Paul Shapshak · Andrew J. Levine
Brian T. Foley · Charurut Somboonwit
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John T. Sinnott *Editors*

Global Virology II – HIV and NeuroAIDS

Springer

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Editors
Paul Shapshak
Department of Internal Medicine,
Division of Infectious Diseases and
International Health
University of South Florida
Tampa, FL, USA

Brian T. Foley
Theoretical Division
Los Alamos National Laboratory
Los Alamos, NM, USA

Elyse Singer
Department of Neurology
UCLA David Geffen School of Medicine
Los Angeles, CA, USA

John T. Sinnott
Department of Internal Medicine,
Division of Infectious Diseases and
International Health
University of South Florida,
Morsani College of Medicine
Tampa, FL, USA

Andrew J. Levine
Department of Neurology
UCLA David Geffen School of Medicine
Los Angeles, CA, USA

Charurut Somboonwit
Department of Internal Medicine,
Division of Infectious Diseases and
International Health
University of South Florida,
Morsani College of Medicine
Tampa, FL, USA

Francesco Chiappelli
Department of Oral Biology and Medicine
UCLA School of Dentistry
Los Angeles, CA, USA

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Preface

The spread of HIV-1 and associated NeuroAIDS commenced in earnest during the last few decades of the twentieth century, and although better characterized by the start of the twenty-first century, the spread of HIV continues in the current decade. The characteristics of NeuroAIDS and treatments have come within reach of practitioners, clinics, research, and development. Presentations in this book include HIV global view, global views in NeuroAIDS, descriptions of NeuroAIDS in several countries, CNS HIV entry, neuropathology, peripheral nervous system illness, genetics, neuroimmunology, perinatal NeuroAIDS, neurocognition in children, human and drug trafficking, drug abuse, oral manifestations, socioepidemiology, HAND and HAART, chemotherapy, genetics and epigenetics, gene expression, multiscale oscillatory biology, new tools and data mining, DNA sequence and database errors, amyloidogenic pattern prediction, miRNAs, neuronal apoptotic pathways, humanized mouse models, psychiatric comorbidities, cardiovascular disease, HCV, Chagas disease, TB, opportunistic infections, Zika virus, Ebola virus, biostatistics, HIV and SIV evolution, and vaccines.

The presentations in this book are a fraction of all that is being done. In addition, there are many books that review many topics during prior years of which a few are mentioned [1–9].

With all this progress, why produce a book such as this? The progress needs to be summarized and described for the global audience: the "cures" for HIV and NeuroAIDS. Moreover, worldwide, with the plethora of various strains of HIV, the work that has been done serves as a paradigm for the continued quest against HIV disease spread and pathogenesis.

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Acknowledgements

This book, for professionals, students, faculty, and interested readers, brings to bear snapshots of where we are with HIV and NeuroAIDS. Clearly, it took many years of work and debate among physicians, scientists, researchers, and other practitioners, including clinicians, interventionists, virologists, immunologists, and epidemiologists—from molecular levels of analysis to patients and clinics—for progress to occur and thus allow us to comprehend and attack the scope of infection, spread, and damage caused by a 9000 nucleotide-base microorganism, a small virus.

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Tampa, FL, USA	Paul Shapshak
Los Angeles, CA, USA	Andrew J. Levine
Los Alamos, NM, USA	Brian T. Foley
Tampa, FL, USA	Charurut Somboonwit
Los Alamos, CA, USA	Elyse Singer
Los Angeles, CA, USA	Francesco Chiappelli
Tampa, FL, USA	John T. Sinnott

Contents

Chapter 1
Multidisciplinary Approach to HIV/AIDS: Historical Perspective

Clyde B. McCoy, A. Jeanene Bengoa, Duane C. McBride, Brian T. Foley, Shikha Puri, Alejandro J. Mendez, and Paul Shapshak

Keywords HIV/AIDS • Epidemiology • Risk activity • Sex • Drug abuse • IDU • NIDA • Transmission • Multidisciplinary • Historical perspective

Core Message

The HIV/AIDS epidemic has persisted over the past three decades due to its adaptability, deleterious effect on the immune system, and various modes of transmission. A multi- and interdisciplinary collaborative approach is one of, if not the best, method in combating the HIV/AIDS epidemic. Specific demographics and high-risk groups dominate this epidemic and are a driving force. Therefore, collaborative approaches must continue to evolve to reduce and prevent the spread of HIV/AIDS. Although the HIV/AIDS epidemic has shown signs of improvement, trends continue in the United States, highlighting the overall global impact of this virus.

Clyde B. McCoy and A. Jeanene Bengoa contributed equally to this work.

C.B. McCoy (✉) • A. Jeanene Bengoa • D.C. McBride • S. Puri • A.J. Mendez
Department of Public Health Sciences, University of Miami Miller School of Medicine, 1120 NW 14 Street, CRB 1507, Miami, FL 33136, USA
e-mail: cmccoy@miami.edu

B.T. Foley
Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM, USA

P. Shapshak
Division of Infectious Disease and International Health, Department of Internal Medicine, Tampa General Hospital, University of South Florida, Morsani College of Medicine, Tampa, FL 33606, USA

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1.1 Introduction

The Body Snatchers, a science fiction novel written in 1954 by Jack Finney set the precedence in portraying the mindset surrounding a plague. Throughout the years, the original novel evolved into subsequent literary works and cinematic movies. In 1994, *Body Snatchers*, a film that starred Meg Tilly and Gabrielle Anwar strangely but accurately portrayed the HIV/AIDS epidemic through a unique perception. The graphic display of individuals who were "normal" and had not yet been subject to the alien seed "pods" clearly depicts the experience of the population throughout the HIV/AIDS epidemic. Those who had not been exposed to those alien "pods" would peer intently at one another, attempting to decipher if they had become alien and fatal. *Body Snatchers* mirrored the feelings and unfortunate fear experienced by those in the forefront of the HIV/AIDS epidemic.

The forefront of the HIV/AIDS epidemic in the Americas was seen in the manifestations of diseases in unusual populations and with no clear explanations of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia (PCP) in the populations that were being seen in major cities such as New York, Los Angeles, and Miami. It is hard to imagine how quickly this epidemic spreads, and it is even more difficult to understand what would have happened if not for global scientific efforts that quickly launched research on these populations using multiple strategies. Among institutes commending such works were the Centers for Disease Control (CDC) and the National Institutes of Health (NIH). The NIH included the National Institute on Drug Abuse (NIDA), which had only become an institute in 1974. NIDA quickly established several research centers that happened to be in the very cities where these populations were being studied clinically. Miami received one of these first centers beginning in 1974 [1].

Furthermore, beginning in 1974 in Miami, there was an additional funded NIH institute center, the Comprehensive Cancer Center. At the advent of the study of this epidemic, there were multidisciplinary and interdisciplinary research teams, including some of this chapter's authors, who worked at both NIH-sponsored centers.

It is unfathomable to imagine the rate at which the HIV/AIDS epidemic would have spread if it were not for the creation of research organization such as NIDA under the umbrella of NIH in 1974 [1]. The first part of the twentieth century saw little to no drug abuse research until the 1960s and 1970s, when the drug epidemic ran rampant [1]. The abuse of drugs provided the need and platform to develop strategies, establish metrics, and institutionalize drug abuse research and prevention to promote multidisciplinary collaboration both domestically and abroad.

The multidisciplinary and interdisciplinary foci that developed throughout the institutionalization of drug abuse research assisted in implementing research priorities within both clinical and research settings [1]. Through this approach, disciplines such as demography, psychiatry, neurology, pediatrics, psychology, sociology, immunology, viral epidemiology, molecular biology, anthropology, ethnography, biostatistics, and public health provided the basis for providing the highest quality of research regarding HIV/AIDS among drug abusers. In addition, development and testing the efficacy of interventions to reduce high-risk behaviors included field

studies regarding drug abuse paraphernalia, efficacy of bleach in eliminating HIV and HCV from needles, as well as many other pertinent vectors of this epidemic [4–8]. This evolutionary process provided the means for extensive community outreach and the acquisition of funding that would allow for crucial information regarding the pathways of transmission, acquisition, and proliferation that manifest within the individual and society [1].

NIDA and other similar agencies at the local, state, and national level through funded infrastructure provided the sustainable foundation for research to progress structure and collaborative support. Unbeknownst to researchers globally, developing NIDA and other scientific oversight would allow for research to develop an understanding of this "strange and pernicious disease" [4, 9]. Although this virus was not studied until the 1980s, the foundation to reduce the impact of the HIV/AIDS epidemic began a decade earlier.

1.1.1 The Initial Years of Fears

Retrospectively, HIV infected humans in the 1920s in the Kinshasa region of what became the Democratic Republic of the Congo and Zaire. In the 1950s and 1960s, the virus embarked on its path as a global pandemic [2, 3]. Once reaching the United States, the HIV/AIDS epidemic forever changed the landscape of the United States. Attempting to understand this inexplicable disease and phenomenon created a sense of fear and apprehension. This virus was first presented to the University of Miami School of Medicine Grand Rounds in 1981, which puzzled physicians as to the cause and effect as well as the potential outcomes and risks associated therewith.

The first reported case in Florida involved a young Caucasian man of Northern European descent who was diagnosed with Kaposi's sarcoma. The physician reporting this case noted how unusual and unique the symptoms were as Kaposi's sarcoma was not known to exist in the age group of the patient or among those of Northern European descent. A second unusual case was also introduced. This time, the young man had been diagnosed with PCP – a disease that, according to the attending physician, usually occurred among the very old who were living in a nursing home. These cases puzzled the group in attendance at the University of Miami School of Medicine Grand Rounds in 1981, and many questions arose from these two cases at hand such as where the patients lived, where they had been, what acute or chronic diseases they had, and with whom they interacted [4]. It was further reported that there was little in the patients' background information that indicated any major acute or chronic diseases that would suggest they would be susceptible to these illnesses.

In the search for the explanation of "this strange and pernicious disease," the University of Miami research centers, departments, and schools had attracted and organized a very effective, multidisciplinary, and interdisciplinary group [1]. This allowed for a very synergistic approach to determining what the origins, consequences, and interventions should be for this "new thing" that initially went by several nomenclatures, such as [1] Gay-related immune deficiency (GRID) and [2] Gay disease. Further, the virus causing AIDS was given various names such as lymphade-

nopathy-associated virus and HTLV-III and even the 4H club which led to increased stigmatization and unnecessary stereotyping [4, 9]. Soon after, AIDS was used to describe this new syndrome that moderately caused a defect in cell-mediated immunity within individuals that had no other known diminished resistance to opportunistic infections such as organ transplant or inherited immune deficiency [10].

The misconception and misinterpretation of the HIV/AIDS epidemic was one of the main reasons for such a rapid increase in the proliferation of this disease. Immediately after this virus surfaced, immunologists were confident that HIV/AIDS could be managed through a simple vaccine and eventually as treatable as other chronic diseases such as asthma and diabetes [4]. Unknown to these scientists was that the AIDS virus was not capable to be overcome by a vaccine that would attempt to trick the immune system into producing effective antibodies [4].

1.1.1.1 AIDS Cases 1981–1991

Misdirection and a lack of scientific understanding led to the rapid increase in the prevalence of HIV/AIDS not only among individuals in the United States, but globally. The exponential rise of HIV/AIDS cases during the first decade of this epidemic shows that although agencies such as NIDA were available to combat drug abuse, the specificity and means by which HIV progresses and becomes AIDS were a mystery to all researchers and healthcare practitioners. Four cases of AIDS were documented in 1981, and by 1991, there were over 261,159; 23,162 and 7488 cases in the United States, Florida, and Miami-Dade County (MDC), respectively [11].

