyond these systems. Systematic examination of the interactions between HIV, HCV, and SUDs remain a relatively recent endeavor. However, we underscore the pressing attention this research area has received: for example, despite a fairly limited pool of existing studies, the literature on effects of HCV on neuropsychological function has been reviewed by many (18–22). A more detailed understanding on how these frequently co-occurring conditions may together affect neurobehavioral functioning is critical for developing appropriate treatments and improving patients' quality of life.

Challenges in Studying Comorbid Consequences of HIV, HCV, and SUDs

Before providing an overview of the literature on possible neurobehavioral consequences of HIV, HCV, and SUD comorbidity, it is crucial that we acknowledge some of the challenges inherent to conducting such investigations. First, it must be kept in mind that findings may often be disparate, in part because participant samples may differ across studies on a number of key parameters. For example, studies that examine HIV may use participant samples that differ in their risk for infection (e.g., MSMs, injection drug users, heterosexual men and women), length of HIV infection, and disease severity (e.g., varying CD4 counts, HIV viral burden in CSF or plasma, presence of opportunistic infection, AIDS diagnosis). As with HIV, individuals with HCV may also differ in their disease severity, as manifest by degree of liver disease, current treatment regimen (i.e., interferon treatment), and whether there are neurological problems due to liver disease (e.g., hepatic encephalopathy). Studies that examine the effects of substance use on neurobehavioral function may employ subject samples that differ significantly in their drugs of choice, amounts of drug use, length of abstinence, and comorbid psychopathology. Consequently, differences in the myriad combinations of parameters that define participants with HIV, HCV, or SUDs across studies may serve to yield conflicting results and make comparisons across studies difficult.

The study of HIV, HCV, and SUDs is necessarily challenging because of the high likelihood of comorbidity between these disorders and a number of other potentially confounding psychopathological and medical factors that may also affect neurocognitive functioning, such as depression, ADHD, antisocial personality disorder, and liver disease. As outlined in Gonzalez et al. (20), a number of steps

can be taken to reduce the impact of these many confounds, such as (1) excluding potential subjects with conditions judged to be significant threats to validity, such as schizophrenia or structural lesions of the CNS (e.g., stroke, gunshot wounds to the head, closed head trauma with significant loss of consciousness); (2) clear dissemination and rigorous enforcement of rules that a positive result on rapid urine toxicology screening or breathalyzer testing is automatic grounds for exclusion and nonpayment; (3) employing a carefully selected series of clinical tests and interviews to assure that groups are closely matched on substance abuse severity and diagnostic composition, current psychological distress, estimated IQ, personality traits such as antisociality and sensation seeking, and symptoms of additional psychiatric disorders such as ADHD. Attention to these potential confounds can strengthen inferences from study findings and also, if carefully examined in data analyses, may yield interesting relationships between variables that would otherwise go undetected.

HIV and Substance Use Disorders

Neural Mechanisms for Interactions

Several mechanisms by which substance dependence and HIV may interface to impair brain functioning have been put forth, and include disruption of immune function, cytokine regulation, cerebrovasculature, and excitatory neurotransmitters (23, 24). Specific drugs of abuse may exacerbate HIV-associated brain injury through one or several of these mechanisms, thus presenting complex pathways for interactions.

Various drugs of abuse are known to increase severity of HIV through suppressing immune function, thus putatively magnifying neurobehavioral dysfunction through increased disease burden. For example, much evidence suggest that opioids may suppress immune function (25, 26), though the mechanisms are complex and remain somewhat enigmatic, particularly in the context of HIV (27, 28). Opioids have been shown to enhance viral replication (29–31) and reduce the effectiveness of CD4 (32) and CD8 T-lymphocyte cells in the presence of HIV (33). It should be noted that the interactions of these substances with HIV have not always been shown to be deleterious; for example, in some circumstances opioids have exerted protective effects (24, 34). Some of the factors that may account for conflicting findings have been discussed by others (35).

Similar to the findings with opioids, cocaine has also been shown to suppress immune response, as well as increase viral replication, and alter cytokine production (e.g, TNF-α), which increases vulnerability to infection (24, 36, 37). Less is known about the impact of central nervous system (CNS) stimulant methamphetamine on the modulation of immune function in HIV, but animal studies suggest it is similar to cocaine in that it may also suppress immune function (38), increase

viral replication (39), and may adversely change cytokine production (e.g., decreases in IL-2 and increases in TNF-α) (40).

There are other known mechanisms by which cocaine and methamphetamine may disrupt brain functioning, namely through direct effects on cerebrovasculature, which may include micro-infarcts and vasoconstriction (41–44). Cocaine has been shown to disrupt blood–brain barrier function, thus causing cerebrovascular complications and allowing greater virus trafficking into brain (45–47). Finally, both cocaine and methamphetamine are known to be neurotoxic and may interact with HIV proteins (e.g., Tat and gp120) to potentiate damage to neurons. These proteins may interact with cocaine and/or methamphetamine to damage neurons through oxidative stress, mitochondrial dysfunction, and inflammation. Indeed, several investigations have suggested that both methamphetamine and cocaine can increase the neurotoxic effects of Tat, and that the striatum may be most vulnerable to such damage (48–53).

More controversy surrounds the impact of alcohol and cannabis on the neuropathogenesis of HIV (e.g., (54)). Not unlike the substances we have already discussed, some have suggested that alcohol may also worsen the effects of HIV on brain through damage to the blood–brain barrier (55, 56), suppression of immune function, damage to immune cells, and modulation of cytokines (37, 57, 58). Less research has been done on the impact of cannabis on immune function in HIV, despite substantial evidence for cannabinoids' ability to suppress immune response (59, 60). Some animal studies report decreased immune function and increased viral replication (61); but recent studies show no effects of cannabis (or THC) on the immune function of HIV+ human subjects (62, 63).

Neuropathology and Neuroimaging

Many neuropathological studies have been conducted to examine the effects of HIV on human brain tissue (e.g., (64–66)). However, there are substantially fewer studies that examine neuropathological changes that occur specifically as a result of comorbid HIV infection and substance use. Notably, examinations of varying cohorts of drug users have often revealed mixed results, and it remains difficult to describe definitively whether substance use exerts additive or synergistic damage to brain tissue. For example, among injection drug users (primarily heroin), investigators have reported greater rates of HIV encephalitis (67, 68). It is thought that HIV and injection drug use may interact synergistically to produce HIV encephalitis (35, 69, 70) and that increased activated microglia among injection drug users is a likely mechanism (71). However, other cohort studies have not found increased prevalence of HIV encephalitis among injection drug users (72).

More recently, neuropathological changes that may occur because of the use of methamphetamine among HIV+ participants has become the subject of study. Langford et al. (73) examined the brains of 28 HIV+ methamphetamine users and 49 HIV+ nonusers that were collected at autopsy. HIV+ methamphetamine users

were more likely to evidence ischemic damage in the neocortex and limbic systems. Further, among patients with HIV encephalitis, those who had histories of methamphetamine use also showed greater microgliosis. In a subset of HIV+ patients from the same cohort, Chana et al. (74) reported that patients with HIV encephalitis and a history of methamphetamine use showed the greatest loss of interneurons compared with those without HIV encephalitis or methamphetamine use. Further, interneuron loss was associated with poorer performance on measures of general neurocognitive function.

Neuroimaging techniques have been used to examine the combined effects of HIV and drug use on brain structure, metabolism, and function among patients, with results from such studies generally suggesting additive or synergistic actions across a variety of substances. For example, a thorough review of studies examining combined effects of alcohol use and HIV concluded that metabolic changes suggestive of neuronal injury were associated with more alcohol consumption among HIV+ persons, particularly within the periventricular white matter, subcortical grey matter, and brain stem (57). More recently, Pfefferbaum et al. (75) used magnetic resonance spectroscopy (MRS) to compare patterns of cerebral metabolites across three groups: HIV+ alcoholics ($n = 15$), HIV+ nonalcoholics ($n = 9$), and 23 healthy controls. HIV+ alcoholics showed significantly lower levels of *N*-acetylaspartate (NAA) and creatine compared with the other groups, suggesting neuronal injury in parietal–occipital grey matter and adjacent white matter. Alcoholism has also been shown to interact with HIV disease severity, such that it may increase damage to corpus callosum among those with more advanced HIV (75).

Metabolic brain abnormalities have also been reported to be magnified by methamphetamine use among HIV+ individuals. Using a small sample of participants ($n = 20$), Taylor et al. (76) reported significantly lower levels of NAA, suggestive of neuronal injury, in the anterior cingulate of individuals with HIV and methamphetamine dependence compared with groups having only one risk factor (HIV or methamphetamine dependence) and healthy controls. Using similar methods, Chang et al. (77) examined brain metabolites in a larger sample ($n = 143$) across groups differing on history of methamphetamine use and HIV. They obtained evidence indicative of additive damage from HIV and methamphetamine, with the group of participants that had both risk factors demonstrating the largest differences from control participants in metabolites suggesting neuronal injury in frontal white and grey matter, as well as basal ganglia. In contrast to the two aforementioned investigations that provide evidence for additive damaging effects, Taylor et al. (78) did not find evidence of additive effects in another investigation they conducted where they examined brain metabolites of 205 participants stratified into four groups based on history of HIV and methamphetamine dependence. Despite this, they did report correlations between markers of immunosuppression and markers of neuronal dysfunction only among the group of participants with both risk factors.

Data from structural brain MRI studies have further complicated the interpretation of additive or synergistic effects from HIV and methamphetamine. Jernigan et al. (79) used MRI to examine the volume of various brain structures in groups of individuals who differed in their HIV serostatus and histories of methamphetamine

dependence. Interestingly, they found that methamphetamine and HIV serostatus had opposing effects on brain volume, particularly in the caudate, with HIV being associated with decreased volumes and methamphetamine with increased volumes. Evidence for additive or interactive effects of methamphetamine and HIV on brain volume were not supported, but may have been obfuscated by the inverse morphological effects of these risk factors.

Neuropsychological Functioning

We have highlighted a few of many mechanisms that have been proposed by which HIV and various drugs of abuse may interact to affect brain functioning. The limited neuropathological and neuroimaging data available lend some support for additive and synergistic dysfunction. Yet, evidence from such studies do not directly inform whether changes in the brains of individuals translate to deficits in their neurocognitive functioning or their ability to function in their daily lives. In this section, we review the neuropsychological investigations of HIV and substance use interactions, which rely on assessment techniques that allow quantification of performance across various cognitive abilities sensitive to brain dysfunction. Furthermore, measures of neuropsychological functions can provide us with information about how a patient's daily functioning may be affected as a consequence of brain dysfunction.

Over the past two decades, several groups have set out to document the neuropsychological impact of HIV infection among substance using populations and/or the effects of substance use among HIV+ cohorts. Studies have often shown that HIV-associated neurocognitive dysfunction can be reliably detected among samples of injection and noninjection substance users (primarily cocaine and heroin). For example, a series of investigations from Chicago have shown that in samples of individuals with substance dependence (primarily cocaine and heroin), those who are HIV+ demonstrate poorer performances on tests of general working memory capacity (80), verbal working memory (81), auditory working memory (82), and nonverbal working memory (83), suggesting that impaired working memory may represent a signature deficit among HIV+ substance-dependent individuals. Also, HIV+ substance users have been shown to demonstrate poorer performances on measures of decision-making (84). Thus, the evidence suggests that HIV worsens neurocognitive functioning among substance users. However, when the effects of substance use have been examined in HIV+ cohorts, the results have been equivocal. For example, some studies report no effects of injection drug use (85–87) or severity of multiple drug use (88) on the neurocognitive functioning of HIV+ participants. On the other hand, others have reported that marijuana use is associated with poorer neuropsychological performance among HIV+ patients in advanced disease stage (89).

The research designs of the aforementioned studies elucidate whether HIV infection worsens neurocognitive functioning among substance users and/or if

substance use exacerbates neurocognitive dysfunction among HIV+ individuals. However, the research designs employed in such studies limit inferences that can be made about possible additive or synergistic effects of HIV and substance use as cofactors, and relatively few studies have employed designs to more conclusively detect such effects (90). To thoroughly investigate the possibility of synergistic or additive effects, studies often include several subject groups: (1) a group with no risk factors (e.g., no HIV and no SUD); (2) two groups with one risk factor each (e.g., a group with HIV but no SUD, as well as a group with SUD but no HIV); and (3) a group with both risk factors (e.g., with HIV and SUD). Such designs allow investigators to isolate the individual contribution of each condition to neurocognitive impairment and to assess if having both risk factors produces greater levels of impairment than what would be expected with one condition alone. It also allows one to determine if the degree of impairment observed in the dual-risk group is consistent with a simple aggregate of the impairment in the single risk factor groups (i.e., additive effects) or if impairment surpasses such expectations. Below, we report results of several investigations conducted in recent years that make use of such designs.

Studies using the earlier-noted four-group design (or similar designs) to examine HIV and alcohol as cofactors generally support both additive and synergistic effects, with groups that have both risk factors typically showing the most pronounced deficits. Green et al. (91) found evidence of additive effects of HIV and alcohol use on neuropsychological functioning, but no evidence of synergistic effects. Specifically, history of alcohol use was not found to affect neuropsychological functioning among HIV− participants, but did result in poorer performance among HIV+ participants on measures of verbal IQ, verbal reasoning, and reaction time. In another investigation (92), HIV was not found to affect performance on a Stroop task, whereas history of alcohol use among HIV− participants worsened performance; however, those with both HIV and history of alcohol use performed most poorly. Rothlind et al. (93) found no consistent evidence of synergistic effects of HIV and alcohol. However, subgroup analyses provided some limited evidence supporting synergistic effects of HIV and alcohol when alcohol users were stratified into current heavy drinkers and current very heavy drinkers. That is, current very heavy alcohol users with HIV showed impaired performances on measures of information processing speed relative to all other groups. Similar findings were also reported by Durvasula et al. (94) with a large sample of African–American men, such that heavy alcohol use had more pronounced effects on the neurocognitive functioning of HIV+ individuals compared with HIV− individuals, particularly on measures of psychomotor speed and reaction time. Thus, it appears that HIV+ individuals are more vulnerable to the negative effects of alcohol on neurocognitive functioning compared with their HIV-seronegative counterparts.

Less-consistent findings have emerged from investigations that have examined whether other substances (besides alcohol) interact in additive and/or interactive ways with HIV. For example, Durvasula et al. (95) found that history of cocaine use and history of HIV both accounted for unique variance in the neuropsychological test performance of a large sample of African-American men. However, no evidence of additive or interactive effects from HIV and history of cocaine use were

observed. Similarly, Basso and Bornstein (96) examined a large sample of HIV+ and HIV− individuals, with and without history of noninjection drug use and found no evidence of additive or interactive effects from substance use. Participants were abstinent and had abused various substances, but the most frequently reported were marijuana and stimulants. In contrast, Rippeth et al.(97) found that participants with both methamphetamine dependence and HIV show greater prevalence of neuropsychological impairment than that observed among groups with only HIV or only methamphetamine dependence. Further, in a separate investigation, poorer immune status was associated with worse neuropsychological functioning among HIV+ persons with methamphetamine dependence compared with those without methamphetamine dependence (98). It may be that methamphetamine and alcohol are more likely than other substances of abuse to compound neurocognitive impairments among HIV+ individuals.

HIV and Hepatitis C

Neural Mechanisms for Interactions

The CNS mechanisms by which HIV and HCV interact remain far from being fully understood, yet several possible avenues have been put forth. For example, it has been argued, and to some extent substantiated, that co-infection with HIV can lead to accelerated progression of symptomatic liver disease and cirrhosis among those with HCV (99, 100). As such, subacute and acute hepatic encephalopathy may contribute to the neurocognitive problems observed. However, most of the studies we review attempt to control for severity of liver disease. Another possibility is that HCV may accelerate HIV-associated neurocognitive problems. Laskus et al. (101) found that HIV infection can augment HCV replication in human macrophages. Further, in a fashion akin to that proposed for HIV, some have presented evidence to suggest that HCV enters and replicates directly in brain (19, 101, 102), perhaps more so among those co-infected with HIV(103). HCV has been shown to replicate in bone marrow, as well as peripheral blood mononuclear cells (104, 105), which are known precursors for microglial cells and perivascular macrophages within the brain. As outlined in a recent review by Perry et al. (22), one manner in which HCV may be introduced into the CNS is through the migration of infected monocytes from the periphery into the brain. These cells then supplant white-matter microglial cells. This method of introducing infection into the brain through peripheral monocytes has been termed the *Trojan horse* mechanism (106). Thus, the brain may be both a reservoir for HCV and/or HIV, as well as a site for further replication. It is important to keep in mind, however, that HCV and HIV viral load (CSF- or serum-based) among patients on highly active antiretroviral therapy (HAART) have not been consistently linked to decrements in neurocognitive performance, nor to the development of HIV-associated dementia (107–109) Hence, other neuropathological

mechanisms must be involved in the effects of HCV and HIV mono- and co-infection on neurobehavioral functioning.

A second neuropathological process that has received increased attention by which HIV and HCV share much in common is the modulation of cytokines and pronounced inflammatory responses in the brain. HCV infection leads to rapid production of cytokines, which can remain elevated for a number of years. Importantly, abnormal or prolonged cytokine production has been recognized as a partial determinant of neurocognitive function (110). One such cytokine, tumor necrosis factor-α (TNF-α), is commonly activated in response to both HCV and HIV infection. Hence, it is possible that increasing levels of TNF-α associated with HCV–HIV co-infection can exert additive and/or synergistic deleterious effects on neurobehavioral function (111). HIV- and/or HCV-induced increases in TNF-α, or other markers of immune system functionality (e.g., MCP-1), may represent a viable pathway by which HCV and HIV can, in combination, exacerbate neurocognitive dysfunction. A comprehensive review of mechanisms for increased cognitive impairment among individuals co-infected with HIV and HCV is presented by Paul et al. (112).

Neuroimaging of HIV and HCV

There is a paucity of neuroimaging studies that examine specifically interactions between HIV and HCV, but in recent years a burgeoning neurophysiological and neuroimaging research into the effects of HCV on neurocognition has shed some light on the potential for interactions with HIV. Specifically, electrophysiological study of cognitive impairments in HCV has revealed abnormal P300 event-related potentials among HCV-seropositive (HCV+) individuals relative to controls (113). These abnormalities may underlie the information processing speed and attention/concentration deficits often observed among HCV+ individuals: deficits that are also common among individuals with HIV and SUDs. Similarly, studies employing MRS have revealed biochemical abnormalities in basal ganglia and white matter that are similar to those also reported with HIV (114, 115). Importantly, these abnormalities have been observed among HCV-infected individuals with and without a history of SUD, suggesting that they may be a consequence of HCV infection and not merely secondary to an SUD. In sum, these studies suggest that some of the brain abnormalities observed with HCV, in vivo, are similar to those observed with HIV; thus, brain dysfunction may be compounded when both are present. However, further research is certainly needed.

Neuropsychology of HIV and HCV

Several studies on neuropsychological effects of HCV and HIV co-infection have focused on comparing HIV+ groups with varying HCV serostatus. The overall findings suggest that a positive HCV serostatus can be an additional risk factor for

neuropsychological dysfunction. Studies of neurocognitive function among HCV+ individuals with varying HIV serostatus have generally but not universally demonstrated greater impairment among dually infected compared with mono-infected subgroups. For example, two recent investigations conducted with a cohort of individuals with advanced HIV disease reported that co-infected individuals tended to perform more poorly than mono-infected subjects, particularly on measures of executive functions (116, 117). Parsons et al. (118) also found poorer performance on tests of visual memory and fine motor function among HIV+ participants who were also HCV-infected compared with those who were not. In contrast, others have found no differences in neuropsychological functioning between HCV+ and HCV– patients with HIV (21).

By using combinations of groups that differ both on HIV and HCV serostatus, several investigators have attempted to examine more conclusively the independent and combined effects of HCV and HIV on neuropsychological functioning. Martin et al. (119) examined performance on a reaction time version of the Stroop task with 156 substance-dependent men with varied HIV and HCV serostatus. They found no conclusive evidence for interactions between HIV and HCV on Stroop performance, but did observe that dually infected individuals performed worse than did mono- or uninfected individuals, consistent with additive effects. Richardson et al. (120) examined the neuropsychological functioning of 220 women stratified into four groups by HIV and HCV serostatus. The groups differed somewhat on several demographic characteristics and history of drug use; however, even when controlling for these factors, the highest odds for neuropsychological impairment was seen in the dually infected group. Controlling for age diminished the strength of these results, and an interaction effect between HIV and HCV was not observed. Similarly, Von Giesen et al. (121) compared the intellectual functioning, gross neurocognitive abilities, and electrophysiological motor performance of three patient groups differing on their HIV and HCV serostatus: individuals mono-infected with HIV ($n = 43$), or with HCV ($n = 44$), and a co-infected group ($n = 44$). They reported no significant difference between the three groups on measures of intellectual functioning and gross neuropsychological functioning, but did find that the groups differed from a control group of uninfected individuals on motor tests.

Reports of the relationships between severity of HIV or HCV disease and neurocognition have been mixed. Richardson et al (120) reported that severity of HIV-associated immunosuppression as indexed by CD4 count mediated the relationship between disease status and neurocognitive function. Conversely, others have reported that markers of liver disease were not significantly predictive of neurocognitive performance (116, 117). These latter findings also suggest that effects of HCV on neuropsychological functioning may be independent of liver disease. However, recent studies of dually infected subjects indicate that neurocognitive function may improve with successful therapy for either disorder (118, 122).

HIV, HCV, and SUDs: Concurrently Examining All Three Risk Factors

Most of the investigations of HIV–HCV co-infection and neurocognition have by necessity included substance-dependent individuals, since injection drug use remains the strongest risk factor for HCV infection. However, only a few studies have treated substance dependence as a systematic variable of interest and examined putative interactions between these three factors.

At present, available "three factor" studies have focused on methamphetamine use. Cherner et al. (123) reported on 430 dually, mono- or uninfected subjects with and without a history of methamphetamine use. They reported that the prevalence of neurocognitive impairment varied according to the number of risk factors, and these effects were most evident on measures of learning, recall, fine motor speed, and abstraction/problem solving. When all three risk factors (HIV, HCV, SUD) were entered into a regression model (along with several covariates), each accounted for unique variance in overall neuropsychological performance. However, the interactive effects of these variables were not systematically examined. A companion manuscript (124) examined the postmortem brain tissues of 25 HIV+ cases (12 with HCV and 13 without) from this cohort and reported that HCV in the CNS was associated with a positive history of methamphetamine use and antemortem cognitive impairment.

To our knowledge, the aforementioned studies are the first to specifically and systematically examine the complex effects of substance use, HIV, and HCV on neuropsychological functioning. They make a valiant effort to tackle an important and complex issue; yet they are also burdened by the challenges inherent in such investigations. Specifically, Cherner et al. (123) noted that some participant groups were not well represented in their sample (e.g., only 2 participants with HCV alone) and that the presence and severity of some confounds were correlated with a number of risk factors (e.g., more alcohol use). Further issues in this work have been highlighted by others (125). Much work remains to be done in this area.

Brief Comments on Treatment-Related Issues in this Population

There are a number of important treatment considerations in the context of the neuropsychology of HIV, HCV, and SUDs that deserve brief consideration. Exogenous administration of IFN-α, either alone or in combination with ribavirin, is the most efficacious treatment choice for HCV infection (126). However, this treatment approach is often associated with subjective and objective complaints of neurobehavioral impairment, as well as depression, apathy, and a number of physical symptoms (e.g., influenza-like symptoms) (22, 126). More specifically, IFN-α treatment appears to be linked to prefrontal cortical hypometabolism, which raises apprehension regarding its effects on neurocognitive functioning (127). Due to the

effects of IFN-α treatment on neurobehavioral and psychiatric status, there have been concerns about employing such treatment among individuals with preexisting complications that already make them vulnerable to neurocognitive disturbances. More specifically, IFN-α therapy is contraindicated in the context of alcohol/substance abuse, severe psychiatric disease, and uncontrolled hypertension. However, empirical evidence supporting such contraindications is far from conclusive (126). Recent studies have also highlighted the potential for drug–drug interactions between HAART, alcohol use, and other psychoactive substances (128). In fact, there is at least one documented report of a fatal interaction between MDMA use and ritonavir (129). Furthermore, co-infection with HIV appears to slow the beneficial effects of IFN treatment, although the reasons for this effect are not yet fully understood (130). Hence, successful treatment of HCV, as well as HIV, in the context of a co-occurring SUD requires special considerations, possibly requiring successful treatment of the SUD prior to implementation of pharmacotherapy.

Reasons for treating SUDs prior to or concurrently with treatment regimens for HIV and HCV extend beyond risk of drug interactions. Individuals with SUDs often lead chaotic lifestyles when actively using that may interfere with almost all aspects of treatment. Compliance with doctor visits and medication regimens would be challenging for such patients. As with ART, adherence is an important predictor of response to IFN treatment among HCV-infected individuals (131). Active substance use would also likely interfere with cognitive functions such as memory and decision-making, which may be important underlying processes critical to successful adherence. Thus, patients with substance use disorders may require more attention, reminders, and motivators to receive optimal benefit from their medical care.

Concluding Remarks

Based on the information presented in this chapter, it can be concluded that current data substantiates interactions between HIV, HCV, and SUDs to potentiate brain injury through a variety of complex pathways. Neurobehavioral disturbances in this population are thought to be in part driven by shared and unique impact from HIV, HCV, and SUDs on immune functioning, cytokine production, and cerebrovasculature. Although each of these conditions appears to affect widespread neural systems, it also seems that each overlaps to some extent in their proclivity to affect striatal structures and associated networks. Nonetheless, the evidence is far from conclusive regarding under which specific conditions co-occurrence of HIV, HCV, and SUDs may yield additive and/or interactive effects on neural systems and neurobehavioral manifestations. It is also important to keep in mind that interactions among these conditions on neurobehavioral functioning extend beyond the molecular level. Indeed, not only do HIV and HCV affect neurobehavioral function, but there appear to be behaviors that are common to their transmission. Although we must make the seemingly obvious assertion that all substance users do not invariably

contract HIV or HCV, and that not all HIV+ or HCV+ individuals are substance users, these conditions do commonly co-occur. The many individuals who suffer from more than one of these conditions appear to be particularly vulnerable to neurobehavioral disturbances and may consequently experience significant difficulties in important aspects of their healthcare, such as maintaining medical appointments, maintaining abstinence, and adhering to prescribed behavioral and pharmacologic treatment regimens. With the lifespan of HIV+ persons becoming progressively longer, the study of co-occurring conditions and their impact on patient health and quality of life become increasingly more important.

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The Functional Impact of HIV-Associated Neuropsychological Decline

Matthew J. Wright, Ellen Woo, Terry R. Barclay, and Charles H. Hinkin

Unlike the relative paucity of research examining the functional impact of HIV-associated neurocognitive decline, there is a mature body of literature with regards to the neuropsychological sequelae of HIV infection (see chapters 7, 8, 9, 15, & 18 in this volume for a thorough review). Briefly, HIV infection is associated with neuropsychological deficits in attention/working memory, motor abilities, memory, and executive functioning (1–5), which are often attributed to disruptions in frontal-striatal circuitry (3, 6). These HIV-associated deficits generally worsen with infection staging (3), and decline in psychomotor speed appears to be the most robust (5, 7). Although dementia occurs in a relatively small number of HIV-infected individuals, between 30 and 50% of those with HIV evidence milder neuropsychological deficits (3, 8). That said, the number of newly diagnosed cases of HIV, in tandem with increased life expectancies resulting from treatment with highly active antiretroviral therapy (HAART), is driving up the mean age of the HIV-infected population (9, 10); older HIV+ individuals have been shown to demonstrate disproportionately greater neuropsychological decline and are about three times more likely to develop HIV-related dementia than are their younger counterparts (11, 12).

Data indicate that activities of daily living (ADLs; e.g., bathing, dressing) and instrumental activities of daily living (IADLs; e.g., financial management, cooking) decline in cases of HIV infection, although these declines tend to be specific to the individual and are somewhat variable (9, 13). Most of the functional declines are observed in IADLs (10). Heaton et al. at the UCSD HIV Neurobehavioral Research Center (HNRC) completed the groundbreaking work in this area via the use of

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laboratory-based functional measures, which indicated that HIV-related IADL declines are predicted by neuropsychological status (9, 14–16), although physical (e.g., fatigue, neurologic symptoms, GI disease) and affective variables (e.g., depression) also play a role in HIV-related functional outcome (17). For example, HIV-associated neuropsychological impairment is predictive of vocational difficulties (e.g., unemployment rates, difficulties completing work-related duties) above and beyond HIV infection itself (18). Furthermore, neuropsychological impairment is predictive of laboratory-based measures, real-world indicators, and self-report questionnaire endorsements of IADLs among HIV-infected individuals (see Table 1 for suggested functional measures) (14). Specifically, HIV-associated deficits in executive abilities (related to declines in vocational, financial, and medication management skills), learning and memory (linked with declines in medication management, shopping, and cooking skills), and language and attention (associated with vocational ability decrements) predict performances on laboratory-based measures of IADLs. Moreover, neuropsychological deficits, poor performance on laboratory measures of IADLs, and depression are predictive of self-reported IADL dependencies in HIV+ persons. Laboratory-based IADL performances and depressed mood are predictive of cognitive complaints and, along with AIDS status, predict declines in real-world measures of vocational functioning.

In summary, HIV infection is associated with neuropsychological deficits, which are predictive of laboratory and real-world measures of functional ability. The current review will focus on medication adherence, driving, and employment, three particular salient areas of everyday functioning.

Medication Adherence

Medication adherence can be assessed via a number of methods, all of which are characterized by unique strengths and weaknesses. These methods fall on a continuum ranging from those that are more objective (e.g., plasma drug levels) to those that are more subjective (e.g., patient self-reports). In this section, methods of assessing medication adherence are briefly outlined and followed by a review of the relationship between medication adherence and neuropsychological function in HIV+ individuals.

Medication Adherence: Methods of Measurement

Although laboratory-based measures can quantify medication management abilities (e.g., Medication Management Test – Revised; see Table 1) (14), accurate real-word measures of actual adherence are difficult to design. Self-report is probably the most widely used methodology for assessing medication adherence in clinical practice. Strengths of self-report include its negligible cost and the simplicity of

Table 1 Suggested Functional Measures for HIV Infected Individuals

Performance Measures	Self-Report Measures
– *Modified Direct Assessment of Functional Status* • A modified DAFS for use with HIV+ individuals that includes: o Financial Skills (from the DAFS): currency calculation and checkbook balancing. o Advanced Finances (from Heaton & colleagues): involves paying three bills, recording a deposit, and active account management to retain needed currency. o Shopping (from the DAFS): selection of goods from a grocery list. o Cooking (from Heaton & colleagues): involves utilizing two recipe cards and completing steps required for preparing pasta and warming bread. – *Medication Management Test-Revised* • The MMT was designed for application with HIV+ individuals. It was later modified by Heaton and colleagues (MMT-R) and entails: o Referencing mock medication inserts. o Sorting, organizing, and making inferences about three fictitious medications (e.g., refill needs). – *MESA SF2* & COMPASS**: computer administered measures of vocationally relevant aptitudes such as: • Academic skills (writing, reading, vocabulary, and mathematical ability) • Cognition (problem solving, short-term nonverbal memory, visual discrimination, and placing and tracking). • Mechanical ability (wiring, alignment and driving, machine tending).	– *Patient self-reported work history** • This can vary form informal interview questions to use of structured questionnaires. – *Patient's Assessment of Own Functioning*: self-report questionnaire reflecting an individuals perception of their functional level with regard to: • Cognition (general intellect, memory, language) • Sensory-perceptual ability • Motor function in hands • Work and recreational activities – *Modified IADL Scale*: assesses current and previous level of IADL dependence on tasks such as: • Financial management • Household repairs & chores • Medication use • Grocery shopping • Telephone use • Use of transportation • Bathing and grooming • Reading and TV comprehension

Notes. For more detail please (14).
IADL = instrumental activity of daily living; DAFS = Direct Assessment of Functional Status; MESA SF2 = Microcomputer Evaluation and Screening Assessment Short Form 2; COMPASS = Computerized Adaptive Placement Assessment & Support System.
* These can be used in conjunction with published vocational profiles to determine level of occupational decline (see 9, 14).

data collection. However, many patients overstate their actual adherence rates. Moreover, research with HIV-infected adults has revealed that patient self-report, relative to electronic monitoring techniques (see below), tends to be accurate among patients who candidly admit to poor adherence but may over-estimate actual adherence rates by approximately 10–20% among the majority of patients who claim perfect or near-perfect adherence (18–20).

Pill counts are a relatively straightforward technique that can be utilized to assess adherence rates. Considering the number of pills dispensed to a patient on a particular date, in conjunction with how many pills they should have ingested in the intervening time period, it is simple to calculate the number of pills that should remain at the end of the study period. Excess doses are therefore considered to reflect doses not taken as prescribed. For example, consider a patient on a 2 pills/day regimen who begins with 60 pills and returns to clinic 20 days later. If 20 pills remain, that would be interpreted as perfect adherence ($60 - (20 \times 2) = 20$). Although it is easy for the researcher/clinician to calculate, a decided drawback is that this is also easy for patients to calculate. Accordingly, prior to their return to clinic, patients may remove extra doses from their pill bottle and thus appear more adherent than is actually the case.

Bansberg et al. at UCSF developed an innovative approach to overcome this limitation (21). They conducted "unannounced pill counts" at participants' residences. They found that this approach correlates well with biologic outcomes (e.g., HIV viral load). Although this methodology works well within dense urban communities (e.g., San Francisco), it would be cumbersome to utilize in sparsely populated rural settings or in a sprawling metropolis. Unannounced pill counts can also be conducted via telephone, an adaptation that at least partially obviates the logistical difficulties introduced by geographical sprawl.

Similar to pill counts, pharmacy refill records have also proven to be a cost-effective measure of medication adherence. This method presumes that patients refilling their medication prescriptions in a timely fashion are more likely to be taking their medication as prescribed in comparison with individuals who are tardy in refilling their prescriptions. This approach works best in settings where pharmacy records are centralized and easily accessed (e.g., in Veterans Administration Medical Centers).

An alternate approach that also minimizes reliance on patient self-report and utilizes electronic monitoring is the use of MEMS caps [e.g., Medication Event Monitoring System (MEMS), Aprex Corp, Union City, California]. MEMS caps employ a microchip embedded in a pill bottle cap that automatically records the date, time, and duration of pill bottle openings. Although electronic monitoring devices may have their own limitations, accumulating data suggest that they often are more accurate than pill counts or self-report, both of which appear to significantly overestimate adherence rates. One disadvantage of this method is the bulky nature of the MEMS cap bottle, which precludes inconspicuous transportation of one's medications. This can lead to "pocket-dosing," where patients remove extra doses from their pill bottle and place them in their pocket (or another less-conspicuous container) to consume at a later time. Also, the use of MEMS devices has precluded the use of daily/weekly pill organizers, which can contribute to

poorer adherence rates. Technological advances are now emerging that will help to overcome this limitation.

Medication Adherence: Neuropsychological Correlates in HIV Infection

The introduction of HAART has led to marked improvement in mortality, functional level, and quality of life among HIV+ individuals (22, 23). However, unless patients are adherent to their HAART regimen (i.e., at least 90–95% of doses taken), viral replication may ensue and drug-resistant strains of the virus can emerge. As mentioned earlier, memory and executive abilities are predictive of performances on objective laboratory measures of medication management (14). Our group has engaged in several studies designed to elucidate the variables that are associated with medication adherence in HIV disease, with a particular emphasis on neurocognitive factors. Below we present an overview of the primary findings from these studies to illustrate how neurocognitive dysfunction can adversely affect medication adherence.

Our laboratory recently conducted an investigation of neuropsychological functioning and medication adherence in 137 HIV-infected adults (24). HIV+ participants were classified as neuropsychologically intact or impaired via a methodology developed by Heaton and colleagues at the UCSD HNRC. Here, neuropsychological test scores were converted to demographically corrected *T*-scores ($M = 50$, SD = 10) and grouped by cognitive domain. A cut-point of 1 standard deviation below the mean (i.e., $T < 40$) was used to classify participants as cognitively compromised. We determined HAART adherence via MEMS caps over a one-month time frame. Participants who took at least 95% of their prescribed doses were classified as good adherers.

