6 THE PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF HIV/AIDS

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AIDS was first clinically identified and described in 1981 in patients presenting with symptoms of severe immunosuppression in the United States (1–3). While the clinical presentations varied among these initial cases, they shared enough features to justify their being treated as part of a syndromic disease caused by a single pathogen. This syndrome was characterized by immune abnormalities resulting from infection and destruction of CD4+ T-lymphocytes, which immunologically compromised the infected person. The term "acquired immune deficiency syndrome" (AIDS) was coined to describe the disease, since the causative agent was not yet known. Prolonged infection resulted in disease with protean clinical manifestations that differed to some degree from country to country and from region to region. Clinicians and scientists realized this new disease had a wide spectrum of signs and symptoms. This variable disease presentation resulted from the capacity of the virus to infect nearly every organ or system, particularly during the more advanced stages of disease.

The emergence of HIV/AIDS was mired in pervasive ignorance, mystery, fear, and stigma, frequently out of proportion to the reality of the situation. As a result, most African countries resisted advocacy and research, making it difficult to engage in informed discussions that would have otherwise promoted awareness of the disease. This was particularly true for Nigeria, where nei-

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ther the transmission modes nor the possible prevention measures could be openly discussed (4). It was against such a background that Nigerians failed to appreciate the need for the education, research, social reorientation, and behavioral change necessary for understanding the disease and planning actions to curtail the epidemic. This explains in part why Nigerians were slow to appreciate the reality of HIV/AIDS, delaying studies even on knowledge, attitudes, and practices until many years later (5–7).

DEFINITION OF AIDS

When first identified, the new syndrome lacked an agreed-upon, accurate definition, and its causative agent was unknown. Therefore, the U.S. Centers for Disease Control and Prevention (CDC) suggested that a combination of opportunistic infections and immunosuppression were indicative of AIDS. Once the causative agent, HIV, was identified, the definition was revised appropriately. The CDC and the World Health Organization (WHO) developed simplified diagnostic criteria that considerably eased the difficulties African physicians encountered in diagnosing HIV-related disease from a clinical standpoint. This definition was based on the presence of certain "indicator" diseases, backed by laboratory evidence of HIV infection (8) (Table 6-1).

At a WHO-sponsored meeting in Bangui in 1985, African scientists agreed upon another definition of AIDS, largely to enable surveillance and to promote a better understanding and diagnosis of the disease. Like the earlier definition, this clinical case definition, known as "The Bangui Definition," promoted more reliable diagnosis of AIDS by identifying certain major and minor clinical features of HIV disease with or without laboratory evidence of HIV infection (Table 6-2).

Although the Bangui Definition was eventually found to be insensitive, at the time it enhanced the diagnostic ability of health workers in developing countries. Many resource-poor sub-Saharan African countries could not even afford the equipment and reagents needed for accurate HIV diagnosis. Yet these were the very countries where such diagnosis was—and still is—needed most because of the enormous burden of HIV/AIDS. Initially, many health care providers were uncomfortable with the imprecise definition of disease; fortunately, significant clinical research during the early HIV epidemic made it possible to revise the definition by introducing more accurate laboratory diagnostic tests. The CDC developed new criteria, which led to an improved clinical classification system (Table 6-3).

Table 6-1. CDC Classification System of HIV Disease

Group	Clinical Stage
I.	Acute HIV infection
III.	Asymptomatic HIV infection
IV.	Persistent generalized lymphadenopathy
IV.	Other diseases
Subgroup A	Constitutional symptoms
Subgroup B	Neurologic disease
Subgroup C	Secondary infectious diseases
Subgroup D	Secondary neoplasms
Subgroup E	Other conditions

Modified from the original U.S. Centers for Disease Control and Prevention classification for HIV disease.

Simplification of methods to identify HIV/AIDS provides easily comprehensible data to clinicians with little training in understanding and interpreting the complicated CDC disease staging algorithm and little time to devote to complicated diagnoses, as they are usually treating hundreds of patients. Several "simple" laboratory tests were recommended to help African health workers make a reasonably accurate diagnosis of HIV infection in the absence of high-technology facilities; to some extent, these simple tests and modified screening algorithms helped achieve the intended objective. An accurate characterization of the disease manifestations and a positive HIV antibody test result enabled reliable AIDS diagnoses. In some settings, though, several of the recommended laboratory tests fell short of the expected accuracy; instead of confirming the diagnosis of HIV and/or AIDS, they gave inconsistent and irreproducible results.

Table 6-2. World Health Organization/Bangui AIDS Case Definition

Major Signs	Minor Signs
• Weight loss > 10% body weight	• Persistent cough > 1 month • Pruritic rash
• Chronic diarrhea > 1 month duration	• Recurrent herpes zoster • Oropharyngeal candidiaisis
• Prolonged fever > 1 month duration infection	• Chronic progressive herpes simplex
	• Generalized lymphadenopathy

Any two major signs, or one major plus two minor signs, constitute an AIDS diagnosis.

As a result of the limited diagnostic capacity in Africa, it was agreed that two positive enzyme-linked immunosorbent assay (ELISA) results using different assay methods were acceptable as confirmatory evidence of HIV infection. In Nigeria, the Federal Ministry of Health decided to establish regional laboratories with equipment and training to confirm ELISA-positive results using the Western blot technique.

