Human Immune Deficiency Virus

Contents

Human Immunodeficiency Virus I: History, Epidemiology, Transmission, and Pathogenesis

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Learning Objectives

- Understand the epidemiology of HIV and AIDS
- Recognize factors that influence the transmission of HIV
- Review the pathogenesis of HIV infection

40.1 Definitions

Lentivirus - Genus of Retrovirus that contains HIV-1 and HIV-2

MSM - men who have sex with men. These individuals may not classify themselves as homosexuals

Retrovirus - Enveloped positive stranded RNA virus that replicated through a DNA intermediate

40.2 Introduction

While research has shown that human immunodeficiency virus (HIV) may have been present in humans as early as the start of the twentieth century in the Democratic Republic of the Congo (formerly Zaire), the diagnosis remained out of the public eye for over half a century [1]. In the 1980s, that all changed. When acquired immunodeficiency syndrome (AIDS) was first described in 1981, acquisition of the disease was considered a death sentence. More than 30 million people worldwide are infected, with the largest number of infected individuals living in resource-poor areas of sub-Saharan Africa and South and South East Asia. Additionally, it is estimated that only half to two-thirds of people with HIV currently have access to treatment [2]. In the United States, an estimated 1,122,900 people were living with HIV in 2015, which includes an estimate of the number of people with HIV who do not yet know of their diagnosis. In 2016, the last full year for which statistics are available, 39,782 new cases of HIV were diagnosed in the United States [3]. Infection with human immunodeficiency virus (HIV) and its end stage, acquired immunodeficiency syndrome (AIDS), is one of the most challenging public health crises of modern times and one of the most disastrous examples of the emergence, transmission, and dissemination of a microbial genome.

40.3 Introduction to the Problem

On June 5, 1981, the case report of five homosexual men with *Pneumocystis carinii* pneumonia, ages 29 to 36 and from Los Angeles, was published in the Center for Disease Control's (CDC) *Morbidity and Mortality Weekly Report*. All five men also had prior or current cytomegalovirus (CMV) infection and mucosal candidiasis. Two died by the time the cases were reported. These cases occurred between October 1980 and May 1981 [4]. At the time, AIDS had not been described and HIV had not yet been discovered. What was clear was that five individuals without a known immune deficiency had contracted infections historically seen only in patients who were profoundly immune-suppressed.

The report ended as follows:

"All the above observations suggest the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections such as pneumocystosis and candidiasis. Although the role of CMV infection in the pathogenesis of pneumocystosis remains unknown, the possibility of *P. carinii* infection must be carefully considered in a differential diagnosis for previously healthy homosexual males with dyspnea and pneumonia [4]."

Soon after the report from Los Angeles, similar reports from San Francisco, New York, and other cities were reported, and the CDC noted that there was an increase in requests for pentamidine, which is used to treat *Pneumocystis* infections. By late 1982, the CDC compiled a set of risk factors associated with the condition which had become known as AIDS. In 1983, two researchers working independently, Robert Gallo and Luc Montagnier, published research manuscripts in Science describing a retrovirus isolated from two patients suffering from AIDS. The virus that they described would go on to be named HIV [5, 6].

Despite having identified the causative pathogen, progress in terms of diagnosis and treatment was slow, and the stigma associated with the disease often lead to discrimination. The first screening test for antibodies to HIV was not approved by the Food and Drug Administration (FDA) until 1985 [7]. Until testing was available, contaminated blood products were unknowingly being provided to patients. Two of the most famous victims of HIV associated with blood transfusions were Arthur Ashe, a tennis player who is believed to have contracted HIV after receiving blood products during heart surgery in 1983, and Ryan White, who contracted HIV from factor VIII infusions required to treat his hemophilia A [8, 9]. A more specific Western blot was approved by the FDA in 1987, which was also the year the antiretroviral for HIV, zidovudine (AZT), was first approved [10]. Prior to the release of AZT, the treatment of HIV/AIDS was limited to the complications and opportunistic infections associated with the diagnosis.

40.4 Epidemiology of HIV/AIDS

40.4.1 Global Epidemiology

Globally, since the start of the HIV/AIDS epidemic, more than 78 million people have been infected, and approximately 35 million people have died from HIV infection. It is estimated that since 2010, there have been no declines in new HIV infections among adults and that every year since 2010, approximately 1.9 million adults become newly infected with HIV each year. By the end of 2015, there were 36.7 million people living with HIV worldwide, and as of June 2016, only 18.2 million HIV-infected people had routine access to antiretroviral therapy. Despite the global impact of HIV,

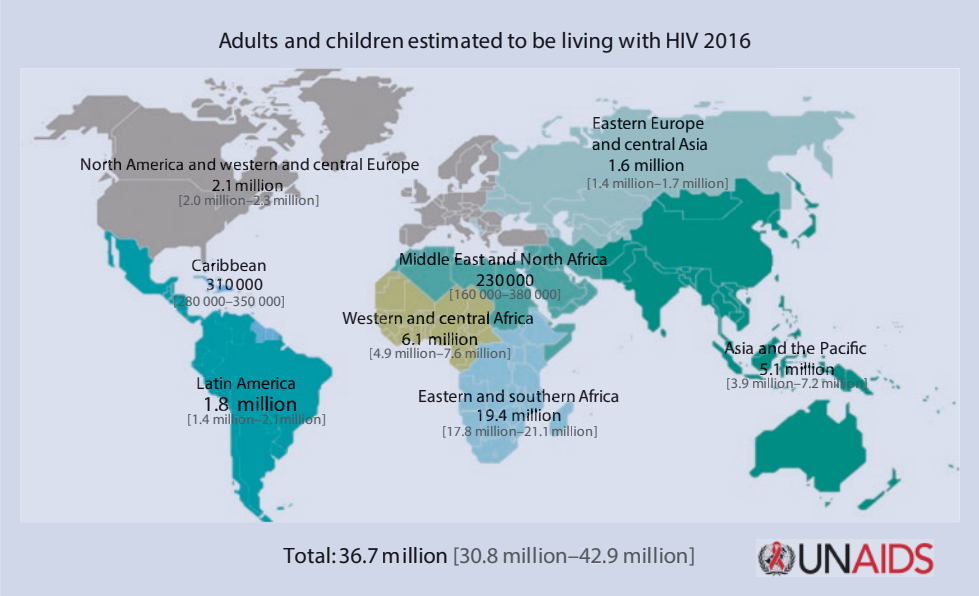

Fig. 40.1 Global and regional estimated of adults and children living with HIV in 2016. (Reproduced from UNAIDS 2017 Core Epidemiology)

the burden of the epidemic varies significantly by geographic location, with eastern and southern Africa remaining the most severely affected (Fig. 40.1) [11].