The surveillance systems that had been established in MDC prior to the rise of the HIV/AIDS epidemic enabled vital data to be collected regarding this virus from the first documented cases. Beginning with four AIDS cases that were presented at the University of Miami Medical Grand Rounds in 1981, there was an exponential increase in the number of HIV/AIDS cases in the following decades [12]. By 1991, nearly 7500 cases were identified in Miami, Florida, which more than tripled to 25,000 in the next decade [7]. The cumulative incidence of AIDS in MDC during 1981–1991 was 85 per 100,000 individuals, the highest rate reached in any decade (see Fig. 1.1) [7].

The first decade (1981–1991) of the HIV/AIDS epidemic in MDC, with 7488 AIDS cases, resulted in ranking only behind the much larger Los Angeles and San Francisco metropolitan areas [12]. Further, MDC was ranked second among US metropolitan areas, with 706 cases attributed to heterosexual contact, third in cumulative AIDS cases among women, and second in the cumulative AIDS cases among pediatric cases [12] (Table 1.1).

The rankings and impact of the HIV/AIDS epidemic within MDC were driven by specific demographics and risk groups which were unknown during the advent of this disease [7]. Men had a higher cumulative incidence when compared to women, and when observed by race/ethnicity, Black/African American had the highest cumulative incidence followed by White/Caucasian and the Hispanics [7]. Although understanding the demographics was essential to understanding and

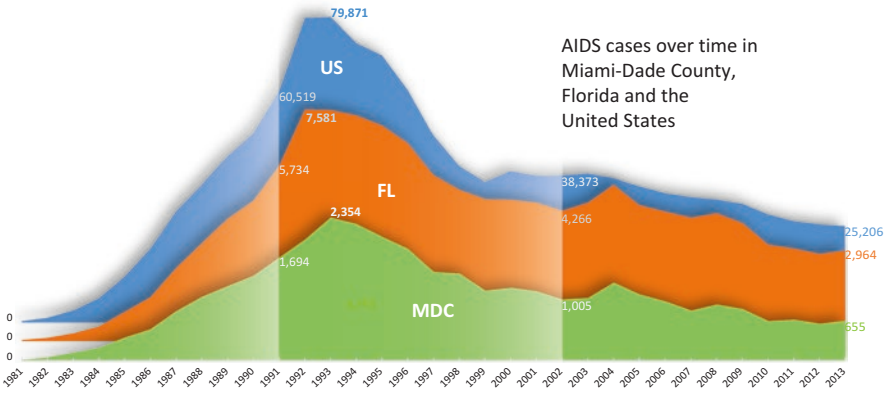

Fig. 1.1 Miami-Dade County vs. State of Florida vs. United States of America. This chart represents the number of AIDS cases per year from 1981 to 2013 [14, 33]

Table 1.1 Cumulative AIDS cases by year for United States, Florida, and Miami-Dade County [14, 33]

		Year		
		1991	2002	2013
Geography	United States	261,159(23)	866,590(16)	1,214,305(10)
	FL	23,162(43)	87,666 (26)	130,099(15)
	MDC	7,488(85)	25,347(43)	34,903(25)

developing methodologies to combat this epidemic, gaining valuable data regarding specific risk groups served as a major contributor in preventing the uncontrollable spread of HIV/AIDS, especially before serological testing for asymptomatic infection became available.

However, the category that accounted for the largest risk group was male-to-male sexual contact (MSM), which represented 45% of the cases irrespective of race/ethnicity [7]. Injecting drug users (IDU) were the next highest group at 23%, followed by heterosexual contact at 20%, unrelated/other causes at 6%, MSM/homosexual/bisexual/IDU at 4%, and blood transfusions at 2% [7]. Once the race/ethnicity was incorporated into the major risk groups, the percentage of high-risk practices differed. Like the overall trend, Hispanics primarily contracted AIDS through MSM at 70% followed by IDU at 10%, while Black/African Americans contracted AIDS predominantly through heterosexual contact and IDU at 37% [7]. Southern Florida was particularly influenced by its proximity to Haiti and thus its influx of Haitian immigrants. It is now well understood that the HIV-1 subtype B epidemic was simmering in Haiti for at least a decade before spreading to the United States and Europe [13].

MDC is an indicator, reflecting the total number of AIDS cases and the impact that HIV/AIDS had in the state of Florida. Although MDC has been one of the major epicenters for the HIV/AIDS epidemic, Florida has experienced its own

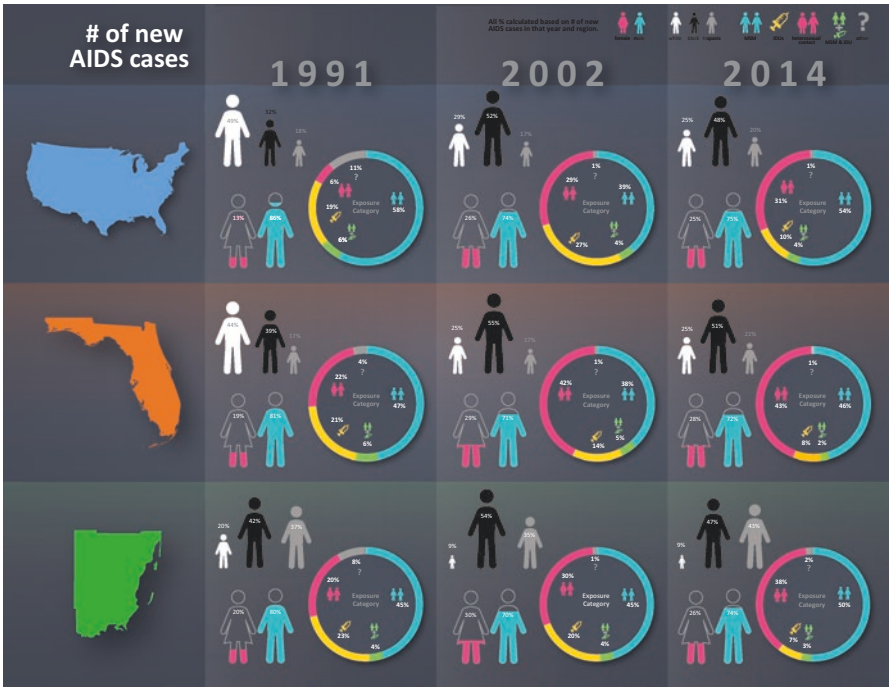

Fig. 1.2 Demographic breakdown of AIDS cases by decade and location [14, 33]

unique challenges distinct from MDC. Like the impact of this epidemic on MDC, individuals who were not white, male, and/or gay had a false sense of security that this virus could not affect them [14]. This misconception, coupled with the initial lack of scientific information, provided the mode for this virus to proliferate among risk groups that were thought to be safe from this epidemic.

The state of Florida saw a consistent increase in the total number of AIDS cases from 0.1 per 100,000 people in 1981 to 43 per 100,000 in 1991 [14]. Like MDC, men dwarfed women in the total number of AIDS cases (see Figs. 1.1 and 1.2) [14]. Further, the greatest number of AIDS cases occurred within White/Caucasian, followed by Hispanics and African Americans [14]. Also, MSM and IDUs served as the largest cluster among all high-risk groups [14]. The proliferation of this virus in MDC and Florida and the widespread increased incidence of AIDS signaled Florida as a major epicenter in the HIV/AIDS epidemic within the United States.

The impact and fear because of the HIV/AIDS epidemic was daunting nationwide. The total number of AIDS cases reported during the first decade showed the proliferation of this virus throughout the United States [15]. The trends experienced within MDC and Florida were also seen in the United States regarding gender. Men accounted for 86% of the total number of AIDS cases when compared to women, which was slightly a larger gap when compared to both MDC and Florida. Further, White/Caucasian individuals accounted for 49% of the total AIDS cases from 1981 to 1991 followed by Black/African Americans with 32% and Hispanics with 18%

[15]. The greatest impact of this epidemic within the United States was among MSM (58%), followed by IDUs (19%) and heterosexual contact (6%) [15].

1.1.1.2 Interventions and Progressive Movements 1981–1991

Social structures within the United States were not necessarily supportive of practices that could help combat an emerging epidemic. Indeed, increased urbanization reduced social structures that constrained sexual behavior [7, 5]. During this initial period of this epidemic, prostitution and venereal diseases increased alongside the abuse of hypodermic needles which became more widespread [1]. Further, changes in sexual mores in the 1960s reduced barriers within the heterosexual population, as also the Gay Liberation Movement in the 1970s presented new and unexpected losses of barriers and an increased severity of this new epidemic [9]. In addition, civic and legal policies produced severe limitations of the availability of clean legally acquired hypodermic needle/syringes, enhancing the conditions for acquiring and transmitting HIV/AIDS among IDUs [4, 5, 16, 17].

Prior to 1981, surveillance tools and agencies such as the Florida Department of Health had been established both within MDC and Florida, which allowed for the prompt documentation of the first AIDS cases. The first AIDS surveillance began within the Florida Department of Health and Rehabilitative Services, and the Centers for Disease Control and Prevention (CDC) declared AIDS a reportable disease in 1983, resulting in a lapse in the reporting of crucial information in the initial years [11]. The delay in recording AIDS as a reportable disease missed the opportunity in documenting the initial cases of IDU, heterosexual contact, transfusions, and infants [11]. In 1983, the HIV/AIDS epidemic was declared a "public health emergency" by the Florida State Health Officer which enforced the responsibility of physicians to report diagnosed cases, which actively began in 1984, mostly in South Florida [11].

In 1984, HIV was determined to cause AIDS with a major impact on the way hospitals, clinics, public health practitioners, and various other healthcare entities in Florida approached this epidemic. This fundamental knowledge directed active surveillance within Florida, and especially in South Florida, which was one of the epicenters for this epidemic [11]. The progression of programs and initiatives continued, and in 1985, the Food and Drug Administration (FDA) approved the first HIV antibody test, and national screening of blood commenced [11]. Further, 26 anonymous HIV counseling and testing sites were established with a statewide toll-free AIDS hotline [11].

After implementing these programs, Jackson Memorial Regional Medical Center, serving as a public hospital and the medical center for the University of Miami, was the primary hospital to deliver comprehensive care to HIV/AIDS patients [11]. Because 75% of all AIDS cases in Florida, health education, and risk reduction programs were established in Miami-Dade, Broward, Monroe, and Palm Beach counties [11]. Statewide public information programs were established to provide vital information and education regarding the HIV/AIDS epidemic to all households in Florida [4]. Six years after the first cases of this epidemic, the first antiretroviral drug, Retrovir, was developed to assist in combating this disease [12].

The expansion of the initial programs and availability of antiretroviral therapy used in AIDS treatment and prevention, coupled with the required notifications to partners of individuals with HIV/AIDS, began the movement in working to contain the impact of this virus.

As the late 1980s approached, new laws, interventions, and programs surfaced and were implemented statewide. In 1987, the World Health Organization (WHO) launched the Global Program on AIDS [11]. The Joint United Nations Program on HIV/Acquired Immune Deficiency Syndrome (UNAIDS) was developed and resulted in more impactful initiatives such as the Multi-Country AIDS Program (MAP) launched by the World Bank, which gave rise to most nations worldwide agreeing to global goals to reverse the spread of HIV [18]. As a result, 700 individuals were enrolled to receive antiretroviral therapy in 1988, which saw one of the first prominent movements in preventing the excessive spread of this virus [11]. In 1989, Project AIDS Care was established by Medicaid, and the FDA approved the use of antiretroviral therapy in mothers, which provided a new mode of preventing the transmission of HIV/AIDS to infants [18]. Although an overall improvement in treatment options occurred just before the start of the 1990s, the 1990s also brought the epidemic of "crack" cocaine in South Florida which led to a substantial increase in the risk factor for AIDS and other related sexually transmitted infections, such as needle-sharing and prostitution in exchange for drugs [19–21].

The Ryan White Comprehensive AIDS Resource Emergency Act was passed in 1990 by the US Congress; this Act provided essential services to those infected with HIV who lacked health coverage. This resulted in Florida obtaining seven million dollars to provide care and support to those living with HIV/AIDS [12]. Also, the second antiretroviral drug was approved by the FDA, and soon after, a combination antiretroviral drug was created that would provide a mechanism that would further assist in preventing the uncontrollable spread of HIV/AIDS. The introduction of Videx in 1991 further enhanced the ability to reduce the impact of the HIV/AIDS epidemic nationwide [12].