Table 6-3. The Modified U.S. Centers for Disease Control and Prevention (CDC) Classification of HIV Infection and Disease

Clinical Stage I	**Asymptomatic disease** Asymptomatic/acute HIV infection, persistent generalized lymphadenopathy
Clinical Stage II	**Early (mild) disease** Weight loss ≥ 10% of body weight; minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infection, recurrent oral ulceration, and angular cheilitis); recurrent respiratory tract infections, such as bacterial sinusitis
Clinical Stage III	**Intermediate (moderate) disease** Weight loss ≥ 10% of body weight; chronic unexplained diarrhea ≥ one month; oral candidiasis (thrush); oral hairy leukoplakia; pulmonary tuberculosis within the past year; severe bacterial infection, such as pneumonia and pyomyositis
Clinical Stage IV	**Late (severe) disease AIDS** HIV-wasting syndrome as defined by the CDC; *Pneumocystis carinii* pneumonia; toxoplasmosis of the brain; cryptosporidiosis with diarrhea ≥ one month; extrapulmonary cryptosporidiosis; cytomegalovirus disease other than in liver, spleen, or lymph nodes; herpes simplex virus infection; mucocutaneous ≥ one month or visdermal of any duration; progressive multifocal leukoencephalopathy; disseminated endemic mycosis, such as histoplasmosis and coccidioidomycosis; candidiasis of the esophagus, trachea, bronchi, or lungs; atypical mycobacteriosis; disseminated, nontyphoidal salmonella septicemia; extrapulmonary tuberculosis; lymphoma, Kaposi's sarcoma; HIV encephalopathy as defined by the CDC.

In 1986, federal health authorities established four centers, only one of which attained acceptable diagnostic competence. This limitation made it impossible to verify the prevalence of HIV infection in Nigeria at that time, and progress in this area was made only years later, after more centers with adequate diagnostic competence were established.

THE HIV LIFECYCLE

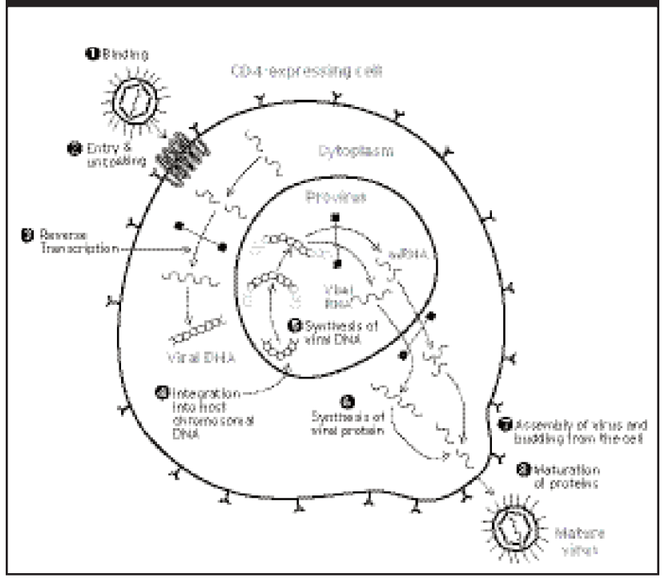
In 1983, and 1984, respectively, U.S. and French researchers isolated and described the causative agent of AIDS, with each group calling the virus a different name: human T-cell lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV) (9,10). Ultimately, the International Taxonomic Association resolved this issue by naming the causative agent human immunodeficiency virus (HIV). The identification and characterization of HIV, apart from enhancing our understanding of the pathophysiology of AIDS, also allowed the development of appropriate diagnostic tests to measure HIV-induced antibodies in the serum, a critical step in diagnosing AIDS. Later virologic studies identified antiretroviral (ARV) therapies to treat this unique and chronic viral infection.

HIV is an enveloped RNA virus whose basic structure consists of an outer bilayer of lipid and glycoprotein and an inner core containing two single RNA strands bound together by a *gag*-derived protein, p24. The outer membrane of HIV contains specific structural elements that play important roles in infectivity and disease progression. The most important of these is the viral envelope glycoprotein 120 (gp120), which is necessary for HIV's interaction with host cell receptors on cells, including CD4+ lymphocytes, macrophages, and monocytes. For this reason, early attempts to develop an HIV vaccine were based on trying to induce production of antibodies directed against gp120. Gp120 is closely associated with the envelope transmembrane viral protein, gp41, which is involved in viral–cell membrane fusion. Both gp41 and gp120 are essential for infectivity.

Gp120 interacts with the CD4+ receptor on the surface of susceptible cells. However, gp120 attachment also requires the presence of chemokine co-receptors, such as CXCR4 or CCR5, which facilitate the process of cell binding and entry. Typically, T-cell-tropic (T-tropic) HIV viruses use the CXCR4 receptor and are syncytium-inducing (SI) viruses, whereas macrophage-tropic (M-tropic) viruses use the CCR5 receptor and are non-syncytium–inducing (NSI) viruses. Other minor chemokine co-receptors—such as CCR1, CCR2, CCR3, and CCR4—may also facilitate the entry of HIV into CD4+ bearing cells (11–16).