The mean adherence rate across all participants was 80.2%; only 34% of participants demonstrated good adherence (95% adherence). Further analysis indicated that neuropsychologically compromised participants' mean adherence was 70% in comparison with cognitively intact participants, who demonstrated a mean adherence of 82%. Logistic regression analyses revealed that neuropsychologically compromised individuals were twice as likely to demonstrate poor adherence. A more detailed inspection of neuropsychological performances revealed that deficits in executive abilities, attention/working memory, and verbal memory were associated with poorer HAART adherence.

Medication Adherence: Neuropsychological Dysfunction and Regimen Complexity

Historically, effective pharmacological management of HIV/AIDS involved adherence to an extremely demanding, often complex, medication regimen [often upwards of 20–30 pills/day, many with specific, compound instructions (e.g., "Take

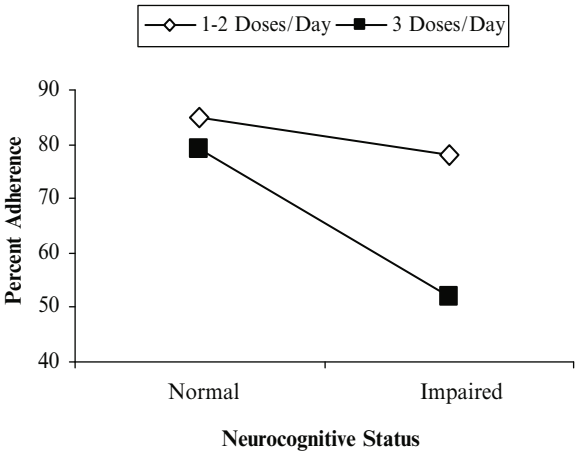

Fig. 1 Relationship between global neurocogniti ve functioning, re gimen complexity, and HAART adherence among HIV-infected participants. Adapted from Hinkin et al. (24)

three times per day on an empty stomach")]. Although considerable progress has been made in simplifying HIV medication re gimens, many regimens remain complex and likely pose difficulties for the cognitively compromised patient. Using the data set mentioned abo ve, we explored the relationship between neuropsychological dysfunction, regimen complexity, and adherence. We found that HAART regimen complexity (1–2 daily doses vs. 3 daily doses) adv ersely affects adherence among neuropsychologically impaired HIV+ indi viduals (see Fig. 1). Complex medication regimens were not signif icantly problematic for the neuropsychologically normal participants. F ollow-up analyses revealed that cognitive compromise in executive abilities and w orking memory interacted with re gimen complexity to produce these marked declines in adherence.

Medication Adherence: Aging and Neuropsychological Impairment

As mentioned earlier, older HIV+ indi viduals evidence disproportionately higher rates of neurocognitive impairment (11, 12). Given these findings, we hypothesized that older HIV+ participants (≥50-years old) w ould demonstrate lo wer adherence than would their younger counterparts (25). However, we found that the older participants were actually f ar more adherent than younger participants. 53% of our older HIV+ participants demonstrated good adherence, whereas only 26% of younger HIV+ participants indicated good adherence. Using a more liberal cutpoint of 90% to define good adherence, 71% of the older HIV+ group were found to be adherent vs. only 37% of the younger HIV+ group.

Nevertheless, a closer inspection of the interaction between adv ancing age and neuropsychological compromise presented a dif ferent picture. When we grouped

participants by medication adherence (using the 95% adherence cut-point) and age (using age 50 as a cut-point) and then compared these groups' neuropsychological test performances, we found little difference in neuropsychological functioning between the good adherers. However, the older HIV+ subjects who were poor adherers performed far worse on neuropsychological testing than did the younger HIV+ subjects who were poor adherers. In fact, 83% of older adult participants demonstrating poor adherence indicated global cognitive impairment. Further analyses showed that this effect was driven by deficits in executive skills, psychomotor functioning, and verbal memory.

This suggests that advancing age in conjunction with neuropsychological decline poses particular challenges regarding medication management for HIV+ persons. Additionally, it must be noted that we have presented these data under the assumption that cognitive dysfunction causes poorer adherence. It is equally plausible that poor adherence results in neuropsychological impairment. In all likelihood, a bidirectional relationship exists, with neuropsychological deficits adversely affecting patients' ability to adhere to their HAART regimen, which in turn results in increased disease progression and a worsening of neurocognitive function.

Medication Adherence: Drug Use/Abuse

Given the high comorbidities between substance abuse and HIV infection, we undertook a longitudinal study examining the impact of drug use and abuse on medication adherence among 150 HIV-infected individuals, 102 of whom were revealed by urinalysis to have recently used illicit drugs (26). Medication adherence was tracked over a 6-month period using MEMS caps. Our data indicated that drug-positive participants demonstrated significantly worse medication adherence than did drug-negative participants (63% vs. 79%, respectively). Logistic regression analysis revealed that drug use was associated with over a fourfold greater risk of poor adherence. Further, stimulant use (i.e., cocaine or methamphetamine) proved to be particularly deleterious to adherence, as participants who tested positive for stimulants were seven times more likely to be poor adherers than those without positive urines (see Fig. 2).

We also compared adherence rates for time periods when subjects were and were not using stimulants. From these data, we computed 3-day adherence rates for visits at which participants tested stimulant-positive as well as adherence rates for visits at which the same participants tested stimulant-negative. The 3-day mean adherence rate for participants who tested positive for recent stimulant use was 51.3% in contrast to the 3-day mean adherence rate of 71.7% for the same participants when they had tested negative for recent stimulant use. These findings suggest that the impact of stimulant use on HAART adherence is a function of state rather than trait. In other words, our findings imply that it is the acute effects of intoxication, rather than stable features, which may be characteristic of the drug-using populace, which adversely affects medication adherence. Related data from our laboratory comparing HIV+ participants who recently used stimulants (cocaine or methamphetamines;

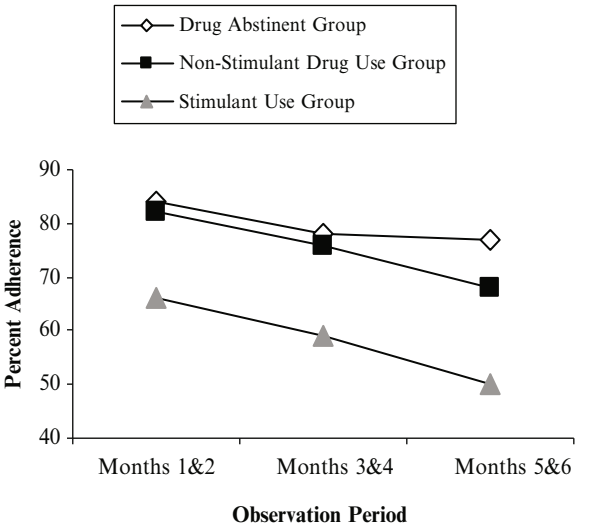

Fig. 2 Medication adherence rates among stimulant using, nonstimulant drug using, and drug abstinent HIV-infected participants over a 6-month period. Adapted from Hinkin et al. (26)

$n = 17$) with those who did not recently use stimulants ($n = 23$) suggest a possible neuropsychological mechanism by which stimulant use decreases adherence (27). In this study, despite similar global cognitive functioning between both groups, we found that recent stimulant use was associated with declines in sustained visual attention as indexed by a computerized continuous performance task. Although we did not assess medication adherence in this experiment, this finding, taken together with other data from our laboratory, suggests that stimulant intoxication impairs attentional abilities, which in turn may result in reduced HAART adherence. Indeed, other work in our laboratory indicates that neurocognitive impairments are predictive of poor medication adherence in older HIV+ participants (28) as well as in stimulant using HIV+ persons (29).

Overall, our work suggests that attention, memory, and executive abilities are particularly important to successful medication adherence in HIV+ individuals (24, 29). One cognitive operation that requires all of these processes and that may account for medication adherence rates among neuropsychologically impaired HIV+ persons is prospective memory (ProMem). ProMem is the ability to remember and correctly execute an intended action in the future at either a specified time (time-based ProMem; e.g., take medication at 5 p.m.) or in conjunction with an event (event-based ProMem; e.g., take medication with dinner). In general, most individuals indicate that time-based ProMem tasks are more difficult to complete than are event-based ProMem tasks. Interestingly, Woods et al. at UCSD HNRC have shown that HIV+ participants demonstrated time and event-based ProMem deficits in comparisons with healthy controls (30). Additionally, these investigators have found evidence suggesting that HIV-related ProMem failures may be due to macrophage activation and axonal injury (31).

Driving

Like medication adherence, driving ability can be assessed in numerous ways. Methods for assessing driving include patient self-report, review of driving history (e.g., records of traffic violations and accidents), driving simulator performances, and on-road evaluations. As mentioned earlier, self-reports can be biased for a number of reasons (e.g., motivation, cognitive impairment). Although state driving records may provide an objective indicator of traffic infractions and accidents, these likely grossly underestimate overall driving difficulties. Driving simulator performances and on-road evaluations almost certainly provide more accurate data on driving ability, although both of these methodologies likely elicit somewhat artificial representations of true driving behavior.

Neuropsychological deficits have been shown to be associated with declines in driving across a number of these methodologies (32–35), although the neuropsychological profile indicative of poor driving is yet to be determined because of methodological and definitional differences among studies. The majority of research regarding the neuropsychology of driving ability in HIV+ persons has been conducted by Marcotte et al. at the UCSD HNRC via the use of driving histories, driving simulators, and on-road evaluations. In the first study of HIV and driving ability, a link between neuropsychological impairments and driving simulator performance was demonstrated (see Fig. 3) (36). Participants evidencing mild

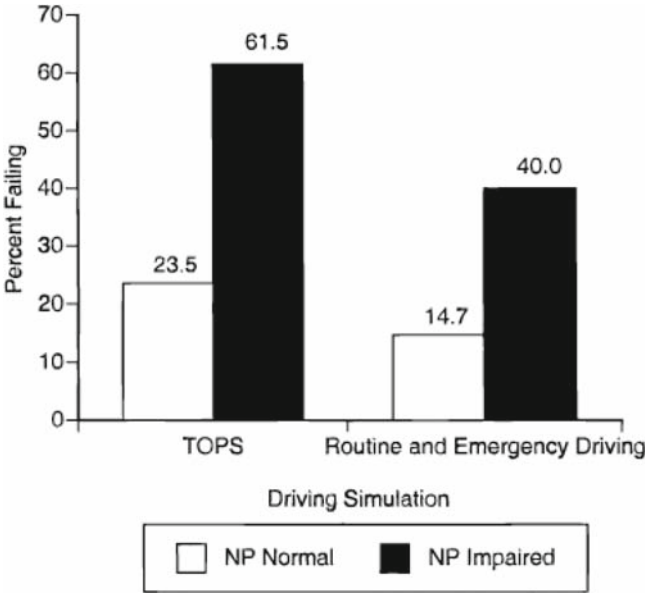

Fig. 3 Percentage of driving simulator failure for neuropsychologically normal and impaired HIV-infected participants. *TOPS* Truck Operator System; a program that assesses maintenance of speed, a straight trajectory, and infrequent divided visual attention. Reproduced with permission from Cambridge University Press (36)

neuropsychological deficits were shown to fail driving simulations at a rate five to six[1] times greater than cognitively intact participants. Also, neuropsychological performances in attention/working memory and fine motor abilities predicted performance across driving simulations (simple and evasive), although visuoconstructive abilities (simple driving) and nonverbal memory (evasive driving) were also found to be predictive.

A later study by Marcotte et al. that included 40 HIV+ participants and 20 healthy controls utilized a comprehensive neuropsychological test battery and two driving simulations to assess navigational abilities and evasive driving: an on-road driving evaluation and the Useful Field of View test (UFOV; a computerized measure of visual processing and attention) (37). Of the HIV+ participants, 11 were neuropsychologically impaired. These impaired HIV+ participants demonstrated increased simulator accidents, reduced simulator driving efficiency (i.e., they drove unnecessary distances to complete a specified task), greater fail rates in on-road driving tests, and decreased visual processing and divided attention on the UFOV in comparison with the neuropsychologically intact HIV+ and HIV− participants. For the whole sample, global neuropsychological functioning, simulator accidents, and simulator driving efficiency accounted for 47.6% of the variance in on-road pass/fail performance. With regard to specific neuropsychological domains, only executive abilities emerged as a significant predictor of on-road pass–fail rates, although attention/working memory, memory, and verbal abilities approached significance.

More recently, Marcotte et al. examined the relationship between visual attention and driving in HIV+ participants more closely (38). In this study, which included 42 HIV+ and 21 HIV− participants, UFOV performances, neuropsychological status, and detailed self-reported driving history were collected. With regard to neuropsychological functioning, 45% ($n = 19$) of the HIV+ group evidenced impairments (mostly mild-moderate), while only 4.8% ($n = 1$) of the HIV− participants showed mild deficits. Overall, the HIV+ participants demonstrated greater difficulties on the divided attention subtest of the UFOV in comparison with controls. In fact, the HIV-infected participants had an 11-fold greater risk of performing in the abnormal range on the UFOV's divided attention subtest than the control participants (36% vs. 17%, respectively). In terms of predicting automobile accidents, high-risk status[2] on the UFOV predicted self-reported accidents, while neuropsychological status approached significance as a predictor. However, when both

[1]Five times worse for simulations of simple driving (i.e., driving on a straight highway at a constant speed with occasional competing responses). Six times worse for simulations of evasive driving (i.e., variable speed driving requiring turns, passage of other vehicles, and avoidance of potential accidents).

[2]Performances across the three UFOV subtests (Processing Speed, Divided Attention, and Selective Attention) are analyzed with regard to an algorithm that classifies risk level (39). Participants in Marcotte et al. (38) with a level five classification (High to Very High risk) were considered high risk.

neuropsychological impairment and UFOV high-risk status were considered together, 93% (39/42) of the HIV+ participants who reported automobile accidents in the past were classified correctly.

In sum, the relationship between neuropsychological functioning and driving ability in HIV-1-infected individuals is complex, but deficits in attention/working memory (particularly in the visual modality), in addition to declines in executive and memory abilities, likely contribute to reduced driving performance in this population. These data argue for driving ability assessments of patients suffering from both HIV and neuropsychological impairments, with a particular focus on deficits in visual attention/working memory. However, it is very important to note that the majority of HIV-infected individuals do not exhibit neuropsychological deficits that would impair their ability to drive.

Employment

Assessment of vocational status in HIV+ persons is of "real world" significance, given that transient employment as well as unemployment is associated with a greater risk of hospitalization and death compared to stable employment (40). Several mechanisms have been proposed to explain the association between poor employment and health status in HIV participants. One mechanism includes the direct physiological effects of stress related to poor employment on the neuroendocrine and immune systems, leading to progression of HIV disease. The second mechanism involves increased risky health behaviors and poor treatment adherence in those without stable employment. Another mechanism is adverse work conditions, such as low control over work scheduling, which can impact health. Finally, participants with a poor vocational situation may have had poorer health prior to HIV infection. Poor employment histories are related to greater overall disability in ADLs (i.e., dressing and grooming, eating, hygiene), IADLs (i.e., reaching, gripping, shopping, and household chores), and mobility (walking, arising) (9), which would have a significant impact on the ability to work.

Employment has been evaluated using a number of different methodologies. One method includes using the Computerized Adaptive Placement Assessment and Support System (COMPASS; Valpar, Inc.). The COMPASS is an objective measure of vocational abilities that can also estimate premorbid work functioning based on a participant's work history. Multiple domains of work functioning are assessed: placing (eye–hand coordination), color discrimination, reading, size discrimination, shape discrimination, short-term visual memory, spelling, vocabulary, mathematics, development/editing (sequentially ordering sentences), problem solving, eye–hand–foot coordination, alignment and driving, machine tending, and wiring (fine motor tasks). Work histories have also been evaluated. Self-report regarding employment status (40, 41) or changes in vocational functioning have also been utilized (14, 40). Current vocational functioning can also be assessed by rating participants' jobs by the skills that the jobs require (14).

The ratings include general educational development (i.e., reasoning, mathematic, and language) and aptitudes (i.e., job-specific skills; learning, verbal, numerical, spatial, form perception, clerical perception, motor coordination, finger dexterity, manual dexterity, eye–hand–foot coordination, and color discrimination). These ratings are used to derive a Department of Labor "Worker Qualifications Profile." These ratings help to determine the number of jobs that people can perform. Heaton et al. (42) suggested that this type of assessment is limited, as they do not account for job-related experience, which can lessen the adverse effect of neuropsychological impairment on occupational performance.

Heaton et al. (42) found that medically asymptomatic HIV-infected patients who exhibited neuropsychological impairment were more than two times as likely to be unemployed (i.e., work less than half-time) than were patients who were not impaired, despite the lack of active HIV symptomatology. In addition, most of these participants were in the earlier stages of HIV infection, suggesting that medical illness was not the primary cause of the lack of employment. Regardless of employment status, HIV+ patients who evidenced neuropsychological impairment perceived themselves to have greater difficulties in vocational functioning than their unimpaired cohorts. The relationship between neuropsychological impairment and employment difficulties could not be explained by depression.

In the HAART era, employment loss is common during the early years of post-HIV infection (40). One out of five patients lose a job after a median time of 2.5 years after infection, even though physical declines are more limited. Dray-Spira et al. (40) found several risk factors that increase the chances of losing employment. These variables include female gender, having a nonpermanent job, poor housing accommodations, and poor health [i.e., advanced HIV disease (viral load > 10,000 copies/mL) and/or hospitalization in the past 6 months]. It was suggested that female gender is already a disadvantage for employment, and this is further compounded by low socioeconomic status (e.g., poor living accommodations) and HIV disease. Other barriers to employment include advanced age and longer duration of unemployment (43). Heaton et al. (42) found that HIV+ persons who were neuropsychologically impaired were more likely to be unemployed. Furthermore, global functional impairment (i.e., on an objective laboratory-based assessment of everyday functioning, self-report of functioning outside the laboratory, and a laboratory assessment of vocational functioning) and depression were more common in unemployed participants. It was suggested that neuropsychological testing and functional assessments could be used together to determine if HIV+ individuals suffer from "syndromic neurocognitive" disorders.

van Gorp et al. (43) found several predictors of return to employment in HIV+ persons who had stopped working after learning of their diagnosis. Effortful learning and memory was a robust predictor of return to work, beyond IQ and health. In addition, motor speed predicted return to work. Taken together, van Gorp et al. suggest that HIV+ individuals seek workplace accommodations while maintaining some employment, as patients who return to employment report less depression and improved quality of life. Furthermore, patients who returned to work often maintained their previous occupational levels. Having a high occupational position

(e.g., managers, executives, craftsmen) decreased the risk of employment loss (40). Furthermore, employed HIV+ participants tend to hold more cognitively demanding jobs and have higher levels of lifetime job skills (44).

In general, loss of employment is common following an HIV diagnosis, and this phenomenon cannot be entirely explained by physical barriers or mood. There are numerous risk factors for unemployment: female gender, temporary employment, poor housing, health problems, older age, an AIDS diagnosis, and increased duration of unemployment. Of note, impairment in neuropsychological skills and everyday functioning should be assessed in HIV+ patients, given that these are the major risk factors for unemployment. Neuropsychological assessments can also help to predict who will more likely return to work, based on higher performances on measures of learning, memory, and motor skills. With the proper workplace accommodations, return to work can be beneficial for HIV patients, as regaining employment can enhance mood and quality of life.

Conclusion

HIV can give rise to neuropsychological deficits in attention/working memory, motor abilities, memory, and executive abilities. Between 30 and 50% of those with HIV evidence such deficits. HIV-infected individuals who demonstrate neuropsychological impairments also tend to exhibit functional declines on real-world and laboratory measures. With regard to the majority of the domains of functional outcome reviewed herein (laboratory ADL/IADL simulations, medication adherence, driving ability, employment status), attention/working memory, memory, and executive deficits tend to be most predictive of functional decline. A complicating factor is depressive symptoms, which interact with cognitive declines and adversely influence the functional abilities of HIV-infected persons. In terms of specific functional effects, deficits in attention/working memory are associated with poorer medication adherence and driving ability (particularly visual attention/working memory); memory impairments correlate with reduced medication adherence (particularly verbal memory), driving ability (particularly non verbal memory), and employment status (chiefly verbal memory); executive problems are related to inferior medication adherence (especially for older adults and complex medication regimens) and driving ability. Additionally, fine motor deficits are predictive of impairments medication adherence (for older participants) and employment status. Overall, research indicates a link between functional outcome and neurocognitive status in HIV+ individuals and strongly suggests the need for repeated neuropsychological evaluations to optimize treatment planning (e.g., tracking cognitive status and diagnostic classification, vocational planning, and recommendations for performance enhancing behavioral and environmental modifications) for HIV-infected persons.

Although our understanding of the functional impact of HIV-associated neuropsychological decline has grown, there are still critical gaps in the literature.

In particular, studies linking structural and functional neural systems known to be affected by HIV disease with their real-world functional correlates are yet to be performed. Such data may not only improve our scientific understanding regarding the neuroanatomy of functional abilities in HIV, but might also suggest neuroanatomical targets for novel pharmacologic and neurocognitive therapies. Additionally, studies deconstructing the neuropsychological deficits (e.g., attention/working memory, memory, and executive deficits) most often associated with functional decline in HIV disease could lead to insights informing neurocognitive rehabilitation strategies (e.g., cognitive strategy use, environmental support, behavioral and environmental modifications) with utility for prolonging functional independence.

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Adjunctive Therapy for Long-Term Support of Cognitive Impairment

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The neurological complications associated with human immunodeficiency virus (HIV) continue to be a problem despite the introduction of highly active antiretroviral therapy (HAART). Current antiretroviral therapies have changed this formerly fatal illness into a chronic disease, allowing HIV-infected individuals to live much longer. But, with increased age and duration of disease, the prevalence of neurological conditions among these individuals has also increased (1).

Before the advent of HAART, dementias related to HIV were common occurrences within the infected population with a prevalence of about 30% (2). The HAART era has shown an initial improvement in cognitive function following treatment (3, 4). However, an increase in the rate of mild and moderate encephalopathy has been reported (5) in the post-HAART era. Autopsy reports show that about 90% of infected individuals have neurological evidence of disease (6).

HAART has altered the expression of dementia associated with HIV, and the nosology for HIV-1-associated neurocognitive disorders (HAND) has recently changed to reflect these differences from pre- to post-HAART era (7). The new criterion has been shown to be more sensitive to diagnosis and better reflective of the state of the brain in patients with HAND (8). As noted in Chaps. 7 and 8, the three types of HIV-associated neurocognitive dementia are asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). ANI, the mildest form of HIV dementia, is characterized by impairment in at least two cognitive domains that are one standard deviation below the mean on neuropsychological testing; however, these impairments do not interfere with the activities of daily living (ADLs). The diagnosis of MND includes the same criteria as the diagnosis of ANI, but these cognitive deficits mildly interfere with ADLs. The diagnosis of HAD is made when there is an impairment in at least two areas of cognitive functioning that fall two standard

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deviations below the mean on neuropsychological tests. These cognitive deficits result in a striking reduction in ADL function.

There are currently no effective treatments for the neurological deficits associated with HIV. While several adjunctive therapies have been considered, the outcomes have not been remarkably positive. In addition, there are no reliable biological assays to monitor the efficacy of the drugs being tested. Current research has focused on interfering with the inflammatory cascade, reducing viral replication, neurotoxin release, oxidative stress, and apoptotic effects, as well as providing neuroprotection. Treatments focusing on prevention early in the course of infection may offer more benefit than attempting to repair damage after it had been done. This chapter provides an overview of the different approaches to adjunctive therapies for cognitive impairment associated with HIV.

Adjunctive Pharmacological Therapies in HAD

HAART has led to significant reductions in symptomology in HIV patients suffering from HAD, as well as the number of patients with HIV who develop these cognitive and motor deficits. However, in those who show cognitive benefit from HAART, the positive effects are often transient and do not wholly ameliorate symptoms. Furthermore, HAART has been shown to exert neurotoxic effects itself (9). As such, HAD remains prominent in the HIV patient population despite the advancements found with HAART (10).

Interestingly, high viral levels in the brain do not represent a valid marker of potential cognitive impairment. In studies conducted before the advent of HAART, CNS viral loads have been low among patients with clinical characteristics of HAD, while patients with low viral loads exhibit significant cognitive impairment (11). The strongest correlation between viral load and HAD relates to peripheral levels in that controlled viral load as seen with HAART is associated with improved cognitive performance. Further, this suggests that brain tissue acts as a reservoir for the HIV virus (12). These findings are consistent with the theory that the development of HAD results from immunological reactions to the presence of HIV as well as direct virus-associated byproducts such as glycoprotein (gp120) and transregulatory protein (Tat) rather than absolute levels of the virus itself. Below we describe different such targeted therapeutic approaches and their findings.

Psychostimulants

HIV patients suffer from a hypoactive dopaminergic system (13). Specifically, dysfunction is noted in the basal ganglia, where these deficits often manifest as movement disorders in HIV patients. Further, the particular pattern of dopaminergic insult in the subcortical area along with the cognitive profile associated with HIV

infection is remarkably similar to that seen in Parkinson's disease. Psychostimulants are one class of drugs that serve as dopamine agonists and have therefore been investigated as possible adjunct therapy for HIV-related cognitive impairments. Studies have investigated the possible therapeutic effects of clinical psychostimulants on cognitive function in HIV patients. Early studies reported that psychostimulants improve cognitive function in HIV patients. Holmes et al. administered either methylphenidate or dextroamphetamine to 17 patients presenting with HIV-related cognitive declines evident through neuropsychiatric evaluation (14). Both stimulants were clinically effective at improving scores on the Efficacy Index of the Clinical Global Impressions in 13 of the 17 patients. However, these results were often short-lived, leading to the interpretation that improvement was perhaps tied to an alleviation of depressive symptoms when considering that four of those patients were diagnosed with major depression. Angrist et al. also found a similar improvement with methylphenidate and dextroamphetamine in seven patients experiencing HAD (15). However, improvement was interpreted as a function of practice effects rather than drug treatment given that the study employed an ABAB design in which the patients did not return to baseline after treatment was withdrawn. More recently, Hinkin et al. found that cognitive processing speed increased following administration with methylphenidate, and these effects were evident in the absence of significant improvement in mood among the subjects (16). As such there appears to be some level of empirical support for the utility of stimulants to improve cognitive function in HIV patients, but as noted by others the pragmatics of this approach need to be weighed in light of common histories of substance abuse in this population.

Selegiline

Selegiline is a monoamine oxidase-B inhibitor approved for the treatment of Parkinson's disease, dementia, and depression. It is speculated that selegiline exerts these effects via reducing oxidative stress. The Dana Consortium conducted a randomized double-blind, placebo-controlled trial evaluating the efficacy of selegiline's neuroprotective actions in 36 patients with mild HAD (17). Selegiline was well tolerated with a few adverse events, and those recipients receiving treatment showed significant improvement on tests of verbal memory. Sacktor et al. then conducted a pilot trial in which nine randomly-assigned HAD patients were given 3.0 mg of selegiline over 24 h via a transdermal patch and five were given placebo (18). The treatment group showed trends toward improvements in delayed recall and psychomotor speed as measured at 4 and 10 weeks. Unfortunately, more recent findings in which the same research group conducted a larger, placebo-controlled, three-arm study across 17 sites yielded less-encouraging results (19). One hundred and twenty eight HAD patients with mild to moderate dementia were given transdermal selegiline in either 3-mg or 6-mg doses, or placebo, over 24 weeks. At the end of the treatment, neuropsychological evaluations revealed no significant differences between doses in terms of cognitive performance and in fact individuals

taking placebo demonstrated some what higher improvement scores. The authors contemplated that perhaps the trial was not of sufficient duration to identify clinical improvements associated with selegiline. However, the results did reveal that cognitive abilities did not worsen among treated patients over the trial period and this was interpreted as a possible neuroprotective effect.

Antioxidants

The presence of HIV in the brain instigates a proinflammatory response. Unfortunately this natural immune reaction cannot eradicate the virus, and the excessive inflammation itself becomes neurotoxic. Further, this reactive activation of macrophages to HIV infiltration and its products may create an uninhibited positive-feedback loop that further feeds HIV replication, which in turn increases neuro-inflammation in a positive-feedback fashion (20). Specifically, macrophage activation is associated with the release of cytokines, including tumor necrosis factor-α (TNF-α). These free radicals trigger excitotoxicity and subsequent cell death.

Treatment approaches involving antagonism of TNF-α include antioxidants that protect the brain from the resulting oxidative stress. CPI-1189 is one such antioxidant that scavenges superoxide radicals (21) and has been shown to exert neuroprotective effects on aggregate brain-cell cultures against TNF-α as well as gp120 (22) and block TNF-α-related deficits such as learning and memory impairments in an animal model of HAD (21). Tested in a randomized and double-blind, placebo-controlled human trial with 64 HAD patients, a 100-mg dose of CPI-1189 was associated with improvement in Grooved Peg-Board Test scores (23). Other compounds with similar antioxidant qualities such as the vitamins α-tocopherol (vitamin E) (24) and selenium (25) have been tested in patients with HAD and shown likewise trends for cognitive improvements. OPC-14117, particularly, is a vitamin E-like antioxidative synthetic that has shown trends toward improvement in memory and timed gait function in HIV patients (26). Recently green tea-derived EGCG has been observed to inhibit neuronal damage by Tat and gp120 in both in vivo and in vitro treated cells (27). Direct, clear-cut evidence of cognitive improvement with antioxidant therapy in HAD patients has however proven elusive to establish largely because of methodological issues such as small sample sizes, primary outcome variables that included only safety and tolerability, and the lack of placebo-controlled studies. Interestingly, in at least one instance an antioxidant has been shown to worsen cognitive impairment. Thioctic acid, along with deprenyl, was evaluated by the Dana Consortium to reveal any effects on HIV-associated cognitive impairment (17). While deprenyl was associated with cognitive improvement, particularly in the domain of verbal memory, thioctic acid was associated with significantly worse performance on the Rey Auditory Verbal Learning Test total score and delayed recall. Additionally the direction of the effects of thioctic acid on the other measures of neuropsychological performance, including the Digit Symbol test, the Grooved Pegboard test, Timed Gait, and Cal Cap, was consistently negative. Still, antioxidant treatment results

overall have reliably been shown to be well tolerated and provide hope for efficacy in additional clinical trials (28).

Valproic Acid

Studies have shown that valproic acid (VPA) inhibits the apoptosis-inducing GSK-3B that is activated by platelet-activating factor (PAF, an inflammatory instrument stimulated by HIV) (29) and protects brain tissue from neuronal and dendritic loss (30). Schifitto et al. recently conducted a small placebo-controlled study and found that 10 weeks of 250-mg VPA treatment in 16 HAD patients induced trends toward cognitive improvement in HIV patients showing cognitive disruptions as measured through neuropsychological evaluations and global screening measures, was well tolerated, and did not affect viral load or CD4 counts (31). Further, magnetic resonance spectroscopy (MRS) revealed a significant increase in brain metabolism in the frontal white matter of those impaired patients receiving treatment. However, concerns remain that while VPA facilitates neurogenesis and acts as a neuroprotectant, it may increase HIV replication in microglial cells, which is the speculated mode of degenerative action in HAD (32, 33).

Lexipafant

Another substance that seeks to act on PAF is lexipafant. Lexipafant inhibits PAF directly, and using a randomized, double-blind, placebo-controlled clinical trial, Schifitto et al. hypothesized that the substance could beneficially affect the cognitive performance of HIV infected people (34). Thirty subjects with HIV infection, evidence of cognitive impairment, and who were on a stable antiretroviral regimen for 6 weeks were enrolled in the study and assigned to receive either placebo or 250 mg of lexipafant twice a day, approximately 12 h apart. The trial was primarily to assess the safety and tolerability of lexipafant, and secondarily to assess cognitive effects as measured by a neuropsychological battery.

Results indicated that the PAF antagonist was as tolerable as placebo, as indicated by similar rates of trial completion, similar incidences of adverse side effects, and similar compliance rates. At week 6 and week 10 after baseline evaluations, the lexipafant group showed trends toward improvement on the Rey Auditory Verbal Learning test as well as the timed gait test. There were no significant differences between the treatment group and placebo on global impression of cognitive ability, functioning mood, or CD4+ lymphocyte count. The trends toward clinical improvement, especially in verbal memory, may be viewed as encouraging particularly given the short duration and size of the trial. Schifitto et al. argue that in the view that it is important to develop an adjunctive therapy that can intervene in the inflammatory cascade triggered by HIV, these results warrant a larger and longer efficacy trial of lexipafant (34).

Calcium Channel Blockers

Other treatment approaches have targeted the prevention of excitotoxicity through mediation of the glutamatergic system reactions. Both immunoreaction macrophage stimulation and direct viral products such as Tat and gp120 bind to the glutamate receptors NMDA and AMPA. This "overstimulation" results in cell loss, most commonly recognized as the mechanism by which ischemia results in brain injury. Nimodipine was one of the earliest of these classes of drugs tested in clinical trials with seropositive patients. Nimodipine is a calcium channel blocker that in preliminary studies demonstrated an ability to block HIV-gp120 and Tat, thereby attenuating over-activity and cell death (35). Navia et al. conducted small phase I and II clinical trials, including 41 mild to moderate HAD patients (36). Nimodipine at 300 mg or 900 mg daily, or placebo, given for 16 weeks resulted in no significant change in neuropsychological Z-scores, although trends for improvement were suggested in the high-dose group. The researchers note that larger sample sizes could have given the power needed to detect any possible significant effects due to nimodipine.

Memantine

The Alzheimer's disease drug memantine, an NMDA antagonist, has shown positive effectiveness in double-blind clinical trials in patients with HIV. Nath et al. have reported blockade of gp120 and Tat-induced neuronal death by memantine in vitro (37). Anderson et al. also found similar results in a murine model specifically outlining neuroprotection in hippocampal cells (38). However, Schifitto et al. conducted a large-scale, double-blind, placebo-controlled multicenter trial testing the effectiveness of memantine in 140 mild to moderate HAD patients on neuropsychological functioning and MRS of frontal white matter and the parietal cortex (39). Results showed that the memantine group did not overall significantly differ than did the placebo group on any measure. Although positive effects of memantine have been reported, conflicting results as well as tolerability issues surrounding memantine warrant cautionary use and more extensive trials.

Minocycline

Minocycline is a broad-spectrum antibiotic belonging to the tetracycline family that has been shown to exhibit anti-inflammatory effects alongside its antimicrobial ability. Studies have shown a neuroprotective component as well in terms of multiple sclerosis (40), ischemia (41), Huntington's disease (42), and other brain insults. Contemporary research has shown that minocycline effectively crosses the blood–brain barrier and decreases the severity of encephalitis (43), inhibits HIV replication in microglia while sparing normal healthy function (44), inhibits microglial activation

(45), and even exerts antioxidative properties (46) and neuroprotective properties by inhibition of the p38 MAPK pathway (43). The long-time proven safety, tolerability, and purported neuroprotective eminence of the antibiotic leave many hopeful that current clinical trials will prove minocycline as an effective and inexpensive adjunct therapy for the treatment of HAD. Minocycline is currently under investigation as part of a large, multisite trial supported by NIH. This study focuses on patients with progressive cognitive decline rather than individuals with static brain involvement. Results from this study will be available shortly.