40.4.2 US Epidemiology

In the United States in 2011, it was estimated that there were 1.2 million people living with HIV, 86% of whom were aware of their diagnosis, and 14% of whom were not [12]. Persons infected with HIV who are unaware of their status are responsible for nearly one-third of newly transmitted cases in the United States [13]. In 2015, 22% of all new HIV diagnoses in the United States were among persons aged 13–24 years, while those between the ages of 50 and 54 years accounted for the largest percentage of persons living with an HIV diagnosis (18%). With regard to race/ethnicity, the highest prevalence rates and highest rates of new HIV infection are found among African Americans, followed closely by Hispanics/Latinos. Although rates of new HIV acquisition are decreasing overall, gender remains a significant risk factor, with men accounting for 81% of all new HIV diagnoses reported in 2015. Seventy percent of new HIV infections are attributed to male-to-male sexual contact, 11% to injection drug use, 10% to heterosexual contact, 7% to male-to-male sexual contact *and* injection drug use, and 1% to perinatal transmission. Currently, the most at-risk group of individuals for new HIV infection includes young Black/African American and Hispanic/Latino gay and bisexual males. Many programs continue to put forth efforts to improve awareness, expand HIV testing to groups at higher risk, retain HIV-infected patients in care, reduce HIV transmission rates, and decrease high-risk behaviors that place individuals at risk of HIV acquisition [14].

40.5 HIV Virology and the Resulting Host Response

HIV is a retrovirus. As part of their replication cycle, retroviruses reverse-transcribe viral RNA into linear double-stranded DNA, which then incorporates itself into the host genome. It is currently believed that HIV-1 and HIV-2 originated in primates and jumped species to humans in Central and West Africa. Four groups of HIV-1 exist: M (for major), N, O, and P. Group M was the main cause of the global HIV pandemic and consists of nine viral subtypes: A–D, F–H, J, and K. Subtype B is the predominant subtype found in the Americas, Western Europe, and Australia, while subtype C is the primary type found in Africa and India [15]. HIV-2 causes a similar illness to HIV-1, but immunodeficiency progresses more slowly, and it tends to be associated with lower viral loads in most individuals. Infection with HIV-2 is largely confined to West Africa and in countries with strong socioeconomic ties to West Africa such as France, Spain, Portugal, and former Portuguese colonies of Brazil, Angola, Mozambique, and parts of India [1, 16]. A distinguishing feature of HIV-1 infection is the progressive depletion of CD4+ T cells, the primary target cell for HIV. Infection and depletion of CD4+ T cells account for many of the manifestations of HIV [17].

HIV enters CD4+ T-lymphocytes via the CD4 receptor and a chemokine co-receptor, either CCR5 or CXCR4, as a dual-receptor system. The virus initiates infection by via the viral glycoprotein, gp 120, which binds to the CD4 receptor found on CD4+ T-lymphocytes and subsets of other mononuclear cells [3] (Fig. 40.2). The HIV envelope fuses with the target, allowing release of the viral core into the host cell. Next, viral DNA is produced through the action of virus-encoded reverse transcriptase on the viral RNA genome. HIV

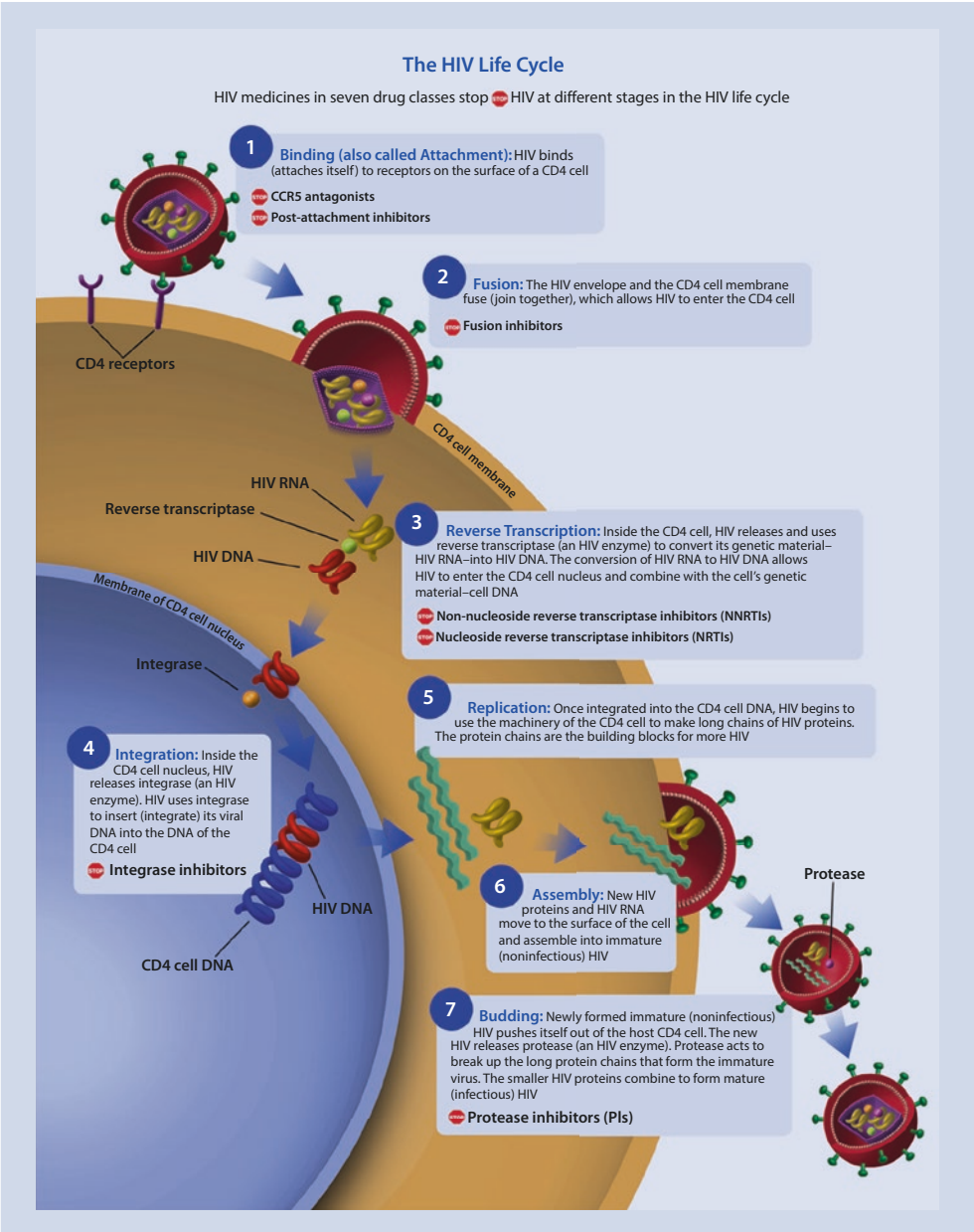

Fig. 40.2 Schematic of the HIV life cycle and associated targets of antiretroviral therapy. (Reproduced from AIDSinfo, The HIV Life Cycle) [31]