To understand how HIV infection progresses from asymptomatic to clinical disease, it is necessary to consider possible modes of virus infection and the mechanisms of progression that result in damage to the immune system. The diversity of HIV-related illnesses requires consideration of these factors to understand the clinical presentation of HIV/AIDS. Thus, it is important to understand the complex mechanism of HIV replication at the cellular level, from the initial stage of attachment of a viral particle to a cell of the immune system—such as lymphocytes and monocytes—to the replication and budding of new viruses from that cell (Figure 6-1). These cellular events lead to the production of massive numbers of new viral particles, death of the infected cells, and ultimately the destruction of the immune system, which leads to the development of AIDS.

Figure 6-1. Replication Cycle of HIV



The HIV lifecycle can be divided into eight stages: binding or attachment; entry into the susceptible cell and subsequent uncoating of the virion; reverse transcription, in which the viral genetic material (RNA) is reverse transcribed into a DNA, or proviral form; integration, in which the viral DNA is inserted into the host cell DNA; synthesis of viral RNA, in which the proviral DNA is transcribed to make multiple viral RNA copies; translation, which involves the synthesis of viral proteins; assembly and budding, in which the new virions complete formation and exit the host cell; and maturation, which involves the processing of viral proteins and is required for the virus to become infectious. This cascade of events has been studied and described in detail (17,18).

Stage 1: Viral Binding

On the surface membrane of all living cells are complex protein structures that may serve as "receptors." A receptor is often compared to a lock into which a specific key or "ligand" will fit. HIV binds to at least two specific receptors on the host cell: the primary receptor, called the CD4+, and a secondary receptor, a chemokine co-receptor, such as CXCR4 or CCR5, as described earlier.

HIV infection of a lymphocyte begins with attachment of the virus, via its gp120, to the cell membrane through both of these "ligand-receptor" interactions. Tight attachment of the viral particle to receptors on the cell's membrane activates other proteins that enable viral fusion with the cell membrane.

Stage 2: Entry and Uncoating

Once the virus has fused with the host cell, the viral core and its associated RNA enter the cell. In order for the genetic material of the virus to reproduce, the coating that surrounds the RNA, or nucleocapsid, must be dissolved. A partial uncoating of the nucleocapsid occurs, resulting in the release of viral RNA into the cytoplasm of the host cell.

Table 6-4. The WHO System for Clinical Staging of HIV Infection and Disease

1. Candidiasis of the esophagus, trachea, bronchi, or lungs
2. Cryptococcosis (extrapulmonary)
3. Cryptosporidiosis (with diarrhea)
4. Cytomegalovirus infection (other than liver, spleen, or lymph nodes)
5. Herpes simplex virus infection
6. Kaposi's sarcoma in people younger than 60 years
7. Brain lymphoma (primary)
8. Lymphoid interstitial pneumonitis/pulmonary lymphoid hyperplasia (LIP/PLH) in a child
9. *Mycobacterium-avium* complex infection
10. *Pneumocystis carinii* pneumonia
11. Progressive multifocal leukoencephalopathy
12. Toxoplasmosis (of the brain)

Stage 3: Reverse Transcription

Conversion of the viral genetic material (RNA) to DNA occurs through the action of an enzyme—reverse transcriptase—that HIV produces. Reverse transcriptase reads the sequence of viral RNA that enters the host cell and transcribes the sequence into a complementary DNA sequence, which can then use the cellular machinery to make viral proteins and additional copies of viral RNA. Without this process, the virus cannot replicate.

The process of reverse transcription is unique to retroviruses as a result of their reverse transcriptase; thus, multiple nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been developed for use as ARVs to treat HIV infection. These ARVs are not as effective in treating HIV-2 infection and disease, however, because of differences in the HIV-2 reverse transcriptase (19–24). Current ARVs also suffer from the drawback that a single nucleotide mutation within the *pol* gene can yield a virus resistant to the ARV.

In the case of HIV, the process of reverse transcription is error-prone; thus, a small number of mutations are introduced in the HIV genome each time it replicates. This error-prone process results in the extreme heterogeneity of HIV (25). At the cellular level, the viruses produced after each round of replication are not identical to the original infecting virions. This variation of HIV within an individual and between HIV isolates from distinct geographic regions has a profound impact on the diagnosis and treatment of HIV, as well as the design and development of potential HIV vaccines.

Stage 4: Integration into Host Chromosomal DNA

During this stage, viral DNA is randomly inserted into the host cell DNA by the viral enzyme integrase. This stage of the HIV lifecycle has enabled the design and development of a new class of ARVs known as integrase inhibitors (26–29); several are still in the testing phase and none is in clinical use currently. Once the viral DNA is integrated into the host genetic material, it can remain there in a latent state for many years. The ability of HIV to persist in this latent state poses a major barrier to eradicating or curing HIV.

Stage 5: Synthesis of Viral DNA

Upon activation of infected cells, viral DNA is transcribed along with the host DNA into messenger RNA (mRNA). The mRNA codes for the production of viral proteins and enzymes. The new viral RNA also serves as the genetic material for the next generation of viruses. Once produced, the viral mRNA is transported out of the nucleus and into the cytoplasm of the host cell.