The AIDS epidemic provided the platform for many initiatives to be developed prior to all the factors associated with HIV/AIDS. For example, the CDC established the National AIDS Information Line (1983), National AIDS Clearinghouse (1987), institution of the nationwide America Responds to AIDS public information campaign (1987), and distributed *Understanding AIDS* (1988), which was the first mailed information regarding a major public health problem delivered to every residential mailing address in the United States [20]. Throughout the advent of these successful programs, the identification of HIV as a root cause of AIDS created the platform to develop serological tests that could detect HIV in the blood [20, 21].

1.1.1.3 Molecular Epidemiology

Beginning with the first infectious molecular clone of HIV-1 to be sequenced in 1985, many more clones from the United States, Europe, and Africa were also sequenced soon, and it became obvious that HIV was a diverse and rapidly evolving

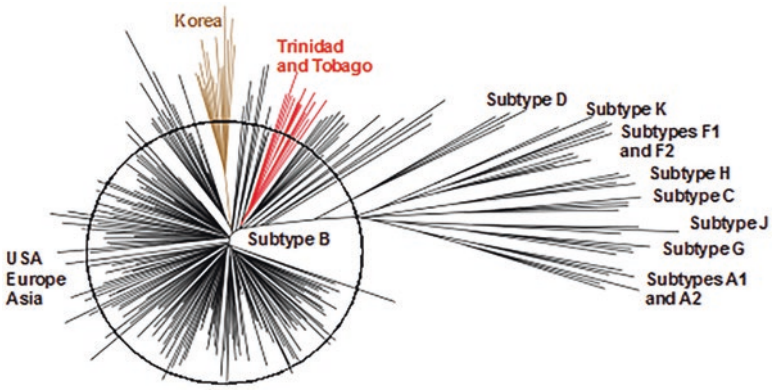

Fig. 1.3 Maximum likelihood phylogenetic tree constructed from HIV-1 subtype B [23]

virus [20, 22]. The rapid rate of evolution of HIV coupled with the knowledge that the virus spreads by direct intimate contact with an infected person allowed the development of a new field now known as molecular epidemiology. Many studies showed that analyzing the virus gene sequences could provide an accurate reconstruction of the spread of HIV within a local group or transmission cluster, and that the same methods can be applied to larger data sets and the study of larger portions of the pandemic [23]. One of the first widely publicized transmission cases solved in part by molecular methods is known as "the Florida dentist case," in which one dentist evidently infected six patients [24].

Misreporting and the resulting lack of public understanding of HIV and AIDS in general, especially during the early years of the pandemic, have resulted in some misreporting and confusion. Although the Florida dentist case was a doctor-to-patient spread of HIV, it was equally clear that this case was very highly unusual, and that dentists and other doctors could continue to work with reduced risk to their patients, assuming appropriate medical precautions.

Although HIV-1 subtype B was present in Haiti before it arrived in the United States and Europe, neither Haiti nor individuals from Haiti are to blame for the US epidemic. Figure 1.3 is a maximum likelihood phylogenetic tree constructed using HIV-1 subtype B complete envelope gene sequences sampled before 1999. Although there are some local subepidemics detectable in such a data set, for the most part the United States and European sequences are intermingled with each other.

Although it is possible to use molecular epidemiology to study HIV transmission patterns in geographical regions such as Florida, the process is fraught with many problems. One of the main problems is detecting and sampling recently infected individuals if the purpose is to study the current trends rather than infections that may have taken place a decade or more prior. Another problem is patient confidentiality and privacy, and the possibility of doing more harm than good by discouraging people from seeking diagnosis and treatment if they fear invasion of privacy or being identified as an IDU.

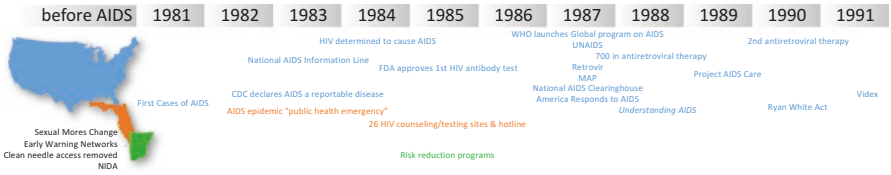

Fig. 1.4 First 10 years of AIDS timeline for key moments [11]

1.1.2 AIDS Cases 1992–2001

The second decade (1992–2001) of the HIV/AIDS epidemic not only saw an increase in the total number of AIDS cases but also new programs, interventions, and initiatives while obtaining crucial knowledge to combat this disease. Although different programs and laws were enacted during this epidemic, comprehensive approaches were not established effectively for targeting and serving the highest risk groups to stem the peaking of the epidemic. This misstep led to an increase in the total number of AIDS cases in the United States, Florida, and Miami-Dade County to more than 260,000; 23,000; and 7500, with new cases peaking: new 80,000; 7500; and 2500 [11, 14].

The total number of AIDS cases within Miami-Dade County continued to rise at an exponential pace throughout the time from 1982 to 1994, with a leveling off in the number of new AIDS cases diagnosed each year in the 1994–2001 time period, mainly due to the development of highly active antiretroviral therapy cocktails. Although Miami, Florida, only accounted for less than 1% of the US population in the early 1990s, it contributed over 3% of all AIDS cases [25]. Miami-Dade County continued to serve as one of the major epicenters during the 1992–2001 time period. AIDS and its impact were ever so present among South Florida and its respective risk groups (see Figs. 1.2 and 1.4). The cumulative HIV incidence of men was 1,703 and for women, 445 per 100,000 [25]. These rates rose exponentially for the first ten years after 1981. Further, African Americans accounted for the largest cumulative incidence of AIDS in MDC at a rate of 2,647 per 100,000, followed by Hispanics at 696 per 1000,000 and White/Caucasian at 657 per 100,000 now had a larger incidence of AIDS when compared to White/Caucasian [25].

As more data was acquired and a better understanding of the epidemic emerged, an understanding of the major risk factors among the demographics in South Florida became more evident. As seen during the first decade, MSM accounted for the largest percentage of AIDS accumulative cases [25]. Further, IDUs followed with the next highest percentage of cases attributed to these high-risk practices at 23% (3,745/19,864) followed by heterosexual risk at 20% [25].

The largest increase in the number of AIDS cases in Miami-Dade County occurred from 1993 to 1996, with the total AIDS cases averaging more than 2000 new cases peaking at 2354 [26]. Following this substantial increase of AIDS cases, a reduction in the total number of new cases began in 1997. From then on, the number of AIDS cases continued to decrease yearly and fell to 1,136 total cases in 2001

[26]. It took nearly two decades to observe a prominent decrease in the number of AIDS cases in the late 1990s, and this was primarily due to effective antiretroviral therapies making HIV treatable, rather than a large reduction in new infections.

Yet, even with the reduction in the total number of AIDS cases that occurred during the latter part of the 1990s, MDC still ranked in the top ten of nearly every AIDS statistic. MDC ranked second in per-capita MSM AIDS cases, seventh among IDU, and fourth in total per-capita AIDS cases among adults/adolescents [25]. As stated above, MDC accounted for <1% of the US metropolitan population yet ranked excessively high among the nation and major metropolitan areas regarding the HIV/AIDS epidemic.

The impact of MDC on Florida exemplified the influence a region can have on its respective state. The number of AIDS cases in Florida rose each year *vis-a-vis* MDC rates of 36.7 per 100,000, 55.1 per 100,000, and 63.7 per 100,000 in 1992, 1993, and 1994, respectively [14]. Males continued to dwarf women in the total number of AIDS cases from 1992 to 2001. For example, in 1994, men had a cumulative incidence of 101.3 per 100,000, whereas women only had an incidence of 28.3 per 100,000. These rates increased during the first half of the 1990s and then saw a prominent reduction in the total number of AIDS between men and women (Fig. 1.4). The epidemics as reviewed by the number of new AIDS cases each year peaked in the early 1990s for the United States, Florida, and MDC. There was a sharp and continuous decline, except for a smaller peak in early 2000s, especially for Florida and MDC (Fig. 1.4).

1.1.2.1 Interventions and Progressive Movements 1992–2001

There were major improvements in both prevention and treatment during the first decade of this epidemic. The evolution of prevention programs continued to progress to combat this epidemic. Further, it was through all these programs and the acquisition of information and knowledge that helped assist in the development of a combination antiretroviral therapy in 1992, and protease inhibitors in 1997, which led to a substantial decrease in AIDS-related deaths while improving the quality of life with those infected with this virus [12]. Preventive strategies continued to be developed, and the fight against this disease had immense momentum as seen by the CDC Serostatus Approach to Fighting the HIV Epidemic (SAFE), providing a framework for improving the health of persons living with HIV and preventing transmission to others [26]. Additional initiatives continued to advance the treatment and prevention of the HIV/AIDS virus [4, 5, 16] (Fig. 1.5).

Finally, in 1993, the CDC recognized and expanded its AIDS case definition to include a CD4 count of <200, and having diseases such as tuberculosis (TB), cervical carcinoma, and bacterial pneumonia if HIV were present [11]. This change in definition resulted in a great increase in reported cases in MDC, Florida, and the United States [11]. The OraSure saliva HIV test was approved by the FDA and supplemented the existing blood tests that provided crucial information regarding the epidemic [11]. The Comprehensive Drug Research Center (CDRC) took a lead

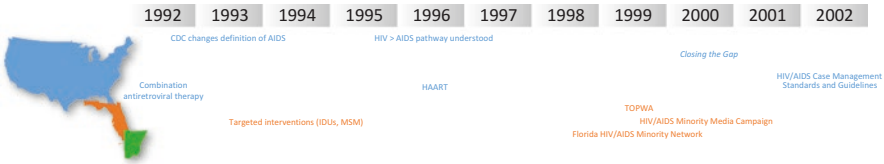

Fig. 1.5 Timeline of the second decade of AIDS [11]

in testing this new tool in our outreach programs. The success of surveillance tools coupled with an extensive classification of this virus provided vital epidemiological profiles that assisted in developing community and specific high-risk group prevention initiatives [11].

Continued acquisition of comprehensive epidemiological profiles nearly 15 years after the first AIDS cases provided the ability to create unique and specific interventions. Combating the impact of IDU within this epidemic was vital as this high-risk group continued to expose themselves to lifestyles that enhanced their probability of acquiring and transmitting AIDS [19–21]. Prevention protocols were then developed regarding the cleansing of needles shared and used by IDUs with bleach in MDC [17, 21].

It was through programs such as these that helped decontaminate needles in an effective and efficient manner. Exemplifying the effectiveness of such programs was highlighted by a study conducted by the CDRC and Health Services Research Center (HSRC) in which needle/syringes from shooting galleries around the Miami, Florida, area were collected and tested without and with cleaning by bleach treatment [4–6, 18, 19]. The study indicated that use of household bleach and proper cleaning techniques by laboratory studies proved that bleach-treated needle/syringes tested negative for HIV whereas those that were not cleaned by bleach tested positive [4–6, 18, 19].

It was innovative and continually developing interventions such as needle/syringe-cleansing programs that promoted cleaning of paraphernalia with bleach and sustained the momentum positively impacting this epidemic. In addition, ancillary paraphernalia were tested for the presence of HIV that included cottons, cookers, and wash-waters used at shooting galleries, which were shown to contain the presence of HIV [17]. In addition, laboratory results indicated that bleach should be utilized for 30 s, which was added to the intervention protocol [6, 7]. Programs and preventive services such as the bleach cleaning of used needle/syringes demonstrated the utility and effectiveness of science-based interventions.