DNA is then transported into the target cell nucleus where it integrates into the host cell DNA genome through the action of virus-encoded integrase. During HIV replication, new viral RNA is used as genomic RNA and as the template for translation of viral proteins. The components assemble and mature into new, infectious virions [18].

It is now known that the cellular and anatomic sites of HIV replication influence the disease progression, the ability of antiretroviral therapy to reduce viremia, and the capacity to establish a viral reservoir. The HIV reservoir is defined as a group of cells that are infected with HIV but that are not actively producing new virions [19].

40.5.1 HIV Transmission

Modes of HIV transmission include direct sexual contact with semen, vaginal fluid, or blood that contains the virus, exposure to blood products derived from HIV-infected individuals, vertical transmission from mother to infant, and accidental occupational exposure. Multiple variables influence the probability of HIV transmission, including the dose inoculum of the virus, the route of exposure, the genetic background of the host, and concomitant infections that are often associated with microscopic breaks in the skin or mucous membranes providing the virus with direct access to the bloodstream [20].

Once infected with HIV, viremia allows for widespread dissemination to target cells of the lymphoid tissue and the central nervous system. During early HIV infection, as the HIV virus infects CD4+ T cells, detectable blood viral RNA levels are quite high, while the CD4+ T-cell lymphocyte count drops only transiently, if at all [21]. Hepatic transaminitis, mild anemia, and thrombocytopenia are also commonly seen during acute HIV infection [22]. HIV has marked genetic diversity because reverse transcriptase does not have proofreading activity like DNA polymerases do. The lack of proofreading during reverse transcription results in a high mutation rate broad genetic variation [1]. HIV also has the capacity to integrate its genome into that of the target cell, so despite treatment with highly effective antiretroviral therapy, the virus maintains a latent reservoir of infected cells [19].

40.6 Basic Concepts

40.6.1 Human Immunodeficiency Virus Replication

HIV is a lentivirus, which is a type of retrovirus. These viruses are enveloped single positive-strand RNA viruses that replicate through a DNA intermediary. There are two types of HIV, HIV-1 and HIV-2. HIV-1 is the most common type worldwide, while HIV-2 is most common in western Africa. The genome for HIV contains ~9000 base pairs that encode 9 genes that produce 15 proteins [23].

HIV is acquired across mucosal surfaces or via direct injection. The cell surface protein gp120 binds to CD4, a marker most commonly found on CD4 T-helper lymphocytes and macrophages. With interactions from the heptahelical transmembrane chemokine receptors CXCR4 and CCR5, the viral transmembrane protein gp41 inserts itself into the T-cell membrane, causing the virus and the cell to fuse. A protein capsid then enters the host cell releasing two viral strands of RNA and three enzymes: reverse transcriptase, integrase, and protease. Reverse transcriptase takes the single-strand RNA and creates an RNA-DNA hybrid. Once the hybrid is complete, the RNase H domain of reverse transcriptase removes the RNA strand prior to reverse transcriptase forming the complimentary strand to the now single-stranded viral DNA. Once a double-stranded DNA copy of the viral RNA is formed, integrase cleaves two nucleotides from each 3-prime end, forming sticky ends. Integrase then transports the DNA into the cell's nucleus and inserts the DNA into the host genome. When the cell becomes activated, host RNA transcriptase copies the viral DNA forming mRNA templates that are cleaved by viral protease, which forms the viral enzymes and cell surface markers needed to generate new viral particles. Once RNA templates of the virus and the necessary proteins are assembled, new viral particles are able to bud off from the infected host cell and migrate to infect other CD4 T-helper cells [24, 25]. ARV medications target key steps in the viral life cycle.

40.7 Risk Factors for the Transmission of HIV

The rate of transmission of HIV is affected by the viral load present in the body fluid that the individual has been exposed to and by the specific nature of exposure. Direct infusion of an HIV-contaminated blood product is associated with more than a 90% risk of transmission (Table 40.1). In the United States, donated blood has been screened since in the late 1980s. Use of screen-negative blood and blood products is associated with an estimated risk of less than one case of transfusion-associated HIV per 1.5 million transfusions. Only one possible case has been identified since 2002 [26]. Receptive anal intercourse, the form of intercourse carrying the highest risk, has a 1.6% risk of transmission per exposure. Needle sharing among HIV-discordant intravenous drug users carries a risk of approximately 0.7% per exposure [27]. HIV transmission risk estimates discussed here and shown in Table 40.1 do not account for variations in the viral load at the time of the exposure. Data are now clear that individuals who have a sustained undetectable viral load are highly unlikely to transmit HIV to a susceptible sexual contact no matter what the nature of the exposure is [28].

One of the earliest and greatest achievements in reducing HIV transmission was the reduction of perinatal

Table 40.1 Risk of HIV transmission by type of exposure [27]

Type of exposure	Risk per 10,000 exposures	Percent risk
Parenteral		
Blood transfusion	9250	92.5
Needle sharing	63	0.63
Needle stick	23	0.23
Sexual		
Receptive anal intercourse	138	1.38
Insertive anal intercourse	11	0.11
Receptive penile-vaginal intercourse	8	0.08
Insertive penile-vaginal intercourse	4	0.04
Receptive oral intercourse	Low	
Insertive oral intercourse	Low	
Miscellaneous		
Biting	Negligible	
Spitting	Negligible	
Skin exposure to body fluids	Negligible	
Sharing sexual toys	Negligible	

acquisition of HIV. Prior to the availability of antiretroviral medications, perinatal transmission of HIV infection from an infected mother to her infant carried a risk of approximately 20%. In 1994, the Pediatric AIDS Clinical Trials Group released the results of protocol 076 which documented a 66% reduction in the rate of transmission of maternal-to-infant HIV when intrapartum zidovudine was administered to the mother during labor and then subsequently administered to the newborn during the first 6 weeks of life [29]. In children born to women with known HIV, the ARV regimen used in the infants is based upon risk factors including duration of rupture of membranes, maternal viral load, the use of fetal scalp electrodes, maternal viral resistance pattern, and compliance with HIV medications prior to delivery. Once delivered, low-risk children are treated with AZT for 4–6 weeks, while those deemed to be at higher risk are treated with AZT for 6 weeks while also receiving other active agents such as nevirapine (NVP) and lamivudine (3TC). For patients whose mothers have an undetectable viral load at the time of delivery and who are treated with AZT after birth, there is a less than 1% risk of acquiring HIV [30].