Stage 6: Translation and Production of Viral Proteins

Translation of viral mRNA results in the production of polypeptide sequences. Each section of the mRNA corresponds to a protein or enzyme that serves as a building block used to construct new HIV particles.

Stage 7: Assembly of Virus and Budding from the Host Cell

This stage of the viral infection is the formation of a new virus particle, or virion, which is preceded by the assembly of functional viral proteins such as the envelope and core proteins (gp120, gp41, and Gag) and necessary viral enzymes (reverse transcriptase, protease, and integrase). Viral polypeptides must be cleaved into smaller parts by the viral protease enzyme. Inhibitors of this viral protease, termed protease inhibitors, block the ability of the protease to cleave the viral polypeptide into functional enzymes or proteins; thus, protease inhibitors interfere with the production of new HIV particles, although they do not prevent infection of the cell in the first place.

When viral RNA and associated proteins are packaged and released from the cell surface as viral particles, they take with them a small portion of the cellular membrane that also contains viral surface proteins. These viral proteins then become the "envelope" of the new viral particles. As described earlier, these envelope proteins then bind to the receptors on other immune cells, thereby facilitating continued infection. If this process of viral replication occurs in CD4+ lymphocytes in a progressive and uncontrolled manner, HIV will eventually destroy them and progressively deplete their numbers. These infected CD4+ cells may also become functionally defective and inefficient in executing their central immunoregulatory functions. An additional consequence of CD4+ cell depletion is the development of opportunistic infections or malignancies that would otherwise not occur in immunocompetent individuals, as the CD4+ cell count is depleted to less than 200 cells/mm^3.

It is well documented that HIV can be cytotoxic to infected CD4+ lymphocytes (30–32). This immune-mediated cytotoxic effect probably involves inhibition of T-cell regeneration in the thymus. For example, T-cell proliferative responses to HIV are quickly lost and the repertoire of antigen recognition diminishes with time. The use of ARVs has provided evidence, however, that some of these immune cells, particularly CD4+ T-lymphocytes, can be reconstituted and become functionally effective once more (33–35). It has been suggested that Africans may have an activated immune system because of chronic exposure or infection with other pathogens, resulting in an unusual susceptibility to HIV infection, which may play a significant role in a more rapid progression of AIDS (7,36,37).

Stage 8: Maturation

The final step in the viral lifecycle, maturation, is required in order for the virus to become infectious. Shortly after budding from the host cell, the protease enzymes in the new viral particle become active and cleave the polypeptides into their appropriate functional subunits, or proteins and enzymes. This processing step results in the generation of a mature and infectious virion.

CLINICAL COURSE OF HIV DISEASE

The pathophysiologic features described in this section refer mostly to ARV-naive individuals, which is what is usually seen in most African settings. While most people are considered typical progressors, with a median incubation period of eight to ten years, a small portion of HIV-infected people are rapid progressors, while still others are long-term non-progressors (29,38).

Primary HIV infection

Primary infection with HIV occurs two to six weeks after infection, a period in which it is extremely difficult to make a specific diagnosis by standard laboratory assays. During this period, viral antigen or RNA detection is required since antibody responses to viral proteins are slower to develop post-infection. Various clinical studies show that many infected people experience flu-like symptoms during primary infection, which they may ignore partly because of the self-limiting and mild nature of those symptoms. Clinical symptoms of primary infection, when recognized, may include mild fever, muscle aches and pains, fatigue, headaches, enlargement of the lymph nodes, rashes, a sore throat, and mild diarrhea. A minority of infected subjects may present with other symptoms suggestive of meningeal, pulmonary, or gastrointestinal involvement (38).

In Nigeria, most of the laboratory and clinical findings associated with primary infection are nonspecific and may mimic other clinical conditions caused by various pathogens. Measurement of levels of HIV-infected peripheral blood lymphocytes, plasma HIV RNA, and HIV p24 antigens—made possible by advances in such sensitive applications as the polymerase chain reaction (PCR)—have greatly facilitated the diagnosis of primary HIV infection (29,38). The fact that early ARVs may delay progression from asymptomatic to symptomatic HIV disease makes early diagnosis of the infection highly desirable.

Asymptomatic Infection

Many HIV-infected persons are asymptomatic for a long time. This stage has a number of important implications for the epidemiology of HIV infection. A lack of awareness and a poor laboratory investigative infrastructure are major impediments to the characterization of the entire disease process, from primary exposure and infection through development of pathophysiologic and clinical features, to relevant diagnostic investigations. Thus, effective control and therapeutic measures (including ARV treatment) that may delay disease progression were slow to be introduced in Nigeria. Fortunately, studies on the course of HIV disease progression have been performed in other African countries.

Symptomatic Infection

Advanced HIV infection predisposes people to many opportunistic infections seen commonly in African patients. The most common of these infections are caused by *Mycobacteria*, exemplified best by *M. tuberculosis*. Tuberculosis develops either by reactivation of latent infection, or primary infection that progresses rapidly in HIV-infected people (39–41). The incidence of tuberculosis in Africa had been declining before the emergence of HIV/AIDS, when the incidence of tuberculosis infection began to increase dramatically. The association between HIV disease and tuberculosis is significant, and some clinicians screen all patients with a diagnosis of tuberculosis for HIV co-infection.