Lithium

Lithium salts, while traditionally prescribed for resistant and recurrent depression as well as bipolar disorder, have been shown to be beneficial against HIV and HAD. Lithium was first studied as an agent to alleviate neutropenia associated with AIDS (47). Lithium has furthermore been observed to carry antiviral properties of its own against HIV, although unfortunately the level required to yield such an effect is much larger than safe therapeutic doses (48). Lithium also boosts the immune system via agonism of T-cell growth factor (49), interleukin-2 and interferon (50), TNF-α (51), and antagonism of glycogen synthase kinase-3 β (GSK-3β), the enzyme activated by Tat involved in the regulation of apoptosis (52). Furthermore, lithium has been shown to protect against neurotoxicity directly from HIV-gp120 (53). Visca et al. have shown this neuroprotective effect specifically in HIV-infected patients with a 900 mg-daily dose significantly increasing CD8+ levels after 4 weeks (54). Clinical trials of lithium in terms of mood disorders have also shown neuroprotective qualities as assessed by increased NAA levels in MRS and MRI analyses in bipolar patients (55), reduced Tau protein production (56), and amyloid-related degeneration (57) in regards to Alzheimer's disease. One small open-label, 12-week pilot study in which eight HAD patients received doses that were titrated to maintain 12-h trough concentrations between 0.4 and 0.8 mEq/L showed improved performance on global neuropsychological tests in all eight individuals after 12 weeks, and became unimpaired in six (58). Furthermore, given the prevalence of depression in HIV patients, lithium's effectiveness against mood dysfunction together with its proven neuroprotective effects lends itself as an appropriate target for more extensive, much-needed clinical trials testing both the safety and efficacy of lithium on cognition in HAD patients.

Treatment of Comorbid Psychiatric Disorders and Its Effects on Cognition

Depression is the most common comorbid psychiatric condition present with HIV infection, affecting between 5 and 25% of the seropositive population (59). Even with this high prevalence, the contributions of depression to neuropsychiatric

impairment in HIV infection have yet to be clearly defined (60). Many empirical studies have found that depression has effects independent of HIV infection in the CNS, and that these effects do not include neuropsychological decline. The relevance of reviewing this literature in the current chapter is related to the question of whether cognitive function can be supported via concomitant treatment of depression and related mood disorders.

Millikin et al. reported that depressive symptoms in HIV-seropositive individuals were not significantly associated with phonemic or semantic fluency performance as measured by the FAS and Animals tests, respectively (61). Cohen et al. conducted a study with HIV infected women, which showed no influence of severity of depressive symptoms on HAART effects with respect to neurocognitive performance in general (4). Cysique et al. evaluated the effects of incident major depression on neuropsychological functioning in HIV infected men (62). They examined 227 HIV+ men and evaluated them for lifetime and current major depressive disorder as well as performance on tests of attention, speed of information processing, language skills, learning efficiency, and motor skills. Results showed no cognitive differences between the depressed and nondepressed HIV+ men, thus supporting the theory that depression is not responsible for neuropsychological impairment in HIV infection. This is a finding that is generally well-supported in the current literature (62).

Yet there are a number of studies that continue to find depression as an influential factor in neuropsychological performance when evaluating HIV+ populations. Vázquez-Justo et al. concluded that seropositive subjects with depressive symptoms performed significantly worse than those without depressive symptoms on measures of attention, verbal and visual memory, motor speed, and frontal functions (60). Chandra et al. state that depression is known to have a role in the causation of neurocognitive problems, particularly in areas of fine motor speed and information processing (59). Over a 2-year study, Gibbie found that only a group of HIV+ individuals without depression, and not one with depression, showed improvement in measures of neuropsychological performance (63). Those individuals without depression at the baseline examination showed significant improvement in cognitive performance following HAART; those with depression at baseline did not show significant improvement. Judd et al. reported a correlation between spatial working memory and subjects' scores on the Beck Depression Inventory (BDI), concluding that HIV may affect the later prefrontal cortex, an area that is involved in working memory and is implicated in major depression (64). Another study, comparing a sample of 47 HIV+ men with concurrent depression against an equal-sized group without depression, reported that the depressed participants showed greater detriment in the domains of memory, attention, and learning (65). More recently, Castellon's group took a novel approach to the evaluation of the BDI by subjecting the test to a factor analysis in order to further determine the specific involvement of depression in cognitive function in HIV infection. The analysis produced three factors: one encompassing apathy items, one encompassing mood and motivation items, and one with somatic items. The mood and motivation factor from the BDI factor analysis was most closely related to neurocognitive performance on verbal memory, executive functioning, and motor performance. The other two factors were not associated with cognitive performance (66).

Clearly there are conflicting results in evaluating the effects of depression on cognition in HIV infection, which raises the question as to whether treating this disorder will result in a significant improvement in cognitive function. The literature cited above is only a sampling of the myriad experiments aimed at determining the true nature of depression's contribution to declining neurocognitive function in HIV seropositive individuals. A complicating factor in many of these papers is the acknowledgement that numerous studies using the same samples and measures have not found significant effects of depression and have, in fact, concluded that depression and HIV infection should be viewed as separate pathologies, with HIV as the major contributing factor to declining cognitive abilities. Still, the discrepant results merit that the issue remains a controversial one.

Even within the established body of research cited above, Gibbie noted that improving symptoms of depression did not improve neuropsychological impairment (63), Goggin explained that depression severity scores did not correlate with any of their cognitive measures (65), and Vázquez-Justo's work revealed that a study performed under the same parameters yielded qualitatively different results from their own (60). Although not definitive, these studies do contribute to the acceptance of the current predominant hypothesis that depression is a disorder commonly occurring in HIV+ individuals, but its contribution to declining cognition is minimal at best (62). As such, treatment for depression has yet to be shown to improve cognition in HIV+ populations, and experiments looking at any such possible effects are a few and far in between. The available evidence indicates that although depression is often present, it is not necessary for cognitive impairment in HIV infection (67). Depressive symptoms and cognitive detriments are currently addressed and treated as separately occurring phenomena and will likely continue to be so.

A somewhat different picture emerges when looking at the domains of apathy and fatigue in HIV infected individuals. Though smaller in number, the studies addressing these sequelae of CNS infection provide more consistent results. Apathy refers to a group of symptoms that include both lack of motivation and reduction in activity in motor, emotional, and cognitive domains (67, 68). Phenomenologically apathy appears similar to depression, but the two constructs can be differentiated and the criteria for HAD define apathy rather than depression as a core feature. Supporting this idea are results from Castellon et al., which showed that apathy, and not depression, was associated with working memory deficits in HIV (69). This led them to conclude that apathy may, on its own, indicate CNS involvement in HIV infection. In later studies, Castellon et al. would produce results showing that apathy is likely to be associated with impairments in working memory and executive functioning; in contrast, depression did not correlate with these two domains (66). On the level of brain organization, Paul et al. state that apathy often occurs in the context of damage to subcortical regions, presumably as a result of the disruption of the flow of information between the frontal lobes and the striatum (70). Importantly, in another study conducted by Paul's lab (2005), apathy as measured by the Marin Apathy Scale correlated with lower volume of the nucleus accumbens (68). Since HIV is found in highest concentrations in deep subcortical nuclei, it is possible that the virus affects the frontal–subcortical circuits, and that this is behaviorally manifested as a deficit

in working memory, executive function, and related cognitive domains. Treatment of apathy in HIV has been minimally examined at the present time.

Like the evidence for apathy, many studies have found that fatigue is significantly associated with depressive symptoms in HIV infection. Fatigue is present in between 2 and 27% of HIV+ individuals, and it is likely present in between 30 and 54% of individuals with AIDS (71). It is widespread among HIV+ patients, but very few studies have assessed effective treatments for it (72). Although there is a limited literature on fatigue as it pertains to cognition, there are many studies explaining its relation to depression in CNS pathology. This body of research has yielded mixed results; some studies have shown no relationship between fatigue severity and cognitive performance (73) while others report that there is an association between the two (74). In 1995, Perkins and colleagues found that there was no relationship between fatigue and neuropsychological function in HIV infection (75). Still, fatigue remains an area of research interest when it comes to alleviating cognitive impairment.

One of the most recent promising avenues of research in this area comes from preliminary studies using modafinil (Provigil). Modafinil is an FDA-approved medication that generally promotes wakefulness. According to Minzenberg and Carter it may improve cognitive function in such psychiatric disorders as depression, attention deficit/hyperactivity disorder, and schizophrenia (76). These authors explain that modafinil acts on catecholamines, serotonin, glutamate, and γ-aminobutyric acid. In particular, though, its primary action may be on the catecholamines, and it appears to be selective for cortical over subcortical sites of action. Though this may not appear to fit with the subcortical profile of HIV-associated dementia, it would help to explain the alleviation of declining working memory and episodic memory shown by the drug. Preliminary results lead Minzenburg and Carter to conclude that modafinil is an excellent candidate for the remediation of cognitive dysfunction across psychiatric disorders, including HIV infection (76). In another study of the drug, Randall et al. (77) elucidated limited evidence for modafinil as enhancing cognition in healthy, middle-aged subjects. A particularly relevant pilot study of the drug was performed by Rabkin et al. in 2004. Of 30 HIV+ patients, 24 were characterized as "responders" to modafinil; this group of responders showed significant improvement on measures of fatigue, depression, verbal memory, and executive function. The authors used these results as evidence for modafinil's potential in alleviating fatigue and related cognitive dysfunction in HIV infection (72).

Potential Targets for Adjunctive Therapy for HIV-1-Associated Dementia

Proinflammatory cytokines, and among them chemokines and chemokine receptors, are currently being investigated for their therapeutic actions in HIV cohorts. When a chemokine binds to its receptor, an induction of calcium ion flux occurs within the cell, which in turn causes intracellular signaling cascades. In the CNS, chemokine

receptors, CCR5, CCR3, and CXCR4, along with the surface receptor CD4, are used by HIV-1 to enter and infect microphages and microglia. Inhibition of HIV-1 entry by antagonists of these receptors is being investigated in clinical trials (78). The novel CXCR4 antagonist neomycin B hexa-arginine has been demonstrated to cross the blood–brain barrier and reduce CXCR4-mediated gp120-induced neurotoxicity (79) .

These chemokine receptors, CXCR4 and CCR5, are also found on neurons and astrocytes, and even though the HIV-1 virus itself does not enter these cells, evidence exists that CXCR4 is involved in HIV-associated neuronal damage while CCR5 may actually have a protective role (as discussed in (78)). The CXCR4 receptor–ligand complex activates p38 mitogen-activated protein kinase (p38 MAPK), which has been shown to promote neuronal death (80). The protective actions induced by the CCR5 receptor–ligand complex involve the activation of the cellular serine–threonine protein kinase, Akt–protein kinase B (Akt/PKB), which has been demonstrated to promote cell survival. Agents that stimulate cell survival through the Akt/PKB pathway and those that inhibit p38 MAPK, e.g., minocycline, have been considered by Kolson to be one of the next investigational steps in HIV-1-associated dementia therapies (80), and development is already underway for p38 MAPK inhibitors for several inflammatory- and stress-related conditions (78).

The HIV-1 protein gp120 can bind to CXCR4 receptors to induce apoptosis in that neuron. However, Kaul and Lipton (as cited in (78)) found that the CCR5 chemokine ligands MIP-1 α, MIP-1β, and RANTES could protect against the gp120-induced toxicity at CCR5 receptors. These CCR5 ligands have been shown to suppress HIV-1 infection in the periphery. Individuals with higher cerebrospinal fluid concentrations of these chemokines, relative to those with low or undetectable amounts, have performed better on neurological measures. Some β-chemokines, the designation of the group of chemokines to which the CCR5 ligands belong, have also been shown to improve NMDA receptor-mediated neurotoxicity; another chemokine, fractalkine, has been shown in vitro to prevent gp120-induced neuronal apoptosis (as discussed in (78)). Selected chemokines may be a potential treatment for HAD, and, as reported in Kaul and Lipton, efforts are underway to develop modified CCR5 ligands that will have the same therapeutic benefits without the adverse inflammatory side effects that have been seen with the administration of these agents (78).

The cytokine erythropoietin (EPO) has also been shown to have neuroprotective properties. Receptors for EPO are found on neurons, and when stimulated by EPO, activate survival pathways that lead to the increased transcription of inhibitors of apoptosis and other pro-survival factors (as discussed in (78)). EPO has been shown in vitro to prevent neuronal death directly caused by HIV-1 through its protein gp120 and indirectly by NMDA receptor stimulation. EPO is already approved for the treatment of anemia, indicating easier passage through clinical trials for the treatment of HAD (78).

Another avenue under investigation for use as adjunctive therapy to HAD is neurotrophic factors. Nerve growth factor (NGF) mRNA and β-fibroblast growth factor (FGF) mRNA levels are elevated in individuals with HIV-1 infection present

in the CNS, suggesting that NGF and FGF are not sufficient by themselves as mechanisms for the prevention of HAD due to the fact that an effective immune action is not seen from the elevation of these agents (81). Brain-derived neurotrophic factor (BDNF) is not elevated in these individuals, yet does show immune reactivity in the striatum and is expressed by neurites and somas in the cortex. As discussed in Nosheny et al., BDNF has been demonstrated to have powerful neuroprotectant effects on the dopaminergic and serotonergic neurons in the basal ganglia and the neurons in the cortex in animal models of neurodegenerative disease (82). These neurons are hit hard by the degenerating effects of HIV-1 on the brain. A rodent model of HAD, created by injection of gp120 into the striatum, demonstrated a decrease in BDNF levels as early as 1 day after injection. Nosheny et al. suggested that this decrease in BDNF may be, in effect, a cause of neurodegeneration rather than a product of cell death (82). Pharmacological concentrations of BDNF demonstrated in vitro neuroprotectant effects in cortical neurons and cerebellar granule cells taken from the rat that were exposed to gp120 for 12 h. BDNF has also been demonstrated to decrease CXCR4 levels and block cell death mediated by the CXCR4 ligand stromal-derived factor 1-α. In effect, the decrease of CXCR4 receptors by BDNF could decrease the damage of gp120 proteins on the cells of the brain. These neuroprotectant influences of BDNF make it a potential candidate for investigation as an adjunctive therapy for HAD.

Lithium has been discussed in regard to neuroprotective effects in HAD by increasing BDNF. However, Dou et al. demonstrated that this was not the mechanism for lithium's neuroprotectant role (83). Blockage of the TrkB receptor, a receptor with a high affinity for BDNF and believed to be involved in BDNF's promotion of cellular survival, did not inhibit the antiapoptotic influences of lithium. This study demonstrated in the mouse that lithium is a neuroprotectant at least in part through the inhibition of glycogen synthase kinase-3 β, an enzyme that is stimulated by HIV-1 mediated neuronal injury. Inhibition of this enzyme allows for the activation of the phosphatidylinositol 3-kinase (PI3-K)/Akt pathways, which have anti-apoptotic effects. These results led Dou et al. to suggest lithium as a possible future adjunctive therapy for HAD.

Another avenue of potential adjunctive therapies for HAD focuses on the mitochondria of neurons infected with HIV proteins. These organelles play an important role in metabolic activities associated with neurotoxicity of HIV-1, such as apoptosis, glutamate-mediated excitotoxic neuronal injury, and regulation of the cellular redox state. Hyperpolarization of the mitochondrial membrane potential in neurons infected by HIV proteins occurs prior to apoptosis (as discussed in (84)). Perry et al. suggest that these bioenergetic changes may be a subcellular mechanism for a reversible metabolic component of HAD. Tolbutamide, an ATP-sensitive potassium (K+) channel antagonist, was found to reverse Tat-induced apoptosis of these neurons by blocking the efflux of K+ across the mitochondrial membrane. This antidiabetic drug has also been demonstrated to possess mitochondrial uncoupling properties, which allow for the inward leakage of protons across the membrane in the absence of ATP. Previous studies have demonstrated mitochondrial uncoupling to protect against ischemic damage in the brain. Perry et al. suggest that this uncoupling may

protect neurons from apoptosis, and along with blockage of K+ channels, tolbutamide, and agents like it such as the β-adrenergic agonist CL-316,243, which express endogenous uncoupling proteins, have potential as adjunctive therapies for HAD.

Estradiol, the most bioactive of the estrogens, has been observed in vitro to protect against the neurotoxic effects of HIV proteins by protecting the mitochondria of neurons through interactions with the mitochondrial enzyme ATP synthase, which is required for moving protons across the mitochondrial membrane, and, thus, normal mitochondrial functioning (81). This is perhaps the mechanism behind the estradiol-induced reduction of oxidative stress produced by gp120 and Tat as described in Wallace (79). These therapeutic properties of estradiol are being considered in terms of HAD therapy. Plant estrogens and selective-estrogen receptor modulators may be therapeutic substitutions for estradiol due to its cancer causing side effects.

Opioid agents that are κ- and δ-receptor preferring have been demonstrated as neuroprotective; however, opioids that preferentially bind to the mu-receptor contribute to the neurotoxic effects of gp120 and Tat, which just happens to include the opioids that are most commonly abused (79). For example, Wallace (79) describes U50,488, an agent that preferentially binds to the κ-receptor, as ultimately reducing excitotoxicity through the inhibition of NMDA receptors by suppressing quinolinic acid, an NMDA receptor agonist, released from microglia. Oxidative stress induced by Tat protein can be reduced by the δ- receptor agonist DPDPE. Research into δ and κ agonists may be a viable therapeutic option.

Kaul and Lipton describe nitroglycerin as a potential therapeutic agent (78). This substance produces nitric oxide-related molecules that can be converted chemically into a substance that resembles nitrosinium, which is one electron away from nitric oxide. This substance has been shown in animal models to protect neurons from NMDA receptor overstimulation and the resulting neuronal injury. However, more research into this potential adjunctive therapy would need to be conducted because of nitroglycerine's cardiovascular side effects.

Many of these potential adjunctive therapies for HIV-1-associated dementia are effective in their suppression of viral replication in the cells of the CNS or their direct protective actions on the neurons bombarded by the neurotoxic effects of HIV proteins. As researchers continue to understand the neurodegenerative properties of HIV-1 in the CNS, more avenues for potential therapeutic interventions will be elucidated.

At a time when HAD is becoming continuously more prevalent in the HIV population, there are still no effective treatments specific to this complicating side effect of HIV. Current research has focused on stopping the neurodegenerative and inflammatory cascade that HIV initiates. Although once hopeful that drugs such as psychostimulants, selegiline, and valproic acid were going to be helpful in eliminating HAD, their results were found to be insignificant and in some instances potentially iatrogenic. New studies focusing on drugs, such as minocycline and a variety of antioxidants, are promising, but further research is necessary to determine the efficacy of these drugs. Other studies are exploring the possibility of attacking the disease by focusing on chemokine receptors, neurotrophic factors, the mitochondria of

cells, and hormone therapy, but all remain in the preliminary stages of development and assessment. Considerably, more research is necessary to effectively treat this debilitating aspect of HIV and fortunately numerous trials are currently underway and offer some hope and opportunities.

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HIV-1 Genetic Diversity and Its Biological Significance

Michael M. Thomson

By means of high mutation and recombination rates, together with point introductions in different populations, HIV-1 pandemic strains have diversified extensively into numerous clades, including nine subtypes, at least 36 circulating recombinant forms (CRF), and diverse variants within subtypes and CRF. Differences between HIV-1 genetic clades on pathogenicity, transmissibility, and other biological features often have been difficult to prove, due to multiple factors, including large intrasubtype diversity, frequent recombination, and methodological issues. In spite of the difficulties and limitations of the studies, evidence of some associations of HIV-1 clades with biological features has been found.

HIV-1, the fastest evolving of known human pathogens, has diversified rapidly since the introduction of the ancestor of the pandemic strains among humans from chimpanzees in West-Central Africa (1) in the first half of the twentieth century (2). Phylogenetic analyses based on full genome sequences have allowed to classify HIV-1 pandemic viruses into discrete clades designated subtypes, subsubtypes, and CRF (3). Far from being constrained to a fixed taxonomy, HIV-1 continues to increase its genetic diversity by generating new variants through interclade recombination and point introductions in different areas. The study of HIV-1 genetic variability may be useful not only to track the epidemic spread of HIV-1, but it also may be relevant for viral pathogenesis, transmission, antiretroviral therapy, or vaccine development. Although some biological correlations of HIV-1 genetic clades have been demonstrated, much of the biological significance of HIV-1 genetic diversity may still remain to be defined. In this chapter, molecular mechanisms of HIV-1 genetic diversification, classification of HIV-1 genetic forms, geographical distribution of major clades, and their biological correlations, including differences in disease progression, transmission, and in vitro biological features, are reviewed. Other implications of HIV-1 genetic diversity, such as those related to immune responses relevant for vaccines, or response and resistance to antiretroviral drugs, have been reviewed elsewhere (4–6), and are beyond the scope of this chapter.

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Mechanisms of HIV-1 Variation

High genetic variability of HIV-1 derives from a combination of multiple mechanisms, including: (a) high mutation rates, derived from an error-prone viral reverse transcriptase (RT), which introduces mutations at an average of approximately one per genome per infection cycle (7), which remains uncorrected because of the lack of proof-reading activity of the viral enzyme; (b) elevated recombination rates, with an estimated average of nine template jumps by RT between both copackaged RNA genomes in T lymphocytes in a single round of replication (8); (c) rapid virus turnover all along the infection, with an estimated production of 10^{10} new virions each day and a mean generation time of 2–3 days (9). HIV-1 recombination rates in vivo are favored by the presence of two or more integrated proviruses in most infected lymphoid cells (10), and may exceed those of mutations in some patients (11, 12).

Viral variants generated through these mechanisms are subject to selective forces, mainly exerted, in the absence of antiretroviral therapy, by the immune system, both by cytotoxic T lymphocytes (CTLs) (13, 14) and, in the envelope, also by neutralizing antibodies (15, 16), which drive the expansion of variants containing escape mutations able to evade selective pressures. CTL escape mutations can be transmitted and remain stable over years (14, 17, 18), and may have contributed to the generation of HIV-1 diversity at a population level (13, 19–21).

HIV-1 diversification in a typical infected individual follows through a series of defined stages. During primary infection, prior to the induction of immune responses, viral populations are usually highly homogeneous (22). Subsequent diversification is driven mainly by immune responses, with genetic diversity increasing linearly (approximately 1% annually in the *env* C2-V5 region) during the period of immune competence, while more homogeneous populations and, eventually, lower diversification rates, develop at late stages, coinciding with the decline of efficient immune responses (23).

Classification of HIV-1 Genetic Forms

By means of high mutation and recombination rates, together with chance point introductions of variants in different populations (i.e., "founder events"), HIV-1 has diversified extensively into multiple genetic forms (3, 4, 24).

In the current classification (3), three phylogenetic groups, M (major), O (outlier) and N (non-M, non-O) are recognized, of which group M is responsible for the global pandemic. Group O viruses circulate only in Central Africa (mainly Cameroon and some neighbouring countries), where they represent a small minority (<1%) of HIV-1 infections (25). Only a few cases of group N infections, all in Cameroon, have been reported to date. The three HIV-1 groups derive from separate introductions from chimpanzees of the *Pan troglogdytes troglodytes* subspecies, inhabiting West-Central Africa (1, 26), although it is uncertain whether group O derives directly from West-Central chimpanzees, or gorillas, among which viruses related to group O have been found (27), served as an intermediate step in a transmission chain originating in chimpanzees. Within group M, nine subtypes are recognized,

designated A–D, F–H, J, and K. Initially subtype E was defined based on *env* sequences, although subsequently it was shown to be a recombinant form (28), currently named CRF01_AE, containing segments of subtype A and an unknown subtype. All subtypes are thought to have originated in Central Africa, with the probable exception of subtype B, which initially propagated in Haiti (29). In phylogenetic trees, subtypes form clusters approximately equidistant with each other, separated by 30–35% amino acid distances in *env*. Within A and F subtypes, subclusters are distinguished, designated subsubtypes A1 through A4 (although the subsubtype status of A3 is controversial (24)), and F1 and F2, respectively. Similarly to subsubtypes, B and D clades are also more closely related to each other than to other subtypes, but their subtype designation has been retained for consistency with earlier literature. Initial diversification of group M most likely occurred in the territory of the Democratic Republic of Congo (DRC), where the greatest HIV-1 group M diversity is found (30), and where the earliest HIV-1 specimens were collected (31, 32). Consistent with this hypothesis, phylogenetic trees of HIV-1 sequences from DRC

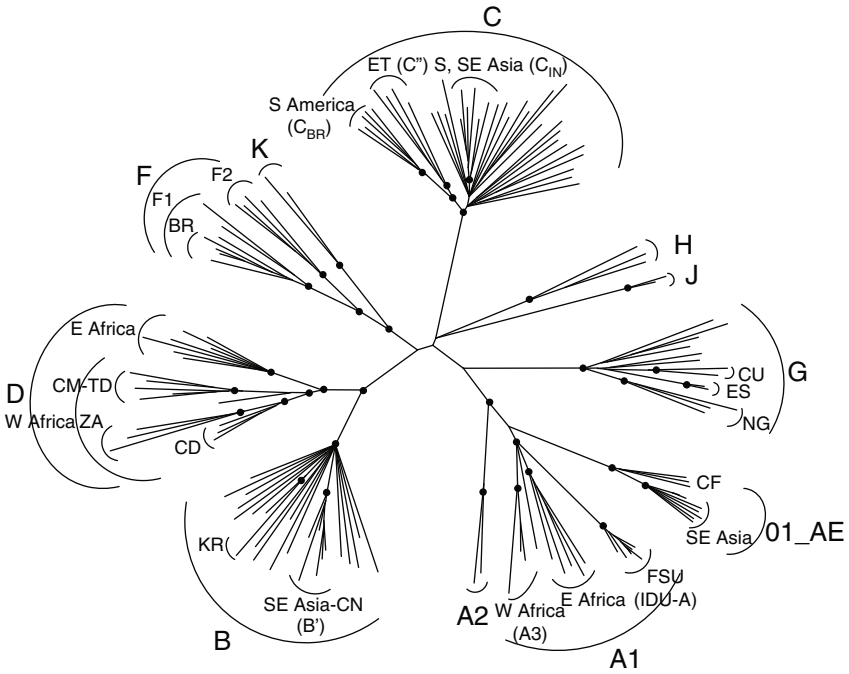

Fig. 1 Maximum likelihood tree of HIV-1 full-length genomes. Clusters corresponding to subtypes, subsubtypes, and geographic variants within subtypes and CRF01_AE are shown. The tree was constructed with Treefinder under the GTR + Γ + I substitution model, with assessment of reliability of tree topologies using 100 bootstrap replicates. Nodes signaled with a dot are supported by ≥90% bootstrap values. In *parentheses* are names given to variants of HIV-1 subtypes. *BR* Brazil; *CD* Democratic Republic of Congo; *CF* Central African Republic; *CM* Cameroon; *CN* China; *CU* Cuba; *ES* Spain; *ET* Ethiopia; *FSU* countries from the former Soviet Union; *IN* India; *KR* Korea; *NG* Nigeria; *TD* Chad; *ZA* South Africa

lack a well defined subtype structure, suggesting that HIV-1 subtypes derive from founder events involving early variants originating from DRC (33).

In areas in which multiple HIV-1 clades are cocirculating in the same population, intersubtype recombinant forms are frequently generated (24, 34), some of which have propagated epidemically. Recombinant forms identified in at least three epidemiologically unlinked individuals, characterized in full-length genomes, are designated CRF (3); these, in turn, may also generate other recombinant forms, including CRF, by successive recombination events (35, 36). Currently, 36 CRF have been reported in the literature, and near full-length genome sequences of 7 more putative CRF have been submitted to the Los Alamos HIV Sequence Database (http://www.hiv.lanl.gov/content/hiv-db/mainpage.htmlp). Some CRF have propagated extensively, such as CRF02_AG in West Africa (37), CRF01_AE in Southeast Asia (38), CRF07_BC and CRF08_BC in China (39), or CRF12_BF in Argentina (40–42).

During the course of their expansion, some HIV-1 subtypes and CRF have entered certain geographic areas or populations through single introductions, generating variants recognizable in phylogenetic trees as subclusters within a subtype or CRF (24) (Fig. 1). Such is the case, for example, of the subtype B and CRF01_AE variants introduced in Thailand among injecting drug users in 1988 and promiscuousheterosexuals in 1989, respectively (43, 44), the subtype C variant introduced in the mid 1980s in south India among commercial sex workers (45), or the subtype A variant introduced in Ukraine among injecting drug users (IDU) in 1995 (46, 47). These are variants that have propagated widely in the countries of introduction and in neighboring countries, although there are several others that have experienced a more limited propagation.

Geographic Distribution of HIV-1 Genetic Forms

Recently, a WHO/UNAIDS study estimating global distribution of HIV-1 genetic forms in 2004 has been published (48). The globally most prevalent clade was subtype C, responsible for approximately 50% infections worldwide, followed by subtypes A and B, representing 12% and 10% HIV-1 infections, respectively. Other genetic forms with more than 1% estimated global prevalences were subtype G (6%), CRF01_AE (5%), CRF02_AG (5%), and subtype D (3%). Recombinant forms collectively represented 18% infections. Globally less prevalent variants circulating as major clades in epidemics of some countries are CRF07_BC and CRF08_BC in China (39), CRF12_BF and related recombinants in Argentina and Uruguay (40–42), subtype F in Romania (49), CRF06_cpx in Estonia (50) and Burkina Faso (51), and CRF11_cpx in Central African Republic (52). A world map graphically representing the main HIV-1 clades circulating in each country is shown in Fig. 2.

Subtype C is predominant in Southern Africa, some countries of East Africa (Tanzania (53), Burundi (54), and Ethiopia (55)), India (56), and among Ethiopian immigrants in Israel (57), and is common in Southeast DRC (58), Sudan (59), Southern Brazil (60, 61), Myanmar (62), and Yemen (63). Subtype C viruses from India (56) (which have propagated to Nepal, Myanmar, and China), Brazil (60), and

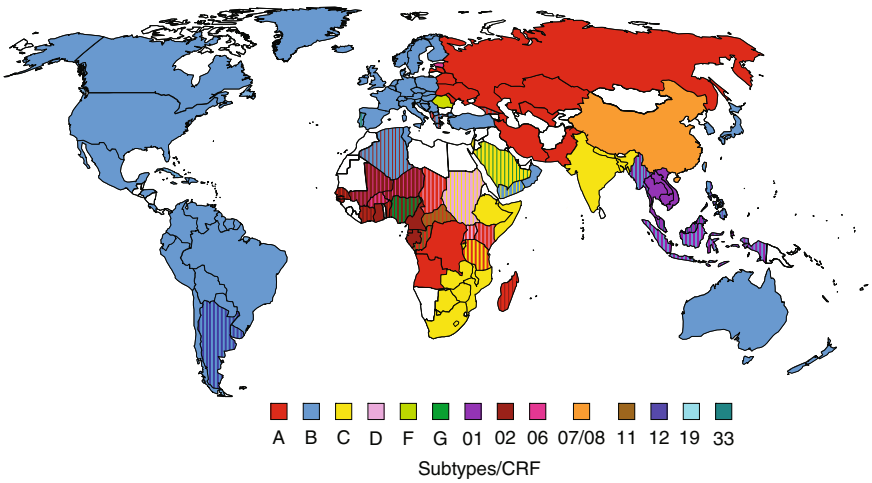

Fig. 2 Geographic distribution of main HIV-1 genetic forms. Only most prevalent genetic forms circulating in each country are indicated with the corresponding color . *Hatched patterns* indicate that a second genetic form is circulating in the country at a prevalence of ≥20%, with *thinner bars* representing the less prevalent form when present in 20–40%, and *thicker bars* indicating >40% prevalences. Subtype or CRF prevalences were determined including URF containing segments of the circulating clades. *White color* indicates no available data from that country. The map is based on published papers, complemented in some cases with information from sequences deposited at the Los Alamos HIV Sequence Database (*See Color Plates*)

some from Ethiopia (55) form three respecti ve monophyletic clusters within the subtype C radiation (Fig. 1), indicating that each represents a v ariant derived from a common ancestor. Subtype C viruses of Indian ancestry ha ve recombined with subtype B viruses of Thai origin to generate the main clades circulating among IDU in China, CRF07_BC and CRF08_BC (64, 65), of which CRF07_BF , has also caused a recent explosive outbreak among IDU in Taiwan (66).

Within subtype A, there are tw o major variants, both of subsubtype A1; one has spread in East Africa (Kenya (67), Uganda (68), Tanzania (69), and Rwanda (70), with the highest prevalence in Kenya, where it frequently recombines with subtypes D and C, and the other in former Soviet Union (FSU) countries (71), where it was introduced among IDU in Southern Ukraine in 1995 (46, 47), constituting the main HIV-1 genetic form in all FSU countries studied, except Estonia (where CRF06_cpx predominates (50)), propagating mainly among IDU. A third subtype A v ariant, designated subsubtype A3 by some authors (72), circulates as a minor form in some W est African countries (73). Subtype A is the most pre valent genetic form in DRC (30, 58) and the Republic of Congo (74), where it is frequently found in recombination with multiple subtypes and CRFs circulating in this area. Recent reports indicate that subtype A viruses are responsible for HIV-1 outbreaks among IDU in Iran (75) and Pakistan (76), and are highly pre valent among se xually infected persons in Albania (77) and among recent diagnoses in Greece (78).

Subtype B is the HIV -1 clade with the earliest epidemic propagation outside Africa and with the widest global geographical dispersal. It is the major clade in the

Americas, although in Cuba multiple variants of African origin and locally generated recombinants collectively predominate over subtype B (79, 80), and in Argentina and Uruguay CRF12_BF and related recombinants are highly prevalent (40–42). The second major area of subtype B distribution is Western and Central Europe, where it was introduced from the USA early in the AIDS epidemic. A subtype B variant was introduced in late 1980s among IDU in Thailand (43), although, since the mid 1990s, it has been replaced by CRF01_AE as the main genetic form transmitted in this population (81). The Thai subtype B variant is predominant in some areas of Myanmar (82) and of the South Chinese Yunnan province (83), is common in Malaysia (84), and originated the epidemic among blood donors in Central China (85). A local subtype B variant is circulating in Korea (86), and in Brazil, a subtype B serotype with a distinctive V3 crown tetrapeptide (GWGR) forming a monophyletic cluster in *env* (87) represents approximately 40% of subtype B infections (88). Subtype B is also predominant in Japan, Australia, and New Zealand, and among homosexual men in FSU and in South Africa.

Subtype G is the most prevalent clade in Northern Nigeria (89), the country with the largest HIV-1 infected population in West Africa. It is also relatively common in the Republic of Congo (74), and circulates as a minor form in other countries of Central and West Africa. A subtype G variant of monophyletic origin circulates widely in Portugal, transmitted via heterosexual contact and among IDU (90, 91), and also among a minority of IDU in Northwest Spain (92, 93). This variant has recombined with subtype B to generate CRF14_BG, which circulates at low prevalences in the Western Iberian peninsula (91–93).

Subtype D comprises two major variants, West-Central and East African (59, 94), of which the later has propagated to a greater extent, being predominant in Uganda (68) and relatively common in Kenya (67), Tanzania (69) and Sudan (59).

CRF01_AE, originating in Central Africa, circulates mainly in Southeast Asia, where, it was first introduced in Thailand among female prostitutes and their clients in 1989 (43, 44) and has subsequently spread widely to all countries of Southeast Asia, where it is the main circulating HIV-1 variant (38), and to areas of South China bordering Myanmar and Vietnam (95, 96). CRF01_AE viruses of Southeast Asian origin recently caused an outbreak among IDU in Finland (97).

CRF02_AG is the main genetic form circulating in most of West Africa (37), except northern Nigeria, where subtype G predominates (89), and some areas of Burkina Faso, where CRF06_cpx is more prevalent (51). CRF02_AG is also predominant in the West-Central African countries of Cameroon (98) and Equatorial Guinea (99).

In areas in which multiple HIV-1 genetic forms co-circulate in the same population, high frequencies of unique recombinant forms (URF) are found, generated in individuals infected with two or more of the locally circulating clades (24, 34, 100). The highest frequencies of URF (over 20%) have been reported in Central Africa, some countries of West Africa (Chad, Nigeria, Ghana, Niger, and Burkina Faso) and East Africa (Tanzania, Uganda, and Kenya), Argentina, Central Myanmar, and Yunnan province in South China. In Ethiopia, 40% viruses were reported to be intrasubtype recombinant between the local subtype C variant (C") and subtype C viruses of Southern African ancestry (C'). It should be noted that the proportions of URF reported in most studies

represent minimum figures, since usually only short genome segments are analyzed and only intersubtype recombination is examined. A recent study reporting intrasubtype recombination in 47% of South African subtype C genomes (101) indicates that recombination in HIV-1 may be much more common than previously estimated.