In 1996, the FDA approved a new regiment of antiretroviral therapy that ushered in the era of highly active antiretroviral therapy (HAART) [11]. The implementation of HAART coupled with innovative programs and initiatives resulted in the first major decrease in the prevalence of AIDS nationwide. Continual efforts promoted development of new therapeutic options including Nelfinavir (Viracept), Delavirdine (Rescriptor), Saquinavir (Fortovase), and Zidovudine (AZT), which provided powerful pharmaceutical and clinical options for combating HIV/AIDS [11].

It was also during this time that the HIV/AIDS pathways were established and explained in a detailed and scientific manner, which allowed for a more precise understanding of the epidemiology and pathogenesis of HIV/AIDS [27, 28–31]. The HIV/AIDS pathways were distinctive; understanding their complexity allowed for a more comprehensive epidemiological profile to be developed of all demographics and high-risk groups. This crucial scientific data further promoted the development of new programs such as Florida's Targeted Outreach for Pregnant Women Act (TOPWA) program (1999), Florida HIV/AIDS Minority Network (1999), and "Closing the Gap" (2000). Additionally, media campaigns were developed to promote and increase awareness of HIV/AIDS throughout the county, state, and national level [5].

A significant shift in the HIV/AIDS epidemic occurred post-1990s. Prevention became more prominent than treatment, which had driven the approach for the first 20 years of this epidemic. HIV/AIDS information, protocols, and interventions were then translated in multiple languages, while increasing the networks and programs for all individuals exposed to this epidemic. Challenges continued to arise and cause barriers within the county, state, and national level, but there was an increasing scientific platform to overcome obstacles. The wealth of scientific information of the HIV facilitates current and future policies and programs.

1.1.3 AIDS Cases 2002–2013 (Figs. 1.1, 1.2, and 1.4)

The trends experienced during the 2002–2013 period of the HIV/AIDS epidemic were evidence that the epidemic was not over and was to be very resistant to the remarkable decline that started in the last half of the 1990s. As matter of fact, both Florida and MDC witnessed increases in new cases at various times during the decade (Fig. 1.2).

The impact of AIDS within the county, state, and national level continues into the third decade (2002–2013) of this epidemic. Even with the newly implemented programs, interventions, and access to antiretroviral drugs, the number of new AIDS cases continued. The total decline in AIDS cases in MDC began in the late 1990s and fell under 1,000 total cases in 2007 [14]. The total number of AIDS cases increased in 2008, but then, once again, fell under the 1,000 mark and has continued this trend ever since. Compared to the previous two decades, MDC continues to experience new cases ranking among the highest in the country [14].

Addressing the major demographics and risk groups has served as one of the most important epidemiological tools. Males continued to have a higher incidence of AIDS when compared to females. The trend persisted throughout the first two decades of this epidemic with men accounting for more than 70% in each decade compared to women [14]. Further, Black/African Americans accounted for the largest percentage of AIDS cases followed by Hispanic/Latino [14].

The incidence of specific high-risk groups, such as MSM and IDU, continued into the third decade of the HIV/AIDS epidemic, with MSM as the largest group

battling AIDS with a total 50% cases, followed by adult heterosexual contact with 38% of these cases [14]. The major shift was that IDU decreased to 7% from more than 20% in the first two decades. Although the overall change was not enormous, occurrences such as these indicate the potential success of current interventions and programs while highlighting the need for implementing new initiatives that adapt to the current needs. With the declines, in new AIDS cases over the third decade, especially in the IDU category, we undoubtedly see the results of the role that NIDA and drug researchers and drug interventions have had in developing the science and interventions directly targeting this major risk group.

However, Florida continues to rank in the top ten in nearly every category regarding HIV/AIDS. As of 2013, Florida ranked first in both newly diagnosed HIV infections and AIDS cases (110,000) [14]. Also, Florida ranked third in the nation for people living with HIV through 2014. Further, consistent with the two prior decades, men accounted for the clear majority of AIDS cases with more than 70% of all cases [32]. Black/African Americans were the largest race/ethnic group living with AIDS at 51% of all cases, followed by White/Caucasian at 25% and Hispanics at 21% [32]. Further, of those living with AIDS in Florida, the greatest transmission mode occurred among MSM (46%), heterosexual contact (43%), and IDU (8%) [32].

The trends experienced during the period between 2002 and 2014 in MDC and Florida differed from that of the United States. That is, the total number of AIDS cases within the United States has continued to see a rise throughout this period and culminated with 1,200,000 estimated cases in 2014 [32]. African Americans account for approximately 48% of all AIDS cases followed by Hispanics at 25% [33]. The rate of new cases for Hispanic males was 2.9 and 4.2 times that for White males and females, respectively [32]. Further, MSM were most severely impacted by AIDS at 54% of all cases followed by heterosexual contact at 31%, IDU at 10%, and MSM + IDU at 4% [33].

The earliest association of AIDS resulted in a stigmatization that those with this disease were considered “untouchable” due to misinformation and prejudice [4]. Irrational fear and paranoia often led to an increase in the discrimination of those battling HIV infection and AIDS throughout the United States. The rapid progression of AIDS led to greater uncertainty and uneasiness among the populations combating this new epidemic. The health inequities present among the different race/ethnicities and risk groups within the United States were the result of the misunderstanding and lack of treatment and care for HIV/AIDS during the decades of this epidemic.

1.1.3.1 Interventions and Progressive Movements 2002 to Present

There were major improvements and progress during the first three decades of the HIV/AIDS epidemic; the evolution of prevention programs must continue to ensure a strong platform to combat this epidemic. Many interventions, testing, and medical advances were and are essential for national initiatives to be effective in treating and managing those who have contracted HIV/AIDS [10, 14] (Fig. 1.6).

Fig. 1.6 Timeline of the third decade of AIDS [11]

After three decades in battling the HIV/AIDS epidemic, complacency settled in among individuals, communities, and the media at the county, state, and national levels. The first HIV/AIDS Case Management Standards and Guidelines were developed with the CARE Act Titles in 2002 [14]. Additionally, the first "entry inhibitors" were introduced into the HIV/AIDS epidemic. Nearly 25 years after the advent of this epidemic, over 500 case managers, supervisors, and other interested staff from the Ryan White Titles I, II, III, IV, and HOPWA were trained in the first statewide HIV/AIDS Case Management Training referred to as the "Nuts and Bolts" [34, 35]. The time it took to fund and conduct scientific research, and turn the science to policy statewide initiatives across the nation highlights one of the main reasons the prevalence of AIDS has continued over time.

These prominent and impactful programs that took nearly 30 years to develop assisted in combating this devastating epidemic [14]. The CARE Act Title program, which was passed by the US government provided substantial support to public programs that combat chronic diseases through various laws and legislation. Additionally, the Ryan White Titles (I, II, III, and IV) provide funding for healthcare entities to provide care and treatment. Initiatives such as these provide those with AIDS or HIV infection the ability to obtain the treatment required to prevent the spread and eventually diminish the prevalence of AIDS worldwide.

Early in 2001, one-on-one capacity building activities and initial prevention programs for individuals testing positive were funded that minimized the unnecessary transmission of HIV. Rapid HIV testing was then developed, and the AIDS Drug Assistance Program (ADAP) continued to proliferate and provide funds for drugs and other essential services. The success of ADAP led to new initiatives which targeted the HIV/AIDS crisis among MSM and other high-risk groups in Florida [14].

Community-based organizations and other similar entities continued which assisted in reducing the prevalence of AIDS and the health gaps present within different race/ethnicities and risk groups. Extensive community mobilization began throughout the nation which provided individuals with the care and access to treatment that could assist in preventing the continual spread of this disease. Further, media and social outreach strategies were improved which provided a means that would contribute to spreading vital information regarding AIDS. Also, programs such as Out in the Open (2007), Organizing to Survive (2008), and Man Up (2009) delivered interventions that assisted groups at the highest risk for contracting and transmitting AIDS [14]. Although there were substantial increases in programs and interventions to combat the HIV/AIDS epidemic, funding constraints

and accessibility prevented critical services to be efficiently and effectively delivered to all needed persons. For example, beginning in 2010, the ADAP saw its first wait list created for services and continued to exist until 2012 when the list was eliminated.

In 2011, world leaders adopted a new declaration that reaffirmed commitments and called for an intensification of efforts to combat the epidemic through new commitments and targets through the United Nations General Assembly and a Special Session (UNGASS) [36]. Most recently, UNAIDS set specific goals and targets to control the HIV/AIDS epidemic by 2020; by 2030 to ensure that 90% of people living with HIV know their HIV status; that 90% of people who know their HIV-positive status are on consistent treatment; and that 90% of people on treatment have suppressed viral loads [36].

Over $30.0 billion is being allocated to AIDS research and programs, prevention initiatives, housing assistance, care, and many other components essential in reducing the impact of the HIV/AIDS epidemic [36]. The momentum to eliminate this disease is in full force and must continue to proactively and aggressively reduce the incidence of new HIV infections. The major impact of AIDS has been consistent among US metropolitan areas with New York, Los Angeles, and Miami topping the list, stressing the importance of improving current programs, initiatives, and interventions to eliminate the spread of the disease [37].

1.1.4 Global Movement

The combined evolution and improvement of the world economy with subsequent increased efficiency and development of the international transport and travel technology has been a major driving force in the global spread of HIV/AIDS [4]. The HIV/AIDS epidemic has affected global populations through many avenues, with MSM, IDU, and heterosexual contact being the predominant risk groups. In addition, newborns and children suffer as well with this disease [38]. This epidemic has spread rapidly among the risk populations around the world, although in some areas it has spread slower and without such a profound impact [36].

Different parts of the world have experienced substantial discrepancies on the progression of HIV/AIDS. Moreover, 95% of HIV cases worldwide are concentrated in developing countries [38]. Further, HIV/AIDS disproportionately impacts distinct demographics and social groups throughout the world. Of the 36.9 million people living with AIDS around the globe, Sub-Saharan Africa accounts for nearly 70% of the cases [39]. Understanding the global network and its unprecedented reach provides the framework for approaching the HIV/AIDS epidemic by developing interventions by focusing on the highest risk networks [40].

Population-based interventions have been very effective in combating the HIV/AIDS epidemic globally [40]. Developing global population-based initiatives through international collaboration has provided a comprehensive approach that recognizes different lifestyles and information regarding this disease which continues to spread, albeit at a slower rate [40]. The specific programs developed throughout

the world provide an expansive resource of enlightened scientific information regarding risk factors such as sex and drug practices, provides better education, health and economic access, and other service components that could have a profound global impact on this epidemic [40]. The success of international programs depends upon a concise understanding and sustainability of modifying interventions to local institutions and communities with distinct cultures and lifestyle practices [40]. It has been consistent international collaboration in striving to break down all the barriers associated with the HIV/AIDS epidemic that led to improved programs and influencing global initiatives. Further, these initiatives have been a major portion of the fight against HIV/AIDS since 1987, when the World Health Organization (WHO) launched the Global Program on AIDS. UNAIDS developed the UN Millennium Development Goals (MDGs) which gave rise to every nation agreeing to global goals to reverse the spread of HIV and AIDS [41]. In the early years of HAART, there was much concern about detrimental side effects of long-term treatment, and thus much study of delaying treatment until CD4 counts fell below some threshold. Recent studies such as the START trial have now proven beyond doubt that treatment should begin as soon as possible [41].

1.1.5 Conclusion

Acquiring a comprehensive scientific understanding of the HIV/AIDS epidemic from a county, state, and national level leads to scientific progress in reducing the prevalence of this disease worldwide. Incorporating a global approach as detailed in this chapter provides a well-defined basis for understanding global epidemics.

Without continued and sustainable funding, initiatives cannot progress, and the HIV/AIDS epidemic will continue to unnecessarily impact millions of people worldwide. Much increased funding at all levels is needed to ensure preventive and treatment services for those affected by HIV/AIDS [36]. The progress of scientific knowledge and a thorough understanding of this epidemic and solid actions taken around the world will be needed to reach the future goal of eliminating this destructive disease, as we have done with other diseases, such as polio and small pox, with global consequences.

Conflict of interest The authors report no conflicts of interest.