Other opportunistic infections associated with advanced HIV disease include candidiasis caused by *Candida albicans* and other *Candida sp*, *Cryptococcal* infections, *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus infections, cryptosporidiosis, and herpes virus infections (42–47). Not surprisingly, patients tend to have multiple opportunistic infections. HIV infection may also occur in association with hepatitis B or C virus infection (48–50). A number of malignancies—including Kaposi's sarcoma, cervical cancer, brain lymphomas, and non-Hodgkin's lymphoma—are also associated with advanced HIV disease (51–54). HIV-infected people with low CD4+ lymphocytes also have an increased incidence of other microbial infections.

Clinical Presentation of HIV Disease

Progression from HIV infection to disease is often insidious, but once sufficient immunologic damage and immunosuppression have occurred, a variety of signs and symptoms appear, depending on the clinical severity and immunopathology of the disease. Nonetheless, the disease course is variable, and patients may present with mild, moderate, or severe manifestations. Diarrhea is a common clinical sign, resulting in rapid wasting, particularly in Central Africa, East Africa, and southern Africa, where this symptomatic complex was initially referred to as "slim disease." In Africa, emaciation or body wasting is often associated with HIV disease, even without formal documentation of HIV infection. AIDS is a clinical syndrome of diseases that results from the profound immunosuppression that permits opportunistic infections to replicate in an uncontrolled manner. This syndromic nature of HIV disease complicates the clinical diagnosis of AIDS, as similar signs and symptoms may be found in a number of other infectious diseases.

Symptomatic HIV disease results from prolonged untreated infection. ARVs and other therapies to prevent and treat the opportunistic infections associated with symptomatic disease have been developed, but their cost renders them beyond the reach of most HIV-infected Africans. Clinical awareness and appropriate diagnostic support are also required in dealing effectively with the disease. Despite the potential of the infection to cause multisystem disease, the manifestations are described according to organ or system, for easier understanding and better appreciation of HIV-associated illnesses.

Skin Manifestations

Dermatologic disease or pathology is almost invariably observed during HIV symptomatic disease. These vary from mild pruritus with or without rashes, to severe coalescent mucocutaneous rashes, such as the kind seen in patients with Stevens-Johnson syndrome. Among people whose behavior places them at high risk, the persistence of skin lesions should lead to a suspicion of HIV infection (55). Similarly, the appearance of herpes simplex or herpes zoster infections in the skin should always prompt testing for HIV infection. These infections may be associated with oral ulcers, sometimes severe enough to cause large and deep mucocutaneous lesions. Orolabial lesions may also occur. Some patients develop Kaposi's sarcoma (56), a

disease caused by human herpesvirus 8. HIV-associated Kaposi's sarcoma is more severe than the endemic African form, which is usually a mild, slow-growing, and fungating tumor. The histological features of the two are broadly similar, however, as both are multicentric tumors with fibroblastic elements (57).

Candidiasis is another significant cause of oral and skin manifestations in many people with HIV (58). Apart from oral lesions, there may be hyperkeratosis of the skin in patients co-infected with *Candida albicans*. Anal warts may be due to human papilloma virus (HPV) or candida infection, while some patients develop generalized mycoses and dermatitis. Another significant oral manifestation of HIV infection is hairy leukoplakia, a persistent white lesion around tongue margins, caused by co-infection with Epstein-Barr virus (59,60). Other skin manifestations of HIV disease include peripheral small arterial lesions, such as angiomatosis, seborrheic dermatitis, and folliculitis (55).

Gastrointestinal Disease

Chronic diarrhea lasting many months is one of the earliest HIV-associated symptoms described in Africa. It can result in progressive weight loss and related metabolic (electrolyte) disturbances. Diarrhea in people with AIDS may be caused by several pathogens, including *Giardia lamblia*, *Salmonella* sp., *Campylobacter* sp., and *Shigella* sp. (61,62). As the patient's clinical condition worsens, other pathogens may be isolated, including cytomegalovirus, *Cryptosporidium*, *Toxoplasma gondii*, *Mycobacteria*, *Cyclosporidia* sp., *Isosporidia* sp., and *Candida* sp. (61–68). Diarrhea may also occur as a result of gastrointestinal cyclosporidiosis, isosporidiosis, and infection by other *Coccidia* sp. (66). The prevalence of these pathogens in Africans with HIV-related diarrhea is difficult to determine, because their isolation requires expensive laboratory equipment not readily available on most of the African continent.

Toxoplasmosis is a protozoan infection that primarily infects the gastrointestinal tract, the central nervous system, and the respiratory tract. Other organs or systems, however, may be involved, although to a lesser extent and with milder clinical manifestations. HIV-associated *Toxoplasma gondii* is isolated in 34% to 80% of asymptomatic individuals, including children and pregnant women in some parts of Africa (69,70).