High prevalences of diverse HIV-1 African clades, mostly among heterosexually infected individuals, are found in several West European countries, such as United Kingdom (102), France (103), Belgium (104) or Portugal (90). However, except in Portugal, where subtype G circulates widely among the native population, most non-B clades are found in African immigrants infected in their countries of origin or in Europeans infected from African individuals.

Correlations of HIV-1 Clades with In Vitro Biological Features

The study of in vitro biological correlations of HIV-1 clades has not been undertaken in a systematic fashion, but rather has been focused on a few particular aspects of HIV-1 biology, mainly the activity of the transcriptional promoter at the 5′ long terminal repeat (LTR) and coreceptor usage, with a more limited number of studies on Tat function and replicative capacity ("fitness").

Viral Promoter Activity

This has been one of the most intensely explored areas of HIV-1 in vitro biology regarding variation among clades. However, results often have been contradictory, which may derive from diverse factors, including the use of different lymphoid and nonlymphoid cell lines, use of promoters from a single or a few isolates from each clade (which may yield results reflecting isolate-specific, rather than clade-specific, differences), or of reconstructed clade consensus sequences (which may differ from actual isolate sequences). Examination of HIV-1 LTR sequences reveals interclade variation in binding motifs for cellular transcriptional factors. One of the most notorious differences is in the number of NF-κB binding motifs just upstream of the transcriptional initiation site: while most clades contain two, most subtype C isolates have three, and CRF01_AE viruses have only one (105). Several studies have suggested that these differences result in different promoter activities. However, only one functional correlation has been uniformly reproducible by different authors in various T lymphoid cell lines, which is a reduced responsiveness of the LTR of CRF01_AE (LTR-E) to TNFα (106–110), a cytokine which enhances HIV-1 transcription by activating NF-κB. Lower promoter activation is reflected in reduced viral replication rates of CRF01_AE in the lymphoid SupT1 cell line in the presence of TNFα (111). Decreased TNFα responsiveness of LTR-E appears to result from the presence of a single NF-κB site, since it was also observed in response to intracellularly expressed Rel A/p65 subunit of NF-κB (105) and to other

stimuli known to activate NF-κB (109), and the response was partially restored by reconstituting the second NF-κB motif (106). Loss of the second NF-κB motif in LTR-E is compensated by its conversion to a GABP binding site, which may promote Tat-induced LTR activation in some cell lines (110, 112). Some authors have reported higher activation of LTR-C by TNFα (107) or NF-κB (105), which would derive from the presence of 3 NF-κB sites. It has been argued that this might contribute to higher efficiency of subtype C transmission through activation of viral replication by elevated TNFα levels in cervicovaginal secretions of women with sexually transmitted infections (107). However, others could not reproduce these results (108, 110). In fact, it was reported that the predicted extra NF-κB site of LTR-C fails to bind NF-κB, thus being functionally inactive (109, 113). Other reported associations of LTR activity with HIV-1 clades include greater responsiveness of LTR-B to NFAT compared with LTR-E or LTR-C (105, 110), and decreased responsiveness to Tat of the LTR-C relative to LTR-B or LTR-E (113).

Coreceptor Usage

Chemokine receptors CCR5 and CXCR4 are the major HIV-1 cellular coreceptors, with viruses using either CCR5, or CXCR4, or both (designated R5, X4, or R5X4 viruses, respectively) (114). Before the discovery of HIV-1 coreceptors, isolates were phenotypically characterized in MT-2 cell cultures as nonsyncytium inducing (NSI) or syncytium inducing (SI), which corresponds to CCR5-tropic or CXCR4-tropic viruses respectively, since MT-2 cells only express CXCR4. In initial studies in subtype B-infected patients, it was observed that in early and asymptomatic stages, viruses are almost uniformly of the SI (R5) phenotype, switching to the SI (X4 or R5X4) phenotype in late stages in approximately half of the patients (115). Subsequently, coreceptor switch was found to occur frequently also in other clades (116–118), except in subtype C isolates, among which this switch is uncommon (117–121) (although one study has reported 50% CXCR4-tropic subtype C viruses in antiretroviral treated – but not in untreated – patients in late stages (122)). Infrequent CXCR4 usage is a biological feature conserved in different subtype C variants from South Africa (120), India (121), Ethiopia (119) and Brazil (123). At the other extreme of subtype C, CRF14_BG viruses, which have a subtype B envelope inserted in an otherwise subtype G genome, and circulates as a minor form in Northwestern Spain and Portugal (91–93), are mostly X4 or R5X4 irrespective of disease stage (124), although longitudinal studies since seroconversion would be needed to confirm this observation. Frequencies of SI viruses in late disease greater than those described in subtype B have been reported also for CRF01_AE in Thailand (117, 125). V3 sequence features associated with coreceptor usage in subtype C, CRF01_AE, and Romanian subtype F differ from those described in subtype B (126–129). In the FSU subtype A variant, the consensus V3 sequences of NSI and SI viruses are indistinguishable, with SI viruses lacking features typically associated with SI phenotype in subtype B (130).

Tat Function

As in the case of the LTR studies, contradictory results on HIV-1 clade correlations have been reported with Tat function, possibly derived from similar methodological limitations. Tat of CRF01_AE (Tat-E) has been reported to be the strongest LTR transactivator compared with Tat from other subtypes (113, 131). Higher Tat-E efficiency was associated with longer half-life, more efficient interaction with TAR, and higher affinity to cyclin T1 compared with Tat-B or Tat-C (131). Other authors, however, have reported greater transactivating efficiency of Tat-C compared with Tat-B or Tat-E (132), or of Tat-C and Tat-B compared with Tat-E (133).

Clade-associated variability in some Tat-mediated effects on cellular genes and functions have also been reported. It has long been known that Tat-B is secreted extracellularly and induces the expression of diverse inflammatory cytokines, among them TNFα by activating its promoter (134). However, recent observations indicate that Tat-E inhibits TNFα gene transcription and protein expression in Jurkat T cells and has no effect on TNFα expression in a monocytic cell line, in contrast to Tat-B and Tat-C, which activate TNFα expression in both cell lines (135). This feature of Tat-E was mapped to W32 residue present in most Tat-E sequences. It was speculated that by inhibiting TNFα expression, and consequently NF-κB activation, Tat-E could promote the recruitment of GABP to its binding site in the LTR-E, thus activating transcription from the viral promoter.

Tat has been implicated in HIV-1 neuropathogenesis through the induction of inflammatory cytokines and promotion of monocyte migration to the brain (136–138). With regard to these activities, Tat-C, compared with Tat-B, has been shown to be defective at induction of chemotactic activity in monocytes (139), correlated with decreased induction of TNFα and CCL-2 (previously known as monocyte chemotactic protein-1) secretion from monocytes and with lack of intracellular calcium flux in these cells (140). These functional defects were mapped to C31S substitution present in 90% Tat-C sequences. Based on these results, it was proposed that the defective chemotactic monocyte activity of Tat-C could contribute to the reported low prevalence of HIV-1 associated dementia in India (141, 142). More recent studies, however, have found frequencies of neurocognitive deficiency in HIV-1 infection in India (143–145) and in South Africa (146) similar to those of Western countries.

Replicative Capacity ("Fitness")

In in vitro pairwise competition assays using primary CD4+ T lymphocytes, R5 subtype C primary isolates from different geographic origins (Nigeria, South Africa, and India) consistently displayed slower replication kinetics than R5 subtype B viruses (147). No differences were found in cocultures of CD4+ T lymphocytes and skin-derived Langerhans cells. Viruses of subtypes A, B, and D, and CRF01_AE showed similar replication kinetics (148). The authors suggested that slower

replicative kinetics of subtype C in CD4+ lymphocytes might result in longer survival, thus increasing the chances of transmitting the virus and contributing to the greater global expansion of subtype C. However, disease progression has been reported to be similar between subtypes A and C in Tanzania (149), and in South Africa, where subtype C predominates, survival in HIV-1 infected patients is similar to Western countries (150). In similar experiments, HIV-1 group O and HIV-2 viruses displayed typically 100-fold less replicative capacity than group M viruses, both in peripheral blood mononuclear cells and in cocultures of dendritic cells with primary quiescent T cells (148), a result which correlates with the much more limited propagation of the group O and HIV-2 viruses. In other studies, CRF02_AG viruses showed higher replicative capacity than subtype A or G viruses, independently of disease stage or coreceptor usage (151, 152), which correlates with the greater expansion in West Africa of CRF02_AG relative to its parental subtypes.

Correlations of HIV-1 Clades with In Vivo Viral Biology

Several studies have found associations of HIV-1 clades with plasma viral loads, disease progression, and transmission.

Plasma Viral Loads

Lower viral loads in the first month after seroconversion have been reported in subtype C infections in Ethiopia compared with subtype B infections in Dutch individuals in the Netherlands, although the difference could be attributable to lower average CD4+ cell counts among HIV-1 seronegative Ethiopians, rather than to clade biological differences (153). In this study, postseroconversion viral loads were on average one log lower in infections with C' viruses (related to South African viruses) than with viruses of the local C" variant, as determined in the V3 *env* region. In another study in Southern Africa, plasma viremia within the first 2 years of infection did not differ significantly from that found in subtype B (154).

Two studies have found higher plasma viral loads after seroconversion in IDU infected with CRF01_AE than with subtype B. In the first study, in Thailand, median plasma viremia was three times higher in CRF01_AE than in subtype B infections in the first month after seroconversion (155). In Finnish IDU infected with CRF01_AE, higher viral loads were observed from 12 to 48 months postseroconversion, compared with subtype B infections among IDU from Amsterdam (156).

In Ghana, increased viral loads have been reported in early CRF02_AG infections compared to infections with other genetic forms circulating in the country (mostly subtypes A and G, and secondary recombinants of CRF02_AG) (157). Similarly, in Senegal, viral loads in primary infection were found to be higher in infections with CRF02_AG than with other clades (158).

Disease Progression

Infections with HIV-2, compared to HIV-1 infections, clearly result in slower disease progression (159), which is associated with lower plasma viral loads (160, 161), and reduced in vitro replicative fitness (148). By contrast, differences between HIV-1 group M clades have been more difficult to prove.

Among seroprevalent infections, similar progression rates have been reported among different ethnic groups residing in one country and harboring diverse HIV-1 clades, such as sub-Saharan Africans and native Europeans in Sweden (162) and England (163), and Ethiopian immigrants and non-Ethiopians in Israel (164).

The first study reporting differences in disease progression between HIV-1 clades was done in Senegal among female sex workers followed since seroconversion (165) .The results indicated that infection with viruses bearing subtype A envelopes, compared to infections with viruses with envelopes of other subtypes (D, G, or C) considered collectively, was associated with an eightfold reduction in progression to AIDS. The results, however, may be considered as inconclusive because of the low numbers of women who developed AIDS and of infections with each of non-A subtypes. In addition, subsequent studies have shown that most A^{env} viruses in Senegal are in fact CRF02_AG viruses (37). A more recent study in Cameroon and Senegal (166), using a much larger number of patients with unknown dates of infection, failed to reveal significant differences in disease progression between CRF02_AG and other clades, adjusting for age, baseline CD4+ cell count, and clinical stage.

Several studies in East Africa have revealed evidence of faster disease progression in subtype D than in subtype A infections among adults. Differences were found in Uganda (167, 168), Tanzania (149), and Kenya (169). In two of the studies the subjects were followed since seroconversion (168, 169). In the Tanzanian study, progression in infections with subtype C and recombinant viruses did not differ from subtype A infections (149). In Kenya, differences in progression were not attributable to differences in viral load (169), whereas in Uganda faster disease progression in D^{env} infections was associated with earlier switch to CXCR4 coreceptor usage (170). In contrast to studies in adults, no differences between subtypes were found in survival among children in Uganda perinatally infected with subtypes A and D (171) .

Three studies in Brazil have found slower disease progression among infections with viruses of the B_{Br} serotype, bearing GWGR in V3, than among infections with subtype B viruses bearing the typical subtype B V3 crown tetrapeptide sequence GPGR (172–174), although in one study the association was found only among women. However, in none of the studies infections were followed since seroconversion.

Transmission

Lower transmission rates have been demonstrated for HIV-2 than for HIV-1, both via heterosexual contact (175, 176) and from mother to child (177), which may be

related to lower viral loads (160, 178). However, differences in transmission among HIV-1 group M clades have not been demonstrated conclusively.

Heterosexual Transmission

Two reports from Thailand suggested higher rates of heterosexual transmission for CRF01_AE, compared with subtype B in Western countries, both from female to male (among military conscripts mostly infected from female prostitutes)(179) and from male to female (among women infected from their male sexual partners), (180). The difference in both studies persisted in the absence of other sexually transmitted infections (STI). However, factors other than genotype could have influenced the results (181), such as frequency of condom use, of STI among prostitutes (in female to male transmission), or the incidence of acute infections (which is associated with increased HIV-1 transmission) during the study period. In another study in Thailand among heterosexual couples, CRF01_AE was associated with higher seroconcordance rates than subtype B. However, different clades in men were associated with different risk groups, with most CRF01_AE infections acquired from female prostitutes and subtype B found mostly among IDU. Presumed increased heterosexual transmission of CRF01_AE relative to subtype B was attributed to differences in replication efficiency in Langerhan's cells (182), but this could not be reproduced by otherauthors (183, 184). In Uganda, a prospective study among monogamous heterosexual HIV-discordant couples found no association between A and D serotypes and frequency of transmission per coital act (185). No study examining the relative efficiency of heterosexual transmission of subtype C, the globally most prevalent clade, has been published, although a higher frequency of vaginal shedding of HIV-1-infected cells among pregnant women in Kenya infected with subtype C than among those infected with subtypes A or D has been reported (186).

Transmission by Needle Sharing Among IDU

In Bangkok, Thailand, a significantly higher probability of transmission per needle sharing among IDU was associated with CRF01_AE compared to subtype B infections, controlling for behavioral risks (187). However, the authors could not exclude the influence of nonviral factors, such as unequal distribution of HIV-1 genotypes among active needle-sharing networks or differences in incidence of acute infections with either genetic form during the study.

Mother to Child Transmission (MTCT)

The largest study on the correlation of HIV-1 subtype on MTCT was carried out in Kenya, involving 414 mothers, of which 80 transmitted HIV -1 infection (188). In multivariate analysis, adjusting for viral loads and other factors, subtype D or AD

recombinant viruses (as determined in gp41 and $p24^{gag}$), were associated with higher MTCT rates compared with nonrecombinant subtype A viruses. In another study in Kenya, however, no difference was found in MTCT between subtypes A and D, as determined in gp120 (189). In Tanzania, subtype C and intersubtype recombinant viruses, analyzed in $p24\text{-}p7^{gag}$ and gp120 (190), or in LTR fragments (191), were associated with increased MTCT rates compared with subtype D. In Brazil, no difference in MTCT rates was found between subtypes B and C (192). Other studies in Tanzania (193) and Ghana (194) failed to reveal associations of subtypes with MTCT rates, although the number of transmitted infections were too low for detection of minor differences. Timing of MTCT transmission and its correlation to subtype was examined in two studies in Tanzania. One revealed that subtype C^{env} was preferentially transmitted in utero (vs. *intrapartum*) compared to subtypes A or D (195). In the other study, intersubtype recombinant viruses were transmitted more frequently during breastfeeding than viruses of nonrecombinant subtype C, or of subtypes A, C, and D combined, as determined in fragments of *env* and the LTR (196).

Concluding Remarks

Biological differences between HIV-1 clades have often been difficult to prove, which seems counterintuitive in view of the great genetic diversity among HIV-1 subtypes. Difficulties in obtaining conclusive results derive from multiple factors, some related to virus genetics and others to methodological issues. Although HIV-1 genetic diversity within group M is large, and increasing over time, intersubtype biological differences do not increase in parallel with growing distances between viruses of different subtypes. These differences were already established at the time of origin of subtypes, and should not be expected to increase with time, since biological features characteristic of a subtype are those derived from its most recent common ancestor that have been preserved among a majority of viruses along subtype diversification. Thus, it is even possible that a clade-specific biological feature is lost if, as a consequence of stochastic events, such as transmission bottlenecks, it is lost in a major variant originated during clade diversification. In this respect, it is important to note, that, according to molecular clock estimates, current intrasubtype genetic distances might exceed intersubtype distances existing when subtypes originated (29, 101, 197). Another factor to consider is the great frequency of interclade recombination, particularly visible in areas in which multiple HIV-1 variants are cocirculating in the same population. These areas (such as East Africa) have frequently been used for studies on biological correlations of HIV-1 subtypes. One factor complicating the interpretation of studies in these areas is that analyzing subtypes in only one or two short genome segments, as is usually done, may be insufficient for the genetic characterization of the virus, given the pervasiveness of recombination. In fact, in one study in Tanzania on HIV-1 transmission through breastfeeding, results were discordant when different genome segments were analyzed (196). A third factor to consider is the existence of different variants within subtypes, which may differ

in their biological features. Some possible variant-specific biological features have been reported in subtype B in Brazil (172–174), subtype C in Ethiopia (153), and subtype A in FSU (130). With regard to studies on transmission, all have compared HIV-1 clades which have spread widely, and which therefore are known to be transmitted efficiently. Differences would be expected to be more easily demonstrable by comparing globally predominant HIV-1 clades with others that have propagated little (such as subtypes H, J, and K, and some "old" complex CRF of Central African origin). Since both transmission and progression correlate with viral loads (198, 199), a similar logic would be applicable to studies on HIV-1 progression. The difficulty in these studies is recruiting sufficient numbers of individuals infected with the genetic form of low prevalence.

With respect to published studies on in vitro biological correlations, there are other methodological issues that may limit the significance of results, as mentioned previously, such as the use of genes or regulatory elements derived from only one or a few isolates from each clade, or differences between cell lines (111).

In spite of difficulties and limitations of the studies, there is reproducible evidence of some HIV-1 clade-associated biological features, such as the lower frequency of CXCR4 coreceptor usage among subtype C viruses, reduced responsiveness of the CRF01_AE transcriptional promoter to TNF α and NF-κB, decreased replicative capacity of R5 subtype C viruses in primary CD4+ T lymphocytes, or more rapid disease progression in infections with viruses of East African subtype D (compared to East African subtype A) variants, which convincingly show that HIV-1 clades do differ in biological properties. Although beyond the scope of this chapter, correlations of HIV-1 subtypes with susceptibility to cellular (200–202) and humoral (203) immune responses and with development of antiretroviral drug-associated resistance mutations (5) have also been reported. These results underscore the importance of continuing and expanding the studies on in vitro and in vivo biological correlations of HIV-1 genetic clades, an area of research which still remains insufficiently explored and in which a major scaling up of efforts would be necessary in the global combat against the disease and the pandemic.

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Opportunistic Infections in the Brain in Developing Countries

Marcus Tulius T. Silva and Beatriz Grinsztejn

Introduction

Since the early stages of AIDS epidemic in the developed world, it has been reported that the nervous system is affected both directly and indirectly by HIV infection (1). Health professionals involved in HIV care recognize that at least one-third of patients with advanced AIDS have some neurologic impairment, and almost 50% will present one or more neurologic complication during the course of HIV disease (2, 3). Several autopsy studies in HIV population show that more than 80% of patients have some nervous system disease (4).

Although less reported in the initial phase of the HIV epidemic, neurologic complications in AIDS patients from developing countries are also quite common. Globally, 40 million individuals are living with HIV in the world, 24.5 million of these in sub-Saharan Africa (www.who.int). From 1980 to June 2006, 433,000 AIDS patients were registered in the database of the Brazilian Ministry of Health (www.aids.gov.br). Unfortunately, the situation is not different in other developing countries, with an increasing number of HIV/AIDS cases each year. Considering that highly active antiretroviral therapy (HAART) access, diagnostic tools, and proper opportunistic infection treatment are not uniformly available in poor countries, we can expect that neurologic diseases associated with HIV infection will have a considerable social and economical impact in these areas.

It is clear that HIV disease is essentially the same in any country, although the course of HIV-2 disease – seen in some places of Africa – appears to be associated with a slower disease progression and to be less severe than HIV-1 disease. However, regarding neurologic diseases associated with AIDS it is possible that some differences

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between developed and developing countries exist. The prevalence and importance of some pathogens vary considerably from the developing to the developed world, changing therefore the pattern of neurologic complications in these regions. Neurotuberculosis, for example, is the most common neurologic complication associated with a focal brain lesion in some developing countries, while cerebral toxoplasmosis is the first one in the developed world. Chagas' diseases, malaria, and paracoccidioidomycosis are other examples of endemic diseases that could have some impact upon neurologic manifestations of AIDS in specific places. These differences are of clinical importance, as people may migrate from poor endemic areas to developed countries, and also to proper management of brain lesions in patients from developing world. For example, it is believed that any focal brain lesion in patients with advanced AIDS is cerebral toxoplasmosis until proved otherwise. This could be true to the majority of countries from the developed and even from the developing world, but not to all (see below). If we strictly adhere to available guidelines from developed countries, a large number of patients from the developing world will be inappropriately managed. This chapter will discuss some infections in the brain and their management in AIDS patients from the developing world.

A Special Consideration in Limited-Resources Areas

Physicians from developing countries involved in HIV care frequently have difficulties to reach a confirmed diagnosis in patients presenting with neurologic syndromes. Unfortunately, an absolute lack of diagnostic tools is the rule in many countries. A recent medical management review done at a hospital in Uganda showed that physicians tended to perform lumbar puncture in patients with acute neurological dysfunction 2.5 days after admission (5). The main reasons for failure or for delayed lumbar puncture were the absolute lack of needles and bottles and limited working hours of the laboratory staff.

Clinical algorithms from developed countries include brain CT scan before lumbar puncture in all AIDS patients presenting with an acute neurological disease. If possible, it is a good practice to submit any patient with probable focal brain lesion to a brain CT scan before lumbar puncture. However, a real difficulty in a normal workday of physicians from some limited-resources area is the lack of any brain imaging study. In some cases it may be difficult to differentiate a focal from a non-focal brain lesion caused by cerebral toxoplasmosis and tuberculous meningitis. For instance, sometimes, cerebrospinal fluid (CSF) analysis is the only neurologic investigative tool available. The decision to not perform a lumbar puncture due to fear of complications in a patient with neurologic dysfunction associated with AIDS could result in delay of diagnosis and inadequate treatment. Even in the presence of a cerebral mass, uncal or tonsillar herniation leading to neurologic deterioration or death is quite uncommon. For example, in a series of 447 lumbar punctures performed on 401 patients with neoplasm, some complication was observed in only one (6). In a metanalysis including 418 patients with papilledema, complications due to lumbar puncture occurred in only

1.2% (7). When the presence of increased intracranial pressure is suspected, a bolus dose of mannitol (1 g/kg of body weight) can be given intravenously and lumbar puncture can be performed 20 min later (8). Performing a lumbar puncture without a previous CT scan in a resource limited setting could be more appropriable than treating patients empirically for two or more possible diseases.

Parasitic Infections

Toxoplasmosis

Toxoplasma gondii, the etiologic agent of toxoplasmosis, is an intracellular parasite for which the domestic cat, a few other mammals, and some ground-feeding birds are the primary hosts. Man, one of the alternative host, acquires infection most frequently by ingestion of both oocysts in contaminated food or water and bradyzoites in uncooked, contaminated meat. Primary infection is more often asymptomatic or results in a mononucleosis-like syndrome in immunocompetent individuals. Soon after primary infection, toxoplasmosis remains quiescent in any nucleated cell.

Antitoxoplasmic antibodies prevalence in both the general population and HIV-infected patients varies according to the region studied and reflects culinary and hygienic habits. It is estimated that in Latin America the seroprevalence approaches 70% in the general population (9). Seroepidemiological studies demonstrate prevalence of 80% in Iran (10), 19% in Turkey (11), 5.17% in China (12), and 0.79% among pregnant woman in Korean (13). Interestingly, 21% of children less than 5-years old in the Democratic Republic of Sao Tome and Principe were positive to anti-*T.gondii* (14). Regarding HIV-infected patients, the available studies show a prevalence of 71% in Brazil (15), 55% in Colombia (16), 54% in Uganda (17), 38% in Nigeria (18), 28% in Burkina Faso (19), and 10.2% in Taiwan (20).

Cerebral toxoplasmosis, one of the most common neurologic diseases in AIDS patients – even in some developing countries -, almost always result from recrudescence of latent infection acquired earlier in life. Its incidence is directly associated with the seroprevalence of anti-*T.gondii* in the general population. It is the most common cause of focal brain lesion in Brazil, being diagnosed in 25–68% of AIDS patients presenting some neurologic dysfunction (9, 21). Other papers from developing world about neurologic diseases among HIV-infected patients shows that cerebral toxoplasmosis is seen in 19% of cases in Republic of Cameron (22), 19% in Mexico (23), about 15% in the Western African (24), 12% in some parts of India (25), and in 4% of the children in Abidjan (26). It is expected that about one-third of HIV-infected people with past *T. gondii* infection develop cerebral toxoplasmosis. For instance, 25% of HIV-infected patients in Brazil with positive anti-*T.gondii* antibodies developed cerebral toxoplasmosis during the course of HIV disease (15).

As in the developed world, headache, seizures, motor impairment, and deterioration of mental status evolving acute or subacutely are the main neurologic findings.

Presumed diagnosis is based on a compatible clinical presentation, CD4+ count less than 100 cells/mm^3, typical abnormalities on brain images, and presence of anti- *T. gondii* antibodies indicating past exposure.

The typical features on CT scan are hypodense, multiple ring-enhanced lesions with surrounding edema and mass effect (Fig. 1a). Ring-enhancement depends on the presence of reactive cells in the lesions. The lack of reactive cells and, consequently, of ring-enhancement is considered a marker of poor prognosis. Expansive lesions without contrast enhancement were seen in 16% of cerebral toxoplasmosis patients from Brazil, being associated with severe immunodepression and poor outcome (27). Unfortunately, MRI, which is more sensitive than CT scan, is not available in most developing countries as effortlessly as in developed countries.

Less than 6% of AIDS patients with cerebral toxoplasmosis had negative anti-*T.gondii* antibodies in a Brazilian series (27). However, in the developed world – where brain biopsy is a vailable more easily than in de veloping countries – 22% of patients with cerebral toxoplasmosis confirmed by biopsy had negative *T.gondii*-IgG antibodies (28). So, the absence of serum antibodies should not exclude the

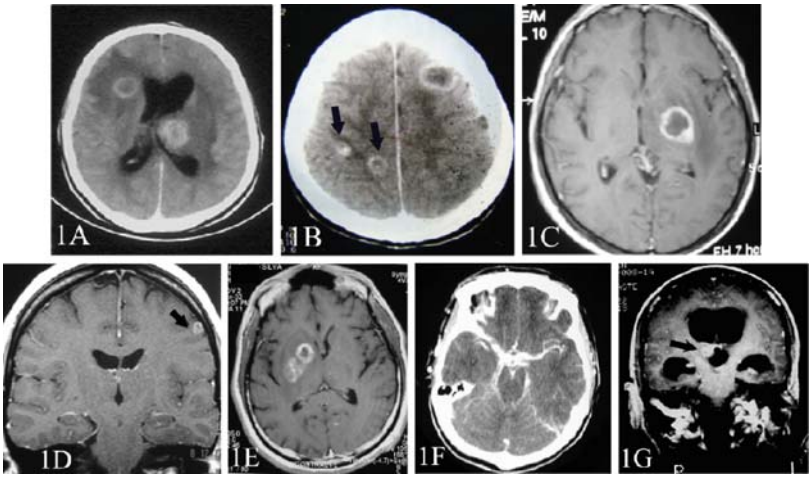

Fig. 1 (**a**) CT scan showing typical hypodense, ring-enhanced lesions of cerebral toxoplasmosis in right anterior limb of internal capsule and left thalamus; (**b**) CT scan showing cystic lesions of neurocysticercosis at cortical–subcortical junction with ring-enhancement. A nodular enhancement inside the cyst corresponding to the scolex is seen in two lesions (*arrows*); (**c**) axial gadolinium-enhanced T1-weighted MRI scan showing left parietal lesion with mild mass effect, perilesional edema, and ring-enhancement in AIDS patient with cerebral Chagas' disease (*Courtesy of Dr. Marcelo Corti, HIV/AIDS Division, Infectious Diseases F. J. Muñiz Hospital, Buenos Aires*); (**d**) gadolinium-enhanced T1-weighted MRI scan showing cryptococoma (*arrow*) and mild meningeal enhancement in a patient with cryptococcal meningitis; (**e**) axial gadolinium-enhanced T1-weighted MRI scan showing two contiguous lesions in right parietal lobe in a man with cerebral paracoccidioidomycosis; (**f**) CT scan showing gross meningeal enhancement in a patient with tuberculous meningitis; (**g**) coronal gadolinium-enhanced T1-weighted MRI scan showing a tuberculoma (*arrow*) and hydrocephalus in a AIDS patients with neurotuberculosis

diagnosis of cerebral toxoplasmosis in the context of a typical clinical picture jointly with classical brain images. The lack of toxoplasmosis prophylaxis history is considered indicative of probable cerebral toxoplasmosis.

The main differential diagnosis of cerebral toxoplasmosis in some developing countries is neurotuberculosis, especially in endemic areas. In Soweto, South Africa, neurotuberculosis was the final diagnosis in 69% of 32 consecutive HIV-infected patients with focal brain lesions (cerebral toxoplasmosis corresponded to only 3% of the cases) (29). Interesting, none of the patients were on prophylactic treatment for *Pneumocystis carinii* or toxoplasmosis. In Bangalore, India, 30% of patients with some neurologic disorder had neurotuberculosis, and only 4% of them had cerebral toxoplasmosis (30). The presence of basal meningeal enhancement on brain images, evidence of pulmonary tuberculosis on chest film, acid-fast bacilli on sputum microscopy, and typical CSF abnormalities (increased protein, decreased glucose, and pleocytosis) are indicative of neurotuberculosis. Other alternative differential diagnoses in an appropriated setting are Chagas' disease, neurocysticercosis, intracranial brain abscesses, and paracoccidioidomycosis.

Cerebral toxoplasmosis has considerable associated morbidity and mortality. In a recent series from Brazil, 13% of patients died in the sixth week of treatment (27). Associated factors related to poor outcome were alteration of consciousness level, fever, multiple lesions on brain scan, CD4+ lymphocytes count less than 24%, Karnofsky scale less than 70, seizures, and atypical brain scan abnormalities.

Treatment should include pyrimethamine, sulfadiazine, and folinic acid. Pyrimethamine is administered orally in an initial loading dose of 200 mg followed by 50–75 mg/day, and sulfadiazine at 4–6 g/day divided in four doses. Folinic acid at 5–10 mg/day is needed to diminish bone marrow suppression. Some alternative drugs to sulfadiazine are clindamycin, azithromycin, and doxycycline. Secondary prophylaxis with trimethoprim–sulfamethoxazole must be maintained until CD4+ count rise up to 200 cells/mm^3.

Cysticercosis

Neurocysticercosis is the most frequent helminthic infection of the central nervous system (CNS) and the commonest cause of acquired epilepsy in the world. It is caused by the encysted larva of the pork tapeworm *Taenia solium*, which can remain latent for years in the brain parenchyma. Symptoms usually coincide with larval death and subsequent intense inflammatory reaction induced by larval antigens. Then, the cyst transforms into a granuloma that shrinks and eventually calcifies or disappears completely.

Cysticercosis is endemic in developing countries of Latin America, Asia, and Africa. Cysticercosis occurs when humans act as intermediate hosts by accidental ingestion of *T. solium* eggs from food – mainly fruits and vegetables – contaminated with feces of human carriers of adult cestodes. The ingestion of cysts present in uncooked, contaminated pork meat results in taeniasis, and not in cysticercosis.

Although neurocysticercosis is not considered a classic neurologic opportunistic infection in AIDS patients, the increasing frequenc y of HIV infection in c ysticercosis endemic areas will render this coinfection to be more frequent. F or instance, neurocysticercosis has been associated with up to 27% of brain lesions in HIV - infected individuals presenting with neurologic symptoms in South Africa (29). However, little is known about the influence of HIV infection on the frequency and clinical course of neurocysticercosis. It is unlikely that HIV infection increases the frequency of neuroc ysticercosis, but AIDS could potentially influence its clinical course. Theoretically, clearance of invasive larvae by immune response at an early stage of *T. solium* infection could be decreased in HIV-infected patients leading to a higher chance for cysticercosis development in HIV-positive compared with HIV-negative patients. Also, the symptoms of neuroc ysticercosis depend more on the host cell-mediated immune response than on the parasite itself (31). Hence, its clinical course could be dif ferent in an immunodepressed setting. It has been reported that giant cysts and racemose forms of neurocysticercosis are more frequent in HIV-infected patients than in HIV-negative patients (32–34). This could be due to an uncontrolled parasitic gro wth secondary to impaired cell-mediated immune response. Furthermore, cases of unusually se vere and disseminated c ysticercosis have been reported in patients with hematological malignancies (35). Together, these reports show that immunodepression alters the clinical course of neuroc ysticercosis. Another interesting and not yet studied issue is the influence of HAAR T on neurocysticercosis course. It cannot be e xcluded that neurocysticercosis can be paradoxically worsened during the immune reconstitution period (36).

Sometimes it is difficult to discriminate a focal brain lesion due to neurocysticercosis from cerebral toxoplasmosis or even neurotuberculosis, the main differential diagnosis (Fig. 1a, b). An additional practical challenge is that approximately one-third of patients with neurocysticercosis and HIV infection could present with at least one other neurologic infection at the same time (36). The clinical manifestations of neurocysticercosis depends not only on the number , size, and location of the brain lesions but also on the intensity of the host immune response (31). Typically, symptoms begin years after initial infection, when host inflammatory response de velops against *T. solium* antigens released after the death of the parasite. Seizures are by far the most common neurologic manifestation, but others symptoms such as headache, motor deficits, and ataxia may be present. Recently, a review showed that 27 cases of neurocysticercosis in HIV-infected patient were reported in the literature. The most frequent presentation was multiple parenchymal lesions (enhanced or nonenhanced cysts), seen in 61% of cases. Other presentations included single parenchymal lesions (17% of cases), atypical forms such as a giant brain cyst and spinal epidural lesion (9%), and mixed forms (parenchymal, subarachnoidal, and ventricular, corresponding to 13% of cases). In 30% of patients another concomitant cerebral infec tion was diagnosed (36) .

Definitive diagnosis is made if (1) there is histopathologic e vidence of neurocysticercosis (brain biopsy is not al ways available in developing world), or (2) a scolex within a c ystic lesion is visible on brain CT or MRI (the last one is more sensitive but almost never available in poor countries), or (3) a suggestive lesion of

neurocysticercosis or a clinical response to treatment is added to serologic evidence of *T. solium* infection by CSF ELISA (37). In a series, more than one-half of patients had a positive cysticercal serology, which underscores its importance for the noninvasive diagnosis of the infection (36). However, 50% of patients with solitary parenchymal lesions are serone gative. This is especially problematic in India, where the majority of patients have single enhancing lesions (37), neurocysticercosis is endemic, and where neurotuberculosis is one of the most common neurologic manifestations in AIDS patients. Imaging and clinical features of cerebral tuberculoma are sometimes very similar to that of neuroc ysticercosis and it is quite difficult to differentiate one from the other. Moreover, because of the high prevalence of both conditions, the presence of these two disorders can occur in the same patient. Generally, neurocysticercosis lesions are usually round in shape, 20 mm or less in size, with ring-enhancement or visible scolex (Fig. 1b), and cerebral edema is severe enough to produce midline shift. Neurologic deficits are not seen in all cases. Cerebral tuberculoma is usually irregular, solid and greater than 20 mm in size, often associated with severe perilesional edema and a focal neurologic deficit (38). Another important differential diagnosis is cerebral toxoplasmosis, which preferably involves subcortical structures as thalamus, basal ganglia, and cerebellum, while in neurocysticercosis the lesions are characteristically located at the cortical–subcortical interface.