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Chapter 2
Global Issues in NeuroAIDS

Jennifer Massey and Bruce Brew

Keywords HIV • Neurology • Immunology • Autoimmune • Infectious disease • Blood borne virus • Dementia • Neuropathy • Meningitis • Myelopathy • Myopathy • HIV associated neurocognitive decline • Immune reconstitution inflammatory syndrome • HIV associated peripheral neuropathy

Core Message
Neurological manifestations and *sequelae* of HIV infection are extensive both as direct and indirect manifestation of the disease, with associated infective, hematological, malignant, vascular, and immune-mediated processes occurring with differing prevalence at different stages of HIV disease and with independent host factors. Additionally, combination antiretroviral therapy (cART) is associated with a multitude of neurological ramifications. As the global burden of HIV continues to predominate in developing nations, neuroHIV and neuroAIDS issues in these settings vary from those seen in developed countries; however, the spectrum of disease remains unchanged and awareness of progress in this field is essential for adequate neurological care for HIV patients universally.

2.1 Direct Neurological Effects of HIV: Primary Infection

Symptomatic primary human immunodeficiency virus (HIV) infection (PHI) will occur in up to 90% of infected patients, with no clear "at risk" groups, or nations identified [1]. Onset of disease following exposure to HIV is typically within 2–4 weeks with the duration of symptoms lasting a median of 18 days [2]. Systemic illness manifests

J. Massey (✉) • B. Brew
St Vincent's Hospital, Sydney, Darlinghurst, NSW, Australia
e-mail: jennifer.massey@hotmail.com

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as fever, lymphadenopathy, headache, rash, myalgia, or arthralgia, with neurological symptoms classically occurring within a fortnight. (Throughout this chapter, the viral type is HIV-1 unless otherwise specified. Viral subtypes are not reported.)

PHI can manifest as a multitude of neurological syndromes ranging from headache, myalgia, cranial nerve palsies, myelopathy, radiculopathies, acute demyelinating neuropathy, and rarely, an acute encephalopathy. The most typical form however is meningioencephalitis, with generalized symptoms including seizures. There are reports of PHI initiating a myopathic process, including cases of florid rhabdomyolysis [3, 4].

Factors influencing the prevalence and severity of primary HIV infection likely relate to the tropism and virulence of HIV and the degree of host immune response. It has been shown that patients with highly replicative viral strains with multitropism are more likely to develop symptoms, particularly if they are unable to mount humoral and cellular HIV-specific immune responses [5]. Host HLA-haplotypes are well recognized to impact on the rate of disease progression, and this is thought to also influence the degree of PHI [6].

Diagnosis is based predominately around a high index of clinical suspicion, as many symptoms are nonspecific. Host immunodeficiency may be reflected through a drop in lymphocyte count. Transient thrombocytopenia is frequently seen, along with elevated serum hepatic transaminases, which normalize within weeks. Evidentially, serum must be tested for HIV RNA, as HIV serology during this time is often indeterminate. In regard to neurological PHI, cerebrospinal fluid (CSF) very often shows a lymphocytic pleocytosis reflecting CD4:CD8 ratios in blood [7], with raised CSF protein and HIV RNA.

Early diagnosis of PHI theoretically allows an opportunity to lower the viral set point, which is determined following established infection. Following initial infection, the HIV viral load rises steadily; however, following immune activation, this falls to a steady-state point of viral replication. Modulation of this set point determines the future progression of the disease, and doing so could suppositionally be established with the use of antiretrovirals. Unfortunately, early trials did not seem to consistently support this [8–10] with only a single study involving zidovudine showing a short-term benefit and others showing no change in this regard; however, emerging trials are pointing toward a beneficial effect of early therapy during acute infection, with early combination antiretroviral therapy (cART) limiting the reservoir size of latently infected cells. To date, however, these benefits appear transient [11, 12].

No study has specifically addressed gross neurological outcomes in this regard; however, increasing work is being done in regard to prevention or improvement of HIV-associated neurocognitive disorders (HAND), which is discussed later. Current WHO guidelines recommend commencement of cART at the point of diagnosis.

It has been postulated that patients' neurological symptoms of PHI may benefit from early cART commencement although again there is no clear evidence base for this. Given the possible effect on viral set point, lower risk of developing both AIDS and resultant benefits with regard to cognitive impairment, most neurologists would at present recommend early commencement of cART [13] preferably using drugs that reach efficacious concentrations in the CNS but avoiding a triple nucleoside combination due to the increased rate of early virologic nonresponders [14]. The

role of drug holidays is no longer supported, and as such, treatment is lifelong. The utility of immunomodulatory therapies such as mycophenolate mofetil (MMF), cyclosporine, or interleukin-2 (IL-2) remains under investigation with no clinically beneficial studies reported [15].

2.2 Direct HIV Neurological Effects of HIV: Meningitis

Aseptic meningitis may develop in the early to medium term following HIV infection, and can be present in patients with otherwise well-controlled HIV disease, with a stable or only mildly decreased CD4 count. There is now evidence that it does however correlate with an elevated HIV viral load in CSF [16], although this was seen nonspecifically in all patients with neurological symptoms.

The clinical picture may be acute, over a period of weeks, and associated with systemic symptoms of fevers, confusion, and seizures or cranial neuropathies. The chronic variant develops over a period of months, with the predominant features being headache or features of raised intracranial pressure. Typically, symptoms are self-limiting, but may recur throughout the course of infection.

Diagnosis on CSF can be made on the basis of a mild mononuclear leukocytosis, although this will vary with differing degrees of immunodeficiency. In patients with greater degrees of immunosuppression, consideration must be given to opportunistic infections. Antiretrovirals including zidovudine, efavirenz, delavirdine, and nevirapine have been associated with nonspecific features of meningitis including headache, malaise, confusion, and stupor [16]. However, these are rare complications and in some cases may relate to immune reconstitution syndrome as discussed later.

Given the nonspecific nature of symptoms and risk of confounding coinfection, correlation of symptoms with HIV viral load is important. Advice regarding how this information should influence treatment is challenging, although commencement of cART with good CNS penetration appears intuitive, and certainly this is recommended for patients with HIV RNA in CSF that is disproportionate to serum levels. Of note, there are limited trials to support this, and given the condition's self-limiting nature, the majority of management is symptomatic. A small trial of zidovudine in 11 patients did not improve symptoms [17]. Anecdotal use supports short courses of steroids for headache if opportunistic infection is excluded.

2.3 Direct HIV Neurological Effects of HIV: Myelopathy

An acute HIV myelitis can occur with primary infective illness, or more commonly with the development of AIDS.

Clinical features relate to the location of the lesion, the typical sites for involvement being the thoracic cord and the conus. Treatment lacks evidence but should be based around the commencement of cART with good blood-brain barrier penetration. The role of steroids is unclear.

Vacuolar myelopathy, as opposed to HIV myelitis, may develop in HIV at any stage but is more common in advanced disease. While the condition is associated with HIV disease, the precise role of HIV in the pathogenesis is unclear. A similar if not identical illness has been described in systemic lupus erythematosus. Vacuolar myelopathy has an estimated symptomatic prevalence in AIDS of 5–10% but is seen in 50% of cases on autopsy [18]. Progression occurs over months typically with spastic paraparesis, hyperreflexia, extensor plantar responses, impaired proprioception, and sensory ataxia. The disease often eventually stabilizes and may not have significant impact on time to death [19]. MRI is typically normal or nonspecific. Further investigations should be performed to exclude other causes of myelopathy, and the diagnosis can only be truly confirmed at autopsy, where intralamellar vacuolation in spinal white matter is seen, typically in the posterior columns of the thoracic cord [18]. There is no known effective treatment [19], although high-dose methionine seems to have modest benefits [20].

2.4 Direct HIV Neurological Effects of HIV: Myopathies

Myopathies in HIV may be secondary to inflammatory conditions related to cART (as discussed in further detail later) or exacerbated in the context of other medications use.

Polymyositis is quoted to occur in up to 2% of HIV patients [21]. The disease occurs with moderately advanced HIV, although rates have not been clearly correlated with CD4 levels in previous reviews [21]. The inflammation is driven by a CD8 cytotoxic T cell response. As more advanced immunosuppression occurs with disease progression however, the condition appears to "burn out," correlating with the declining ability to mount an inflammatory immune response [22].

Creatinine kinase (CK) will be elevated, although this is nonspecific, and myositis antibodies appear to be of lower yield in these cases. EMG will support a myopathic process with small duration, low-amplitude polyphasic motor unit potentials, fibrillations, and positive sharp waves. Muscle biopsy remains the definitive investigation, showing CD8+ driven endomysial inflammatory infiltrates [22]. Treatment should be with intravenous immunoglobulin (IVIg) to minimize immune compromise; corticosteroids and other immunosuppressants are reserved for more refractory cases. The role of cART in treatment of this condition is not established, though theoretically at least it is likely to be beneficial [21].

Inclusion-body myositis has also been associated with HIV infection [20]. The HIV-associated variant differs from the nonimmunocompromised form of the disease, with earlier age of onset and higher CKs. It has been established that the virus does not replicate within muscles but is present in endomysial macrophages, although the autoimmunity occurs as a result of specific CD8+ T cells invading muscle fibers, recognizing muscle antigens and inducing inflammation. Again, trials of IVIg can be considered [23]. There is no clear role for steroids, but up to 25% of patients have been shown to transiently respond to IVIg, and T cell immunotherapy remains under investigation [24].

As seen in the general population, drug-induced myopathies remain the most common cause of raised CK in the developed world. With increasing understanding of long-term vascular effects of HIV and hyperlipidemia, and treatment of this, statin-associated myopathy prevalence is increasing. This can be exacerbated by interactions with protease inhibitors, particularly ritonavir.

2.5 Direct Neurological Effects of HIV: Peripheral Neuropathy

Peripheral neuropathies can occur as a direct consequence of HIV infection early or medium term into the disease, typically when immunodeficiency is significant [25]. Peripheral neuropathy also occurs in conjunction with HCV in the context of coinfection, medication side effects, or other associated conditions.

Lumbosacral polyradiculopathy, which develops subacutely, typically manifests as asymmetric leg weakness, saddle anesthesia, bladder and/or bowel dysfunction, and sensory loss. Most commonly, this is secondary to cytomegalovirus infection, suprainfection, or reactivation in the setting of immunosuppression. However, it can occur with other viral coinfections, particularly herpes simplex. Nonetheless, 30–50% of patients have no coinfective illness, and radiculopathy is thought to be mediated by HIV itself [26].

Plexopathies characteristically occur as part of a seroconversion illness or during seroconversion of a coinfection with another blood-borne virus. Mononeuropathies of cranial (typically facial) and peripheral nerves may occur as isolated events, or progress to a mononeuritis multiplex syndrome. These may occur as a consequence of coinfections including varicella zoster virus, syphilis, and hepatitis C or secondary to HIV alone.

Mononeuritis multiplex can also be directly related to HIV through vasculitis. Other causes include cryoglobulins, lymphoma, and the coinfections previously mentioned. Interestingly, HIV patients may develop an early hyperlymphocytic reaction to the virus with proliferation of CD8 cells resulting in a Sjogren's-like neuropathy and associated sicca symptoms [27].

Patients are also susceptible to Guillain-Barre syndrome as well as a chronic inflammatory demyelinating polyneuropathy. This is characterized by weakness, areflexia, and an elevated CSF protein, and typically occurs in a bimodal pattern either at seroconversion or chronically, later in the illness [28]. It may also occur with immune reconstitution. First-line therapy is based around IVIg or plasmapheresis.

Distal symmetrical polyneuropathy is the most common peripheral nerve complication of HIV. Typically, it occurs late in the disease; there appears to be an increased incidence in patients with lower CD4 counts (30% of patients with CD4 <200).

Overall, the incidence has declined in the cART era (despite certain patient cohorts showing the opposite) [29]. Contributing factors to disease include vitamin deficiency, alcohol abuse, medications (particularly D4T as will be discussed), glucose intolerance/diabetes, and renal impairment.