Hepatic Disease

Clinically relevant involvement of the liver is not common during the early stages of HIV infection, even though mild "hepatitis-like" self-limiting symptoms may occur in some people with acute or primary infection with HIV. Chronic active hepatitis in people with HIV is a progressive illness that is often difficult to treat. Although the transmission modes of HIV and hepatitis viruses are similar, co-infection with hepatitis C virus is both more common and serious in terms of morbidity than co-infection with hepatitis B virus (48–50,71,72). There is no evidence that HIV infection per se is directly oncogenic to primary liver cells; thus, any increase in the number of people with primary liver cancer in Nigeria and other African countries may be due to increased incidence of infection by hepatitis B and C viruses and/or improved diagnostic capabilities. Certain ARV therapies may also act on hepatitis viruses and therefore slow the progression of HIV co-infection with hepatitis B or C viruses (48–50). ARVs may also exacerbate liver disease in people co-infected with HIV and hepatitis C virus, however, through increased hepatotoxicity (48,49).

Respiratory Disease

The respiratory tract may be involved in various ways during symptomatic HIV disease. Upper respiratory infections may occur early in some patients, caused by common respiratory pathogens, such as *Haemophilus influenzae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*. Respiratory disease may also be caused by opportunistic infections as a result of prolonged HIV infection. Patients with HIV-related pneumonia or pneumonitis often present with cough, fever, and shortness of breath, which may become severe as the disease progresses.

Limited facilities and poor manpower capacity make diagnosis of *Pneumocystis carinii* pneumonia (PCP) difficult in most resource-poor African nations (42,73–75). Although sputum tests are easy to perform and are routinely done, they do not yield the necessary accuracy for diagnosis. Moreover, the more reliable and sensitive investigative techniques used for diagnosing PCP — such as PCR — are not generally available in sub-Saharan countries because of their high costs and the lack of adequate laboratory expertise. Therefore, they are neither in routine use nor satisfactorily standardized. Additionally, the signs and symptoms of PCP may closely mimic those of pneumonia from causes other than HIV infection. This may partly explain why PCP has not been reported commonly in Nigerians or other Africans with HIV disease.

In terms of numbers, complications, and severity, co-infection with *Mycobacterium tuberculosis* is one of the most common and serious respiratory diseases in people with symptomatic HIV disease (76–78). Pulmonary tuberculosis is the most common form. The diagnosis of tuberculosis is simple, as sputum examination may be all that is required in most patients when a positive smear stained with Ziel-Nielsen shows acid-alcohol-fast bacilli. Other diagnostic methods can increase the sensitivity to nearly 100% (79). In some cases, HIV-infected people suspected of having tuberculosis on clinical or radiological grounds may be sputum negative, in which case it may be necessary to employ other rigorous diagnostic procedures, such as sputum culture or PCR. Patients with suspected HIV-associated tuberculosis and possible brain lesions of other etiologies should undergo computerized tomographic (CT) scanning and magnetic resonance imaging (MRI) to rule out brain tumors.

The incidence of tuberculosis is significantly higher in HIV-infected people than in those without infection (39–41,80). The clinical presentation of tuberculosis is the same regardless of association with HIV infection; however, the disease severity may be higher in people with immunodeficiency. For instance, those with tuberculosis may present with bilateral hilar adenopathy, interstitial fibrosis, collapse/consolidation, pleural effusions, and cavitating disease. Tuberculosis associated with HIV infection may also affect the cardiovascular system and present as pericarditis with or without effusions. Central nervous system infection by *Mycobacteria* may cause meningitis, while ascites may occur in gastrointestinal involvement. Disseminated tuberculosis is a serious condition predisposing to miliary presentation, polyarthritis, osteolytic lesions, and paravertebral abscess.

Hematologic Disease

The cardiovascular system may be directly affected in a number of ways during symptomatic disease, with manifestations ranging from minor peripheral immune-complex–mediated vascular lesions to

septicemia. Common hematologic disturbances in HIV-infected people include anemia, thrombocytopenia, lymphopenia, lymphocytosis, and mild lymphadenopathy. Lymphopenia results from persistent HIV infection, concomitant with progressive destruction of CD4+ lymphocytes. As depletion of CD4+ cells continues, the imbalance between CD4+ and CD8+ lymphocytes progresses, often reversing the CD4+/CD8+ cell ratio. The reversed ratio is attributable largely to severe depletion of CD4+ cells, rather than an absolute rise in CD8+ lymphocyte numbers.

Persistent generalized lymphadenopathy (PGL) is one of the earliest clinically recognized features of symptomatic HIV disease. For this reason, it was one of the first illnesses used to diagnose AIDS before definitive laboratory indices were developed. PGL is thought to result from progressive and rapid turnover of infected lymphocytes in the lymph nodes (81). The lymph nodes are clinically indistinguishable from other causes of lymph node enlargement, underscoring the need to exclude other causes, such as tuberculosis and lymphomas.

Lymphomas and Kaposi's sarcoma are among the opportunistic tumors that occur in HIV-associated disease. Both Hodgkin's and non-Hodgkin's lymphoma may occur in patients with HIV disease, the most common forms being diffuse large-cell lymphomas with widespread extranodal involvement (54). Moreover, an association exists between HIV-related lymphomas and Epstein-Barr virus, as well as human herpesvirus type 8 (52,54,82). HIV-related Hodgkin's lymphoma occurs late during HIV disease and is more advanced than autonomous Hodgkin's disease.