Treatment of neuroc ysticercosis can be done with albendazole (15 mg/kg/day for 7–21 days) or praziquantel (50 mg/kg/day for 14 days). Steroids can be used in some cases to prevent neurologic complications produced by edema following the antigens' exposure after the c ysticercus's death. The response rate to c ysticidal therapy in HIV patients is about 85%, similar to that reported in the literature for the general population (36).

Malaria

As with neuroc ysticercosis, malaria is not an opportunistic infection b ut will be briefly discussed here because there is e vidence that HIV infection has a ne gative impact on its natural history, which could predispose HIV-infected patients to cerebral malaria.

The intracellular protozoan *Plasmodium sp.* is the etiologic agent of malaria, being transmitted to mammalians by the female of *Anopheles* mosquito. Any of the *Plasmodium* species can cause malaria (*P. falciparum*, *P. ovale*, *P. vivax*, and *P. malariae*) but most severe cases, as cerebral malaria, are associated with *P. falciparum*.

The importance of HIV–malaria coinfection is ob vious since almost 90% of the annual 300 million infections tak e place in sub-Saharan Africa, where about 24 million people are living with HIV today (39). Other possible convergence zones for HIV and *Plasmodium sp* are located mainly in Haiti and Latin America, e ven though in this last one *P. vivax* is more common. Although seminal papers did not

find any association (40), recent reports have demonstrated that the course of malaria can be altered by HIV infection and *vice-versa*. This is particularly true to pregnant women and patients with advanced AIDS. HIV-infected patients have 2.3 more chance for severe malaria, as cerebral malaria, and 7.5 more chance for fatal outcome than HIV-negative patient (41). Other reports have also demonstrated that clinical severity of malaria worsens with advanced immunosuppression (42–44). On the opposite side, malaria appears to alter HIV viral load, which theoretically could have an impact on HIV disease. Plasma HIV levels were tested in coinfected patients at baseline, during malaria, and post-malaria: HIV-1-RNA concentration was twice between baseline and parasitemia, falling to baseline levels two months later (45). Interestingly, patients who remained aparasitaemic showed no changes in HIV-1-RNA concentration.

Cerebral malaria is defined as impairment of consciousness varying from somnolence to unarousable coma and hyperparasitemia (>4%; in hyper or holoendemic areas, 20% or more) (46). Diagnosis is not easy in some situations because malaria may mimic many infections of the CNS and the demonstration of the parasite in the blood is sometimes hard. Classically, patients present fever, severe headache, delirium, and progressive stupor. Occasionally, focal neurologic manifestations may occur. Systemic features that corroborate the diagnosis of cerebral malaria are splenomegaly, hepatomegaly, severe anemia, icterus, and surface-core temperature dissociation. Hypoglycemia may be encountered and can indicate a poor prognosis. Seizures can also be seen in some cases, especially in children. Mortality rates can reach up to 30% in some series (47).

The Brazilian Ministry of Health recommends as first line therapy intravenous artesunate (loading dose of 2.4 mg/kg followed by a dose of 1.2 mg/kg in 4 h, 24 h, and 48 h later) or intramuscular artemeter (3.2 mg/kg in the first day followed by 1.6 mg/kg each day for 4 days). After this, clindamycin (20 mg/kg for 5 days divided in two doses) or doxycycline (3.3 mg/kg/day divided in two doses for 5 days) are used. Alternative drugs to artesunato and artemeter are intravenous quinine with or without intravenous clindamycin (48).

American Trypanosomiais (Chagas' Disease)

Chagas' disease is an antropozoonosis caused by the flagellated protozoa *Trypanosoma cruzi*, which is transmitted to human and animals by a group of hematophagus triatominae insects. These bugs live in rural areas, doing their nests in precarious houses, which are generally made of wood and clay. Besides the inoculation of *T. cruzi* by the bite of these bugs, Chagas' disease can also be transmitted to humans by blood transfusion, transplacental route, or contaminated transplanted organ.

Chagas' disease occurs only in the American continent, affecting almost 18 million people. It is estimated that chronic infection is present in 22% of the general population in Bolivia, 7.2% in Argentina, 10% in Chile, and 4.3% in Brazil (49).

The growing number of AIDS cases in Latin America and the spreading of HIV infection to rural areas will potentially result in an increasing number of HIV-*T. cruzi* coinfection cases. This is relevant as the natural history of Chagas' disease can be modified by immunosuppression. The CNS, which is almost never damaged during the course of the disease except in very young children is the most affected organ in the reactivation of chronic, asymptomatic *T. cruzi* infection when the immunodeficiency evolves (see below).

There are two distinct phases during the course of Chagas' disease. In the acute phase, which last for 1–2 months, the majority of patients are asymptomatic, although very young children may develop myocarditis or meningoencephalitis, the latest being fatal in almost 50% of the cases (50). Parasitologic tests detect *T. cruzi* trypomastigota bloodforms by microscopic examination and are useful in the acute phase, as there are large numbers of parasite circulating in the bloodstream. Importantly, these tests may also be employed in the CSF. In fact, since the seminal description of Chagas' disease by Carlos Chagas (a Brazilian researcher), in 1913, it has been reported that the detection of *T. cruzi* in the CSF is possible in the acute phase of the disease (*apud* (51)). In the chronic phase, *T. cruzi* infection may remain dormant for decades. About 15% of the patients will develop myocarditis or digestive tract alterations, but the CNS is never affected in immunocompetent patients. Since in this phase the parasites are not seen in the bloodstream, the main diagnostic tool for chronic Chagas' disease is the detection of parasite antigen by serologic testing such as ELISA, indirect immunofluorescence, and indirect hemagglutination.

Reactivation of chronic Chagas' disease is observed in immunodeficiency states, as in prolonged corticosteroids use, after organ transplantation, and lymphoproliferative diseases (51). It is expected that the spreading of HIV in endemic areas will result in an increased number of reactivated diseases. Most often, Chagas' disease reactivates when CD4+ count is less than 200 cells/mm^3 (28). Both acute myocarditis and cerebral involvement may be observed, the last one associated with high morbidity and mortality if not promptly recognized. Acute meningoencephalitis, tumor-like lesions, and granulomatous encephalitis have been described (52). Neurologic symptoms depend on the number and location of the lesions, and include headache, fever, cognitive disturbances, seizures, and hemiparesis. Meningeal signs are rarely seen. Unlike cerebral toxoplasmosis, which typically involves basal ganglia and thalamus, brain focal lesions of Chagas' disease are seen preferentially in the subcortical white matter of the cerebral hemispheres (53). The cerebellum and brain stem are less frequently affected. In a clinical series of 23 HIV-infected patients with Chagas' disease, 87% had multifocal or diffuse acute meningoencephalitis (54). CSF analysis disclosed pleocytosis with a predominance of lymphocytes, protein increase, and presence of protozoa in the majority of cases. Pseudotumoral lesions were seen in 15 out of 16 CT scans, and in 50% of patients only one lesion was observed. Typically, brain scans disclose ring-enhanced lesions similar to that of cerebral toxoplasmosis, but involving preferentially the white matter (Fig. 1c). Anatomopathological studies show that the brain of a HIV-infected patient with cerebral Chagas' disease has increased weight and volume, with enlargement and flattening of the gyri and narrowing of the sulci (53). Microscopy

reveals meningoencephalitis with necrosis and hemorrhages, the presence of microglial nodules in the gray and white matter, and edema. Amastigote forms of *T. cruzi* may be encountered within the glial cells and macrophages but also in the periphery of microglial nodules. Neuronal parasitism is uncommon.

If not properly treated, cerebral Chagas' disease is fatal. Nifurtimox for 2–3 months and benznidazole for 1–2 months are the drugs used in all stages of *T. cruzi* infection, including cerebral Chagas' disease. Benznidazole, which is the recommended drug in Brazil, is used for 2 months at 8 mg/kg/day divided in two doses. In HIV-infected patients, lifetime secondary prophylaxis with benznidazole is recommended (200 mg three times a week).

Strongyloides stercoralis

Although extra-intestinal strongyloidiasis is no more considered an opportunistic infection in AIDS, a brief consideration about this will be included in this chapter due to some reports about severe meningitis associated with *Strongyloides stercoralis* infection in HIV-infected patients.

S. stercoralis is an intestinal nematode endemic in many developing countries, which may cause an asymptomatic, lifelong infection. This is explained because *S. stercoralis* larvae may directly pass to an infective larval form inside the host gut, resulting in autoinfection. The dissemination of *S. stercoralis* throughout the body (disseminate strongyloidiasis) is possible and fatal in the absence of therapy. Disseminated strongyloidiasis is almost always associated with host immunosuppression, and Human T Lymphotropic Virus type 1-infected patients appear to be more susceptible to both *S. stercoralis* infection and disseminated strongyloidiasis (55). Both hyperinfection and disseminated infection are uncommon in HIV-infected patients, but can occur in those with more severe immunosuppression (CD4+ count less than 200 cells/mm^3).

The occurrence of bacteremia in *S. stercoralis* infection is well documented. Enteric organisms may enter the bloodstream either by bowel wall ulceration or carried by invasive *S. stercoralis* larvae. There are reports of disseminated strongyloidiasis in HIV-*S. stercoralis* coinfected patients resulting in bacterial meningitis. In one of these reports, a HIV-infected woman developed bacterial meningitis (56) .During the investigation, *Streptococcus bovis* was cultured in the CSF and *S. stercoralis* was identified in specimens from the colon obtained by colonoscopy. Direct brain involvement by filariform larvae was documented in the past in two AIDS patients. The authors observed granulomatous ependymitis and identified the filariform larvae in the brain (57). In another report, a HIV-infected patient with Burkitts lymphoma developed lymphomatous leptomeningeal involvement, and filariform larvae of S. *stercoralis* were seen in CSF cytology (58). *Escherichia coli* meningitis was diagnosed in a man who had recently started antiretroviral therapy (59). The authors speculated that disseminated strongyloidiasis occurred due to immune reconstitution syndrome and that *E. coli*, part of the gastrointestinal tract

flora, was carried by *S. stercoralis* to the CNS. Although uncommon in HIV disease, physicians in developing countries with endemic *S. stercoralis* infection should consider that disseminated strongyloidiasis can be more diagnosed in AIDS patients receiving antiretroviral therapy. In some of these, the CNS can be affected.

Ivermectin (200 mcg/kg/day) or thiabendazole (25 mg/kg twice a day) are the main drugs used to treat *S. stercoralis* infection and should be maintained for at least 7 days.

Leishmaniasis

Leishmania sp is a dimorphic, obligate intracellular protozoa mainly transmitted by the bite of a female sand fly. There are reports showing that *Leishmania sp.* can also be transmitted by needle sharing in intravenous drug users. Leishmaniasis is endemic in many developing countries, affecting almost two million people each year (60). The majority of leishmaniasis cases are due to the *Leishmania donovani* group. Cutaneous, mucocutaneous, and visceral involvement are seen in patients infected by some *Leishmania sp*, some of these affecting one or more of these organs.

Immunologic impairment seen in HIV disease alters the clinical manifestations of *Leishmania* and their response to treatment. HIV-*Leishmania* coinfection is associated with a higher risk for disseminated infection, atypical localization of the lesions, chronic and relapsing diseases, and poor response to therapy, especially in patients with CD4+ cell counts less than 50 cells/mm ^{3} (61). Although rare, CNS involvement is possible and has been described as a result of a contiguous infection (62). In fact, multiple visceral localizations of *Leishmania* outside the reticuloendothelial system such as in the CNS are one of the features of leishmaniasis as an AIDS-defining disease. Most neurologic cases are due to cranial nerve or meningeal involvement throughout paranasal sinuses infection (63).

Diagnosis of leishmaniasis is difficult in HIV-infected patients since less than 50% of patients have typical features of visceral disease, as fever, splenomegaly, and hepatomegaly. Also, characteristic antibodies can be detected only in 50% of the cases (61). Definitive diagnosis is achieved mainly by direct identification of amastigote forms in biopsy tissue or in leukocytes on peripheral blood smears. Amastigotes have been detected in CSF in a boy with visceral leishmaniasis (64). Brain CT scans disclose bone invasion or sinus destruction in some cases, but there are no specific abnormalities associated with leishmaniasis.

Although the majority of coinfected patients initially respond well to both pentavalent antimonial and anphoptericin B, 25–80% relapse later (9). Worthy of note, HAART reduces the incidence of visceral leishmaniasis but even combined with secondary prophylaxis only a group of patients will be free of relapses in the future. Treatment is with intravenous or intramuscular *N*-glucantine antimoniate at 20 mg/kg/day for up to 40 days. An alternative drug is amphotericin B at 0.6–1 mg/kg/day for 14 days.

Fungal Infections

Cryptococcosis

Worldwide, cryptococcal meningitis is one of the most common opportunistic infections in AIDS patients. Although probably underestimated, the incidence of cryptococcosis in Latin America is expected to be around 4.5–16.2% in Argentina, 10.2% in Peru, and 4.3% in Brazil (65). In Brazil, cryptococcosis was the AIDS-defining disease in 6% of the AIDS patients reported to the Brazilian Ministry of Health AIDS case surveillance system (www.aids.gov.br). Analysis of cryptococcosis cases in a Brazilian hospital revealed that from 1984 to 1996 its incidence was 3.5 times higher than that observed up to 1983 (66). In Central Africa, the prevalence of cryptococcosis ranged from 8 to 36% (67). In a serological screening performed in HIV-infected patients from Zaire, cryptococcal antigens were detected in 44 out of 450 individuals. In 66% of these CSF analysis resulted in the detection of *Cryptococcus neoformans* by direct microscopy or culture (68). Seroepidemiological surveillance in a rural zone from Uganda disclosed that 5.8% of 377 HIV-infected patients had positive serological results. More death was observed among these patients compared with those without cryptococcal antigenemia (the calculated risk of death was 6.6) (69).

Regardless of the country, more than 95% of cryptococcosis cases in AIDS patients are caused by *C. neoformans* variety *neoformans*. A few cases of disease caused by *C. neoformans* var. *gattii* have been described, mostly in Brazil (65). *C. neoformans* var. *neoformans* is a cosmopolitan fungus encountered mainly in soil and feces of several birds, especially pigeons. Infection occurs via the respiratory system. From the lung, the fungus disseminates to other organs, including the CNS, which is susceptible to infection due to the lack of complement and immunoglobulins in the CSF. Worthy of note, the immune reconstitution secondary to HAART may unmask latent infection and precipitate clinically apparent meningitis (70). Due to increased availability of HAART in the developing countries, health care providers in these places will increasingly face this situation.

Cryptococcal meningitis is one of the most common neurologic manifestations of AIDS in developing countries. In Brazil, several series shows that cryptococcal meningitis is the second most frequent neurologic disease, occurring in 13–33% of the neurologic patients (21). In a series of 177 consecutive autopsies in AIDS patients from Mexico, the CNS was the fourth most affected system (11% of patients) (23). Among these neurological cases, cryptococcal meningitis was diagnosed in 10%, the second most common after cerebral toxoplasmosis. In a clinical series of 500 HIV-infected patients with neurologic disease from India, cryptococcal meningitis was detected in 25% of them, preceded only by neurotuberculosis, diagnosed in 30% of patients (30). In sub-Saharan Africa, it is the third most common neurologic disease and AIDS-defining disease for 90% of patients (71). In a prospective cohort about natural history of HIV disease in Uganda, cryptococcal meningitis was the cause of death in 13% of the patients, being preceded by wasting

syndrome (diagnosed in 31% cases), and chronic diarrhea, which was the death cause in 22% (72). In Singapore, cryptococcosis was the fourth most common cause of all deaths occurring in a cohort of 504 AIDS patients (73).

Normally, cryptococcal meningitis occurs in patients with CD4+ count less than 100 cells/mm^3. The main clinical symptoms are headache and fever, present in more than 80% of cases. Neck stiffness is seen in less than one-third of patients (74). Typically, the symptoms develop over several weeks but some patients have a more acute course, which is associated with a worse outcome. Also, altered mental status, high CSF pressure, and a higher number of organisms in the CSF are indicative of poor prognosis. Cryptococcal meningitis is an important contributor to mortality in developing countries. In sub-Saharan Africa, cryptococcosis cases have shown a tendency to be more acute and lethal compared with cases from the developed world (67). In Uganda, the median survival time after cryptococcal disease diagnosis is 22 days (43). In Zimbabwe, median survival time from diagnosis was only 14 days, with less than 25% surviving more than 30 days (75).

About 75% of patients with proven cryptococcal meningitis had mild mononuclear pleocytosis, elevated CSF protein, and raised opening pressure. Cryptococcal antigen is positive in almost all cases and the India ink test detects the organism in about 70% of them. Fungal culture is important to determine species and document sterilization of the CSF. Brain imaging can reveal meningeal enhancement, hydrocephalus, and even cryptococomas, the later seen in about 10% of cases (Fig. 1d).

The main drugs used to treat cryptococcal meningitis are fluconazole and amphotericin B. Although previously tested as primary therapy (76), fluconazole alone appears to be an unsatisfactory choice for the treatment of this disease (77). In a recent report from South Africa, patients treated with fluconazole as monotherapy had a higher chance to develop symptomatic relapse of cryptococcal meningitis (78). Worthy of note are the multiple drug interactions, which can determine inadequate CNS levels of fluconazole. One special situation is the frequent concurrence of tuberculosis along with cryptococcal meningitis in patients with AIDS in developing countries. It is well known that rifampicin substantially increases the clearance of fluconazole, lowering its serum levels and CSF concentration. This way, amphotericin with or without flucytosine has been considered as a first line therapy. In resource limited settings, where adequate administration of amphotericin B is not possible, fluconazole in higher doses can be a reasonable alternative (79).

Paracoccidioidomycosis

Paracoccidioidomycosis is endemic in Latin America. In Brazil, it is the most common deep mycosis and is prevalent mainly in rural areas, with an estimated annual incidence of 1–3 cases in 100,000 inhabitants (80). Habitually, patients are infected inhaling the conidia of the dimorphic fungus *Paracoccidioides brasiliensis,* present mainly in the soil. Early infection results in a primary pulmonary infection. In most individuals, the innate or acquired immune defenses can eliminate the agent or

establish equilibrium between host and fungus. Only in a minority of the patients does the infection progress to overt disease, evolving into one of the two major clinical forms, namely acute/subacute or juvenile type and chronic or adult type (81). In some patients, the fungus may remain viable in latent foci of infection. A disturbance on cellular immune response may result in overt paracoccidioidomycosis originating from the primary infection complex or from the reactivation of quiescent foci (82).

Most frequently affected organs are lymph nodes, skin, lungs, oropharyngeal mucosa, liver, and spleen. In HIV-negative individuals, CNS involvement is detected in 9.9–27.3% of cases (83, 84). In autopsy series, CNS involvement is around 27% (85, 86). Preferentially, the lesions are located in the cerebral hemispheres, but can also be observed in cerebellum, brain stem, and spinal cord. CT scans of patients with cerebral paracoccidioidomycosis show hypodense, mass effect enhanced lesions, sometimes resembling cerebral toxoplasmosis (Fig. 1e). Even in a country as Brazil, endemic to paracoccidioidomycosis and where the HIV epidemic is spreading to rural areas, HIV-*P. brasiliensis* coinfection incidence appears to be less than expected. The prevalence of paracoccidioidomycosis in AIDS patients varies from 0.02 to 1.5% (65). The lower numbers of paracoccidioidomycosis in HIV-infected patients compared to other systemic mycoses could be explained by the widespread use of trimethoprim–sulfamethoxale as prophylaxis for *P. carinii* pneumonia, which is also very effective against *P. brasiliensis*. HIV-paracoccidioidomycosis coinfection cases has been described both in Brazil and in other Latin American countries such as Venezuela and Colombia (87). In 74% of the patients, paracoccidioidomycosis was the first life-threatening disease to be diagnosed. The clinical presentation resembled the acute/subacute form of classical paracoccidioidomycosis, usually with a short course of fever, weight loss, fatigue, and anorexia, associated with lymphadenopathy (81). Involvement of the CNS or bone was detected in two cases each.

Several treatment regimens are used and sometimes more than one drug is need. The main drugs used in paracoccidioidomycosis are amphotericin B, trimethoprim–sulfamethoxazole, itraconazole, and fluconazole.

Histoplasmosis

Histoplasmosis is a systemic mycosis produced by the dimorphic fungus *Histoplasma capsulatum* variety *capsulatum*, which is acquired via the respiratory system. Histoplasmosis is endemic in many countries of the Americas, Asia, and Africa, and its prevalence has been estimated by the histoplasmin skin test. In Brazil, for instance, the positive skin reaction prevalence ranges from 2.6 to 93.2% (*apud* (88)). Approximately, 5% of the AIDS patients had disseminated histoplasmosis in Buenos Aires, Argentina (65). With an incidence of 2.9/100 person-years among HIV-infected patients, disseminated histoplasmosis was the second most frequent opportunistic infection and the first cause of death in a series from French Guiana (89).

Skin testing showed that 29% of individuals in Guyana and 42% in Trinidad were reactive to histoplasmin (90). In a recent series of 74 patients with histoplasmosis from Rio de Janeiro, 49% occurred in HIV-infected patients who presented with disseminated disease. Histoplasmosis was the AIDS-defining disease in one-third of those (88).

Generally, the primary infection is asymptomatic, but more severe cases may be seen either when a great inoculum is aspirated or in a setting of immunosuppression (91). Reactivation of quiescent infection occurs during immunosuppression (92). The clinical manifestations of disseminated histoplasmosis are prolonged high fever, weight loss, asthenia, anorexia, diarrhea or vomiting, hepatosplenomegaly, multiple adenomegalies, and skin lesions. CNS involvement may be a manifestation of widely disseminated disease or an isolated illness, and is clinically recognized in 5–10% of disseminated histoplasmosis cases (93). In a case series from Brazil, 39 out of 164 HIV-infected patients with disseminated histoplasmosis had some neurologic manifestation, which was independently associated with an increased risk of death (OR 5.8) (94). Neurologic syndromes include subacute or chronic meningitis, focal brain or spinal cord lesions, stroke syndromes, and encephalitis. Focal brain or spinal cord lesions, so-called histoplasmomas, are also described.

Histoplasmosis is a challenge for clinicians because the clinical symptoms are not specific and no diagnostic test is at the same time specific and sensitive. So, multiple tests make the clinical investigation truly expensive for many countries. Also important is the possibility of false-positive results from nonculture-based tests, including the *Histoplasma* antigen assay. Although diagnosis may be simple for patients with disseminated disease, since organisms may be identified in multiple organs, difficulties occur to diagnose those with isolated CNS involvement. For such patients, positive results may only be found through CSF, meningeal, or brain tissue evaluation. At least 10 mL of CSF should be cultured to increase the sensitivity for isolating small numbers of yeast organisms (95). Serologic tests for anti-*Histoplasma* antibodies in the CSF are also helpful, having positive results in up to 80% of cases. However, the antibody response may be impaired in immunosuppressed individuals. For example, in patients with disseminated histoplasmosis, anti-*Histoplasma* antibodies were present in serum in samples from 67% of patients with AIDS, 80% of those with other immunosuppressive disorders, and 86% of those without underlying immunosuppression (96). Also, serologic tests may have false-positive results due to cross-reactions caused by infection with other fungi, including *C. neoformans* (97).

Optimal treatment for CNS histoplasmosis is presently unknown, but amphotericin B and fluconazole are the main options.

Sporotrichosis

Sporotrichosis is endemic worldwide. It is caused by *Sporothrix schenckii,* a dimorphic fungus that is mostly encountered in plants and soil. Therefore, agricultural workers are most at risk for infection. People can be infected mainly by direct inoculation

of spores after a traumatic skin lesion, but infection via respiratory system is also possible. The disease is generally restricted to skin and subcutaneous tissues, but it has been well recognized that AIDS patients can develop a severe and disseminated form of this fungal disease (98–100).

The CNS is rarely involved in sporothricosis, but some cases of meningitis due to *S. schenckii* have been described in HIV-infected patients with disseminated sporothricosis. In a Brazilian case description, a farm-worker developed meningitis after irregular therapy with itraconazole for cutaneous sporothricosis. CSF analysis disclosed a moderate lymphocytic pleocytosis and moderate increase in protein level. The CT scan showed small hypodense lesions in temporal and parietal lobes. Chronic granulomatous inflammation was seen in the meninges mainly in the basal skull, and yeast-like forms similar to *S. schenckii* were identified (101). Other similar reports from the developed world showed that brain MRI may disclose nonenhanced lesions in the brainstem, basal ganglia, thalamus, and centrum semiovale along with meningeal enhancement (99, 102). CSF antibodies specific to *S. schenckii* and fungal cultures are crucial to the diagnosis.

Cutaneous sporothricosis is treated mainly with itraconazole. Since itraconazole shows poor penetration into the CSF, amphotericin B is the best option to treat meningitis due to *S. schenckii*.

Bacterial Infections

Tuberculosis

The prevalence of tuberculosis is directly associated with poverty. More than 80% of cases worldwide are seen in developing countries. Of 8.8 million new cases of tuberculosis worldwide registered in 2005, 1.9 million occurred in India (www.who.int). A socio-economic survey in a rural population in South India disclosed that the prevalence of tuberculosis was 343/100,000 in areas with a low standard of living index, while in areas with a high index the prevalence was 92/100,000 inhabitants (103). Actually, in Brazil, 50 million people are infected by *Mycobacterium tuberculosis*, and 116,000 new diagnoses are made each year (prevalence of 68/100,000 inhabitants). In 2005, 4278 out of 1,006,827 deaths that occurred in Brazil were directly associated with tuberculosis (www.datasus.gov.br).

Overall, it is assumed that HIV-infected individuals are six times more likely to develop tuberculosis than individuals who are not HIV infected (104). HIV-infected patients are particularly susceptible to extrapulmonary tuberculosis. Furthermore, HIV infection is associated with increased mortality in patients with neurologic manifestations of tuberculosis, especially meningitis. HIV-infected patients with tuberculous meningitis had higher rates of multidrug-resistant tuberculosis and mortality than HIV-negative controls in Vietnam (105). High mortality rates are mainly associated with late diagnosis, which is common in poor countries due to lack of appropriate diagnostic tools.

It has been estimated that the CNS is affected in 5–10% of patients with pulmonary tuberculosis, corresponding either to quiescent infection reactivation or spreading of *M. tuberculosis* from other infected tissue in disseminated tuberculosis. By far tuberculous meningitis is the most common neurologic manifestation of *M. tuberculosis* infection, but tuberculoma and abscess can also be encountered. The highest rate of neurotuberculosis in AIDS patients from a developed country is 1.4% (half of patients were drug users) (106). In developing countries, the prevalence of neurotuberculosis is approximately 12% in unselected autopsies (tuberculoma and tuberculous abscesses were seen in 6% of the cases) (24, 107). In Latin America, neurotuberculosis is diagnosed in 4–14% of AIDS patients (9). Probably these figures are underestimates, as tuberculosis is highly prevalent in many Latin American countries. This can be due to the difficulty in diagnosis. In a recent series from Brazil, tuberculous meningitis was the third most common neurological disease in AIDS patients, occurring in 10.8% of patients (108). In an autopsy study from Mexico, tuberculous meningitis was the third most common diagnosis, encountered in 7% of 160 patients who died of neurological complications during HIV disease (23). In South Africa, where the general prevalence of tuberculosis is 315/100,000 inhabitants, neurotuberculosis was the most common diagnosis in 32 consecutive patients with a focal brain lesion (69% of cases, while cerebral toxoplasmosis corresponded to only 3%) (29). Tuberculous meningitis was seen in 11% of adult AIDS patients in 294 autopsied patients from Côte d'Ivoire, West Africa (24). Among 500 cases of HIV/AIDS with neurologic manifestations from Bangalore, India, neurotuberculosis was the most prevalent one (25).

Tuberculous meningitis typically present as subacute meningitis evolving in several days or weeks, characterized by signs of meningeal irritation, headache, low and persistent fever, irritability, and altered mental status (109). Focal neurological signs such as cranial nerve paralysis along with seizures can appear later. In non-treated patients coma and high fever herald death, which occur 5–8 weeks after the beginning of symptoms (110). CT scanning is abnormal in more than two-thirds of patients, and most of them show hydrocephalus or meningeal enhancement (Fig. 1f). Focal brain lesion can be observed and are characterized by iso- or hypodense rounded lesions with ring or nodular enhancement. MRI is more sensitive to disclose such lesions but is not available in many poor settings. Presence of meningeal enhancement is the most important characteristic to discriminate a focal brain lesion due to tuberculosis from cerebral toxoplasmosis or neurocysticercosis (29).

Clinical features of focal forms of neurotuberculosis, namely tuberculoma and tuberculous abscess, are similar to other expansive lesions in AIDS patients and include headache, fever, seizures, and focal deficits on neurologic examination, with or without meningeal signs. CT scans are nonspecific, but a relationship among histopathologic findings and radiological characteristics can be observed. Noncaseating granulomas are rounded, multiple hypodense lesions that show a nodular enhancement after contrast injection (Fig. 1g), while caseating granulomas are hypodense, ring-enhanced lesions (111). The so-called "target sign," a central nest either of calcification or of contrast enhancement surrounded by a hypodense, ring-enhanced lesion is unique but an infrequent finding of tuberculoma.

CSF analysis in neurotuberculosis typically discloses lymphocytic pleocytosis, increased protein levels, and decreased glucose levels. Sometimes, neutrophils can predominate, and this finding was associated with a higher chance for positive *M. tuberculosis* CSF culture in a Brazilian series (112). Direct smears of CSF are positive in minority of patients. In Brazil, none of proven tuberculous meningitis cases were positive on direct examination (112). However, a detailed microscopic examination and a greater volume of the fluid could result in an increase in the sensitivity of this method. Although CSF culture is the gold-standard method for a correct diagnosis, it is not useful to make a rapid clinical decision because *M. tuberculosis* shows a slow growth in the Lowenstein-Jensen medium (30–60 days). PCR test has a reasonable sensitivity (56–70%) and high specificity (98–100%), but is not available in the majority of the developing countries (113, 114). An elevated concentration of adenosine deaminase in the CSF may be useful as an auxiliary diagnostic tool, but lacks specificity since that is elevated also in many other neurologic disorders, such as bacterial or fungal meningitis and lymphoma (115).

Tuberculous meningitis treatment is with isoniazid (300 mg/day), rifampin (600 mg/day), and pyrazinamide (1–2 g/day) plus ethambutol (800–1,600 mg/day) or streptomycin (1 g/day). A scheme of four doses should be used for 2 or 4 months, followed by a course of isoniazid plus rifampin for 7–9 months. Instead of tuberculous meningitis and tuberculoma, which are treated clinically, tuberculous abscess requires both surgical and pharmacological treatment.

Viruses

Only JC virus infection will be discussed here because the prevalence of the disease associated with this poliomavirus is different from developing to developed world.

JC Virus

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the CNS. It is the result of a productive infection of the oligodendrocytes by the ubiquitous JC virus. Since the beginning of HIV epidemic, PML has been described as one of the most frequent opportunistic disease in AIDS patients in developed countries. The incidence of PML in AIDS patients in this setting has been estimated to be around 4% (116, 117). In Italy, PML was the third most common neurological disorder in a cohort of HIV patients (118). However, a few cases have been reported in developing world. Difficulty in rendering a diagnosis, which requires either molecular techniques or brain MRI, is probably the main but not the only reason that explains the few PML cases reported in limited-resource areas, especially in Africa and India.

In Brazil, in spite of a JC virus seroprevalence of 92%, only a few PML cases have been described. Since 1998, only 10 cases of PML were seen in a large

University Hospital in Rio de Janeiro (Chimelli, personal communication). In our cohort (unpublished data), only 17 cases were diagnosed since 1985, 16 of these in the post-HAART era. Nevertheless, a 48.2% prevalence of JC virus in 56 Brazilian AIDS patients with focal brain lesions but without mass effect was recently reported (119). Maybe the scaling up of HAART use in Brazil and in other developing countries could result in an increasing number of PML cases since its incidence appears to have increased compared with other opportunistic infections or tumors (120). On the other side, there are reports showing that both infection by HIV clade C and different JC virus types could justify the low incidence of PML in patients from Africa compared with patients from the Western world (121–123). It has been reported that the majority of Caucasians from United States and Europe excrete JC virus types 1 or 2B (124), while different strains, namely African genotypes of JC virus types 3 and 6, were observed in individuals from West Africa (121).

There are no differences in the clinical presentation of PML patients either from the developed or developing world. The most common neurologic abnormalities are hemiparesis, ataxia, cognitive disturbance, and visual impairment. MRI is by far more sensitive than CT scan and shows hypodense, nonenhanced lesions without mass effect predominately localized in the white matter. CSF is usually normal and amplification of JC virus DNA by PCR from spinal fluid is a very useful diagnostic tool but not available in the majority of developing countries. So, spinal fluid analysis is important to exclude alternative diseases but not to diagnose a PML case in a limited-resource area that is not possible to perform molecular tests.

The best treatment to PML is HAART. In countries where HAART is not available, PML follows its lethal course in a couple of months.

Conclusion

Neurologic manifestations in AIDS patients from developing countries are as common and relevant as in the developed world. However, the majority of guidelines for management of these patients was elaborated in the developed world and includes expensive diagnostic methods such as molecular biology and stereotaxic cerebral biopsy. Also, very few papers have been published about neurologic disturbances in HIV-infected patients from developing countries, which result in dubiousness about the real prevalence of certain pathogens. This way, physicians working in poor countries frequently encounter limited information in the literature about neurologic diseases in their areas and have difficulty to ascertain the right diagnosis due to lack of complementary exams. Another important aspect is that some neurologic diseases caused by certain pathogens endemic in developing countries may be encountered in the developed world due to immigration of people. So, physicians from developed world should consider alternative diagnosis in patients from poor countries presenting a neurologic disturbance, such as cysticercosis and Chagas' diseases.

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Impact of Clade Diversity on Neuropsychological Outcomes

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Introduction

Studies of clade diversity and cognitive function associated with HIV are effectively studies of cross-cultural neuropsychology, given the global geography of the different clades. This produces unique challenges in understanding the impact of HIV on the brain, since cross-cultural neuropsychology requires careful attention to the translation and modification of cognitive tests, as well as concerted efforts to assure cultural relevancy. In some developing countries this may pose even further challenges, as few if any neuropsychological measures may exist and research teams might be required to develop a battery from scratch. The effort, however, is important because our knowledge regarding HIV brain involvement is limited to the genetic strain of the virus present in North America, Europe and Australia, while little is known about the more prevalent genetic strains in the world. Yet, when considered globally, it is estimated that HIV is one of the most common causes of dementia among individuals under the age of 40 (1). As such, there is a significant need to understand the neuropathogenesis of cognitive impairment across the major clade subtypes.

As described by Thomson in Chap. 13, it is possible that the different clade subtypes exhibit unique biological characteristics that lead to differential levels of vulnerability within the CNS. For example, differences may exist across clades in specific protein binding sites and binding characteristics, replicative capacity (2), and possibly in the development of treatment resistance (3, 4), though much more work is needed in this area. Evidence of faster disease progression among individuals in Africa infected with clade D virus offers yet additional evidence that the viral clades may exert unique biological impact on body systems (5). Yet the nature and direction of these differences, particularly in terms of the brain, are not well described and in some cases they have been inconsistently described. For example, some authors have suggested that a defect in the Tat protein in clade C may result in less

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neurovirulence (6), whereas others have suggested that clade C may be associated with higher rates of dementia because this clade has a strong affinity for the CCR5 receptor, which is itself associated with macrophage infiltration into the CNS (7).

The purpose of this chapter is to describe the current state of knowledge regarding clade subtype and the expression of HAND. As noted earlier, such a review almost inherently becomes organized by geography, but we have elected to identify each clade as the primary principle of organization below. It should be noted that a few studies have actually confirmed the clade subtype in studies, and it is possible that recombinant forms render the outcomes less clear. With these caveats noted, the following chapter describes the impact of clade diversity on cognitive function. Subsequently we review recommendations for future neuropsychological studies based on international settings.