Exercises are included at the end of ► Chap. 41**.**

40.8 Summary

HIV remains a disease that can easily mimic the signs and symptoms of other illnesses, and coupled with the stigma of diagnosis, the disease is often not tested for as frequently as it should. However, a careful review of a patient's history, and a thorough examination, will often provide clues that HIV should be expected. Moreover, it should become common practice to test all sexually active individuals during their annual wellness checks. Should HIV be suspected, there are now tests that are both highly sensitive and specific for the diagnosis. And while HIV does not have a cure, advances in therapeutics since HIV/AIDS was first described in the early 1980s have significantly reduced the morbidity and mortality associated with the disease so that it is now thought of more as a common chronic medical condition as opposed to the uniformly lethal diagnosis of the 1980s and early 1990s.

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Human Immunodeficiency Virus II: Clinical Presentation, Opportunistic Infections, Treatment, and Prevention

Fever, Pharyngitis, and Lymphadenopathy with Prolonged Fatigue Weight Loss with Recurrent Infections

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Learning Objectives

- Understand the clinical presentation of acute HIV infection
- Recognize the appropriate laboratory tests used for the diagnosis of HIV infection
- List the classes of and uses for antiretroviral medications
- Describe AIDS defining conditions, including opportunistic infections
- Discuss effective strategies used to prevent HIV infection

» "There is no story in global health as transformative, awe-inspiring, and yet as tragic as the AIDS pandemic. The disease was unknown only a generation ago – a medical curiosity among young gay men in New York and San Francisco in June 1981. Within a few short years, AIDS could be found on every continent, enveloping the world to become one of the most devastating pandemics in human history. It has caused untold human suffering, social disintegration and economic destruction." – Lawrence O. Gostin [1]

41.1 Introduction

Since it was first described in the medical literature in 1981, the battle led by scientists, physicians, advocacy groups, educators, activists, and policy makers has resulted in dramatic advances in the diagnosis and management of HIV/AIDS that are changing this disease from a "death sentence" to a more manageable chronic disease [2–4].

Diagnosing HIV infection requires a high index of suspicion, recognition of the clinical manifestations, as well as knowledge of the diagnostic tools required in order to make an accurate and timely diagnosis [5]. Infection with HIV/AIDS can be a shocking and isolating diagnosis for an individual to receive. Today, access to care, early diagnosis, regular monitoring of the disease, treatment with highly active antiretroviral therapy (HAART), and prophylaxis and treatment of opportunistic infections have increased survival rates and changed the natural history of HIV infection wherever these resources are made generally available [6].

41.2 HIV Disease Progression

41.2.1 Acute HIV Infection

Individuals acutely infected with HIV can present with a constellation of symptoms ranging from an influenza-like illness with a maculopapular rash to a nonspecific chronic illness with fatigue and wasting [6]. The symptoms experienced during acute symptomatic HIV infection are referred to as the acute retroviral syndrome [7]. Individuals with acute HIV infection commonly complain of fever, fatigue, myalgia, skin rash, and headache, with or without pharyngitis, cervical adenopathy, arthralgia, night sweats, or diarrhea [5]. Clinically, the constellation of fever, fatigue, myalgia, rash, pharyngitis, and cervical adenopathy is quite typical for acute mononucleosis secondary to infection with Epstein-Barr virus or cytomegalovirus. Individuals with a mononucleosis-like syndrome should be tested for acute HIV infection unless the etiology of their illness has already been otherwise established. It is important to note that up to 60% of individuals with acute HIV infection do not recall experiencing a recent medical illness suggesting that many episodes of acute retroviral syndrome are minimally symptomatic [23, 24].

41.2.2 Early HIV Infection

Early HIV infection generally refers to the first 6 months of the infection. During this time many patients experience transient or vague symptoms. Some are asymptomatic. Initially, there is a robust and rapid period of viral replication with infection of CD4+ T-cells. Blood viral RNA levels are generally very high (>100,000 copies/mL) and can be associated with a transient drop in the CD4+ T-cell count. During the ensuing 3–6 months, the HIV viral load (quantitative HIV RNA level) will drop 3–5 logs, in association with CD4+ T-cell recovery [8]. HIV RNA levels may reach a steady state, or set point, by 3–6 months after the primary HIV infection. HIV RNA levels may be variable, but, overall, the viral load is directly associated with the rate of disease progression [8, 9]. CD4+ T-cell counts recover during the first month after infection as CD8+ T-lymphocytes help to control viral replication [10]. Without treatment, the decline in CD4+ T-cell counts occurs over time, occurring more rapidly in those patients with prolonged symptoms at the time of primary infection [8]. Though there may be clinical latency during this period, there is great replicative activity within lymphoid tissue, which acts as a major reservoir for the virus [11]. As HIV infection progresses, there is a gradual loss of this partially effective immune response. Even the once-limited control over virus replication is lost, leading to more active viral replication and further impaired cellular immune function.

41.2.3 Chronic HIV Infection

Chronic HIV infection occurs after the set point has been reached during early infection but before the occurrence of severe immunosuppression, defined as a peripheral CD4+ T-lymphocyte count of fewer than 200 cells/mm^3. During this time, HIV RNA levels are typically stable as the patient experiences a gradual but progressive decline in circulating CD4+ T-cell numbers. This decline is most rapid during the first year of infection, after which the drop slows to a rate of about 50 cells/mm^3 per year [12]. The rate of CD4+ T-cell loss is highly variable from patient to patient, but on average the threshold of fewer than 200 cells/mm^3 is reached over an 8- to 10-year period. [13–15].