Clinically, the neuropathy is symmetrical, predominantly sensory, and distal, rarely extending above the knees. Ankle jerks are absent or depressed as are knee jerks later in the illness. Weakness is very unusual, and when present is confined to the feet. Pain is a common feature. An autonomic neuropathy may occur in conjunction, typically manifesting as postural hypotension and gastroparesis [29].

HIV neuropathy is a length-dependent axonal degeneration. Differential diagnosis should include coinfection with other blood-borne viruses including hepatitis C and HTLV, hematological conditions including lymphoma, autoimmune conditions such as Sjogren's disease, and sarcoidosis or medication side effects. There is an inflammatory monocytic infiltrate associated with decreased numbers of dorsal root ganglion neurons. Treatment in addition to cART is symptom-based management [29].

2.6 Direct Neurological Effects of HIV: HIV-Associated Dementia and Lesser Forms of Impairment

HIV-associated dementia (HAD) or AIDS dementia complex (ADC) is a well-recognized condition often described under the subheading of HIV-associated neurocognitive disorders "HAND." HAD presents as a subacute dementing illness in patients usually with advanced HIV disease. Milder variants as per the HAND classification are minor neurocognitive disorder and asymptomatic neurocognitive impairment.

Overall, it is thought that approximately 40% of HIV-infected patients have some form of HAND [30, 31], not excluding the confounding effects of psychiatric disorder, substance use, coinfection, etc.; if the latter are taken into account, the percentage drops to approximately 20–25% [32, 33]. As life expectancy of HIV patients increases with advances in treatment regimens, prevalence continues to rise [34]. Incidence appears to be stable, though rigorous prospective data from the current HIV population are lacking. The development of HAND is not universal and appears to relate to both host and viral factors. Of note, HAND is a distinct entity from the disease HIV encephalitis, which should be reserved for patients who have pathologically proven features of a multinucleated giant cell encephalitis with HIV in the brain parenchyma [35].

HAD is typically subcortical, lacking features of aphasia, alexia, and agraphia. Motor dysfunction is frequently seen early in the disease [36]. Progression previously occurred over weeks to months, but this has now typically extended to months to years in the cART era. The three classically affected cognitive domains include cognition with changes to memory, concentration and reasoning, and motor function specifically gait unsteadiness, clumsiness, and a decline in fine motor skills as well as behavioral change most classically progressive apathy or disengagement from daily activities. Primitive reflexes may be elicited on examination [36].

In patients on cART, the disease can be tentatively classified into active or inactive states with the defining feature being clinical, immunological (CSF viral immunological activity), or radiological (on MRI spectroscopy) progression of the disease

Table 2.1 Classification of HAND [37]

Inactive	The disorder has not changed clinically or neuropsychologically for more than 6 months
	The CSF has no evidence of viral or immunological activity
	MR spectroscopy does not show evidence of increased glial turnover
Active	Progressive: the disorder is worsening clinically or neuropsychologically
	Stable: the disorder has not changed for more than 6 months, but there is activity in the CSF (viral or immunological) or by MRS
	Regressive: the disorder is improving

(Table 2.1) [37]. Validation of activity status by these measures, while intuitively reasonable, awaits large studies. Currently, it appears the disease phenotype is much the same between treated and untreated patients; however, with increased life expectancy, more "typical" causes for dementia may overlap with HAND, causing a confounding clinical picture. The increased prevalence of CNS vascular disease in the HIV population may also contribute to the clinical overlap syndrome. Interestingly, the only clear risk factor associated with HAND progression in the recent MACS study was hypercholesterolemia [33].

Not only does HAND contribute to a growing burden of HIV-associated neurological complications, but increasing evidence exists that HIV may facilitate other neurodegenerative conditions.

Common understanding regarding neurodegeneration relates to a breakdown of protective cellular mechanisms resulting in accelerated neurotoxicity. Alzheimer's disease and other neurodegenerative conditions are understood to occur subsequent to aggregation of misfolded proteins, which in turn activate cellular defense mechanisms. Subsequent activation of inflammatory pathways includes excitotoxicity, oxidative stress, and mitochondrial dysfunction. In CNS HIV infection, activated microglia and astrocytes contribute to neurodegeneration via upregulation of proinflammatory molecules, including TNF-α, IL-6, and MCP-1, resulting in a neurotoxic environment. Oxidative stress is thought to be the final common pathway in the majority of neurodegenerative diseases including HAND. HIV also affects normal aging processes. Aging results in frontal and hippocampal neuronal loss and less efficient myelination. Similar regions are affected by HIV. Aging disturbs cellular disposal of toxins via increased abnormal ubiquitin inhibiting protein degradation. Inhibition of the ubiquitin-proteasone complex, as is seen in AD, Parkinson's disease, and motor neuron disease also occurs in HIV [38].

Investigations are predominately focused around exclusion of differential diagnoses. Routine serum testing for metabolic causes of dementia should be performed including thyroid function, B12, and folate levels. Neuroimaging should include CT or preferably MRI to assess the degree of atrophy, exclusion of mass lesions, and exclusion of progressive multifocal leukoencephalopathy. MRI may show periventricular T2 changes in the white matter, which are associated with HAND. MRI spectroscopy can contribute to diagnosis by showing reduced levels of N-acetyl aspartate and increased levels of choline and myoinositol in the deep frontal white

matter and especially the basal ganglia. CSF should be performed to assess for HIV RNA, exclude coinfection, test for drug resistance of the virus, and assess for immune activation markers or other features of CNS inflammation.

While HIV-1 is the cause of HAD in patients with unsuppressed HIV, the cause in milder forms of HAND in the context of viral suppression is still unclear. Evidence now shows that HAND continues to be a progressive neurological syndrome in the cART era, even as frequency declines.

Potential explanations include poor CNS drug penetration and a dissonance between serum and CSF virologic control; the "legacy effect" where cognitive dysfunction has occurred in the pretreatment period; CNS toxicity from antiretrovirals; and possible contribution by immune restoration in an IRIS-type phenomenon [39]. Normal aging degenerative changes as outlined earlier are also relevant. HIV presumably accesses the CNS within infected mononuclear cells [40]. HIV strains vary in their degree of neurotropism and neurovirulence, likely explaining at least in part why only some HIV-infected patients develop HAND [41].

Studies that have attempted to assess the "legacy effect," specifically neuropsychological status early in infection, and whether cognitive function can be altered by early commencement of cART have been limited by access to populations at this stage of disease. One small study reported approximately 25% of newly diagnosed HIV patients had impaired neuropsychiatric performance at a median of 19 days post infection, and that this correlated with CSF HIV RNA. These outcomes were not reversed by cART introduction at the time of diagnosis on testing at 3 and 6 months, suggesting limited reversibility in this group [42]. Another study showed slightly more promise, indicating initiation of cART can improve but not restore brain integrity [43]. Adding weight to the evolving picture of early neurological complications of HIV is a report of perinatal HIV children with adequate viral suppression on cART having lower brain volumes, more white matter disease, poorer brain structural integrity, and poorer cognition compared to age-matched controls on neuropsychological performance and imaging [44].

Much of HAND pathogenesis is still to be elucidated. It is recognized that the inflammatory cytokines released in the brain and spinal cord in response to viral infection play a more dominant role than direct virally induced brain damage; however, the detailed pathogenetic pathways including host genetic influences remain only partially answered [45].

cART should be commenced if there is evidence of HAND. If the patient is already on cART but not suppressed (either in the blood or the CSF), then antiretroviral (ARV) resistance studies should be done to determine which ARVs should be included in a revised cART regimen. If the patient is virally suppressed in both blood and CSF, then the management path is unclear. Theoretically at least, it would be reasonable to alter the cART regimen if there was evidence of inflammation in the CSF, for example, an elevated neopterin. If there is no inflammation in the CSF, then management is even less clear – the patient may have inactive or "burnt out" disease in which case a wait-and-see approach would be reasonable [45].

Another approach would be to intensify cART by the addition of another ARV known to be effective in HAND. This would be reasonable if there was clinical

suspicion of progression of HAND despite any other evidence of activity. There is some emerging evidence for this [91]. The role of MRI spectroscopy in guiding management in such scenarios is still in evolution. Adjunctive therapy in the form of neuroprotectant medication has no clear role currently. The exact ARVs that should be included in a cART regimen for the treatment of HAND is controversial, with some studies favoring ARVs with higher CNS penetration and efficacy while others find no superior benefit [46]. There are methodological issues with most of these studies; when these are taken into account, the evidence does seem to favor ARV regimens with better CNS penetration and efficacy, though not conclusively. A review of observational studies investigating this question concluded that in well-conducted trials neuroHAART was effective in improving neurocognitive function and decreasing viral load, but large randomized trials are required in this field [47].

2.6.1 Indirect Effects of HIV: Infective – Tuberculosis

Tuberculosis (TB) coinfection occurs predominantly in the developing world where it remains a leading cause of death in patients with HIV. Not only does HIV increase the risk of disseminated tuberculosis, but coinfection poses challenges to treatment and is known to be a risk factor for poor clinical outcomes. Central nervous system (CNS) TB can manifest as tuberculous meningitis, tuberculoma, and tuberculous abscesses.

Tuberculous meningitis (TBM) may occur in up to 10% in coinfected patients where TB is endemic [48]. The majority of patients who develop TBM have a CD4 count <500 cells/μL, and more frequently <200 cells/μL. Common systemic features include fever, headache, and altered mental state. Two-thirds of patients will have meningeal signs and approximately a third of these, focal neurology [49]. TBM has the highest morbidity and mortality compared with other end-organ TB infection. Early diagnosis is critical and notoriously challenging due to the relatively nonspecific signs and the fastidious nature of the organism. Diagnosis of TB from the CSF has improved significantly with the use of PCR, which has a sensitivity and specificity of 70.5 and 87.5%, respectively [49]. Treatment for tuberculosis should be commenced immediately. In patients who are not already on cART, this should ideally be delayed until after TB treatment is complete, if not 6–8 weeks underway to prevent immune reconstitution inflammatory syndrome (IRIS); however, the safety of doing so will depend on the CD4 count: in patients with CD4 counts <50, delay in antiretroviral therapy should be minimized [50]. The routine use of steroids is not currently advocated for HIV-infected patients with TBM. However, corticosteroids are the treatment of choice in patients with TBM and HIV who develop IRIS. Drug interactions must be carefully considered, particularly in regard to Rifampicin. Prognosis is poor, and 30–50% of patient with TBM will die, although outcomes appear similar to those in the non-HIV population.

Both tuberculoma and tuberculous abscess typically present with a constellation of systemic features, seizures, and focal neurological deficits related to the site of the lesion. A more fulminant course is expected in abscesses. Imaging confirms a solid-

enhancing or ring-enhancing lesion which may mimic the imaging appearances of cryptococcomas, proving to be a management challenge with regard to empiric treatment [49]. Confirmatory tests include screening for pulmonary TB with chest x-ray, CSF (where safe to do so), MRI possibly with MR spectroscopy. In developed nations where tissue biopsy is more readily attainable, PCR and culture of tissue will be beneficial. In developing nations, it is reasonable to commence empiric TB treatment in patients with respiratory symptoms, negative serology for toxoplasmosis, and recent co-trimoxazole treatment on the basis that this argues against CNS toxoplasmosis [49].

2.6.2 Indirect Effects of HIV: Infective – Toxoplasmosis

Toxoplasmosis remains the commonest cause of focal cerebral lesions in the developing nations' HIV population. The infective agent is *Toxoplasmosis gondii*, an intracellular protozoa. The tachyzoite represents the acute infective organism and the bradyzoite the organism responsible for latent disease. Both cellular and humoral immunity are required to prevent parasitic proliferation. CD4 T cells and gamma interferon are essential in this process, and when CD4 counts fall in HIV, latent toxoplasmosis can be reactivated [51].