Clade C

Clade C accounts for more than half of all HIV cases worldwide and early studies suggested that the brain was less vulnerable in clade C HIV (e.g., 8, 9). Based on clinical studies, the prevalence of HIV-associated dementia was reported to be less than 5%, roughly one-fourth the rate that was often reported in association with clade B HIV in North America (10, 11). Interestingly, Ranga et al. (6) demonstrated an important natural variation in the dicysteine motif of the Tat protein (C31S) that was conserved only in clade C virus. Further, the authors demonstrated that the variation was functionally significant, as the mutation diminished monocyte chemokine migration properties. Since the Tat protein promotes viral replication directly and it reduces HIV-resistance in uninfected cells, a functional change in the Tat protein could significantly impact the virulence of the virus. Indeed, studies have demonstrated that Tat is selectively involved in the migration of monoctyes into the brain via upregulation of inflammatory cytokines and adhesion molecules (12). Tat has also been shown to disrupt the tight-junction proteins that support the blood–brain barrier (13), and therefore a defect in the Tat protein could offer some protection against CNS involvement. Another recent study suggests that the Tat gene in subtype C is associated with increased cell survival in rat hippocampal neuron cultures compared with subtype B (Li, unpublished data, personal communication).

Consistent with the biological properties described earlier, Clifford et al. (14) did not find significant neurocognitive differences between nontreated HIV+ individuals and demographically matched HIV− counterparts in Ethiopia, a region that is presumed to be largely associated with clade C virus. In this study, a brief neuropsychological battery was administered to treatment-naïve patients and a group of well-matched control subjects. The battery included the International HIV Dementia Scale, finger tapping, timed gait, and the grooved pegboard test. Of these tests, the HIV patients exhibited significantly slower performances on the finger tapping test, but performances were similar between the groups on the other measures. The authors offered a number of possible explanations for the lack of group differences, including the

possibility that clade C is less neuro virulent, though they also cautioned that the restricted cognitive battery may not have provided sufficient sensitivity to detect the presence of actual group differences.

In contrast to the results from Ethiopia, several studies have now identified significant cognitive impairment associated with clade C HIV in India. Riedel et al. (7) reported a prevalence of 35% of HAND using the international HIV dementia scale in a large, untreated urban cohort from Pune, India. Another study in South India provided a much higher rate using a more comprehensive assessment (15). This study was conducted by members of our group with funding from the NIH. In this study, 30 HIV+ individuals infected with clade C virus in India were compared with 30 healthy controls from the surrounding community on measures of neuropsychological function. The healthy controls were matched to the HIV group according to sex, age, and education. All subjects were administered a battery of neuropsychological measures that had been adapted from traditional US-based tests. The tests were translated and back-translated and adapted for cultural relevance. Comparisons of HIV+ patients and the seronegative controls demonstrated significant differences between the two groups for verbal list learning total recall, verbal list learning delayed recall, visual learning and memory, fine motor speed and dexterity, and cognitive flexibility. Performances did not differ between the groups on the response inhibition. Overall, the range of impairment was 4% (Stroop incongruent) to 40%, with the largest percentages evident on the test of visual learning and cognitive flexibility. Further, 46% of the HIV participants with advanced HIV met criterion for impairment on two tests.

Nearly identical results have been obtained in a study conducted by Gupta et al. (16) .In this study 119 HIV+ untreated individuals with clade C HIV underwent neuropsychological testing, and performances were compared with 126 seronegative individuals similar in demographic characteristics. The neuropsychological battery consisted of tapping, animal fluency, phonemic fluency, verbal working memory, visual working memory, executive function (Tower of London), and verbal auditory memory. Results indicated that more than one half of the HIV sample exhibited mild to moderate cognitive impairments in the domains of verbal fluency, working memory, verbal learning, and verbal memory. Overall immune system status did not correlate with cognitive function, though patients with CD4 counts below 200 or viral loads greater than 1,000,000 copies demonstrated poorer performance on a test of visual working memory. The investigators examined the percentage of patients with deficits (defined as performance below the 16th percentile) on each test, and reported that as many as 30% of patients were impaired on the 2-back verbal working memory test, and nearly 35% of patients were impaired on the test of verbal auditory learning

These results along with the results of our own study indicate that cognition can be impaired among patients with clade C infection. Of particular interest is that the pattern of cognitive deficits associated with clade C is highly consistent with the pattern evident in clade B, and suggests that the same subcortical regions of the brain (including white matter) are impacted in this viral clade. Given the empirical evidence that cognition is affected in clade C, it is possible that the reported low

prevalence of HAND associated with clade C may be due to the fact that most other studies did not employ standardized cognitive tests to determine the presence of impairment rates, and therefore the prevalence of significant impairment may be higher than that initially reported. It is also possible that less severe, but still clinically meaningful, difficulties on cognitive tests are present among individuals with clade C virus. Clearly, more comprehensive studies are needed, given the disparate results from Ethopia using the smaller battery. Members of our group are now working with the University of Cape Town, University of Stellenbosch, and University of Western Cape to complete comprehensive cross-clade studies of HIV neuropathogenesis in South Africa. These studies include neuroimaging and we believe these studies will significantly advance our understanding of clade C HIV and the brain.

Clades A and D

Several recent studies have been completed that examined cognitive function in patients residing in Africa with clades A or D. Sacktor et al. (17) examined the utility of an international HIV dementia scale in Uganda, an area of Africa known to be predominately A and D. In this study, 81 HIV+ individuals in Uganda and 61 HIV+ individuals in the US completed the screening measure, which includes tests of psychomotor speed, tapping, and recall. Neuropsychological assessments were also completed in order to test the sensitivity and specificity of the screening measure. In this study, the screening measure demonstrated a sensitivity of 80% and specificity of 55% in the Ugandan sample and nearly identical psychometric properties in the US sample.

More recently, Robertson et al. (18) reported that the neuropsychological battery administered in the Sacktor et al. study identified significant differences in verbal learning and memory, speed of processing, attention, and executive function, with HIV patients in Uganda performing significantly more poorly than seronegative controls from the same region of Africa. Further work from this group has demonstrated that cognitive function improves with HAART among individuals from Uganda, and to our knowledge this is the first evidence of cognitive benefit from HAART in the context of clade diversity. Additional follow-up studies have been conducted on this cohort from Uganda, with a recent report from Wong et al. (19) that the prevalence of HAD was 31% in an urban cohort attending an AIDS clinic. The authors also showed that age and current CD4 cell counts were the only factors associated with HAD. This prevalence estimate is likely to be an underestimate considering the selection of their study population, which was likely to be healthier than some of their HIV+ counterparts in the rural areas of the country. In another study from Uganda, subtyping was performed in 60 HIV+ individuals who received detailed neurocognitive assessments. Eight of nine (89%) HIV+ individuals with subtype D had HIV dementia, compared with 7 of 33 (24%) HIV+ individuals with subtype A (Sacktor et al., CROI abstract 2008) (43). These findings are the first results in well-characterized HIV+ individuals in sub-Saharan Africa to demonstrate that HIV subtype may have different biological properties with respect to its capacity to cause HAND.

The reported prevalence of dementia in sub-Saharan Africa noted above is greater than the prevalence reported in the pre-HAART WHO study, which noted a 7% dementia prevalence in Nairobi and Kinshasa (20). Despite being different countries, it is likely that the prevalence may have been higher, but this study did not include many patients with AIDS. As noted by Wong et al. (19), differences in study method, type of clinics, type of HIV population studies, advancement of the disease, and use of nonstandard criteria may significantly affect the prevalence rate. These results demonstrate the feasibility of translating traditional US-based neuropsychological tests into local non-English languages in developing countries. Further, the results of these studies provide additional evidence that cognition appears to be affected in the A and D subtypes of HIV in addition to the B subtype.

Clade E

Circulating recombinant form (CRF) 01_AE, commonly referred to as clade E virus is one of the predominant circulating subtypes in Thailand, an area where some neurocognitive data have been acquired. Bangkok was one of the original five sites evaluated in a cross-cultural effort conducted by Maj et al. in the early 1990s (21). Here, the authors identified significant differences in neuropsychological testing among seronegative controls, symptomatic HIV adults, and asymptomatic HIV adults using their newly compiled neuropsychological battery designed to minimize cross-cultural influences (21). Specifically, symptomatic HIV patients showed deficits in the color trails one test, the grooved pegboard dominant hand, trail making A, and two tests of verbal fluency. In contrast, asymptomatic HIV patients differed from controls only in the grooved pegboard dominant hand. This early study identified neuropsychological deficits in Thai nationals with HIV, although clade determination was not included in this study.

More recently, members of our team replicated this work among 15 individuals diagnosed by a Thai neurologist to have HAD and matched HIV individuals without cognitive complaints of similar age and CD4 counts(22). Thirty age-and education-matched controls were used for comparison. Performance on a global composite score differed by serostatus. As a group, HAD cases performed worse than did HIV+ controls in verbal learning and recall, psychomotor speed, and in one test of visuospatial skill, a pattern that is relatively similar to that previously described in clade B virus. All HIV cases were naïve to HAART and confirmed to be infected with the CRF AE_01 subtype. With near uniformity, cases exhibited a robust cognitive response to HAART (Valcour, personal communication).

To our knowledge, HAND prevalence estimates have not been determined for clade E virus. Meanwhile, focused studies have identified clade-specific alterations that may impact cognition. Ranjbar et al. evaluated Tat proteins in clade E compared with clade B and C viruses, identifying selective inhibition of TNF gene transcription and gene production in clade E associated with a tryptophan substitution at residue 32 of the clade E Tat gene. Such down-regulation in clade E may be expected to

impact neurovirulence. More recently, investigators in our group failed to identify differences in cellular activation markers (CD14+/16+) and inflammatory protein profiles in HAD compared with non-HAD patients in this Thai cohort in stark contrast to that previously described in presumably clade B infected subjects from the US (23, 24) This study provides an added cellular basis for differences by clade. Interestingly, this work also identified higher rates of cellular activation in seronegative controls from Bangkok when compared with seronegative controls in the US, highlighting the challenges in distinguishing cultural, environmental, host, and HIV genetic factors when interpreting the prevalence of neurocognitive impairment across international sites (23).

Further International Studies

In Latin America where the dominant clade is B, studies specifically dedicated to investigate the rate of HAND are lacking. An epidemiological study of HIV+ neurological complications (25) reported a prevalence of 4.6% for dementia in an infectious disease clinic, in Brazil. Trujillo et al. (26) conducted a study in the pre-HAART era comparing US and Mexican samples on the prevalence of neurological complications. They found that dementia was the most common neurological manifestation in both groups, while intracranial tuberculoma was present only in the Mexican population. A recent panel of experts from the US and Brazil reported several strategies to start to carefully study HAND in Brazil (27). It is hoped that from these initiatives, a more accurate picture of HAND will emerge in the near future for Latin America.

In China where clade B is predominant with some clade E in the South and other recombinants, two studies have provided preliminary results. Pilot results from a study, including subjects from Beijing and the Anhui province, found that HIV+ individuals performed worse than did their HIV− counterparts, who were matched for age, education, and gender on all standard neuropsychological tests included in the battery. On a global neuropsychological summary score, the difference between HIV+ and HIV− yielded a medium effect size ($d = 0.55$). The HIV+ group included mainly individuals with AIDS (28). In addition, the authors also found that the magnitude and pattern of neuropsychological testing did not differ compared with a US cohort matched for age and disease severity. This pilot study was the first phase of a larger investigation in former plasma donors in the rural area of Anhui (China) for which detailed results are forthcoming (29). Briefly, the authors developed demographically corrected norms (T-score conversions) on a comprehensive battery of neuropsychological tests using uninfected individuals for both HIV and HCV. Using a global summary score, neuropsychological impairment was found in 34.2% of the HIV mono-infected group as compared with 12% in the controls ($p < 0.0001$ (30)). Finally, the Asia Pacific NeuroAIDS Consortium (APNAC) conducted a multisite study in HIV-infected outpatient from a wide range of clinics in China, Malaysia, Thailand, Cambodia, India, and Papua New Guinea (31). Their brief

neuropsychological battery included the timed gait, finger tapping (nondominant), grooved pegboard (dominant hand), and semantic fluency (category animal). Their criterion for significant neuropsychological impairment was defined as minus 2 SD in two of the four tests detecting moderate to severe impairment levels (i.e., HAD). Using local norms, they found that 12% of their cohort met the criteria for neurocognitive impairment.

The Assessment of Cognitive Functions in Developing Countries

The assessment of cognitive functions in developing countries in HIV-infected individuals poses a number of challenges to the adaptation of the neuropsychological method that have initially been developed in Western countries. First, it is often that in limited resources settings brief neurological and neuropsychological assessment will provide the most efficient mode of evaluation. To this effect, Sacktor et al. (32) have developed the international HIV dementia scale (IHDS) and a brief timed gait scale, respectively, with normative standards. However, as in Western countries, these instruments should be primarily used for screening purpose and caution should be applied when deriving prevalence of HAND only from them. Ideally an assessment similar in length to the one recommended by Antinori et al. (33) is necessary for reliable diagnosis of HAND and effort to accomplish this kind of studies is underway.

Second, educational attainment in developing countries varies much more widely than in Western countries and includes individuals with very low or no formal education. In addition, differences in educational attainment may vary in function of gender, and whether individuals reside in urban vs. rural areas. It is known that poor educational attainment and illiteracy render the interpretation of conventional neuropsychological tests difficult (34). Indeed, most neuropsychological tests are based on the use of symbols, letters and numbers, visuo-spatial skills, and conceptual rules that will favor individuals with high educational achievement. Reversely, these tests may compound poor performance in individuals who already exhibit cognitive deficits due to HIV and have very low educational achievement. In this extreme case, even normative data may not adequately translate the extent of cognitive impairment due to HIV, because the performance will reach the lowest level in many instances. The WHO studies (20) made recommendations for the use of tests that are less biased in that sense (e.g., Color Trails rather than Trail Making Test). In addition to the careful selection of test measures, adequate selection of control population matched not only for age, education and gender, but also residence area is certainly required in developing countries. In fact large-scale normative studies (inclusive of a wider range of educational levels) are required, such as the ones originally conducted in Western countries (35). In these forthcoming studies, it would be hoped that the effects of age, education, and gender as well as extended demographics are thoroughly explored on the most commonly used neuropsychological tests in NeuroAIDS research.

Third, specific considerations for translation need to be implemented. This means that literal translation of tests is not appropriate. The adaptation will ideally require the involvement of bilingual neuropsychologists in order to have the assurance that the conceptual basis of the test is respected in the translation. Moreover, in the case of language based tests, frequency of use, and semantic adequacy of the translation will have to be determined. For example, as noted earlier, the WHO battery (20) included a test of verbal memory that appears not to have been modified for cultural relevancy in that the verbal memory test was translated but not modified to ensure that the target words retained similar meaning in the local languages. This is an important point, because simple translation does not equate to cultural relevancy and in many circumstances modifications will be needed. In our work (15), we replaced an entire semantic category from the Hopkins Verbal Learning Test-Revised, because the existing category did not provide the same meanings and task demands once translated into the local languages, Tamil and Telugu. Similarly, we have modified the WHO battery for cultural relevancy in Thailand, because some words from the verbal memory test did not have equal meaning in Thai. Investigators are truly obligated to take any necessary steps to ensure optimum cultural relevancy. This is a prerequisite to correctly interpret the nature and prevalence of HAND in developing countries, and guidance from the International Test Commission Guidelines can provide a meaningful starting point for investigators beginning this work (wwwintestcom.org/).

Fourth, certain comorbid conditions, either preexisting HIV infection (e.g., malnutrition as children) or sometimes concomitant to HIV infection (e.g., tuberculosis, malaria, and other endemic diseases), need to be carefully recorded in limited-resource settings. Ideally, their independent effects on neuropsychological performance would need to be evaluated. In addition, HIV-related brain opportunistic infection, almost eradicated in Western countries with the widespread use of HAART, could account for some of the clinical impairment identified. This may happen especially in limited-resource settings where exclusion of opportunistic infections is often impossible to complete with certainty. Therefore, reports should make an effort to record as carefully as possible the prevalence of brain opportunistic infection in their study population. Major psychiatric illnesses should be evaluated, such as major depressive disorder or substance use disorders, as their prevalence may vary significantly between countries or geographic regions within a same country. Ideally again, their potential confounding effect on neurocognitive outcome should be independently evaluated.

Finally, investigators should take advantage of the research strategy gained from testing minority populations in Western countries such as in Hispanic-Americans (36, 37), African-Americans (38, 39), and in Aboriginal-Australians (40) as well as some guidelines to foster good ethics practice in the context of cross-cultural neuropsychology (41). In this respect local collaborators are essential interlocutors for providing and assessing the relevant information to their countries, cities, or villages reinforcing the need for a collaborative cross-cultural scientific strategy. International studies are also likely to involve training of some local collaborators, ideally again the training strategy should be reported by investigators to forge standardized practices.

Discussion

Overall it appears that cognitive function is impaired across most clades. There remains some uncertainty regarding clade C, but the two most comprehensive studies suggest that impairment is evident. Collectively these results provide further support for the possibility that HIV may be the most common form of dementia globally among individuals under the age of 40. Much more effort is needed to determine whether the impairment evident across clades reflects a common neuropathogenic pathway, as it is possible that the outcomes are similar but the routes are different (Jernigan, personal communication). If true, and studies are able to delineate the pathways, then we will have learned critical information about how this virus, and perhaps other viruses, negatively impact brain structure and function.

Fortunately, there is strong interest to develop this area of research. In 2007, investigators at the University of California, San Diego, initiated the International Consortium of NeuroAIDS Scientists; a major focus of this group is to promote and facilitate cross-clade and international neuropsychological studies. It is certainly timely that the Western scientific community is allocating some resources to study HAND in the developing countries (42). It is hoped that this strategy will inform us about the characteristics of HAND in developing countries as well as assist the training of local clinicians to correctly diagnose and address the manifestations of cognitive disorders. Reciprocally, the local clinicians are valuable and essential collaborators as well as interlocutors in order to better understand the characteristics of HAND in their countries.

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The Effects of Aging on HIV Disease

Robert C. Kalayjian and Lena Al-Harthi

Characteristics of Older Persons Living with HIV

Because of marked improvements in survival as a result of combination antiretroviral therapy (cART), persons older than 50 years constitute a rapidly growing segment of the prevalent, HIV-1 infected population. This age cutoff, although arbitrary, has prognostic validity in identifying a subset of persons who experience a greater rate of HIV disease progression, who are at a greater risk for cardiovascular and renal disease, and who are more likely to experience neurocognitive impairment. This chapter reviews the epidemiologic and the clinical characteristics of HIV disease in older adults, and summarizes the current understanding of the effects of aging on the immunopathogenesis of HIV disease.

Persons 50 years or older have represented approximately 12% of the newly diagnosed AIDS cases in the US since 2005 (1). In an analysis of such cases between 1991 and 1995, older persons were more likely to present with encephalopathy and wasting syndrome, and were more likely to die within one month of presentation, (2). Although the largest HIV transmission category in this analysis were men who have sex with men, several studies also have demonstrated lower rates of HIV seroconversion and lower rates of unprotected anal intercourse among older men, however (3–5).

In a recent community-based survey of sexuality among older Americans, although the majority of respondents were sexually active with a partner (83.7% of men, and 61.6% of women), and reported at least one bothersome sexual problem, only a minority of these older persons (only 38% of men, and 28% of women) had disscussed sex with their physicians (6). Together, these observations suggest that

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older persons are tested for HIV-1 infection later during their HIV disease course, because of lower self-perceived risks for infection, or lower risks as perceived by their health care providers.

Older Age and Accelerated HIV Disease Progression

A strong, detrimental contribution of older age to the natural history of HIV disease was recognized early in the AIDS epidemic. Significantly lower survival rates were evident among older persons with AIDS (40 years or older) compared with younger ages, in one of the earliest large cohorts involving 5,833 AIDS cases diagnosed in New York city before 1986 (7). Because this association may have been confounded by longer durations of infection among older persons, stronger evidence for the contributions of age to the natural history of HIV disease was derived from a cohort of hemophiliacs with AIDS that included 319 persons with known dates of HIV-1 seroconversion, in which significant reductions in survival were associated with older age at seroconversion; this age-effect was evident as early as the second decade of life (8). These observations were confirmed in an analysis from 38 studies, before the availability of cART, that included 13,030 persons with known dates of seroconversion, in which each 10-year increment in the age of seroconversion was associated with a 1.47-fold increased risk of death (9). In this analysis, the median time to an AIDS diagnosis fell from 11 years to 8.6, and 4 years, for persons who seroconverted between the ages of 15–24, 35–44, and 65 or older, respectively.

The detrimental effects of age on the natural history of HIV persist despite cART. Older age at the time of cART initiation was associated with a higher probability of a new AIDS defining event or death in three large cohort studies that included 3,015 participants in the French Hospital Database, 12,574 participants in the International Antiretroviral Therapy Cohort Collaboration, and 16,198 participants in a rapid scale-up project of cART application in Zambia (10–12). Despite adjusting for relevant baseline differences, analyses of these cohorts demonstrated more rapid HIV disease progression in persons who began cART at the age of 50 or older, in the studies from industrialized settings, and at the age of 41 or older, in the resources limited setting.

Additional, compelling evidence for the detrimental effects of age on HIV disease progression were derived from a population-based cohort of 3,990 HIV-1 infected Danish patients during the late cART-era (from 2000 to 2005) that included 379,872 persons from the general population (13). Although the relative mortality rates for HIV disease decreased in association with older age, because of age-dependent increases in mortality within the general population, the excess HIV-attributable mortality rates increased in association with older age; this rate did not exceed 12.3 per 1,000 person-years for persons younger than 50, but increased to 19.5, and 53.8 per 1,000 person-years for those aged 55–60, and 65–70, respectively. These studies confirm the strong effect of age on HIV disease progression, which

in the absence of antiretroviral therapy, is evident at young ages, within the second decade of life. This effect is reduced, but is not eliminated by the application of cART, and is apparent in industrialized, and in resources limited-settings alike.

Adherence, Tolerability, and Viral Suppression with cART

Despite concerns of reduced tolerability and increased medication-associated toxicities among older persons, adherence to antiretroviral medications appears to be at least as good, if not better in older patients compared with their younger counterparts (14–18). This was most evident in an analysis of self-reported adherence in the Anti Protease Cohort that included 970 patients with at least 12 months of follow-up, in which moderate and poor medication adherence was independently associated with younger age; additional correlates included treatment side effects, more frequent dosing, and protease inhibitor-based regimens (18).

Consistent with these adherence differences, several studies also have demonstrated that older persons were more likely to achieve sustained viral suppression in association with cART (19–21). For example, older age was the most significant baseline predictor of viral suppression over 144 weeks of cART, as demonstrated in an observational cohort study of 1,083 subjects in the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trial, in which subjects began their first cART regimen through one of several randomized clinical trials. Similarly, older age was associated with a longer time to the emergence of indinavir resistance, in a multivariable analysis to identify correlates of resistance among demographic, immunologic, virologic and pharmacokinetic factors from five randomized clinical trials (22).

The association between older age and cART-related toxicities are less clear. In a single-center, retrospective cohort of 222 subjects from Madrid, older age was associated with an increased risk of hepatic toxicity in association with cART (23). No significant age-group differences in any medication-associated toxicities were observed in a prospective, multicenter, age-differentiated cohort study (ACTG Protocol 5015) of 90 subjects; however, who were evenly divided into older (median age 50, range 45–79) and younger (median age 26, range 18–30) age-groups, and who received 192 weeks of a uniform protease inhibitor cART regimen (24). Older persons were significantly less likely to modify or to change their initial cART regimen due to toxicity, in an analysis of 556 subjects of the Royal Free Hospital in London, and there were no differences according to age in subsequent modifications of cART due to toxicity, in the multicenter ATHENA cohort of 2,470 subjects (25, 26).

Several studies have documented a significantly higher risk of lipoatrophy in older persons, in association with cART (27–30). Therefore, although older persons are at a greater risk of lipoatrophy and possibly hepatotoxicity, they often exhibit better adherence to cART, and they are more likely to achieve superior levels of viral suppression than younger persons.

Comorbidities and Adverse Clinical Events

Older persons have more comorbid conditions, and take more medications for these conditions (31, 32). In ACTG Protocol 5015, older persons were more likely to receive a new diagnosis of hypertension or cardiovascular disease during the 192 weeks of follow-up (24). In a retrospective cohort of 165 older patients (ages 55 years or older) from three outpatient clinics in New York city, 147 patients (89%) had a mean of 2.4 comorbid conditions (32). Although 133 patients (81%) received a mean of 2.7 medications for these conditions, the likelihood of viral suppression was not adversely associated with either the presence of comorbidities, or with the number of concurrent medications that were prescribed.

The risk of cardiovascular and kidney disease is strongly associated with older age among HIV-1 infected persons, as it is in the general population (33–37). In the large prospective data collection on adverse events of anti-HIV drugs study group of 23,468 HIV-1 infected patients who were followed between 1999 and 2001, each 5-year increment in age was associated with a 38% increased risk of myocardial infarction (34). Older age was associated with higher hospitalization rates for cardiovascular or cerebrovascular disease among 36,766 HIV infected patients who received care at veterans affairs facilities (between 1993 and 2001),(33) and older age (greater than 45 years) was associated with a greater risk of venous or pulmonary thrombosis, in the multicenter adult/adolescent spectrum of HIV disease project of 42,935 HIV-1 infected outpatients (38). HIV disease has been associated with an increased risk of cardiovascular disease in some, but not all studies (39, 40). In one study of more than three million California medicaid recipients, this increased cardiovascular risk was evident among younger (up to the ages of 34 in men, and 44 in women), but not in older persons (39).

HIV disease is associated with both primary and secondary causes of kidney disease, and the risk of acute and chronic kidney disease increases with age (35–37). Several studies have demonstrated increased mortality rates in association with acute, and chronic kidney disease (defined by either proteinuria or reduced serum creatinine) among HIV-1 infected persons, which were independent of other relevant baseline factors (35, 36).

As the incidence of AIDS defining malignancies has fallen markedly in association with cART, accounting for 1.1 deaths/1,000 person-years in a recent analysis from the Data Collection on Adverse Events of Anti-HIV Drugs Study Group (D:A:D), the death rate from non-AIDS defining malignancies, including lung, gastrointestinal, hematologic and anal cancers have increased, to 1.8 deaths/1,000 person-years (41). The risk of death for both AIDS defining, and non-AIDS defining malignancies in this study was associated with $CD4^+$ cell depletion; older age, cigarette abuse and active hepatitis B infection were additional risk factors for death from non-AIDS defining cancers.

In an analysis of 319 lung cancer cases in persons with AIDS, HIV disease accounted for higher than expected rates of lung cancer, when adjusted for age, race, sex and smoking intensity (42). This excess risk was evident in men who were

Table 1 Significant epidemiologic and clinical differences in older HIV-infected persons, compared with younger HIV-infected persons

Comparisons of older vs. younger persons with HIV-1 infection	Comment
Epidemiologic differences	
Accelerated HIV disease progression (9– 12)	Evident during the second decade of life in the pre-cART era, and after the fourth decade of life in association with cART (9, 10–12)
Lower rates of HIV seroconversion and unprotected anal intercourse, among men who have sex with men (3– 5)	
Clinical differences	
More advanced immunodeficiency at presentation, with more encephalopathy and wasting (2)	
Better adherence to cART (14– 18)	
Higher proportions of persons with sustained viral suppression (19– 22)	
Greater risk of lipoatrophy in association with cART (27– 30)	
Greater risk of cardiac, cerebrovascular and peripheral vascular events (33, 34, 38, 39)	HIV was associated with greater cardiovascular risk among younger, but not older persons, however (39)
Greater risk or renal disease (35–37)	
Greater number of co-morbidities (31, 32)	
Greater risk of death from non-AIDS defining malignancies (41, 42)	HIV was associated with higher than expected rates of lung cancer, among women, ages <50 years, and among men, ages <60 year (42)

IDU injection drug use

younger than 60, and in women who were younger than 50, but it was not evident among older men or women. Therefore, the increased risk of lung cancer that is attributable to HIV may be the result of higher than expected cancer rates among younger persons, but lung cancer rates among older, HIV-1 infected persons may not exceed those of the general population.

Finally, older HIV-1 infected persons may have a higher risk of AIDS dementia complex, as was demonstrated in a cross-sectional analysis of the 202 HIV-1-infected subjects in the Hawaii Aging with HIV-1 Cohort (43). After adjusting for education, race, current substance dependence, depression, cART use, HIV-1 viral load and $CD4^+$ cell counts, participants over 50 years old were 3.26 time more likely to meet criteria of HIV-associated dementia complex than were younger subjects in this cohort.

Aging and the Immunopathgenesis of HIV Disease

HIV disease and normal aging are both associated with enhanced susceptibility to infections by encapsulated organisms, increased risks of tuberculosis and varicella zoster reactivation, and higher rates of malignancy (44, 45). Because many of the same immunologic changes that develop during normal aging also arise as a consequence of HIV disease [Table 2], this has lead to the hypothesis that HIV disease induces an accelerated aging of the immune system, resulting in the premature exhaustion of immune resources (46). A better understanding of the mechanisms that underlie the association between aging and HIV disease progression may facilitate a better understanding of the immunopathogenesis of both processes.

Both normal aging and HIV disease are characterized by a shift from a predominance of naïve to memory T-cell phenotype (47, 48). Both conditions also are associated with: T-cell dysfunction and reduced proliferative responses to antigenic and to mitogenic stimulation;(49, 50) reduced IL-2 production in response to T-cell receptor (TCR)-mediated stimulation; (51–53) post TCR-mediated signal transduction abnormalities with impaired cell cycle progression;(54, 55) lower expression of the costimulatory molecule, CD28 on $CD8^+$ cells;(56, 57)B-cell dysfunction that

Table 2 A comparison of similar immunologic parameters that have been observed, both in association with normal aging, and in association with HIV disease

Immune differences	Aging	HIV	Comment
T-cells			
Thymic output	↓	↓	Thymic involution with aging, impaired intrathymic proliferation with HIV-1-infection (65– 68)
Circulating naive T-cells	↓	↓	Involves $CD4^+$ and $CD8^+$ cells in both aging and HIV disease (47, 48)
T-cell proliferation	↓	↓	To both antigenic and mitogenic stimulation with both aging and HIV disease (49, 50)
Expression of the coactivation molecule (CD28) on T-cells	↓	↓	Expansion of CD28 negative cells, and contraction of CD28 positive cells with both aging and HIV (56, 57)
TCR signal transduction	↓	↓	Abnormalities in cell cycle progression following TCR stimulation (54, 55)
T-cell activation	↑	↑	Heightened HLA-DR, Fas and FasL expression on $CD4^+$and $CD8^+$cells with both HIV and aging (60– 62)
Replicatitve senescence	↑	↑	Telomere shortening involves $CD4^+$and $CD8^+$cells with aging, and CD8+cells with HIV disease (105– 108)
sTNFR-II	–	↓	sTNFR-II is elevated with HIV, particularly in older persons with HIV, but not with normal aging (68)
B-cell proliferation	↓	↓	B-cell proliferation defects with both aging and HIV disease (58, 59)

TCR T-cell receptor; *FasL* Fas ligand; *sTNFR-II* soluble tumor necrosis factor receptor II

impairs the generation of high affinity antibodies;(58, 59) and heightened immune activation with enhanced susceptibility to activation induced cell death (60–62).

CD4+ Cell Regeneration in Response to cART

Older age is associated with reduced CD4+ cell restoration in response to cART (63, 64). Among 1,956 patients who initiated a cART regimen in the prospective, multicenter EuroSIDA cohort, older age (greater than 40 years) at cART initiation was associated with a lower likelihood of achieving circulating CD4+ cell count increases of 100 or 200 cells/μL above baseline, and with a longer time in achieving absolute CD4+ cell counts greater than 200/μL (63).

Similarly, greater CD4+ cell recovery was associated with younger age, in a multivariable analysis that was adjusted for sex, baseline HIV-1 viral load, baseline CD4+ cell counts, and included post-baseline contributions by viral suppression, from a multicenter, prospective, randomized ACTG trial of 980 subjects who began their first cART regimen (64). In this study, older age (greater than 40 years) was associated with lower median CD4+ cell increases from baseline (by 40–50 cells/μL), over 144 weeks of observation.

Naïve T-Cell Depletion and Thymic Dysfunction

This reduced capacity to restore total CD4+ cells may result from a diminished capacity to generate naïve CD4+ cells, because of impaired thymic output from age-associated thymic involution, or because of HIV-associated impairments in thymocyte proliferation (65–68).

Involution of the thymus follows a biphasic, exponential pattern of volume contraction that begins at puberty but may be accelerated beyond the third decade of life (69). Despite this process, however, several lines of evidence suggest that thymopoiesis and de novo T-cell synthesis continues throughout adulthood (70–73). Specifically, this evidence includes the isolation of functional thymocytes from the thymic tissue of older adults, and the measurement of signal-joint or coding-joint TCR gene rearrangement excision circles (sjTREC or cjTREC) (70–73).

TRECs are DNA plasmids that are products of TCR gene rearrangement, encoding the δ locus of the α-TCR chain, which occurs in the thymus during the double positive stage of T-cell development ($CD3^+$ $CD4^+$ $CD8^+$). TREC containing cells, therefore, identify recent thymic emigrants, and reductions in TREC concentrations within lymphocytes indicate reduced de novo T-cell synthesis. When measured in this way, reduced thymic output has been demonstrated in association with both aging and HIV disease (70, 72). Lower TREC concentrations independently predicted accelerated HIV disease progression in the absence of antiretroviral therapy, when adjusted for the age at HIV-1 seroconversion(74), and increases in TREC concentrations were observed in association with cART application, suggesting that HIV-associated thymic dysfunction may be reversible (70, 75).

Because TRECs do not replicate, however, their concentrations within recent thymic emigrants may be diluted with each cycle of cell division. Therefore, in an environment of accelerated cell division, reductions in TREC concentration may indicate a higher rate of cellular proliferation, from the dilution of TREC signal, rather than reductions in de novo T-cell synthesis. These dilutional effects can be avoided by measuring β-chain TCR gene rearrangement products (βTREC), a process that occurs earlier in thymocyte development, during the triple-negative stage of T-cell development ($CD34^+$ $CD1^+$ $CD3^-$ $CD4^-$ $CD8^-$) (76). Intra-thymic proliferation can then be estimated by the ratio of βTREC: sjTREC, and this ratio is not susceptible to these diluting effects on TREC concentration. When measured in this way, impairments of intrathymic proliferation with reduced thymic output have similarly been demonstrated, both in association with HIV disease and with aging, and enhanced thymic output also was demonstrated in HIV disease with cART application (76).

Thymic volume can be estimated by noncontrasted chest CT (77), and larger thymic volumes also have been correlated with higher circulating naïve and total $CD4^+$ cell counts, and with greater $CD4^+$ cell increases in response to cART (78–82). These associations similarly support the importance of thymic contributions to $CD4^+$ cell homeostasis in adults.

Thymic independent pathways of peripheral T-cell expansion in response to cART also have been demonstrated in adults with HIV disease; however, and in other T-cell depleting conditions including bone marrow transplantation, and normal aging (83–86). A better understanding of the extent to which total and naïve $CD4^+$ cell restoration in response to cART is limited by thymic output, and the ability of these thymic independent pathways to compensate for reduced thymic output may be informative in devising strategies to enhance $CD4^+$ cell recovery in HIV disease, and in other T-cell depleting conditions.