While patients are generally asymptomatic during this period, clinical manifestations may include generalized lymphadenopathy, peripheral neuropathy, or illnesses heralding the decline in effective immune function including recurrent or persistent oral or vulvovaginal candidiasis, reactivation of varicella zoster virus causing shingles, immune-mediated thrombocytopenic purpura, or oral hairy leukoplakia [16].

41.2.4 Advanced HIV and AIDS

Uncontrolled HIV eventually causes sufficient loss of CD4+ T-cells leading to significant immunosuppression. From the laboratory perspective, acquired immunodeficiency syndrome (AIDS) is defined by a CD4+ T-cell count of 200 or fewer cells/mm^3. While this threshold is commonly used to categorize the HIV patient as having AIDS, there are other illnesses that are also considered AIDS defining. These illnesses typically occur when the CD4+ T-cell count falls below 200 cells/mm^3 for a sustained period of time; however, they can also occur at higher cell counts [16, 17]. Prior to the era of antiretroviral therapy (ART), AIDS-defining illnesses accounted for most of the morbidity and mortality associated with HIV infection. AIDS-defining illnesses include opportunistic infections, certain malignancies, and syndromes associated with HIV infection that may not be otherwise clearly defined. A complete list of AIDS-defining conditions is presented in Table 41.1. In the USA, the most common AIDS-defining illnesses seen in HIV patients during the 1990s included *Pneumocystis jirovecii* pneumonia, esophageal candidiasis, Kaposi sarcoma, wasting syndrome, and disseminated *Mycobacterium avium* infection [18]. Once the CD4+ T-cell count falls below 200 cells/mm^3, the median time to developing an AIDS-defining condition is 12–18 months without ART [19]. Patients who progress to advanced HIV infection, commonly defined as a CD4+ T-cell count of less than 50 cells/mm^3, have a median survival of 12–18 months [20, 21].

Table 41.1 AIDS-defining conditions in HIV-infected individuals [57]

Bacterial infections, multiple or recurrent[a]	Disseminated or extrapulmonary infection with *Mycobacterium avium* complex or *Mycobacterium kansasii*
Candidiasis of the bronchi, trachea, or lungs	Kaposi sarcoma
Candidiasis of the esophagus	Lymphoma, Burkitt (or equivalent term)
Cervical cancer, invasive[b]	Lymphoma, immunoblastic (or equivalent term)
Coccidioidomycosis, disseminated or extrapulmonary	Lymphoma, primary, of the brain
Cryptococcosis, extrapulmonary	*Mycobacterium tuberculosis* of any site, pulmonary, disseminated, or extrapulmonary[b]
Cryptosporidiosis, chronic intestinal (>1 month's duration)	*Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
Cytomegalovirus disease (other than the liver, spleen, or nodes), onset at age >1 month	*Pneumocystis jirovecii* pneumonia
Cytomegalovirus retinitis (with loss of vision)	Pneumonia, recurrent[b]
Encephalopathy attributed to HIV[c]	Progressive multifocal leukoencephalopathy
Herpes simplex virus infection causing chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age > 1 month)	*Salmonella* septicemia, recurrent
Histoplasmosis, disseminated or extrapulmonary	Toxoplasmosis of the brain, onset at age > 1 month
Isosporiasis, chronic intestinal (>1 month's duration)	Wasting syndrome attributed to HIV[c]

[a]Only among children aged <6 years
[b]Only among children aged ≥6 years, adolescents, and adults
[c]Suggested diagnostic criteria for these illnesses, which might be particularly important for HIV encephalopathy and HIV wasting syndrome, are described in MMWR Recomm Rep 1994; 43 (No.12) and MMWR Recomm Rep 1992; 41 (No.17)

41.2.5 HIV Controllers

A small percentage of HIV-infected individuals not on ART do not develop significant progression of disease. These individuals tend to remain asymptomatic with stable CD4+ T-cell counts and low levels of HIV viremia. Long-term non-progressors are individuals without significant disease progression for many years while maintaining a minimal CD4+ T-cell count of 500 cells/mm^3, likely as a result of sustained immune control limiting their HIV viremia to fewer than 10,000 copies/mL [22, 23]. An even smaller percentage of individuals are considered elite controllers. Elite controllers have no detectable viremia and preserved CD4+ T-cell counts for a prolonged period of time without any disease progression [23]. Despite the ability to control HIV viremia without ART, these individuals may still be at risk of other complications of chronic HIV infection including noninfectious complications such as cardiovascular disease [24]. While viral loads are low in non-progressors and absent in elite controllers, significant immune activation does occur. These individuals, therefore, still benefit from ART [11].

41.3 Clinical Evaluation of the HIV-Infected Individual

41.3.1 Physical Examination

Initial evaluation of the HIV-infected patient includes a comprehensive medical history, including a thorough social, travel, and medication history, and a complete physical examination. During the physical examination, the provider should be sure to complete an assessment for palpable lymphadenopathy as nonspecific, small, mobile nodes are frequently seen in HIV-infected patients [6]. Examination of the head, eyes, ears, nose, and throat should note any presence of pharyngeal edema or hyperemia or mucocutaneous ulcerations [7, 25]. One should also evaluate for oropharyngeal candidiasis (thrush), angular cheilitis, stomatitis, and oral hairy leukoplakia, a manifestation of infection with Epstein-Bar virus in immunosuppressed individuals. A complete eye examination should be performed at baseline. If the patient's CD4+ T-cell count is below 50 cell/mm^3, and there are changes in vision, a detailed ophthalmologic examination is important to evaluate for the possible presence of cytomegalovirus (CMV) retinitis or ocular syphilis. The cardiopulmonary examination should focus on any symptoms of shortness of breath, cough, or hemoptysis to help assess for pneumonia, pneumothorax (which can be related to *P. jirovecii* pneumonia), pericarditis, or cardiomyopathy [6]. The gastrointestinal examination should start by assessing for the presence of nausea, dysphagia, or anorexia. Right upper quadrant abdominal pain should raise concern for cholelithiasis or hepatitis, while left upper quadrant pain is more concerning for pancreatitis or disease associated with the stomach or spleen. Diarrheal illness is common in HIV infection and can be caused by a wide variety of pathogens including bacteria (e.g., *Salmonella* species, *Shigella* species), viruses (e.g., CMV), or parasites (e.g., *Cryptosporidium parvum*). The presence of rectal pain should be evaluated for signs of trauma, abscess, proctitis, fissures, or masses [6]. The genitourinary examination should evaluate for findings that may consistent with the presence of other sexually transmitted diseases, all of which can be more difficult to diagnose and treat in the setting of HIV infection. HIV-infected women should undergo a full pelvic examination with regular Pap smear screening because of their increased incidence of cervical dysplasia and more rapid progression to cervical cancer [6]. Neurologic signs and symptoms associated with HIV infection and its complications are highly variable. Acute complaints of headache or visual loss may be an evaluation for meningitis, encephalitis, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy, retinitis, or CNS lymphoma. Memory loss with poor concentration may be a sign of HIV-associated dementia. The dermatologic examination should focus on any type of rash or change in skin pigmentation, including careful visual inspections of the palms, soles, and anogenital area [6].