The majority of patients with toxoplasmosis have a CD4 count <100 cells/uL. Clinical manifestations reflect a focal lesion and include headache, focal neurological symptoms and signs, and sometimes seizures. Disseminated infection, a much less common form of the disease, leads to headache and confusion usually. Diagnosis can be made on the grounds of a typical history, imaging features, and serological testing, given that the majority of HIV-related cases are reactivation. Antibody-negative cases can occur with advanced immunodeficiency and loss of prior antibody, and rarely, disease may be a result of primary infection. If CSF can be safely obtained, it will typically show a pleocytosis, raised protein, and normal to low glucose. Culture takes weeks in duration, and PCR is the test of choice on CSF; however, it is only positive in about 60% of patients, dependent on the proximity of the lesion to the ventricles [51]. Imaging with contrast CT or MRI is beneficial with lesions showing heterogeneous contrast enhancement. Typically periventricular lesions are less likely to represent toxoplasmosis. In HIV-positive patients, MRI spectroscopy has limited benefit in differentiating toxoplasmosis from CNS lymphoma; however, FDG PET-CT may be beneficial in this situation [51].

A provisional diagnosis of cerebral toxoplasmosis can be made when there is no history of toxoplasmosis prophylaxis (low-dose co-trimoxazole), a CD4 count <200, particularly <100, positive toxoplasmosis serology, and brain imaging consistent with multiple enhancing mass lesions.

Empirical therapy with pyrimethamine, sulfadiazine, and folinic acid often results in clinical response in 1–2 weeks. cART should probably be delayed for several weeks to decrease the risk of IRIS which may result in clinical deterioration [52]. Primary therapy is given for 6 weeks followed by long-term maintenance therapy at reduced doses, with duration determined by response to cART. Therapy can be discontinued when there is a persistent CD4 count >200 [52].

2.6.3 *Indirect Effects of HIV: Infective – Cryptococcus*

Currently, cryptococcal meningitis is the largest single cause of neurological infectious death worldwide [53]. Consistent with other CNS infections in immunosuppressed patients, cryptococcal disease may manifest as either meningitis or mass lesions, cryptococcomas. Crytpococcal CNS disease is particularly prevalent with a CD4 count <100cells/μL [54]. Cryptococcal meningitis is almost exclusively caused by *Cryptococcus neoformans* var *neoformans* serotype. Meningitis is a much more common clinical presentation compared to cryptococcomas.

Patients with meningitis typically present with headache and sometimes fever [54]. Generalized symptoms of drowsiness, visual obscuration, cranial neuropathies, and seizures may occur over time if untreated and typically reflect raised intracranial pressure. Cryptococcomas typically present with relevant focal neurological changes. Serum cryptococcal antigen is almost always positive in meningitis, but it can often be negative in cryptococcomas. Imaging should always be performed prior to lumbar puncture to assess the presence of raised intracranial pressure and other potential diagnoses. CSF cryptococcal antigen has a sensitivity of 88–90% in HIV-positive patients [54]. Treatment with amphotericin and flucytosine as induction therapy for 2 weeks is followed by fluconazole. The duration of therapy varies according to clinical response and CSF but is of the order of a year [55]. Recent studies have demonstrated the balance between a CNS response facilitating fungal clearance and an excessive damaging response. The Cryptococcal Optimal ART Timing trial found that antiretroviral therapy given later in the course of meningitis (>5 weeks after diagnosis) had better outcomes than treatment in the initial fortnight [56].

2.7 Indirect Effects of HIV: Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) continues to be a major contributor globally to neurological disease in patients with HIV and remains a treatment dilemma for clinicians. Although the use of cART worldwide has resulted in a decline in the incidence of the disease in the HIV population, it remains a condition without specific treatment.

PML is a subacute demyelinating disease of the CNS affecting oligodendrocytes and astrocytes. It is a consequence of reactivation of latent infection with the polyomavirus, John Cunningham (JC) virus. The site of latency is controversial with most considering it to be in the bone marrow, kidney, and possibly brain. JCV is a ubiquitous organism with antibody prevalence in the general population of approximately 50–60% [57]. The features of primary infection are not known to cause clinical disease. Viremia recurs in cases of immunodeficiency and correlates with CD4 count, but does not appear to correlate with HIV plasma viral load [58]. PML is the AIDS-defining illness in approximately half of HIV-positive patients. Average survival is 3–4 months in the absence of cART [58].

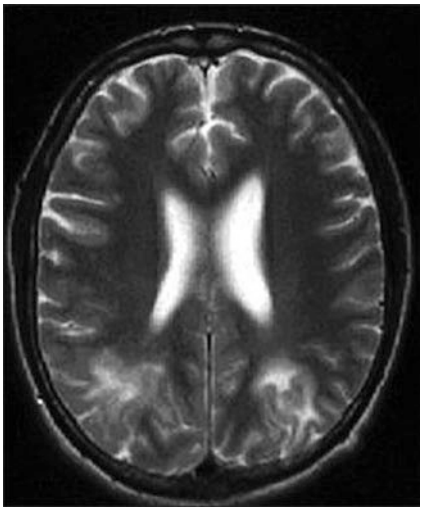

Fig. 2.1 T2-weighted magnetic resonance image shows hyperintense signal abnormalities in the white matter of the parieto-occipital lobes due to progressive multifocal leukoencephalopathy [60]

Clinically, PML is defined by subacute focal neurological deficits in the infected region. Fever is absent. Localizing features include hemiparesis, speech and language disturbance, cognitive dysfunction, headache, and ataxia. Serum JCV DNA is not useful as it does not correlate with PML. The best diagnostic test is CSF JCV DNA, which is detectable in 80–90% of cases who are not on ARVs [59]. Although diagnostic sensitivity has declined in the cART era, it remains useful. Brain biopsy for immunohistochemical detection of JCV is the gold standard but rarely required. MRI will show subcortical and deep white matter signal change on FLAIR and T2 sequences, typically with a ribbon of cortical sparing. Lesions typically do not enhance with gadolinium (Fig. 2.1).

In the HIV-positive PML population, treatment is centered on cART with response rates of approximately 50% likely relating to the degree of immune recovery achieved by cART. Cytosine arabinoside, cidofovir, and other agents have been trialed without benefit. Initiation of cART may result in IRIS, which can cause life-threatening cerebral edema, and steroids may be required [61].

2.8 Indirect Effects of HIV: Hematological

Primary CNS lymphoma and Kaposi's sarcoma, which were commonly seen in HIV patients in the pre-cART era, are now becoming increasingly rare. Challenges remain however in recognition, diagnosis, and management of both diseases.

Primary CNS lymphoma (PCNSL) is a diffuse non-Hodgkin's lymphoma that, in contrast to the nonimmunosuppressed population, develops secondary to reactivation of latent Epstein Barr virus (EBV) in HIV-positive patients. All cases contain the EBV viral genome [62]. Incidence differs depending on the presence of cART and remains higher in the developing world. The benefit of

cART on incidence is reflected in the decrease of PCNSL from 313.2/100,000 person-years to 77.4/100,000 person-years after 1996 [63].

Typically, the disease develops as in intracranial mass, but it can also involve the spinal cord, meninges, and eyes. Symptoms relate to the focal location of the lesion, in addition to the generalized symptoms of mass lesions, headaches, cognitive changes, altered alertness and less commonly seizures, which are seen in approximately 10% of cases [64]. Given radiographic features of PCNSL are nonspecific; differential diagnoses for consideration include other demyelinating or inflammatory conditions such as sarcoidosis or, in cases of single lesion disease (which makes up between 60 and 81% of cases), other space-occupying lesions [64].

Diagnostic work-up involves MRI brain with gadolinium. Stereotactic biopsy is the only certain means of diagnosis, although CSF for flow cytometry in case of leptomeningeal spread, or micro-RNA, can be useful, though the yield is low [65]. MR spectroscopy may aid diagnosis if it shows changes of metabolites, specifically phosphorylethanolamine, consistent with lymphoma [66]. SPECT in HIV patients is beneficial as the absence of Thallium-201 uptake on early images at the site of a CT/MRI abnormality excludes the diagnosis of lymphoma with a high degree of confidence [66].

Once diagnosis is confirmed, patients should have ocular assessment for involvement, as well as systemic staging, because they have a higher incidence of extranodal lymphomas. Although survival outcomes are improved in the cART era, overall prognosis is poor [67]. The AIDS population has a median survival of 2–5 months following commencement of treatment which typically involves combined chemoradiotherapy as well as commencement/continuation of cART [67]. In patients with poor functional status, treatment is typically limited to cranial radiotherapy; in patients with more aggressive treatment aims, high-dose methotrexate is used.

It should also be noted that HIV patients are at greater risk of metastatic lymphoma invading both the CNS and PNS. There may be an increased incidence on patients with advanced HIV/AIDS of cerebral gliomas, although there is no clear correlation with CD4 count. Rarely, Kaposi's sarcoma may cause intracerebral mass lesions associated with hemorrhage.

2.9 Indirect Effects of HIV: Cerebrovascular Disease

In comparison to other neurological complications of AIDS, cerebrovascular events are relatively uncommon, although HIV is recognized as an independent risk factor for stroke [68–70]. Typically, stroke occurs in the context of aforementioned opportunistic infections and associated metabolic syndrome, linked with certain antiretroviral regimens.

HIV predisposition to stroke is thought to be predominantly driven by atherosclerotic mechanisms. The prolonged life expectancy seen in accordance with the introduction of cART has correlated with not only higher rates of hyperlipidemia and hypertension but also the translation of these risk factors to predominately isch-

emic stroke. Both the older generation protease inhibitors and nucleoside reverse transcriptase inhibitors may be associated with hyperlipidemia. Protease inhibitors have been associated with the development of the metabolic syndrome although a causal relationship has not come to fruition in larger studies, with the caveat that patients responding well to treatment might have increased risk of atherosclerosis-related strokes after prolonged exposure [71]. Hypercoagulability may also be an important consideration, with protein S deficiency being frequently encountered in the HIV stroke population but rarely the cause of stroke [71].

It is now well recognized that HIV creates a chronic inflammatory state with increased rates of atherosclerotic disease compared with age-matched population. Both HIV and immunosuppression contribute to atherogenesis, and it remains unclear which correlated greater with risk: viral load or immunosuppression.

Studies of carotid artery atherosclerosis show HIV is an independent risk factor for arterial stiffness, with similar magnitude of risk to smoking. An inverse relationship has also been shown with CD4 count and carotid distensibility. Probable mechanisms include both procoagulant and endothelial dysfunction in response to inflammatory cytokines. This inflammatory response is modulated by host factors, specifically genetic variants that increase activation of monocytes and macrophages that accelerate atherosclerosis [72, 73].

Although immunodeficiency (as measured by CD4) count) influences stroke risk [74, 75], a direct virotoxic effect of HIV on arteries cannot be excluded. A recent study in sub-Saharan Africa not only demonstrated risk of stroke associated with HIV infection but notably higher risk in patients commencing treatment in the preceding 6 months [70]. Although this may be explained by a greater degree of immunosuppression seen with lower CD4 counts in this population, an immune reconstitution phenomenon against target antigens from HIV-mediated cell damage or the virus itself is plausible [76].

Differential consideration in patients presenting with stroke-like symptoms must include cerebral vasculitis/HIV vasculopathy, occurring as an inflammatory response to the viral antigen, although this is rare. If this is the cause of vascular events, treatment with cART alone is unlikely to be adequate and immunosuppressive agents are typically required [77]. Tuberculosis can cause an invasive/obliterative arteriopathy, either directly or in the context of meningitis. VZV recurrence/reactivation can also cause a large vessel vasculopathy.

2.10 Indirect Effects of HIV: Seizures

There is an increased seizure frequency in the HIV population, which is likely to be multifactorial. Not only do coinfections and associated lesions, as well as inflammatory states cause seizures, but the direct neurotropic effect of HIV lowers seizure threshold [78]. Around 10% of patients will develop epilepsy without an associated cause [78]. Confounding factors include substance abuse, trauma, and coinfection. cART which crosses the blood-brain barrier including efavirenz has also been

anecdotally associated with seizures in the pediatric population. It is also important to consider interactions with protease inhibitors and anticonvulsants in known epileptic patients commencing treatment for HIV [79].