Central Nervous System Disease

Numerous central nervous system (CNS) manifestations of HIV disease occur, as well as peripheral neuropathies, neuronitis, and mononeuritis. Neuropsychiatric manifestations also arise in people with HIV-related CNS disease (83,84). Dementia is common in patients with advanced HIV disease and is often known as AIDS dementia complex (83,84). While the exact mechanisms by which HIV causes CNS manifestations remain unclear, the virus infects and is cytopathic to neuronal cells (85–89). In addition, some patients present with features of meningeal irritation or meningitis because of opportunistic infections by *Mycobacterium tuberculosis*, *Cryptococcus* sp., *Streptococcus pneumoniae*, *Meningococcus* sp., or *Toxoplasma gondii*. Primary brain lymphoma, characterized by focal or multifocal neurologic deficits, is another clinical CNS manifestation of HIV disease, the diagnosis of which is facilitated by CT and MRI scans (54). Progressive multifocal leukoencephalopathy occurs in association with human polyoma JC virus (90). Other CNS pathologies include astrocytomas and ependymomas, although these are rare. Bacteremia due to co-infection with *Streptococcus pneumonia* or *Escherichia coli* may cause meningitis, thereby increasing mortality among HIV-infected people with severe immune dysfunction (91).

HIV INFECTION IN NIGERIA

The minister of health announced Nigeria's first confirmed case of HIV infection in 1986, followed by a formal report from the National Institute of Medical Research, the one institution with the appropriate facilities to confirm HIV infection at the time. Studies that began soon afterward demonstrated that the HIV seroprevalence rate in the general population ranged between 0.15% and 1.3% (92–95). The authors of these initial publications concluded that the incidence of HIV infection in Nigeria was low, and that Nigeria was the African country least affected by HIV at the time. The same researchers also reported that the highest incidence of infection was among female sex workers and their patrons, commercial blood donors, long-distance truck drivers, and those with sexually transmitted infections. A one-year follow-up study by one group showed a 9.81% rise in seroprevalence among sex workers and concluded that the rate of HIV infection would increase sharply within a few years unless appropriate preventive measures were taken (96). Unfortunately, the lower rates of infection found among "low-risk" groups is these early studies contributed to the country's denial about its growing epidemic.

Since these early studies, the estimated seroprevalence of HIV infection in Nigeria has risen to 5.0% overall (97). Considering the size of Nigeria's population, this means that as many as six million Nigerians may be infected with HIV. Thus, although no longitudinal investigations of rising HIV prevalence were carried out at the time, by the late 1990s it had become clear that Nigeria's epidemic had changed from one concentrated in high-risk populations to a more generalized epidemic, resulting in an epidemic that resembled those in Central Africa and southern Africa (98).

One of the problems that delayed early action on the HIV epidemic in Nigeria was the lack of political and financial commitment at the highest level. The National Expert Advisory Committee on AIDS, which the minister of health instituted in 1986, was full of ivory-tower clinicians and scientists and short on social workers, counselors, health education specialists, media and communications experts, and people living with HIV/AIDS. No community, religious, or traditional leaders were involved—a serious omission in Nigeria. Real progress began only in 2000, when a new political leadership placed HIV/AIDS at the top of the national agenda, with President Olusegun Obasanjo himself chairing a new National Action Committee on AIDS (NACA). The president also personally led advocacy campaigns, a significant undertaking in Nigeria, making citizens appreciate the serious nature of the epidemic and the need to take preventive measures. For the first time, the government provided substantial funding for multimedia communication and research. The levels of denial, shame, stigma, discrimination, and similar negative perceptions of HIV/AIDS decreased, making way for more honest and open discussions of the epidemic. In 2001, the government also committed to providing a heavily subsidized ARV program.

With published data on HIV in Africa relatively sparse, the paucity of scientific information, particularly on the pathophysiology and clinical manifestations of infection, has continued. In Nigeria, such data are especially limited, as research has generally been a low priority, leading to a lack of funding for scientific investigations (99). Most of the early seroprevalence studies on HIV/AIDS in Africa were carried out in East Africa, Central Africa, and southern Africa. Nigeria's need for additional research to characterize the pathophysiology HIV infection and disease progression has grown critical.

Initially, sentinel surveillance was conducted with considerable difficulty in Nigeria, leading to insufficient data on which to plan or base intervention strategies. For many years seroepidemiology remained the only method for ascertaining HIV prevalence in Africa, though a few sophisticated investigations were also

carried out (100); at same time, many African clinicians questioned whether seroepidemiology or clinical epidemiology should be used to estimate prevalence. Despite being asymptomatic, HIV-infected people have laboratory abnormalities, many of which may be nonspecific in nature. For instance, some may have moderately low hemoglobin levels, neutropenia, lymphopenia, and other hematologic abnormalities, such as low platelet counts (101). In much of Africa, including Nigeria, the inability to run confirmatory tests for HIV infection has contributed to the rapid spread of HIV infection. Inexpensive, simple assays, such as ELISA, are now available in Africa, but monitoring the progress of HIV disease, with or without ARV treatment, requires more complex and expensive assays that tend not to be generally available, such as quantitating the amount of virus in the blood, or viral load. Thus, many people perceived the overall threat of HIV/AIDS to be low until a critical threshold of "visible" HIV infections or AIDS cases became evident in society.