41.3.2 Laboratory Evaluation

The initial symptoms of HIV infection can be nonspecific and difficult to distinguish from other viral illnesses unless appropriate laboratory testing is performed [5]. A diagnosis of HIV should be made from two separate blood samples with the tests performed varying based on a patient's age. As antibodies to the HIV virus cross the placenta and may persist in the blood of the child born to an infected mother for up to 15 months, antibody-derived tests are of no utility in the diagnosis of exposed newborns. Instead, in an exposed newborn, qualitative RNA PCR is the test of choice. DNA PCR has been well studied and is reliable; however, commercially available and FDA-approved DNA PCR tests are not available. Beyond the newborn period, fourth-generation antibody and antigen tests are preferred; however, for very early acute infections, viral load testing (quantitative HIV RNA PCR) may be necessary. Fourth-generation combination antigen and antibody immunoassay, **and** a quantitative RNA polymerase chain reaction-based assay to determine the HIV viral load [26, 27]. Current fourth-generation HIV-1 antibody tests and p24 antigen tests typically become positive approximately 15–20 days after HIV exposure. A detectable HIV RNA viral load is present within 5–15 days post-HIV exposure [28].

Perinatal transmission of HIV infection from an infected mother to her infant is preventable with proper intrapartum and postpartum management. Women who have not had HIV testing during the current pregnancy who present in labor should have a rapid HIV test performed so that results are available as soon as possible. Rapid HIV tests are preferred in this setting because they allow the initiation of ARV therapy in the expectant mother, if she has not yet delivered, and the initiation of ARV therapy in the newborn as soon after birth as possible. This strategy dramatically reduces the risk of perinatally transmission of HIV from the mother to her child.

When a patient is newly diagnosed with HIV infection, additional laboratory testing is necessary to establish baseline laboratory values, to document the current degree of immunosuppression, to estimate the likelihood and rate of HIV disease progression, and to guide decisions regarding optimal and appropriate ART. During subsequent clinical evaluations, laboratory testing is used to monitor the virologic response to ART, to monitor for potential toxicities of medications, and to continue to screen for common and/or preventable associated illnesses [6] (Table 41.2).

41.4 Treatment

41.4.1 Basics of ART: Antiretroviral Therapy

The first antiretroviral medication, zidovudine (ZDV), was introduced in 1996. Since that time, dozens of highly effective medications have become available for use in combination

Table 41.2 Diagnostic laboratory testing used for the diagnosis and monitoring of HIV infection

Laboratory test	Rationale	Suggested monitoring interval
CD4+ T-cell count May include additional lymphocyte immunophenotyping, often referred to as "lymphocyte subsets"	Evaluation of degree of immunosuppression Guiding initiation of prophylaxis for opportunistic infections Prognostic information Monitoring of efficacy of therapy	Baseline, then every 3–6 months if not on ART, every 3–6 months for the first 2 years of ART and for patients who struggle with adherence Every 12 months after 2 years of ART with sustained, suppressed viral load
Quantitative HIV RNA PCR, commonly referred to as an HIV viral load test	Monitoring of HIV replication activity Evaluating the efficacy of the current ART regimen	Baseline, then at time of ART initiation or modification Repeat 2–8 weeks after ART initiation or modification Every 3–6 months for the first 2 years of ART, then every 6 mos if stable
HIV genotyping Commonly referred to as HIV resistance testing	Evaluation for mutations associated with resistance to ART medications To guide changes in treatment regimens	Baseline At time of ART initiation If patient has virologic failure
CBC with differential	Monitoring for hematologic drug toxicities	Baseline At time of ART initiation or modification Every 6 months Every 3–6 months if not on ART or as clinically indicated
Serum electrolytes, creatinine, and hepatic transaminases	Evaluation of baseline renal and liver function Monitoring for drug toxicities	Baseline At 2–8 weeks after ART initiation or modification Every 3–6 months More frequently in patients as clinically indicated Every 6–12 months if not on ART
Fasting lipid profile	Monitoring for drug toxicities	Baseline At time of ART initiation or modification Every 6 months if abnormal Every 12 months if benign
HLA-B*5701	Assess genetic risk of hypersensitivity reaction to abacavir	Prior to initiation of abacavir as part of an ART regimen
G6PD activity	Screening for G6PD deficiency prior to starting therapy with an oxidant drug	Baseline
Tropism testing	When considering the use of a CCR5 antagonist as part of an ART regimen	Prior to initiation of a CCR5 antagonist
Urinalysis and creatinine clearance	Evaluation for the risk of nephropathy and prior to using potentially nephrotoxic medications	Baseline Prior to initiation or modification of ART Every 6 months if tenofovir is included in the ART regimen, otherwise every 12 months
Acute hepatitis profile	Diagnosis of viral hepatitis Evaluation for prior vaccination and immunity to hepatitis A and hepatitis B	Baseline During potential acute infection
Rapid plasma reagin	Screening for syphilis Monitoring of response to syphilis therapy	Baseline Annually During new symptoms
Anti-toxoplasma antibody (IgG)	Screening for prior exposure to *Toxoplasma gondii* Guide future diagnostic and empiric management	Baseline Annually in patients who are IgG negative
Tuberculosis screening May be done using tuberculin skin testing or interferon gamma release assay	Screening for active or latent tuberculosis	Baseline Annually if possible exposures

ART regimens. The availability of ART has been associated with a tremendous decline in the morbidity and mortality associated with HIV in all areas of the world where it has been made available. In one study, mortality declined from 29.4 per 100 person-years in 1995 to 8.8 per 100 person-years in 1997, just from the introduction of ZDV [29]. Reductions in mortality were noted regardless of factors such as age, sex, race, or mode of HIV transmission [29].