2.11 cART and the Neurological System: IRIS

Immune reconstitution inflammatory syndrome (IRIS) was first clinically recognized in the context of advancements in HIV treatment in the late 1990s. Successful treatment and rising CD4+ve lymphocyte counts were associated with a paradoxical clinical deterioration, an immunological reaction to opportunistic infection or tumor. IRIS in the settling of PML, crytpococcal meningitis, and HIV encephalitis is of relevance in neurology.

IRIS classically develops in the most immune-deficient patients who experience the greatest immune reconstitution following commencement of ARVs. HIV treatment induced IRIS is particularly important in the developing world, given the frequent delay to commencement of cART and high opportunistic infection burden. It is also frequently underrecognized, being difficult to differentiate from the underlying infection or inflammatory process itself.

PML is characterized by minimally enhancing MRI lesions (Fig. 2.2). As the immune system is restored, PML lesions in IRIS frequently contrast enhance and result in significant amounts of edema, although this is seen less reliably in milder lesions. The presence of punctate or linear enhancement is notably consistent with inflammatory PML [61]. MRS can be used to show elevated myoinositol and lipid/

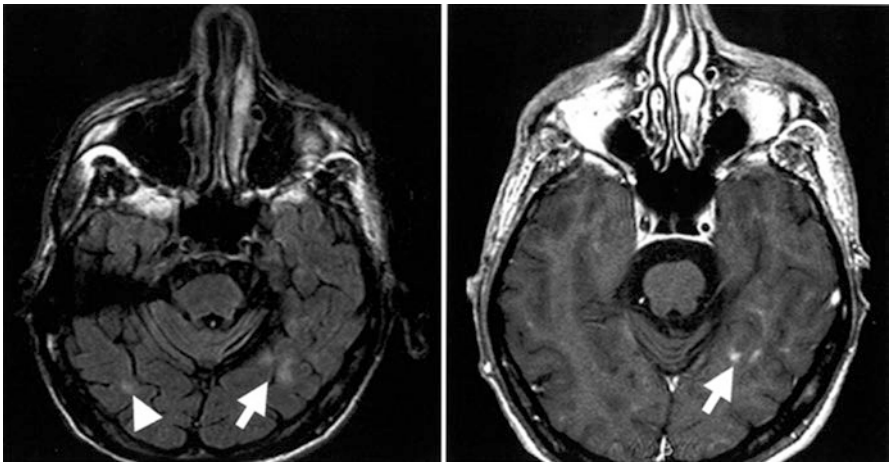

Fig. 2.2 Contrast enhancement of PML lesions in a patient with IRIS. A left temporal lobe lesion seen in FLAIR (*arrow, left panel*) minimally enhances after gadolinium injection in T1-weighted image (*arrow, right panel*), whereas a right temporal lobe lesion is only detected in FLAIR sequence (*arrowhead, left panel*) [80]

creatinine peaks in lesions with inflammation [61]. Prognosis is usually reasonable. PML with cART immune reconstitution can be treated with high-dose corticosteroid therapy – typically 1 g for 3–5 days, occasionally repeated fortnightly to monthly. Steroids should only be used in conjunction with ongoing cART. Cryptococcal meningitis and IRIS are a common clinical scenario. Increasingly, it is recommended that cryptococcus treatment precedes HIV treatment by at least 5 weeks [56]. Treatment efforts include removing the antigen burden with large-volume lumbar punctures and steroids to "dampen" the immune response. Case reports also exist of a syndrome in treated HIV patients of severe CD8 infiltration to the brain, essentially an IRIS to HIV itself. IRIS and the balance between inadequate and overactive immune response to neurological complications of HIV, particularly opportunistic infections, will continue to challenge clinicians, and early awareness/recognition of this entity is likely key to ongoing management.

2.12 cART and the Neurological System: Adverse Effects – PNS Toxicity

In addition to the direct HIV-related distal sensory polyneuropathy seen in the HIV population, cART is also associated with a toxic neuropathy and may cause over a third of cases of DSPN in patients with HIV on treatment [81]. This may be distal, affecting the arms and legs and resulting in pain, paresthesia, and gait instability, or involve the autonomic nervous system.

It largely relates to the use of nucleoside reverse transcriptase inhibitors: didanosine, zalcitabine, stavudine [81]. There have been reports of protease inhibitors inducing neuropathy although evidence remains insubstantial. The clinical presentation is frequently indistinct from that due to direct HIV toxicity, and as such the importance of early recognition lies with the physician who must be aware of the association with certain antiretrovirals. Drug toxicity neuropathy is typically more painful, has a more abrupt onset, and progresses rapidly [82]. Nerve excitability studies can aid in differentiating direct viral effects versus antiretroviral drug therapy neuropathy; one report described normal properties of the axonal membrane in sensory and motor nerves demonstrated in patients with viral neuropathies with excitability changes indicating pathology of the internode in nucleoside neuropathies [83].

The mechanism of action relates to mitochondrial DNA damage and is typically dose-dependent. There is classically partial to complete reversibility with cessation of the offending agent. Although serum acetyl-L-carnitine levels are decreased in cART-related neuropathy, there is no good evidence for replacement/supplementation [84]. The mitochondrial haplogroup T has also been associated with an increased risk of development of antiretrovirus-induced neuropathy.

cART-induced myopathy with zidovudine can also occur during treatment for HIV. Again, the effect is dose-dependent, with lifetime doses >200 g being the highest risk, but the incidence also appears to increase with advancement of disease [85]. The frequency of AZT-induced myalgias is 8–10%, and myopathy is up to 18% [85]. Presentation is with proximal weakness and atrophy predominantly involving the buttocks. CK is typically elevated, and a biopsy may be required to delineate the cause of the myopathy. Termination and substitution with another antiretroviral is indicated; typically, there is a period of 1–2 months of improvement followed by plateau [86].

The integrase inhibitor raltegravir is also reported to have caused a handful of cases of rhabdomyolysis with significant CK elevations and has subsequently been associated with symptomatic myopathy manifest as myalgia and proximal myopathy with normal CKs [87]. This does not seem to be a concentration or time-dependent effect, and the mechanism is unknown, but in cases where the antiretroviral agent was changed due to intolerance, objective improvement occurred indicating reversibility [87]. Implications for therapy remain unclear; myalgia alone, if tolerable, would not routinely necessitate change of agent, but change may be required by weakness or rising CK.

2.13 cART and the Neurological System: Adverse Effects – CNS Toxicity

ARVs have variable CNS penetration. Recognition of this heterogeneity has resulted in measurements such as the CNS penetration effectiveness score (CPE) and the observation in some studies of worse neurocognitive function with certain ARVs with higher CPE, contributing to HAND in the cART era [88]. There has been some in vitro and in vivo support for this concept. NRTIs are believed to cause mitochondrial toxicity, and this appears targeted, with lower NAA levels in MRI spectroscopy in patients on stavudine and didanosine [89]. Efavirenz is known to damage dendritic spines in neuronal culture [90], and has been well described as causing generalized neurobehavioral side effects. Management is on an individual case-by-case basis, but if patients are clearly intolerant, adjustment of regimen is recommended.

2.14 Conclusions and Future Directions

HIV-related neurological complications continue to be a challenging field for neurologists in the developing and developed world. While CNS opportunistic infections and early HIV-related complications such as HIV myelopathy and encephalitis are increasingly rare in the developed world, they continue to burden patients

globally. In the developed world, neurologists are frequently called upon to investigate the causes of cognitive impairment, peripheral neuropathy, and immune-mediated syndromes related to HIV, as well as complications of treatment. Early recognition and intervention remain key to impacting ultimate patient outcome and quality of life, and future progress in immune-based therapies will likely broaden the field of HIV neurology in the coming years.

Conflict of interest The authors report no conflicts of interest.

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Chapter 3
HIV-1 Related Central Nervous System Diseases: Pathogenesis, Diagnosis, and Treatment – An Indian Scenario

Sudharsana Sundarrajan, Sajitha Lulu, and Mohanapriya Arumugam

Keywords India • HIV • NeuroAIDS • Neurological complications • Dementia • Antiretroviral therapy • Adherence to treatment • Follow-up • Opportunistic infections • Toxoplasmosis • Cryptococcal meningitis • TB • PML • Seizures • Central nervous system lymphoma • Non-Hodgkin's lymphoma • Hospital-based reports

Core Message
The advancement of medical sciences in India has recognized an increase in the prevalence of neurological complications associated with HIV infection. Infection with HIV continues to be a major contributing risk factor for the development of neurological complications. The limitations of the studies from India primarily are attributed to the lack of a complete knowledge of the disease, a lack of adherence to treatment, as well as loss during follow-up. In the current scenario, early diagnosis of HIV and access to care and treatment are most vital.

3.1 Introduction

3.1.1 AIDS in India

India ranks third in its HIV-infected population of around 2.1 million people (UNAIDS Gap Report 2016[1]). India has different epidemics in various parts of the country. The epidemic episodes in the southern and western states are primarily

[1] http://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf.

S. Sundarrajan • S. Lulu • M. Arumugam (✉)
Department of Biotechnology, School of Biosciences and Technology, VIT University, Vellore, Tamilnadu 632014, India
e-mail: mohanapriyaa@vit.ac.in

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heterosexual. The northeastern states initially experienced HIV in the injection drug user population and sexual partners; however, the distribution due to heterosexual population has been increasing. In 2015 alone, around 87% of new infections were reported. Five states with highest prevalence, which includes Manipur, Mizoram, Nagaland, Andhra Pradesh, and Karnataka, are in the east and south of the country. Few states in the north and northeast India also are contributing now to high prevalence. The Indian population is primarily infected with subtype "C" HIV-1. Broad intervention programs were launched by the government of India along with international, nongovernmental, and community-based organizations. The main barriers to effective control are the low literacy levels, insufficient resources, stigma, and widespread migrations [1].

3.1.2 NeuroAIDS: An Overview

HIV-1 infects the nervous system of almost all the patients with systemic infection leading to disorders related to central and peripheral nervous systems (CNS and PNS). Autopsy studies revealed that around 75% of patients dying with AIDS had neurological abnormalities [2]. The virus is neuroinvasive (enters the CNS), neurotropic (replicates and survives in neural tissue), and neurovirulent (causes nervous system diseases) [3]. The presumed overall mechanism of CNS invasion is that virus-infected monocytes cross the blood-brain barrier (BBB), mature, and infect perivascular macrophages, choroid plexus, and capillary endothelial cells [4]. Oligodendrocytes and neurons are rarely infected, and indirect mechanisms are postulated for their damage [5]. BBB breakdown and persistent infection lead to neurotoxicity, axonal and neuronal injury, and clinical symptoms. Damage includes immune system dysfunction and paves the way for the development of opportunistic infections [6]. The CNS is permeable to antiretroviral drugs to various degrees, making the management and eradication of reservoirs of virus infection difficult. The virus can evade the immune system creating an environment to replicate, mutate, and reinfect via the circulation. The persistent inflammatory response may induce pathways leading to other neurodegenerative changes and diseases.

During early stages of infection, HIV-1 induces polyclonal hyper-gammaglobulinemia leading to demyelinating diseases of the CNS and PNS. The virus induces progressive multiple symptoms of motor, behavioral changes, and cognitive impairment. The development of these neurological syndromes in HIV-positive patients is consequent to a chain of events, which is determined by the properties of the virus itself, genetics of the host, changes in gene expression, and interaction with the environment. The neurological syndromes associated with HIV can be categorized into three classes: (i) primary HIV neurological disease (HIV is both required and sufficient to cause illness), (ii) secondary/opportunistic neurological disease (where HIV infection leads to infection by other pathogens – opportunistic infections), and (iii) treatment-induced neurological diseases [1–7].