The response to HIV/AIDS in Africa is accentuated by large-scale poverty, limited access to education, inadequate health care, and poor health care systems. As resources become available for ARVs, the requisite needs for adequate infrastructure and human capacity will slow the scale-up efforts. Furthermore, the migration of many highly qualified professionals from poor developing countries ravaged by the HIV pandemic to countries in North America and Europe compounds the problem (102,103).

The early studies in Nigeria showed that the HIV seroprevalence rate was highest among the 16-to-30-year age group (94). One epidemiologic study revealed that within one year (1987 to 1988), the seroprevalence rose from 0.2% to 1% (96). It was widely believed that HIV first arrived in Nigeria several years after high rates of HIV infection were reported from Central Africa, then regarded as the focus of the infection (104,105). The clinical manifestations and disease progression of HIV/AIDS in Nigeria resemble those found in other African countries.

MANAGEMENT AND CONTROL

Early in the HIV epidemic, no drugs were capable of reducing HIV replication, slowing disease progression, or prolonging the life of people with HIV. Consequently, the management of HIV/AIDS was extremely difficult and frustrating. Effective ARVs became available only much later. Yet unlike developed countries, the resource-poor countries of Africa could not — and most still cannot — afford to procure or regularly supply the drugs to people with HIV/AIDS to prolong their lives. In addition, facilities for clinical and laboratory diagnosis were — and in many countries remain — poor or nonexistent, so even when ARVs were affordable and available, treatment safety and efficacy could not be properly monitored. Ignorance, discrimination, stigmatization, denial, and poverty remain major factors driving the HIV/AIDS epidemic and hindering effective control measures.

ARV therapy has, no doubt, provided greater hope for longer lasting survival and improved quality of life (106,107). Apart from their high cost, however, the need for combination therapy — a minimum of three drugs — may be problematic. In addition, the treatment is not always tailored toward individual patient responses to the particular drugs being used. For many years, effective ARVs were unavailable, and when they became available, it was difficult to make decisions about their use in Nigeria, as was the case in much of sub-Saharan Africa. These drugs have progressively become more available largely on account of reduced costs brought about by allowing developing countries to manufacture generic formulations. Intervention by international agencies and donor countries has contributed significantly to the campaign to make ARVs more affordable to the people in poor developing countries who are the most in need of these drugs. On a number of occasions, ARVs have not reached the individuals for whom they were intended. Instead, officials responsible for distributing or administering them have diverted them inappropriately, charging patients more for the drugs.

Logistical problems, political considerations, and the weakness and incapacity of the health systems have further compromised the fair and equitable distribution of ARVs in many African countries. In some developing countries, ARV access has been subject to political considerations; rather than allowing clinical or professional criteria to determine which people received ARVs, governments have withheld drugs from people perceived as their political opponents. Education of clinicians on the multiple combinations of the drugs most appropriate for individual patients or access to these combinations continues to be problematic, impeding rapid progress in treatment and control of the infection. The infrastructure is still poor and the capacity to monitor ARV therapy inadequate. Moreover, patient education, acceptance, and adherence continue to hinder treatment efforts. Many infected people are reluctant to be tested for HIV, even after they develop signs of HIV disease. When they agree to be tested, they are often reluctant to reveal their HIV status because of the stigma. In Nigeria, all these constraints are gradually giving way to more openness and a better understanding of HIV/AIDS. At the same time, caregivers and physicians are becoming more familiar with combination ARV therapy, and facilities for diagnosis and monitoring treatment continue to improve.

Management and control of the HIV pandemic and disease progression depend heavily on international assistance to poor developing countries. Rich developed countries were slow to come to the rescue of sub-Saharan Africa. Even after realizing the gravity of the socioeconomic damage and the sharp rise in disease burden from HIV/AIDS, these countries offered assistance that has not been able to make a significant difference to the affected countries. The more recent establishment of large-scale intervention initiatives — such as the Global Fund for HIV/AIDS, Tuberculosis and Malaria; the Millennium Development Goals; and the Global Alliance for Vaccines and Initiatives — are laudable (108–110). Logistical problems and incapacity in poor countries are hampering progress, however, making timely attainment of the intended goals unlikely (111–114). Some countries, including the United States, have already served notice that the Millennium Development Goals must be re-focused or even abandoned.

CONCLUSION

The general clinical and pathogenesis features of HIV infection and disease are no different in Nigeria than in other African countries. Although the early epidemic was thought to be less pronounced in Nigeria than elsewhere in Africa, the country's estimated 5% prevalence rate is equivalent to the current estimates for the rest of the continent. This underscores the need for increased prevention efforts and support services, including access to ARV treatment and care.

The clinical and diagnostic limitations that have hindered progress in understanding the pathophysiologic basis and clinical manifestations of HIV infection are diminishing. Improved infrastructures and capacity are infusing the health care system, and increased access to HIV/AIDS education, prevention, and treatment is reducing stigmatization and encouraging a more open approach to the crisis. This new positive approach to HIV/AIDS in Nigeria provides hope for efforts to curb the epidemic and control the disease.

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