Heightened Immune Activation

Heightened immune activation is a cardinal manifestation of HIV disease, and to a lesser extent, is also associated with normal aging. Substantial elevations in the expression of the activation markers HLA-DR, CD38, and Fas (CD95) on $CD4^+$ and $CD8^+$ cells have been consistently demonstrated in HIV disease (61, 87), and elevations in HLA-DR expression on T-cells also has been observed in association with normal aging (60). In HIV disease, markers of immune activation were better correlates of $CD4^+$ cell depletion than were plasma HIV-1 RNA concentrations, and more rapid disease progression was predicted by higher HLA-DR/CD38 expression on $CD8^+$ T-cells in untreated patients, independent of baseline plasma HIV-1 RNA concentrations (88–90). Reductions in T-cell activation in response to cART also correlates with $CD4^+$ cell increases when adjusting for suppression of HIV-1 plasma viremia (91–93). Although heightened T-cell activation may persist despite

several years of antiretroviral therapy, normalization of this activation marker was demonstrated in one cohort after 6 years of cART (64, 94, 95).

Fas is a member of the tumor necrosis factor (TNF) receptor superfamily, and is a major mediator of apoptosis. Fas binding by Fas ligand (FasL) initiates apoptosis by the activation of caspases, which activate cellular proteases and endonucleases that cleave host cell structural and regulatory proteins and nuclear DNA (96). The soluble TNF receptor type II (sTNFR-II) is derived from proteolytic cleavage of the cell-surface receptor, p75TNF-R, and modulates TNF-α activity through competitive binding with this cell-surface receptor (97). T-cells from HIV-1-infected donors and older, healthy donors (65–95 years), exhibit heightened susceptibility to apoptosis in association with increased Fas and FasL expression, and cART reduces apoptosis in association with reductions in Fas expression (62, 98). Soluble TNFR-II was a strong, independent predictor of HIV disease progression in three cohorts of subjects who did not receive cART (99–101). $CD4^+$ cell increases during cART also were associated with polymorphisms in several TNF-related genes, including TNF-α, TNFR-I, TNFR-II, TNF-related apoptosis inducing ligand (TRAIL), and caspase-8, and higher sTNFR-II concentrations were associated with less naive $CD4^+$ cell recovery in a case-controlled study of immunologic nonresponders to cART (102, 103).

These studies support a growing consensus of a major role by heightened immune activation in AIDS pathogenesis. Among the many unanswered questions are included: what are the causes of immune activation in HIV disease, and to what extent does immune activation represent a cause, rather than a consequence of immune damage? (104).

Replicative Senescence

Telomeres are repeating DNA–protein structures located on the ends of chromosomes that shorten (by approximately 50–200 base pairs) with each cell division. In the absence of compensatory mechanisms to lengthen telomeres, by telomerase, cell death ensues when a critical telomeric length is achieved (105). As such, telomeres may serve as a mitotic clock in predicting the replicative capacity of a cell.

Telomere shorting in peripheral blood mononuclear cells (PBMC) of HIV-1-infected persons is accelerated compared with healthy adults (to 100–300 base pairs/year, compared with 30–50 base pairs/year). This shortening is consistently observed within $CD8^+$, but not $CD4^+$ cells; however, and is associated with reductions of CD28 cell-surface expression, the primary costimulatory molecule for naïve T-cells (106–108). Circulating lymphocytes from HIV-1-infected persons, and from healthy older adults have increased frequencies of terminally differentiated, $CD28^-/CD8^+$ cells. Telomere lengths within this terminally differentiated subset were comparable to those of PBMC from centenarians (109). This terminally differentiated subset is also characterized by the cell-surface expression of CD57, and the absence of CD27 expression. In HIV disease, this subset also was inversely correlated with circulating $CD4^+$ cell counts (110). These observations suggest that elevated and

chronic immune activation in the context of HIV-1-infection may drive $CD8^+$ cell differentiation towards a state of replicative senescence and may contribute to an exhaustion of immune capacity.

Age-Associated Immunologic Differences in Response to cART

In ACTG protocol 5,015, older HIV-1-infected subjects had significantly lower naïve $CD4^+$ and $CD8^+$ cells, lower total $CD4^+$ cells, lower frequencies of $CD8^+$ cells that expressed CD28, and higher Fas (CD95) expression on T-cells at baseline (111). They also had lower thymic volumes as estimated by CT, and lower sjTREC concentrations within PBMCs and higher sTNFR-II plasma concentrations compared with their younger counterparts (68). Despite more durable HIV-1 suppression during 192 weeks of follow-up among older subjects, they exhibited lower naïve CD4 cell increase but demonstrated substantial B-cell expansion, to levels that were significantly higher than age-matched, healthy controls (24).

Greater rates of naive $CD4^+$ and $CD8^+$ cell increases were predicted by lower frequencies of $CD8^+$ cells that expressed Fas, in longitudinal, multivariable models; larger thymic volumes and viral suppression to <400 copies of HIV-1 RNA/mL also were associated with greater rates of naïve $CD4^+$ cell increase (112). These observations highlight the complex, detrimental contributions by immune activation to cART- mediated $CD4^+$ cell restoration, and implicate heightened TNF-activity and reduced thymic output as potential mediators of impaired naïve $CD4^+$ cell recovery among older people in response to cART. A better understanding of these contributions may inform more effective strategies to restore immunity, in addition to that which is achieved with antiretroviral therapy alone.

Concluding Remarks

The challenges that are imposed by HIV disease include not only viral eradication but also the reconstitution of a battered immune system. Because of the strong effects of age on HIV disease progression, and the similarities between the immunopathogenesis of HIV disease and that of immunosenscence, a better understanding of aging in the context of HIV disease may provide important insights into both processes. Correlates of age-associated differences in HIV disease outcomes may help to identify underlying mechanisms that are responsible for this effect, and may lead to interventions that enhance thymic output, improve T-cell survival or selectively reduce immune activation, so as to augment the beneficial effects of HIV-1 viral suppression and improve immune restoration. A better understanding of the unique challenges that are associated with the care of older HIV-1-infected persons is essential for optimal care and improved outcomes in this rapidly growing segment of the population.

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Neuropsychology of Healthy Aging

Molly E. Zimmerman and Adam M. Brickman

Introduction

As the population of adults with HIV continues to grow older, clinicians and researchers are becoming increasingly interested in the unique health care needs of older adults with HIV. Cognitive abilities are one aspect of general well-being and health that are compromised in older individuals with HIV. However, it is also well-established that cognitive abilities decline among healthy older adults without HIV or other frank neurological conditions. Therefore, an emerging scientific challenge is the systematic exploration of the synergistic impact of both HIV and age on the cognitive abilities of older adults. To facilitate an understanding of this complex relationship, the cognitive changes that accompany healthy aging have to be characterized, and this is the purpose of this chapter. Subsequent chapters will address specific relationships between advanced age and cognitive impairment in individuals with HIV.

The number of adults over the age of 65 is projected to represent a relatively greater proportion of the general world population in the coming years (1). As the number of older adults continues to increase, so does the critical importance of an expanded characterization of biological and behavioral manifestations of aging. Cognitive (from the Latin *cognoscere*, "to know") processes are a fundamental aspect of the human experience, mediating individuals' understanding of both themselves and their relation to a broader environmental and social context. Accordingly, fear of cognitive decline is a ubiquitous concern among older adults (2). Deterioration of cognitive abilities may have deleterious effects on the psychological well-being of affected individuals and their caregivers (3). In addition, substantial health care costs associated with cognitive dysfunction are likely to increase as the proportion of older adults in the general population rises.

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There is an important distinction between cognitive change due to pathological processes and cognitive change due to normal aging. As an individual grows older, they may experience cognitive decline as a result of a degenerative condition (e.g., Alzheimer's disease, Parkinson's disease), infection with HIV, vascular disease, or other pathological conditions. The degree of cognitive change can range from mild to severe and is likely to have a detrimental effect on activities of daily living. Healthy older adults may also experience cognitive decline, albeit to a lesser degree, that is associated with normal biological aging processes of the brain. The extant literature suggests that advancing age in healthy adults is associated with heterogeneous cognitive decline across a variety of cognitive domains, including memory, language, and higher-order executive processes (4–6). In addition, cognitive abilities are highly variable in healthy older adults, with substantial evidence of both intra- and inter-individual variability in test performance compared with younger adults (5). An enhanced understanding of normal age-related cognitive change provides an important context in which to interpret disease-related cognitive decline.

This chapter seeks to provide a broad overview of the cognitive changes that occur in healthy older adults; that is, older adults that are free of known disease. We will use a neuropsychological assessment framework to summarize recent research findings, focusing on the cognitive domains of attention, executive function, memory, language, visuospatial abilities, and speed/information processing.

Attention

Consideration and manipulation of attention as a cognitive process has long been of interest to researchers and clinicians. The term "attention" broadly refers to complex, multifaceted cognitive processes that serve to orient an individual toward a stimulus (7, 8). Assessment of various forms of attention is an important aspect of the neuropsychological evaluation because attentional processes frequently support performance on many other tests of cognitive function, such as memory and executive function (9). Although not exhaustive, the primary components of attention that will be discussed herein include selective attention, sustained attention, and divided attention.

Selective Attention

One of the more thoroughly explored aspects of attention, selective attention is characterized as the filtering of stimuli in order to process relevant information and ignore or inhibit a response to irrelevant information. A commonly used selective attention paradigm is "visual search," in which an individual is directed to identify the location or presence of a target in a visual display. In general, older adults exhibit poorer performance on selective attention tasks compared with younger adults (10, 11) particularly when executing a demanding task that requires selection of a complex target (10, 12). Researchers have suggested, however, that this age-associated performance decrement may be largely a function of the older adult's

difficulty inhibiting an inappropriate response (13) or to an overloading of attentional capacity demands (14). Importantly, age-related impairments may be attenuated if an older individual is given specific cues to direct their focus (15) or if the individual has previous experience with the target (16, 17). Presentation of easily discernable targets (e.g., using contrasting colors or easily distinguishable forms) has also been shown to facilitate selective attention abilities in older adults (18–20).

Divided Attention

Divided attention refers an individual's ability to allocate resources in order to simultaneously perform two or more tasks. Research paradigms that utilize relatively simple task designs, such as perceptual identification, suggest that older and younger adults demonstrate comparable performance (21). As task complexity increases, however, older adults are more likely to exhibit impairments in performance (22, 23). For instance, McDowd and Craik (22) conducted a study in which younger and older adults were asked to monitor a list of words while simultaneously discriminating between visually presented letter and number characters. Older adults demonstrated marked difficulties performing this dual-task compared with younger adults, providing support for age-related declines in divided attention processing. Hartley and colleagues have also shown that older adults exhibit declines in performance on dual-tasks when both tasks require a manual response (24, 25). Similar to selective attention abilities, however, the amount of practice or previous experience with a stimulus has been shown to facilitate performance in healthy elderly (26, 27). Attentional switching is another type of divided attention in which an individual alternately monitors two or more stimuli. Research provides support for age-associated declines in attentional switching for auditory information but not visual information in older adults (28). Although both younger and older adults demonstrate task switch costs, or task switch declines in efficiency (29), older adults demonstrate relatively poorer efficiency compared with younger adults (29, 30).

Sustained Attention

Sustained attention is conceptualized as an individual's ability to maintain mental performance over time. This aspect of attentional processes is most commonly measured as performance on a vigilance task in which an individual is asked to direct his or her attention to a display in order to identify targets presented at infrequent intervals over an extended period of time (see (31) for a review). In general, researchers have reported that younger and older adults demonstrate comparable rates of decline in performance on vigilance tasks, although age-related deficits have been demonstrated on tasks that require distinctions between targets and nontargets that are not readily discernable (32). These results suggest that the older adult's difficulty with vigilance tasks may be secondary to impairments in other aspects of cognition that are tapped by general task demands, such as target detection (33).

Executive Functions

Executive functioning refers to a set of cognitive processes involved in complex goal-directed behavior, planning, cognitive flexibility, and allocation of attentional resources (34). Although the construct is somewhat heterogeneous, there is some consensus in the neuropsychological literature for its standardized assessment (35). Executive functioning is thought to be mediated by the frontal lobes (36) and frontal-subcortical circuitry (37, 38). Because reports from the neuropsychological, cognitive neuroscience, and neurobiological literatures indicate that there are relatively greater rates of age-associated decline in executive abilities than other cognitive domains, it is often thought of as the cognitive domain most sensitive to normal aging (39, 40), although this view has not gone unchallenged (41, 42). In this section, we briefly discuss the construct of executive function and review recent evidence of changes in executive functioning that accompany normal aging.

Defining Executive Function

As noted previously, the construct of executive functioning captures a number of related cognitive abilities. In neuropsychology, authors sometimes define the concept as performance on a specific test or use the term to mean "frontal lobe functioning" specifically. Lezak (43) discusses executive functioning in general terms, describing it as "those capabilities that enable a person to engage successfully in independent, purposive, self-serving behavior (p. 42)," comprising four components that include goal formation, planning, goal execution, and effective performance. However, a range of other concepts have been assigned to the category of executive functioning (reviewed in (44)), such as cognitive flexibility or concept formation (45); strategy control (46); goal setting (47); planning, impulse control, concept formation, flexibility (48); reasoning (49); problem solving, generation of strategies, sequencing complex behaviors (36); and coordinated organization of behavior (50). Although some of these ideas appear conceptually unrelated, what unifies them is their "executive" nature. That is, much like a business executive, they all view executive functioning as having some "supervisory authority" over more basic cognitive processes.

Executive Functioning and Aging

When considering the role of executive functioning in aging, it is important to establish whether executive functioning represents a unique construct, whether executive functioning mediates age-associated decline in other cognitive domains, and whether there is decline in executive function per se even in the absence of its secondary impact on other cognitive domains. Salthouse and colleagues (e.g., (42, 51))

have conducted among the most elegant work to address these issues. They showed that performance on tasks ostensibly measuring executive functioning showed relatively good convergent validity, but the shared variance among tests of executive function was highly related to other constructs, most notably fluid intelligence (51). This overlap between variance attributed to executive function and variance attributed to fluid intelligence was interpreted as lack of evidence for discriminant validity of the former. In a follow up study (42), two large, independent data sets were used to show that performance on tests hypothesized to reflect executive functioning were highly related to perceptual speed and reasoning abilities. Further, few of the tests of executive functioning were related to age after the association between age and performance on the other cognitive tests was taken into account statistically. The researchers interpreted the findings as evidencing weak support for an independent construct of executive functioning. However, these findings may also be interpreted to suggest that reasoning ability might be a central feature across various tasks of executive functioning.

A number of studies from the neuropsychological literature have supported the idea of pronounced and consistent decline in executive abilities with normal aging. In our own work (52), we used a cluster analysis approach applied to performance across a range of neuropsychological tests to categorize the cognitive profiles of older, neurologically healthy adults compared with younger controls. We identified three groups of older adults: those with selective impairment in executive functioning (defined as performance one standard deviation below the mean of the young control group on a computerized set shifting test), those with deficits in three domains (i.e., attention, executive function, and motor speed), and those with global cognitive deficits across all domains. The findings highlight the heterogeneity in patterns of cognitive aging among healthy adults. More importantly, they demonstrate that executive dysfunction was a characteristic of all three of the cognitive profile groups, suggesting that it is a ubiquitous component of cognitive aging.

Among the most popular measures of executive functioning is the Wisconsin Card Sorting Test (WCST; (53, 54). The test involves sorting cards using rules based on one of three characteristics of the card stimuli (i.e., color, shape, and number), which systematically change throughout the test trial. The number of correct categories and number of perseverative errors are the most common performance measures. A recent meta-analysis showed that, across studies, both measurements decline markedly with age (55).

Tests of executive functioning can also be divided grossly into subdomains, including attentional control, planning, set shifting, and verbal fluency (44). Attentional control includes abilities such as inhibiting irrelevant information and is often evaluated with tests such as the Continuous Performance Test and Stroop Test (56, 57). There are a number of examples of significant age-associated performance decrement on these tests (58–60), even after control of processing speed ((61) reviewed in (44)). The Tower of Hanoi Test (62), in which subjects are required to rearrange different sized and colored rings across three pegs, is commonly used to assess planning ability. Several studies have shown age-associated decreases in performance on this task, which may begin as early as age 60 (63). Age-associated performance differences on the Tower of Hanoi Test are characterized by a greater

number of moves required to reach criteria and increased number of rule violations (64). As noted above, there are consistent findings in the literature of age-related decline in performance on set shifting tasks, as measured by the Trailmaking Test or WCST. Although Salthouse et al. (65) found little evidence for aging effects on performance on a test similar to the Trailmaking Test after accounting for age-associated differences in perceptual speed, others have found that aging effects persist even after control of motor and perceptual speed (66). Tests of verbal fluency may also be considered executive abilities, although they can clearly be considered primary tests of language as well. In typical tasks of fluency, the subject is asked to generate as many words as possible within an allotted time period. In a large, cross-sectional aging analysis, we found that both letter verbal fluency and semantic verbal fluency showed a linear age-associated effect, but the degree of age-associated decline was greater for the latter (67). A recent meta-analysis is consistent with these findings in showing a significant age effect on verbal fluency performance (68).

Though not without controversy, there is evidence in the neuropsychological literature of a relatively pronounced age-associated decline in executive abilities. Age-associated changes in executive function have been linked to concomitant declines in instrumental activities of daily living (69) and linked to age-associated reductions in frontal lobe grey and white matter volume (70, 71).

Memory

Memory refers to the ability to explicitly or implicitly recall information that has been encoded in the recent or distant past. Current conceptualization of this cognitive domain usually divides the construct into hierarchical taxonomic modules based on the type of information that is being retrieved and the duration of the retention interval. For the purpose of the current discussion, we frame our discussion of memory in the structure put forth by Squire and colleagues (72, 73), in which long-term memory is divided into declarative and nondeclarative subcomponents. Declarative, or explicit, long-term memory is the ability to recall facts (semantic memory), events (episodic memory), or perceptual information (perceptual memory). Nondeclarative memory refers to the implicit recall of information and is often divided into procedural, priming, or simple conditioning.

Short-term memory is distinct from long-term memory and refers to the retention of information on a time scale on the order of seconds or minutes. Working memory is a type of short-term memory in which certain mental operations are performed during the retention period. Because working memory involves the manipulation of stored information during short-term memory, it is often included as a type of executive functioning, which is discussed in greater detail earlier in the chapter.

Memory functions are of particular interest in the study of older adults, as most diagnostic schemes for neurodegenerative disorders, such as dementia, incorporate significant memory loss as central to the diagnostic criteria. Cross-sectional and longitudinal studies of healthy aging demonstrate that different subcomponents of memory show a differential vulnerability to the effects of age.

Long-Term Memory

Declarative Memory

Semantic Memory

Despite the common anecdotal report of difficulty recalling the names of objects, names, or other well-learned information among older adults, semantic memory is among the more stable memory systems across the adult lifespan. Semantic memory is often evaluated by asking an individual to define words or provide answers to factual questions, such as on the Vocabulary and Information subtests of the Wechsler Adult Intelligence Scales (74). Longitudinal data from the Canberra Study (75), which followed neurologically healthy adults over age 70, showed performance stability on semantic-based tasks over an 8-year period (5). Other reports have demonstrated a gradual improvement in semantic memory (e.g., word knowledge) in later adulthood (76), suggesting that semantic knowledge accumulates across the lifespan with little or no age-associated decline. Perceived difficulty with semantic memory among older adults may be attributable to a tip-of-the-tongue phenomenon, in which older individuals have the feeling that they know a piece of information, yet have difficulty recalling it explicitly (77, 78). This common experience is discussed in greater detail in the Language section of this chapter.

Episodic Memory

The distinction between episodic and semantic memory was introduced by Tulving in the 1970s (79). Episodic memory is the "what," "where," and "when" of information storage (80) and interacts with semantic memory. The observation that episodic memory declines markedly with normal aging has existed in the literature for decades (81) and has been well-documented. Neuropsychologists typically evaluate episodic memory by asking subjects to learn information explicitly (e.g., a list or story) and recall it after a delay period. This paradigm permits the evaluation of three aspects of episodic memory – encoding, storage, and retrieval – that show differential aging effects. Older adults evidence a more shallow depth of encoding than younger adults. After a delay period, they recall less information than their younger counterparts, but the degree of retrieval differences between younger and older adults is somewhat attenuated when the amount of forgetting (i.e., the amount of information lost during a delay relative to the amount of information encoded) is considered (82, 83). Furthermore, older adults tend to endorse more distracter stimuli, or foils, in during recognition paradigms (84). Salthouse (85) recently proposed three important observations regarding episodic memory decline and aging. First, patterns of age-associated differences in performance on tasks of episodic memory are similar across modalities (e.g., story recall, paired associated learning, etc.). Second, cross-sectional evidence suggests that episodic memory begins to decline as early as age 20 and continues linearly until

about age 60, at which time there is a more precipitous age-associated decline. Third, in well-screened samples of healthy older adults, there does not appear to be increased variability in performance on tasks of episodic memory compared with younger adults, although some investigators have noted increased variability with age (e.g., (86)).

Source memory, a component of episodic memory, refers to the context in which information is learned. Even with successful episodic recall, older adults may have exaggerated difficulty recalling the source from which the information was acquired (87–89). For example, older adults often have the experience of recalling a news item, but have difficulty recalling whether the information was acquired from television, the radio, or newspaper.

Nondeclarative Memory

Nondeclarative memory, sometimes referred to as implicit memory, describes the occurrence of learning and recall outside of conscious awareness. The construct is generally divided into procedural memory and priming. Nondeclarative systems are relatively spared across the adult lifespan.

Procedural Memory

Nondeclarative memory encompasses procedural or skill learning. Procedural memory involves the nonconscious acquisition and retention of motoric sequences. Among the most common examples is the process of learning how to ride a bicycle. A novice cyclist needs to recollect consciously how to maneuver the bicycle, yet with practice, the skill enters procedural memory and control becomes automatic. Very little work has examined age-associated changes in procedural memory. Although there is clearl motoric slowing with age, results of studies examining procedural memory with age have been somewhat equivocal (90, 91). Studies that examine aging experts, such as typists or pianists, report a trend for slowing but maintenance of performance with age (92, 93). Further, while older adults may learn motoric sequences at a slower rate than their younger counterparts, they are able to retain procedural knowledge similarly (94). Problems with studying procedural memory among older adults include the potential confounding effects of motoric speed, other cognitive abilities (e.g., working memory), and distinction between learning and memory.

Priming

Repetition priming is special type of implicit memory that describes the phenomenon of enhanced recall of a stimulus based on prior exposure. For example, a subject would be more likely to complete the word stem “STR___” with “EET” (to form the

word "STREET") than with "ONG" (to form the word "STRONG") if the word "STREET" had been previously exposed. Although priming is not typically evaluated clinically, the topic has a long history of research in the cognitive aging literature. Earlier reports in the 1980s suggested minimal aging effects across a number of priming modalities, including picture naming (95), word identification (96), and word stem completion (reviewed in (97)). More recent investigations have shown small, but statistically reliable, decrements in priming with age (98).

Short-term Memory

In contrast to long-term memory in which information is stored on the order of minutes to years, short-term memory is defined by memory storage in conscious awareness for seconds. Short-term memory is a qualitatively distinct memory system that interacts with long-term memory; for information to enter long-term memory, it must first enter short-term memory. The "modal model" of information transfer (99) remains a popular conceptual framework for short-term memory. Briefly, information from the environment enters primary sensory stores and then a short-term store, which can include rehearsal, coding, or decision. From there, it is either forgotten, leads to some form of behavioral response, or enters long-term storage, which is relatively permanent. When information is drawn from long-term memory, it exists in short-term memory while in conscious awareness. For many years, psychologists believed that the average capacity of short-term memory was seven plus or minus two items or chunks (100). However, more contemporary theorists believe that short-term memory span is closer to four items (101) or dependent on individual differences in processing speed (102).

The term "short-term memory" makes reference to the passive storage of information. There is little evidence for significant change in short-term memory *per se* with normal aging. However, it is difficult to discuss the effects of age on short-term memory without consideration of the process by which information is retained in storage. Working memory is the cognitive manipulation of information that is contained within short-term memory. Indeed, there is ample evidence of significant age-associated decline in working memory abilities (103). In a typical working memory paradigm, a subject is asked to perform mental operations on items held in conscious awareness (i.e., short-term memory), such as reordering numbers or solving simple arithmetic problems while remembering a digit from each problem (104). Efficacy of inhibition (13, 105) and shortened span (104) are two components of working memory that decline most rapidly with normal aging. Age-related decline across working memory task modalities, such as letter rotation, reading span, computation span, and line span, appears to decline with age at a similar magnitude as age-associated decline in episodic memory or speed of processing (76). There is also some evidence that age-related decline in working memory mediates age-associated loss in other cognitive domains (104).

Course

Several studies suggest that normal age-associated memory decline may begin as early as the early- or mid-twenties and decline linearly (106, 107). Longitudinal studies highlight more precipitous decline with memory after about age 60 (108).

Language

Human language processing and production is a rich arena of cognitive study. Our understanding of language function encompasses a wide range of complex abilities that include spontaneous speech, repetition, speech comprehension, naming, reading, and writing (35). The effect of age on each of these functions is heterogeneous, with preserved and even improved abilities in some areas and decrements in other areas as an individual grows older (109, 110). In general, older adults have a more extensive vocabulary range than younger adults, yet they experience more difficulty with the production of words in both spontaneous speech and controlled laboratory settings (111, 112). In this section we will focus on two broad categorizations of language function: expressive and receptive language.

Expressive Language

One of the more common objective research findings and subjective complaints of older adults is the tip-of-the-tongue phenomenon, in which an individual is temporarily unable to orally express a word that they feel they know (113). Typically, lexical retrieval is most difficult for proper names compared to other words (78, 114). This difficulty is ameliorated; however, when older adults are asked to pronounce phonologically similar words (115), particularly words sharing an initial syllable with the target word (116).

Slips of the tongue, or the misproduction of a sound in an intended word or sentence (e.g., saying "bobbin" instead of "robin") are also quite common in elderly adults. Studies have shown that older adults are more likely to omit sounds when required to produce words to a task demand, while younger adults are more likely to substitute different sounds (117).

Older adults are also slower and less accurate when performing confrontational naming of pictures of common and uncommon objects, such as the Boston Naming Test (118). Zec et al. (119) reported data from a longitudinal study of 541 healthy older adults who demonstrated relatively preserved lexical retrieval until the age of 70, at which point only very minor declines in performance were observed. Findings from a more recent cross-sectional study (120), however, indicate more severe naming deficits in a healthy elderly group compared with younger adults.

A similar pattern of findings was reported by Connor et al. (121), with cross-sectional analyses indicating relatively greater performance declines in the naming abilities of older adults than longitudinal analyses. Other researchers (122) have found no differences between object and action naming in older adults, although there was an age-associated decline in overall naming abilities. A study (123) examining both confrontational naming and spontaneous discourse found that older adults exhibited significantly more word-retrieval errors, but had a higher overall naming accuracy than older adults. The authors speculated that this unexpected latter finding may be related to generational familiarity with some of the items.

Finally, healthy older adults frequently demonstrate difficulty expressing complex ideas in written autobiographies (124) and spoken responses (125). Similarly, elderly adults also display relatively increased off-topic verbosity when compared with younger adults, which may be due to an inability to inhibit inappropriate responses (126).

Receptive Language

Consistent findings have emerged that are supportive of the relative preservation of general word, sentence, and discourse knowledge in old age (111, 127). Older adults have a larger vocabulary than younger adults (125) and perform better than younger adults when pronouncing irregularly spelled words (e.g., the National Adult Reading Test; Nelson, 1985) even after controlling for education (128). Some studies have reported that vocabulary may even continue to improve in old age (5, 129). However, longitudinal studies have shown that healthy older adults may begin to exhibit a relative decline in vocabulary comprehension following the age of 90 (130).

Beyond single word knowledge, sentence comprehension declines in healthy older adults, including the ability to characterize details and generate inferences (131, 132). Comprehension of grammatical rules, or syntax, has also been shown to decline with age (133). Compared with younger adults, older adults also exhibit relatively increased difficulty accurately identifying language that is presented at an increased rate of speech (134). Provision of a meaningful context may be a useful comprehension aid for the elderly (135). For instance, older adults' comprehension of "real world" information presented in a television newscast was found to be relatively well-preserved compared with younger adults (136).

It is important to consider the effect of age-related memory declines on receptive language processes, as older adults have been shown to exhibit declines in comprehension measures that rely on working memory processes (125, 133). Also important are the effects of hearing loss on language abilities. Both clinically significant (137) and nonclinically significant (138) age-associated hearing loss has been shown to exert negative effects on auditory processing abilities (see (127) for further discussion). Finally, age-associated inhibitory control difficulties may also have a deleterious effect on language abilities, where irrelevant thoughts and associations intrude on cognitive processes necessary for efficient language function (139, 140).

Visuospatial, Visuoconstructional, and Visuoperceptual Abilities

Visuospatial, visuoconstructional, and visuoperceptual abilities are utilized for the processing, manipulation, or reproduction of visual information. Visuospatial abilities refer to an appreciation of spatial aspects of the visual environment, including localization of points in space, judgment of direction and distance, and topographical orientation (e.g., route descriptions) (141). Visuoconstruction refers to the motoric action of assembling parts to form a unified whole, exemplified by the performance demands on the Block Design subtest from the WAIS-III (142). Visuoperceptual abilities comprise fine visual discriminations, separations of figures from ground, or synthesis of disparate components into a meaningful unit or object (141). Although the general literature on this topic is broad, herein we highlight selective research findings as they relate to the healthy aging process.

Older adults perform more poorly than younger adults across a variety of spatial, constructional, and perceptual information processing tasks (143). Healthy elderly exhibit lower total scores and poorer quality of responses on the visual reproduction subtest of the Wechsler Memory Scale (144–146). Shay and Roth (147) examined cognitive performance in 105 men across the age spectrum and found decrements in an older adult group aged 60–73 on visuospatial and visuoperceptual tasks that included visual reproduction from the WMS (144), the Digit Symbol subtest from the WAIS-R (148), Hooper Visual Organization test (149), and the Rey-Osterrieth Complex Figure Test (150, 151). Within the older adult group, performance differences on these tasks were noted between individuals divided into low and high aerobic fitness groups. This finding suggests that older adults who participate in physically stimulating exercise may demonstrate relatively better visuospatial and visuoperceptual performance than their nonexercising age-matched peers. A large community-based study of 219 healthy older adults aged 75–96 reported age-associated impairments on tests of both visuospatial abilities and spatial orientation (152). In a recent study of spatial abilities, Driscoll et al. (153) reported age-associated declines in performance on a virtual spatial learning task and a mental rotation test. Finally, using a comparative neuropsychology approach in which tasks originally developed to examine cognition in animals are adapted for use in humans, Boutet and associates (154) reported that older adults performed more poorly than younger adults on a spatial discrimination task.

Speed and Information Processing

Speed, accuracy, and motor control are important aspects of task performance under laboratory conditions and in everyday life. It is well known that as an individual grows older, motor behaviors executed in response to a stimulus are disproportionately slowed (155, 156). Performance on a commonly used neuropsychological measure, finger tapping, has been shown to decline with age (157, 158). Age-associated declines in the time taken to complete a letter cancellation task have also been

reported (159). A recent examination of perceptual and cognitive speeded tasks requiring a verbal response revealed age-associated declines in performance (160). In addition, statistical control of generalized slowing has been reported to minimize age-related changes in performance on tasks of other cognitive functions. Both cross-sectional and longitudinal studies have reported that many age group differences observed in cognitive performance may be better accounted for by age-relatedchanges in processing speed and psychomotor speed (161–163). For instance, Pietrzak et al. (164) report an age group difference on a task of spatial learning efficiency that was attenuated when measures of processing speed were considered. Age-related psychomotor slowing in word production speed has also been shown to be an important predictor of performance on a verbal fluency task (165). An enhanced understanding of speeded processing measures provides an important context in which to interpret both healthy age-associated and pathological changes in cognition.

One of the most common indices of speed of information processing is reaction time (RT), a measure of the amount of time utilized to detect a stimulus and execute a response. There are several types of RT, including simple reaction time and choice reaction time, in which an individual is required to select a correct response from several possible responses. Longitudinal studies have shown that simple RT increases with age at a rate of approximately 0.5 ms/year (166). Researchers have also reported that total RT measures are at least 25% longer in older adults compared with younger adults (167–169). Interestingly, an increase in preparation time prior to task performance actually results in an increase in RT differences between younger and older adults, indicating that older adults do not benefit from extended preparation times (167, 170). Older adults asked to perform choice RT tasks are approximately 30–60% slower than younger adults (171, 172). Choice RT rates have been shown to increase at a rate of 1.6 ms/year in longitudinal studies (166). Performance is further impaired in older adults when stimuli become more difficult to discriminate (173) and as the number of choices increases (166, 169). Age differences in choice RT have also been noted for nonverbal information, but not verbal information. These differences are somewhat attenuated when opportunities for practice are provided, but they are not entirely eliminated (174). Importantly, studies have revealed that level of physical fitness may have a beneficial effect on RT in older adults (175).

Conclusions

Clinical and research reports have generated a wealth of information on the cognitive aging process of the healthy older adult. A review of the findings suggests that age-related changes in cognitive processing are heterogeneous, with both declines and preservation evident across cognitive domains. Performance on selective and divided attention tasks generally declines with age, although older adults may benefit from previous experience or practice with attentional stimuli. Executive function abilities, such as problem solving and concept formation, are frequently

compromised as an individual ages, and may be the abilities most sensitive to the biological sequelae of healthy aging. Older adults commonly report decline in memory abilities, particularly in the areas of episodic memory. However, semantic memory abilities are relatively preserved across the lifetime. Older adults also exhibit difficulties with expressive language, such as confrontational naming and the tip-of-the-tongue phenomenon, while receptive language abilities remain generally intact. Spatially-mediated tasks evidence age-associated decline, particularly visuospatial and visuoconstructional tasks. Finally, generalized slowing is a common feature of the cognitive aging process, with declines noted on tasks of motor control and speed of information processing. This brief review of the recent literature on the neuropsychology of healthy aging may be used to better understand the behavioral and cognitive manifestations of cognitive aging in older adults with HIV and other pathological processes.

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Interactions Between Advanced Age and HIV Cognitive Impairment

Victor Valcour and Aaron M. McMurtray

Epidemiology of Aging with HIV

Age-Related Demographic Changes in HIV Infection

Important changes are occurring in the frequency of HIV in older adults, driven in large part by extended survival due to effective antiretroviral treatment (1, 2). With no effective cure in sight, HIV infection has entered the realm of chronic diseases that require long-term management. Moreover, it is often accompanied by a multitude of comorbidities, both medical and psychiatric. This is common in geriatric medicine and typically requires a multidisciplinary approach. Most older HIV patients acquired infection at a younger age and aged with HIV; however, older individuals also acquire infection in their sixth or older decade of life and remain an often hidden population. Not surprisingly, the frequency of becoming infected in older age may also be rising (3). Epidemiological trends indicate greater risk behaviors in this population with insufficient public health emphasis for safer sexual practices (3). New infections occurring in older adults are disproportionately occurring in women and the majority of these older female cases occur in minority populations (4).

It is currently estimated that there are over 114,000 adults over 50 years living with HIV in the United States (Fig. 1) (5–8). In 2005, 15% of new infections occurred in individuals over 50 years of age (6); while in some states, the rate approached 30% (9). While coming into greater attention more recently, these changes were suggested even in the early 1990s, prior to HAART, where the rates for developing AIDS rose twice as fast in persons 50 plus years than it did in persons younger than 50 (22% compared with 9%, respectively) (6, 10). A recent statement by a member of the US Senate Committee on Aging estimated that up to 50% of

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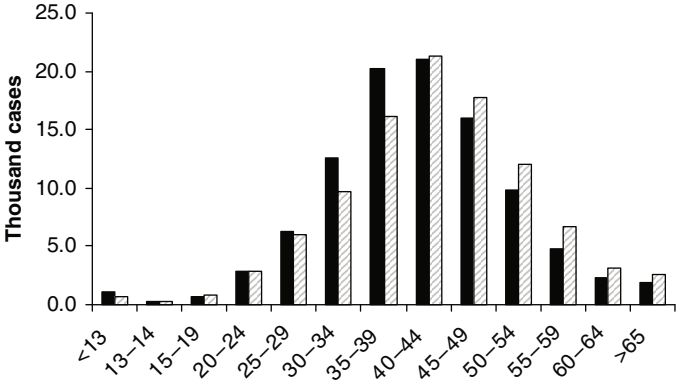

Fig. 1 Changing demographic distribution of prevalent HIV cases as reported to the Centers for Disease Control and Prevention (CDC) between 2001 (*black bars*) and 2005 (*open bars*)

US prevalent HIV cases will be over 50-years old by 2015 (11). There is little doubt that this is a burgeoning population.