Historically, guidance and opinion on when to start a patient on antiretroviral therapy have varied. Individuals with CD4+ T-cell counts less than 350 cells/mm^3 who are treated with ART have reduced morbidity, slower progression to AIDS, and lower mortality from opportunistic infections [30–32]. In contrast, ART was once delayed in those with preserved CD4+ T-cell counts given the potential toxicities associated with treatment and lack of known benefit for patients with higher CD4+ T-cell counts. More recent data clearly supports the use of ART regardless of CD4+ T-cell counts [33–36]. Many of the newer antiretroviral medications are much better tolerated and are associated with fewer toxicities than their predecessors. Thus, the current goals of treatment for HIV infection are to prevent or reduce HIV-associated complications by suppressing any HIV viremia, thereby preserving immune function and preventing progression to AIDS. Suppression of HIV viremia also significantly reduces the risk of transmission to HIV seronegative sexual partners by as much as 96% [37, 38].

Some individuals are at particularly high risk for HIV-associated morbidity and mortality warranting urgent evaluation and initiation of treatment. Conditions of elevated risk include pregnancy, coinfection with hepatitis B virus, and patients who have already developed complications from HIV. Individuals with acute HIV infection (acute retroviral syndrome) should also be considered for immediate therapy to reduce their potential for transmission to others during their period of highest viremia.

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41.4.2 Antiretroviral Therapy Options

Currently six classes of medications are available for the treatment of HIV infection (Table 41.3). Combination therapy is warranted to reduce the emergence of drug resistance.

Nucleoside reverse transcriptase inhibitors (NRTIs) are nucleoside analogs, and once they are phosphorylated by the host cell, they compete with other nucleosides for inclusion into DNA copies being created by reverse transcriptase. Once NRTIs are included into a growing DNA chain, transcription is terminated. Nucleotide reverse transcriptase inhibitors (NrTRIs) are similar to NRTIs except that they do not require phosphorylation by host kinases. Tenofovir disoproxil fumarate (TDF) was first approved in 2001, and a revised formulation, tenofovir alafenamide (TAF), was approved in 2016.

Unlike NRTI, non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to reverse transcriptase, inactivating it.

Table 41.3 The six classes of available antiretroviral medications

	Class	Examples
1	Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	Zidovudine (ZDV), lamivudine (3TC), emtricitabine (FTC), abacavir (ABC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF)
2	Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz (EFV), rilpivirine (RPV), nevirapine (NVP), etravirine (ETR)
3	Protease inhibitors (PIs)	Atazanavir (ATV), darunavir (DRV)
4	Integrase strand transfer inhibitors (INSTIs)	Raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG)
5	Fusion inhibitor (FI)[a]	Enfuvirtide (T-20)
6	CCR5 receptor antagonist[a]	Maraviroc

[a]Typically used in salvage regimens for treatment-experienced individuals with HIV infection

Common FDA-approved NNRTIs are nevirapine (NVP) 1996, efavirenz (EFV) 1998, etravirine (ETR) 2008, and rilpivirine (RPV) 2011. NNRTIs are not used as monotherapy and are always combined with medications from other classes owing to the rapid development of resistance if used as monotherapy.

Protease inhibitors (PIs) bind to and prevent the action of HIV protease, which is needed to cleave viral proteins into their appropriate shape and length. PIs were the first class other than NRTIs and NNRTIs to be developed.

Integrase Inhibitors: first approved by the FDA in 2007, integrase inhibitors (II) prevent insertion of viral DNA into the host genome. Commonly used integrase inhibitors include raltegravir approved for use in 2007, dolutegravir approved in 2013, and elvitegravir approved in 2014. Integrase inhibitors are included in several of the most recent multi-medication combination tablets including Genvoya ® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) approved in 2015 and Juluca (dolutegravir and rilpivirine) approved in 2017.

Fusion and entry inhibitors aim to stop the earliest stages of the viral replication cycle. Maraviroc first became available in 2007. This drug prevents the HIV transmembrane protein gp120 from associating with CCR5, a co-receptor with CD4, on the surface of T-helper lymphocytes and macrophages. By blocking gp120's interaction with CCR5, the entry of the viral protein capsid into the host cell is prevented. Enfuvirtide (T-20), FDA approved in 2005, is a fusion inhibitor that binds to the viral protein gp41. After the interaction between gp120 and CD4 and either CCR5 or CXCR4, gp41 undergoes a conformational change and inserts itself into the host membrane, allowing fusion. By binding to gp41, T-20 prevents this step.

Table 41.4 Opportunistic infection prophylaxis based on CD4+ T-cell counts [58]

CD4+ T-cell count	Opportunistic infection	Recommended prophylaxis
All patients	Tuberculosis (TB)	Latent TB therapy if warranted based on testing
≤250 cells/mm^3	Coccidioidomycosis	Fluconazole in patients who live in endemic regions and have positive serology
≤200 cells/mm^3	*Pneumocystis jirovecii*	Trimethoprim-sulfamethoxazole discontinue once CD4 > 200 cells/mm^3 for more than 3 months
≤100 cells/mm^3	Toxoplasmosis	Trimethoprim-sulfamethoxazole in patients with positive serology discontinue once CD4 > 200 cells/mm^3 for more than 3 months
≤50 cells/mm^3	*Mycobacterium avium* complex (MAC)	Azithromycin; discontinue when CD4 > 100 cells/mm^3 for more than 3 months

In patients who are treatment naïve, the initial ARV regimen mainly consists of two NRTIs, as the backbone of therapy, plus a third drug from another class of medication, such as an NNRTI, PI, or INSTI. Medication formulations now exist that include two, three, or four medications in a single pill in an effort to reduce the burden of taking multiple pills at one time. Several of the available medications now have serum half-lives that permit once-daily dosing. Available treatment regimens now include several "one pill, once a day" options to deliver the necessary combination therapy. Current guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents from the US Department of Health and Human Services include options such as tenofovir alafenamide with emtricitabine, plus either dolutegravir or raltegravir; tenofovir alafenamide with emtricitabine, elvitegravir, and cobicistat; or abacavir with emtricitabine and dolutegravir (in patients who are negative for HLA-B*5701) as preferred regimens [11, 39, 40].

Other factors should also be taken into consideration when choosing a regimen, including patient preference regarding pill burden, dosing frequency, comorbid conditions such as cardiovascular or renal disease, drug interactions, side effect profile, and known potential toxicities. Treatment-experienced patients who have failed prior regimens should undergo HIV genotype testing to assess for resistance mutations that may impact HIV suppression before choosing a new treatment regimen [41].