Clinical Factors Associated with Aging in HIV Infection

The demographic and clinical features of these older HIV individuals may differ from that of younger populations in a manner that could be expected to impact cognition (Table 1). Older adults tend to have a longer overall duration of infection and possibly a longer duration of exposure to antiretroviral medications (12, 13). In the Hawaii Aging with HIV Cohort (HAHC), patients over 50 years reported 11.8 years of HIV infection, on average, compared with only 7.2 years in their counterparts who were younger than forty (14). Based on this range of duration, many older individuals would be expected to have survived a period of time when HAART was not yet conceived, thus opening up the possibility that survivorship tendencies exist in this population, whereby unrecognized host or viral factors are associated with long-term survival in the absence of effective treatment. Older patients may be more likely to have been exposed to more toxic antiretroviral medications, such as dideoxy-nucleoside reverse transcriptase inhibitors (NRTI), which are currently less commonly used in the developed world, but were very commonly employed in the early HAART era. Limited magnetic resonance spectroscopy (MRS) data suggest that such treatment could impact brain health (15). The extended duration of illness also implies the possibility that many of these individuals were treated with mono or dual therapy, increasing the likelihood of periods of incomplete viral suppression and therefore, possibly increased resistance. Central nervous system compartmentalization of resistance patterns has been described and demonstrated to correlate with neurocognitive deficits (16). Perhaps least studied, but of potential great importance is the role of chronic low-level immune activation that likely

Table 1 Clinical factors potentially associated with HIV at older ages

Longer duration of infection and chronic immune activation
Longer duration of ARV exposure
Greater risk for previous exposure to more toxic ARVs
Greater risk for incomplete viral suppression with past mono or dual therapy, possibly increasing ARV resistance patterns
Delayed diagnosis with greater duration of immunosuppression
Possible survivorship tendencies

occurs in patients with controlled infection that is below the level of detection (17). This might be represented as so called "viral blips" of intermittent plasma HIV RNA detectability, which may be larger with chronic disease (18). Continued infection of the monocyte cellular subset (reservoir) of peripheral mononuclear cells is well described in successfully treated HIV patients with known implications on HIV disease progression (19), monocyte activation (20), and cognition (21). Whether these relationships are due to immune activation is an area of ongoing study.

Individuals who become infected in older life may have unique cognitive risk factors. Several groups have identified delayed diagnosis to occur more commonly in older adults (22–25). This has lead some to speculate that the pre-AIDS phase in older adults may be less symptomatic (24, 26). HIV and other lentiviruses are known to have neurotropic qualities (27) and HIV is known to enter the brain early in infection (28). The cognitive implications of early compared with late initiation of HAART are incompletely studied. However, the delayed diagnosis translates to longer periods of time with untreated HIV, continued HIV viremia and likely with a prolonged period of immunosuppression, which is a known risk factor for HIV dementia (29). A diagnosis of dementia concurrent with first identification of HIV infection occurs more frequently with advanced age (30).

The relationship between age and HIV clinical outcomes including progression, immunological response to HAART, and mortality is the subject of numerous publications. Advancing age was recognized early in the epidemic as a risk factor for more rapid progression of disease (31, 32); a finding that remains present in the era of HAART (33, 34); although argued by some to possibly reflect access to care(2). Most authors also identify a blunted immunological response to HAART in older individuals despite comparable virological responses (35–37) with some discrepant reports (26). Despite increases in complications (38, 39), older patients tend to have greater rates of adherence to medications (40), possibly making up for limitations in HAART response. We refer the reader to these excellent reviews of clinical outcomes in aging HIV patients, a topic that is beyond the scope of this chapter.

Evidence That Age Impacts Cognitive Performance in HIV

Several groups have investigated the effects of aging on development of cognitive dysfunction in HIV, yielded conflicting results possibly associated with methodological challenges. The majority of these studies, but not all, suggest that age detrimentally impacts cognitive performance with advancing age, increasing the risk for clinically

relevant cognitive dysfunction. These findings are more robust for clinical outcomes than they are for neuropsychological findings, where most published studies have been limited in power or methodological approaches. More consistent findings in clinical or epidemiological outcomes compared to neuropsychological outcomes may also reflect the importance of motor and behavioral symptoms in HIV dementia, items captured less well in neuropsychological testing. We will first present the epidemiological data, which relies upon physician reporting of illness, and one report that utilized clinical endpoints diagnosed with structured neuropsychological and neurological evaluations. We will then review available studies of age effect on neuropsychological performance.

Epidemiological and Clinical Diagnostic Outcomes

The introduction of HAART changed the epidemiological and clinical characteristics of cognitive disorders in developed countries (41–43). Data reported from the pre-HAART era provides a glimpse at HIV-specific effects on age-related brain function, since during this period, control of HIV replication was sub-optimal and the confounds of antiretroviral medication effects were generally absent. During this period, several epidemiological studies identified age as a robust risk factor for HIV-associated cognitive disease (30, 44). The AIDS in Europe study, which evaluated the AIDS cases reported between 1979 and 1989, identified a 14% increased risk for AIDS Dementia Complex (ADC) at the time of AIDS diagnosis per 5-year increase in age (44). This was accompanied by a 19% increased risk of developing ADC during follow-up. In the United States, investigators from the Multicenter AIDS Cohort Study (MACS) reported a relative hazard ratio for dementia of 1.60 per decade of life at AIDS onset (29). Using data from 1987 to 1991, Janssen et al. reported an age-related risk for HIV encephalopathy based on US Centers for Disease Control and Prevention (CDC) reports (30). They identified that 19% of reported AIDS cases over 75 years had HIV encephalopathy compared with only 6% among patients between 15- and 34-years old.

This increased risk appears to carry forward in the era of HAART. Age was one of the few risk factors that emerged from the Concentrated Action on Seroconversion to AIDS and Death in Europe (CASCADE) in the era of HAART with a relative risk of 3.24 per 10-year increase (45). Age was also associated with an increased risk for transition from a non-dementia status to dementia in the Northeast AIDS Dementia cohort (46). A similar increase in cognitive diagnoses has been reported using structured clinical assessments in the HAHC. Using a consensus conference and American Academy of Neurology 1991 criteria (12, 47), this work identified that patients over 50 years have greater than twice the risk of meeting HIV-associated dementia (HAD) criteria. At the time of publication, this cohort was comprised of 202 HIV patients living in Hawaii, 96 with ages younger than 40 years and 106 with age $\geq$50. Outcomes were adjusted for education, race, substance dependence, antiretroviral medication status, plasma HIV RNA (viral load), CD4 lymphocyte count, and depression scores (Fig. 2). Although

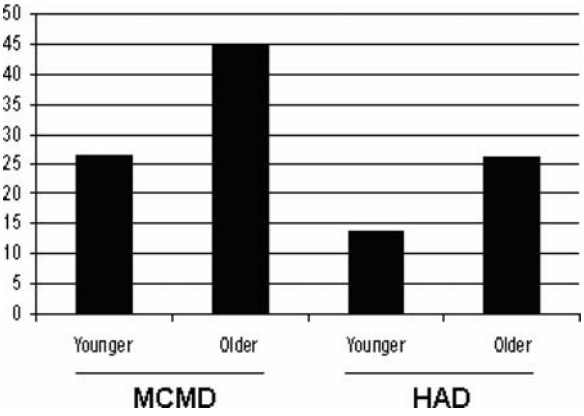

Fig. 2 Cognitive diagnostic outcomes in the Hawaii Aging with HIV Cohort

these data are compelling that age impacts cogniti ve outcomes in HIV, the etiology of the impairment remains less clear. Most cases in this cohort were cate gorized as "possible" rather than "probable" dementia, a qualif ier that indicates the lik elihood that comorbid illness impacted cognitive performance. This finding highlights the heterogeneous etiology of cognitive deficits in HIV.

Neuropsychological Performance Outcomes

Despite a number of reports addressing the ef fect of aging on neuropsychological performance in HIV infection, the relationship remains incompletely understood (Table 2). Both aging and HIV infection are associated with declines in neuropsychological performance, a factor highly suggestive that at least additive effects may be found (re viewed in (48)). Some authors describe domain-specif ic overlap of performance deficits with both age and HIV dif ferentially affecting psychomotor speed and cognitive flexibility (49, 50). However, conflicting findings are noted in other studies, and, if present, the age at which these f indings would translate into clinically relevant outcomes remains to be defined.

In the pre-HAART era, van Gorp et al. reported an e valuation of age effects on cognitive performance in two studies, one using the MACS cohort (study one) and a second using a clinical cohort (study two) (51). The first study compared neuropsychological performance among 1,066 HIV+ and 1,004 HIV− MACS enrollees, of whom only five HIV cases were over the age of 55. They identified age effects; but interestingly, failed to identify HIV or HIV -age interaction ef fects. The second study investigated relationships within a clinical cohort that included 76 HIV+ individuals, 29 of whom were o ver the age of 55. Both age and HIV ef fects were noted on most measures with interaction ef fects limited to the groo ved pegboard test, a test of psychomotor speed and manual de xterity. They did not report the

Table 2 Selected reports of neuropsychological outcomes associated with aging in HIV infection

Author and reference	Patient population	Outcome measure	Major findings	Limitations
Becker et al., AIDS (53)	22 HIV+ age 50+ vs. 100 age<50	Dementia and cognitive impairment not dementia (CIND) defined by neuropsychological measures	22% of older compared with 9% of younger patients with "dementia" at baseline; 14% of older compared with 22% of younger with CIND; 1-year incidence of dementia at 7% older vs. 4% younger	Limited age matching to controls; NP abnormality requirements for mild impairment were mild (0 to −1 SD abnormality); 40% classified as "dementia" denied symptoms
Cherner et al. AIDS (13)	67 HIV+ age 50+ vs. 52 < 35 years	Cognitive impairment rating scales based on neuropsychological performance	Trends for age-associated differences were noted on most ability domains. Age–CSF HIV RNA interaction effects identified	Preliminary report, unclear if sample size was adequate
Hardy et al. (49)	257 HIV+ b/w 1989 and 1995. Divided into 2 groups (older/younger) at the median of 36 years	Neuropsychological testing battery	Age effects were seen on most neurocognitive measures in HIV+ patients	No seronegative control group to determine HIV × age effects
Kissel et al. (59)	66 HIV− (10 over 45 years old) compared with 188 HIV+ (25 over 45 years)	Neuropsychological testing battery	Both age and HIV effects noted on summary deficit score; interaction effects not identified	Limited HIV− individuals over 45 years of age
Van Gorp 1994	*Study 1*: 1,066 HIV+ (<1% over 55-years old) and 1,004 HIV−; *Study* 2: 76 HIV+ (age 29–55, 41 of whom had symptomatic HIV disease) and 47 age-matched HIV− controls	Neuropsychological testing battery	*Study 1*: age (but not serostatus) was associated with poorer performance on most tests; age × serostatus effects not detected. *Study 2*: age × serostatus interaction effects seen only in grooved pegboard test on nondominant hand	Patients in study one were relatively young (5 greater than 55-years old)
Wilkie et al. (50)	Younger groups (age 19–39): HIV− (n = 30), HIV+ (n = 56); Older groups (age 50+): HIV− (n = 29), HIV+ (n = 36)	Neuropsychological testing scores	Age × HIV effects were not identified	Preliminary report, not clear if sufficient power existed

presence or absence of neuropathy symptoms, an aspect of the clinical examination that may have impacted performance on this test and is known to be more frequent with aging (52).

Several important points can be drawn from these two studies that may provide insight into the challenges of studying age effects in HIV and that may have influenced other studies attempting to identify HIV-aging interaction effects. The MACS reports an educational cohort effect whereby older enrollees have higher educational attainment. This has been confirmed in other studies (12, 49). Since lower educational attainment is an independent risk for cognitive impairment in HIV (53, 54) and other neurodegenerative disorders (55), such a finding will impair our ability to identify age-specific HIV effects in cohorts with insufficient sample sizes to properly adjust for this covariate. Educational attainment, age, and depression scores were included as covariates in both the MACS and HAHC reports. In addition, the second study revealed a greater representation of individuals with advanced disease (AIDS) when compared with the MACS study. Advanced HIV disease is a well-accepted risk factor for cognitive impairment (29) and likely represents a sub-population most vulnerable to the effects of age. It is not surprising that interaction effects are more readily identifiable in this population, and less identified in other studies largely composed of asymptomatic subjects. Interaction effects between age and advanced disease (AIDS) are noted in other studies (49). Neuropsychological performance in asymptomatic HIV patients is a past topic of great controversy and is beyond the scope of this chapter; but is likely associated only with modest group effects, requiring large sample sizes and detailed batteries to confidently identify (48). Thus, population-based studies of predominantly asymptomatic or minimally symptomatic patients may be less likely to identify relationships with age.

This study also highlights a potential methodological challenge in the interpretation of neuropsychological data in HIV. As described by Wilkie et al. (50) and recommended in a National Institutes of Mental Health workgroup (56), comparison of group mean scores may not be sensitive in identifying HIV effects, since it is suspected that only a proportion of these individuals will ultimately develop cognitive dysfunction and relevant findings may be obscured due to inclusion of individuals with less overall risk. Even in the pre-HAART era, when HIV infection was largely untreated, only a portion of individuals developed clinically important cognitive dysfunction, suggesting that host or viral factors are critical (29). These authors recommended approaches that utilize cut-points to evaluate proportions of individuals in each group who may be exhibiting neuropsychological compromise, rather than comparing group means. Should age impact cognitive performance, one would expect to identify a higher proportion of individuals meeting impairment criteria in older ages. Other studies have employed this technique resulting in more suggestive associations.

For example, a recent study conducted by Cherner et al. evaluated patients from the HIV Neurobehavioral Research Center (HNRC) using the recommended cut-point approach to identify rates of impaired performance by age group. They compared 67 HIV individuals over 50-years old with 52 individuals aged 35 or less. The younger group was chosen to best match the demographics of the older group; but reported shorter HIV duration (8 years compared with 12 years). Over half of both older and

younger patients were categorized as having stage C disease. They identified a tendency for greater impairment in older subjects compared with younger subjects in most ability domains. Statistically significant differences were not identified, perhaps owing to the relatively small sample size and limited power in what the authors define as a preliminary report.

Importantly, these investigators identified an interaction between age and CSF HIV RNA levels whereby older individuals with detectable CSF HIV RNA had twice the rate of impairment than did their older counterparts who had undetectable CSF HIV RNA. In contrast, they detected no relationship to detectability of CSF HIV RNA among younger individuals. The authors speculate that CSF virus in younger individuals may be more representative of "transient" seeding (transfer across the blood–brain barrier); whereas, in older patients it may represent more permanent autonomous virus (derived from independent replication in the nervous system), which could be considered to be more deleterious. An alternative interpretation is that older individuals exhibit a greater degree of CNS vulnerability and cannot withstand higher levels of CNS HIV viremia. This vulnerability factor may be suggested by their finding that 76% of older patients not receiving HAART compared with 57% of older patients on HAART met impairment criteria while the rates in younger patients were unchanged by HAART status (54% vs. 52%); although, this interaction did not meet statistical significance.

Similarly, data from the HAHC identified an age-associated cognitive vulnerability associated with having at least one apolipoprotein epsilon 4 allele. In this population, the presence of an epsilon E4 allele did not appear to impact cognitive outcomes in younger adults; however, a significant risk was identified in older adults (57). Arendt et al. identified age-associated changes in cognitive information processing in HIV using cognitive event-related potentials, similarly identifying age-associated vulnerability in HIV (58).

Other groups have attempted to identify age-associated differences on neuropsychological performance in HIV with mixed results. Becker et al. reported rates of neuropsychological testing abnormalities among older compared with younger participants in the Allegheny County Neuropsychological Survey, which included 290 HIV+ and 114 seronegative individuals. They identified 37% of older ($n = 22$, >50 years) compared with 31% of younger individuals (<50-years old) tested in an impaired range, with most of the older patients having greater degrees of impairment (23% defined as "dementia" compared with 9% in the younger group). In this work, a dementia designation was based on neuropsychological performance rather than clinical diagnostic characterization. Consequently, they report that 40% of such subjects were clinically asymptomatic. Other methodological challenges were identified, including use of normative data that were not well-matched for age and the potential to rate individuals as impaired with only minimal standard deviation abnormality on individual tests.

Hardy et al. identified differences by age in performance among HIV patients; however, they were unable to evaluate HIV-age interaction as they did not have a comparative seronegative group (49). They identified age-effects on most neuropsychological tests. Kessel et al. compared the performance of 25 individuals over 45 years with 155 HIV individuals who were less than 35 years. They identified HIV effects

and age effects but failed to identify age-HIV interaction effects (59). Their sample included only 6 HIV– individuals over 45 years. Goodkin et al. identified higher rates of minor cognitive motor disorder (MCMD) symptom reporting among older patients (41). This finding should be interpreted with caution given that symptom reporting is often more reflective of affective state rather than objective cognitive functioning (51, 60, 61), although, this report carefully adjusted for such factors in the analyses.

The age at which individuals are considered "old" varies in these studies and does not appear to be based on clear physiological criteria. Previously, it was suggested that 50 years was appropriate. This age represented an approximately 2 standard deviation cut-point from the mean for age of HIV patients in the mid 1990s (62); however, this distinction has very little pathological or physiological significance and has likely been altered with the changing demographics of HIV/AIDS in developed countries. Early epidemiological data hinted at an age threshold effect, whereby risk increased to a greater degree above 65 years (30) (reviewed in (51)). This cut-point needs to be considered cautiously as this study relied on physician reporting of diagnoses, a factor that may be influenced by the patient's age. In many studies, the chosen age cut-point appears to be based on practical issues of sample availability. There are no reported studies in HIV with sufficient enrollees to consider the neuropsychological interaction effect in populations over 60. Another approach is to consider age as a continuous variable in regression analyses, but this approach risks obscuring thresholds where brain vulnerability may sharply increase.

We conclude that the interaction effects between age and cognitive function are most robust for epidemiological studies and clinical diagnostic studies. The effects identified in neuropsychological performance are less clear owing to methodological limitations in available studies. The likelihood that age impacts cognitive performance in HIV is supported by the recognition that CSF HIV RNA levels, apolipoprotein E4 status, and cognitive information processing by cognitive event-related potentials may have an age-associated impact in HIV and the recognition that such an age effect is common in other dementias such as Alzheimer's (63) (reviewed in (51)). Proper longitudinal evaluations with adequate samples of older age subsets are needed.

Age-Specific Risk Factors for Cognitive Impairment in HIV

To our knowledge, no other group besides the HAHC has evaluated age-specific risk factors of cognitive impairment in HIV. This evaluation is not only limited by the small number of aging cohorts with cognitive characterization, but also by the changing characteristics of cognitive diseases in the era of HAART, resulting in a need to re-analyze the applicability of most pre-HAART risk factors in all age groups (42, 64). One might anticipate that duration of infection would impact either frequency or severity of impairment; however, self-reported duration of infection has not emerged as an important risk factor in the HAHC (12). In both young and old patients, nadir CD4 lymphocyte count appears to be an important predictor of neurological and cognitive outcomes in HIV (52, 65, 66). This factor may be more

applicable to older patients who would be expected to have had a greater risk of low CD4 counts prior to initiation of ARV therapy due to longer duration of illness or delayed diagnosis. Metabolic dysfunction in the HAHC, including diabetes (67) and insulin resistance (68), as well as apolipoprotein epsilon 4 status (57) appear to have increased applicability to middle aged and older adults. This topic is discussed further in a later portion of this chapter. Due to the lack of data in this field, neuropathogenic models are necessarily speculative.

Age-Related Comorbidities That May Influence Cognition in HIV Infection

A Model for the Role of Comorbidity in HIV Cognitive Outcomes – Brain Reserve

As presented above, epidemiological and neurocognitive clinical outcome studies suggest the possible role of aging in augmenting the risk for cognitive outcomes in HIV; although it is not clear that the etiology of the increased risk is directly attributable to HIV itself. A finding that diabetes and insulin resistance contribute to cognitive impairment in older patients suggest a need to consider heterogeneous etiologies that include ARV side effects (short and long-term), chronic inflammation, and concurrent neurodegeneration.

The concept of brain reserve is a useful model to compile these factors (Fig 3.). This construct has been considered in the context of other dementias (69, 70) and suggests that the symptoms of dementia will be more prominent and/or present earlier in individuals with a decreased reserve of brain function. In other dementias, postulated reasons for a decreased reserve include factors such as low education, head trauma, developmental factors, and genetic factors (70–73). Among patients with HIV infection, we must consider the possibility of concurrent neuropathology relating to age-associated neurodegenerative processes including Alzheimer's disease and cerebrovascular disease (resulting from hypertension, diabetes, hypercholesterolemia, or cardiac disease). Immunological factors and the long-term effects of ARV therapy may contribute as well. The effects of these factors may be counter-balanced, at least partially, by increased adherence rates with older age (40). Although mild cognitive impairment is known to negatively impact adherence and may minimize the impact in this older population (74). It is possible that complicated interaction effects exist among comorbid illness, chronic antiretroviral treatment and age-related brain changes, such as cerebrovascular disease (75)

Vascular Complications

Cerebrovascular disease either alone or in combination with other neurodegenerative disorders is a common cause of cognitive impairment in the general population

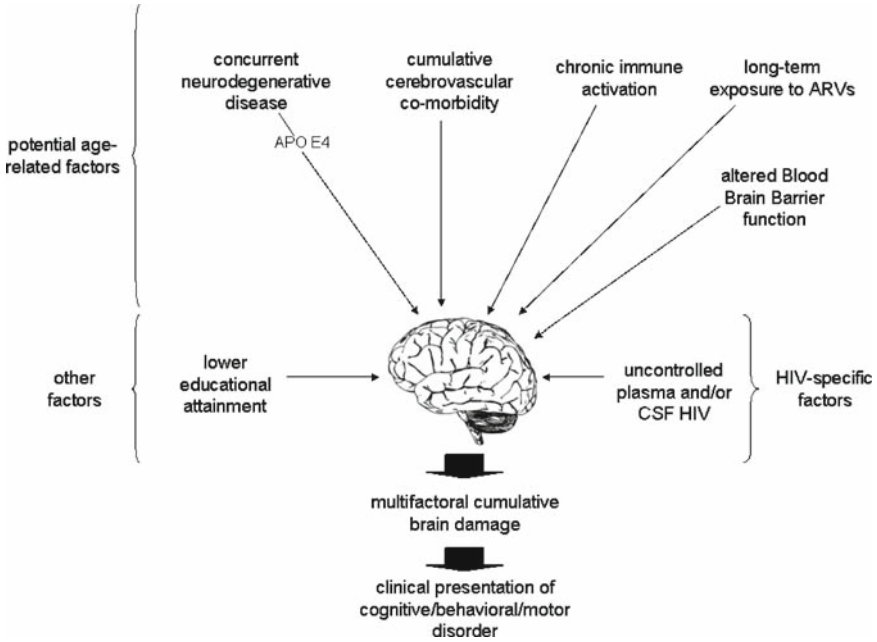

Fig. 3 A model for the multifactoral etiology of cognitive/behavioral/motor disorders in older adults

(76). The types of cerebrovascular damage that can cause or contribute to cognitive impairment vary greatly and include large cortical strokes, small lacunar infarcts in strategic locations, small vessel vascular disease, and hemorrhage. Although not all patients with such lesions develop dementia, several studies report a high frequency of cognitive impairment among patients admitted for stroke, with up to 32% developing impairment sufficient to meet clinical diagnostic criteria for dementia (77, 78). Since stroke is relatively common among older individuals, with a lifetime risk for ischemic stroke alone approaching 20% (79), the potential contribution of vascular damage to cognitive dysfunction in aging HIV patients can not be o verlooked.

In HIV, cerebrovascular disease can be caused by both HIV and non-HIV related factors (75). Specific to HIV, reports suggest a potential relationship to HIV-related cardiac disease (80), arterial thromboembolism of cardiac source (81), hematological disorders affecting clotting ability such as antiphospholipid antibody syndrome or protein S deficiency (82), and v asculitis secondary to opportunistic infections or substance abuse. Treatment with certain antiretroviral medications are also associated with changes in blood lipid levels that may contribute to arterial clot or plaque formation, such as decreased HDL cholesterol, increased LDL cholesterol, and ele vated triglycerides (41, 83–86). Protease inhibitors have been particularly linked to increased risk of myocardial infarction (87) and may be related to v asomotor CO_2 reactivity by transcranial Doppler, particularly among patients who develop lipoatrophy (88). The presence of chronic inflammation and activated monocytes, even at low levels, may be expected to contribute to accelerated atherosclerosis as well (89).

Risk factors for cerebrovascular disease that are not directly related to HIV infection will likely play an increasing role in HIV patients as they age, since many of the risks increase with age. Such factors include hypertension, diabetes mellitus, cardiac disease, and dyslipidemia. Smoking is a robust risk for cerebrovascular disease and may be of particular interest for older HIV patients where this behavior is more frequent, reported to be as high as 54% among individuals living with HIV in San Francisco and 55% and among 881 HIV-seropositive veterans in the Veterans Aging Cohort Three-Site Study (VACS 3) (90, 91). In a study of 3,221 HIV+ men and women enrolled in the Terry Beirn Community Programs for Clinical Research on AIDS, current smokers were more likely than individuals who never smoked to develop AIDS dementia complex after adjustment for CD4 count, prior disease progression, and use of antiretroviral therapy (92). These findings suggest that cerebrovascular disease prevention and control will be important for the cognitive health of aging HIV patients.

To date, there is very little published work on small vessel cerebrovascular injury in HIV. The large D:A:D (data collection on adverse events of anti-HIV drugs) study identified an increased risk of cardio- and cerebrovascular events in HIV associated with antiretroviral medication use (93). Described in the literature infrequently (94), lacunar strokes do not appear to be a major component of MRI abnormalities seen in HIV infected patients. Series that have described an increase relationship are often confounded by opportunistic infections or illicit drug use and are commonly compiled from younger populations, where traditional risk factors may have less barring (95–99). Patients with HIV infection are reported to have an increased rate of cerebral infarction at autopsy compared with the general population, with the prevalence ranging from 4 to 29% (99, 100). In these series, vasculitis does not appear to be a major determinant. The relationship with hypercoagulable states remains controversial, but does not appear to be a major determinant (82, 101, 102). Although classically associated with dementia in younger HIV patients and thought to possibly represent gliosis, the periventricular white-matter changes identified in older HIV patients may be more closely related to cerebrovascular risk factors than to HIV parameters in the era of HAART (103). This circumstantial evidence may suggest that considering a cerebrovascular ischemic etiology may be of increasing importance when interpreting such MRI data in older HIV adults. These findings support increased concern for cerebrovascular contributions to cognitive impairment in older HIV patients (104).

Neurodegenerative Disorders

It is theorized that HIV infection may synergistically or additively impact neurodegenerative disorders, possibly altering disease characteristics such as age of presentation, rate of cognitive decline and mortality. To date, this topic has not been thoroughly investigated or defined; although, some groups have started to investigate the relationship between classic Alzheimer's disease (AD) risk factors and cognition in

HIV patients, including apolipoprotein epsilon 4 genotype, the presence of brain amyloid, and AD-like plaque formation.

Apolipoprotein E is an essential element in the metabolism and transport of serum lipids and is involved in cholesterol metabolism within the brain where it is produced primarily by astrocytes (105). Polymorphisms in the gene that encodes for Apo E are associated with a number of detrimental neurological processes including increased amyloid beta deposition in cerebral vessels [cerebral amyloid angiopathy (CAA)] (106), both the accelerated loss of synaptic connections and the development of plaques in Alzheimer's disease (AD) (107), and poor outcome following head trauma (108). Carrying an E4 allele nearly doubles the lifetime risk of AD (109). Although independent of classic cerebrovascular risk factors such as hypertension and hyperglycemia (110, 111), the risk associated with Apo E4 may be partially mediated through vascular mechanism (112).

Among patients infected with HIV, there are mixed reports regarding the influence of having an apolipoprotein E4 isoform and neurological disease. In one series, dementia was twice as prevalent among E4 carriers and was further associated with neuropathy (113); while in another study, no statistically significant relationship was identified (114). Data from the HAHC suggest the role of APO E4 may be more important in older HIV patients compared with younger HIV patients (57). In this cohort, older patients were 50 or more years, and the vast majority of dementia cases were recognized to have had potential contributions from non-HIV factors, including the possibility of concurrent neurodegenerative disease or vascular complications; although no patients had overt AD. It is nevertheless possible that such confounding underlies this finding.

Both intracellular and extracellular amyloid is a common finding in the brains of HIV infected patients, particularly in the frontal cortex, and may be more frequent among patients with an apolipoprotein epsilon 4 allele (115). In the era prior to HAART, argyrophilic amyloid plaques were identified in AIDS patients with an age-related increased frequency (116). In the era of HAART, the pattern of CSF amyloid and tau levels in HIV dementia patients is similar to that described in AD; although a clear age-association has not been described (117).

There is a limited but growing cadre or reports exploring the biochemical basis for an interaction between HIV infection and neurodegenerative disorder such as AD. Increased expression of beta-amyloid precursor protein (β-APP), a protein implicated in the early cascade leading to amyloid plaques in humans with AD, has been described in the brains of asymptomatic HIV patients (118) and may be related to the presence of inflammatory mediators, such as interleukin-1 (119) .The presence of gp41 correlates to the degree of β-APP staining in the corpus callosum of HIV patients (120). Furthermore, inflammatory markers, such as tumor necrosis factor (TNF)-α and interferon-γ increase the degradation of APP to amyloid beta by stimulating gamma secretase-related cleavage (121). More recently, the HIV protein tat has been associated with inhibition of the amyloid beta degradation enzyme, neprolysin (122). These findings provide a theoretical framework for an increased amyloid burden in HIV patients. Knowledge that insulin degredation enzyme (IDE) may modulate intracellular amyloid processing (123) has lead to speculation that aging

and prolonged HAART may be accompanied by even larger risks for amyloid deposition in such patients (115).

From a clinical perspective, the investigation of interaction effects between HIV dementia and non-HIV neurodegeneration may present substantial challenges (53). Accepted definitions for probable Alzheimer's disease, exclude individuals where another medical condition that could potentially account for the cognitive symptoms is present (124). Similarly, consensus diagnostic criteria for HIV cognitive disorders exclude patients from a diagnosis of clinically probable HIV-associated dementia when another condition exists that may cause cognitive decline (47). The paucity of substantial markers for either disorder further complicate the dilemma(42). The more general descriptions suggested in a revised consensus report for HIV cognitive disorders in the era of HAART may provide greater flexibility (125); however, prospective observational trials that include excellent neuropsychological and neurological characterization, the best available biomarkers, and, critically, neuropathological correlation, will be needed to fully address these important questions.

Physiological Changes in the Aging Brain That May Impact HIV Cognitive Disorders

There is a robust relationship between failure of the immune system and the development of clinically significant cognitive disorders among individuals without access to HAART and likely among those failing HAART (29, 45). It is therefore reasonable to consider age-related changes in immune function to potentiallyimpact cognition in older patients. Older age is associated with more rapid immunologic decline and poorer survival (32, 126). Advanced age is associated with a lower magnitude of rise of naïve CD4 cells specifically (127), possibly due to thymic involution with age and failure of thymic productivity (128). Many aspects of HIV-related immune dysfunction mirror that of aging, including a shift from a naïve to a memory T-cell phenotype, reduction in T-cell proliferative ability (associated with reduced telomere length and increase in CD8 cell population that are CD28-), and decreased production of IL-2 and IL-2 receptors (129–132). The expansion of CD8+ CD28− cells that have been described in typical aging (133) may be considered to augment the pathogenic tendencies of HIV in older adults. Enhanced IFN-γ and TNF-α production by the CD8+ CD28− subset has been described in both HIV+ individuals and aged blood donors (134). An age-associated increased expression of other proinflammatory cytokines in the brain, including IL-1a, IL-6 has been described (135, 136).By virtue of their inflammatory roles, such cytokines may play an important role in cognition among aged HIV patients.

A second potential immunological mechanism relates to the increase in activated monocytes/macrophages (CD14+/CD69+) seen in the context of HIV dementia and Alzheimer disease (137, 138). Activation of peripheral monocytes may enhance transmigration of these cells into the brain consequently allowing the initiation of

inflammatory processes leading to HAD (139, 140). It is possible that common shared inflammatory pathways of both HIV infection and aging may synergistically effect cognitive function in older HIV-seropositive adults (141). Age related changes in brain glial cells may impact brain vulnerability in older adults. Glial cells are critical to brain neuroplasticity (142). Based on human and rodent models, aging is associated with detrimental effects of brain repair processes, such as attenuated neurotrophic responses (143), weakened astrocytic responses (144), and a reduced capacity for neuronal sprouting (143).

HIV infection is associated with both structural and functional changes in brain microvascular endothelial cells causing alterations of the blood–brain barrier, which may contribute to cognitive dysfunction. Structural changes observed in HIV infection includes: increased diameter of cortical vessels, disruption of tight junctions, apoptosis of brain microvascular endothelial cells, thinning of the basal lamina, and loss of membrane glycoproteins (145–147). Disruption of tight junction proteins, such as occludin and zona occludens-1, is thought to be the most important and characteristic feature of blood–brain barrier disruption in HIV infection(148). Chemokines secreted by infected CD4+ T-lymphocytes and monocytes, such as monocyte chemotactic protein-1 (MCP-1), contribute to upregulation of adhesion molecules, chemotaxis, which result in increased transmigration of infected and non-infected monocytes, lymphocytes, and granulocytes (149–153). The aging brain may be more vulnerable to blood–brain barrier disruption through the effects of the inflammatory response and HIV infection (154, 155). The increased microglial production of proinflammatory cytokines (135, 136, 156)contribute to blood–brain barrier dysfunction and, potentially, to increased transmigration of infected microglial cells into the CNS (140).

Successful Cognitive Aging in HIV

The over-arching aim for successful cognitive aging in patients living with HIV is to minimize the frequency and severity of CNS complications and to maximize the quality and duration of life. Successful strategies are not currently tested in this population and must be largely drawn from our knowledge of risk reduction for other cognitive disorders and our knowledge of high quality HIV care. Some broad recommendations can be made.

The basic principles of excellent HIV care may be the most important recommendation. Adherence to medications is of highest priority as immune suppression is known to increase the risk for dementia. At present, there are no strong data to recommend specific antiretroviral regimens in a population basis. However, the importance of CNS penetrating ARV regimens is an active area of research and new recommendations may be forthcoming. Among individuals who exhibit cognitive decline on HAART, this issue is clearer and recommendations are currently published (64). In the cognitively impaired population, extant data suggest that higher penetrating regimens are likely associated with improved outcomes (157–159). It is premature to consider that older individuals are at sufficient increased risk to

support use of more penetrating regimens as first line therapy; however, this is an area of research that might be particularly valuable. Early diagnosis of HIV is mandatory and among older individuals likely represents an area where there is room for improvement.

Given the emerging evidence that cerebrovascular risk factors are more prevalent in aging HIV patients and, in preliminary studies, may impact cognition, this is another area where vigilance may be valuable. HIV infection, itself, by virtue of its inflammatory characteristics, may increase cardiovascular and cerebrovascular risk. Therefore, it may be reasonable to consider HIV infections as a cardiovascular risk equivalent when choosing lipid goals for treatment (160). Regular evaluations for diabetes with timely initiation of appropriate interventions are recommended. Physical exercise and maintenance of proper weight not only assists in minimizing cerebrovascular risk factors, such as diabetes, hyperlipidemia and hypertension, but may also have a direct positive impact on cognition (161). Smoking cessation should be strongly encouraged as should absence from illicit drug use. Finally, close attention should be paid to proper psychiatric care including careful observation for depression to allow early intervention. These strategies provide hope that healthy aging can be realized, regardless of HIV status.

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