41.4.3 Other Treatments for HIV Infection

Patients with HIV infection may also benefit from treatment with other medications depending on the clinical circumstances. Patients with low CD4+ T-cell counts, for example, may need to take antibiotics to help prevent specific opportunistic infections (OIs) such as *Pneumocystis jirovecii* pneumonia [16, 18]. Table 41.4 outlines the common OI prophylaxis recommendations based on the patient's CD4+ T-cell count.

Treatment innovations for the pediatric population, even in the developed world, have lagged behind. Not all medications are available as a child-friendly preparation (liquid or sprinkles), and some liquid medications are very unpalatable. Owing to the need for weight-based dosing, most single-pill combinations are not available to pediatric patients. However, in 2017, single-pill combinations had started to be investigated in patients weighing at least 25 kilograms.

41.5 Complications Associated with HIV Infection

41.5.1 Immune Reconstitution Inflammatory Syndrome

While ART has dramatically reduced morbidity and mortality in HIV-infected individuals, complications associated with the initiation of ART have been noted. Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical worsening of preexisting infections or noninfectious conditions that were previously controlled or treated or an unmasking of subclinical or unknown infections or noninfectious conditions [42, 43]. IRIS occurs as a result of improved immunologic function as the individual's CD4+ T-cells repopulate during the treatment of their HIV infection. Although the exact mechanisms of action are unclear, it is felt that there is a restoration of pathogen-specific immune responses [44, 45]. It is estimated that as many as 30% of HIV-infected individuals will experience IRIS. Symptoms typically occur between 30 and 40 days after starting ART [45, 46]. Risk factors for IRIS include younger age at time ART initiation, lower CD4+ T-cell count at the time ART is initiated, and high viral load [46]. Typically, the inflammatory response associated with IRIS occurs at the site of the pre-existing infection and is generally self-limited. More severe, even life-threatening IRIS occurs rarely. Common opportunistic infections that are associated with the development of IRIS and general management considerations are summarized in Table 41.5 [42, 46, 47]. Generally speaking, ART should be started early and within 2 weeks of starting treatment for an existing opportunistic infection [11, 38]. ART should be maintained through the clinical course, unless life-threatening symptoms occur requiring that ART be temporarily held

Table 41.5 Infections associated with the development of IRIS following treatment for HIV infection [42, 45, 46, 47]

Infection	Clinical manifestation of IRIS	Management
Cryptococcus neoformans	Meningoencephalitis Pneumonia	Antifungal therapy Consider corticosteroids for severe disease Consider delaying ART by 2–10 weeks
Cytomegalovirus	Uveitis Retinitis	CMV antiviral therapy Consider corticosteroids (topical, intraocular, or systemic) Continue ART
Mycobacterium tuberculosis	Pneumonia Lymphadenitis Meningitis Central nervous system (CNS) tuberculoma	Treatment for tuberculosis Consider delaying ART by 8–12 weeks or continue ART if already initiated For severe disease or CNS involvement, use corticosteroids
Mycobacterium avium complex	Pneumonia	Continue ART
JC virus	Progressive multifocal leukoencephalopathy	Continue ART Consider corticosteroids
Pneumocystis jirovecii	Pneumonia	Continue ART PJP treatment
Herpes zoster virus	Worsening vesicular/ulcerative rash	Antiviral therapy Continue ART
Hepatitis B virus	Hepatitis	Continue ART Consider a TDF- or TAF-based regimen
HHV-8 (associated with Kaposi sarcoma)	Rapid lesion progression, fevers	Continue ART

and adjunctive therapies with anti-inflammatory medications such as corticosteroids or nonsteroidal anti-inflammatory medications be utilized [11].

41.5.1.1 Opportunistic Infections in AIDS

Pneumocystis carinii (now *jirovecii*) (PJP) pneumonia, an unusual fungal infection, was described in all five patients reported in the first case series of what was eventually called AIDS [48A]. Prior to the HIV era, this infection was only seen in severely malnourished infants and among individuals with profound deficiencies in cellular immunity. Among HIV-infected patients, PJP occurs when the CD4+ T-lymphocyte count falls below 200 cells/mm^3. Patients with PJP present with cough and shortness of breath associated with hypoxemia. The chest radiograph typically shows bilateral chest infiltrates. The diagnosis can be made by performing direct fluorescent antibody staining or pathogen-specific PCR on sputum or bronchoalveolar lavage fluid. Prevention of PJP is most effective with trimethoprim-sulfamethoxazole; pentamidine, inhaled or intravenous monthly, or atovaquone can be used in patients who have a sulfa drug allergy or G6PD deficiency [48B].

The fungus, *Cryptococcus neoformans*, also causes opportunistic infections in HIV-infected patients with low CD4+ T-lymphocyte counts. *C. neoformans* is an encapsulated yeast acquired by inhalation. Once inhaled, the organism disseminates hematogenously with a proclivity to seed the meninges. Mortality in AIDS patients with cryptococcal meningitis exceeds 10% [48C].

Mycobacterium species are responsible for the majority of bacterial opportunistic infections in patients with AIDS. *Mycobacterium avium* complex (MAC) is a ubiquitous environmental pathogen that affects both immunocompromised and immunocompetent hosts. Infected immunocompetent hosts typically develop a chronic lymphadenitis, while severely compromised individuals, such as those with AIDS, develop fevers, weight loss, and anemia from disseminated disease. Prophylaxis against MAC is achieved by administering azithromycin daily once the patient's CD4+ T-lymphocyte counts fall below 50 cells/mm^3. Patients who are infected with HIV are also at elevated risk for infection with *Mycobacterium tuberculosis* [48D].

Protozoa can also cause infections in severely immunocompromised patients with HIV infection. The three most common opportunistic protozoal infections seen among patients with AIDS include *Toxoplasma gondii*, *Cryptosporidium* species, and *Isospora belli*. *Toxoplasma gondii* causes chorioretinitis or encephalitis, while *Cryptosporidium* species and *Isospora belli* cause chronic diarrhea, malabsorption, and wasting.

Viral infections can also be problematic for patients with AIDS. Viruses in the *Herpesviridae* family are some of the most troublesome. Herpes simplex viruses 1 and 2 cause intermittent outbreaks in some immunocompetent individuals and can become chronic and/or disseminated in patients who lack cellular immune function, such as those with advanced HIV disease. Cytomegalovirus is associated with esophagitis and retinitis, while Epstein-Barr virus is associated with hairy leukoplakia and may play a role in the development of HIV-associated lymphomas. Human herpesvirus-8 (HHV-8) also has oncogenic potential, being most infamous for its role in causing Kaposi sarcoma, the most common malignancy diagnosed in individuals with HIV infection [48E].

Non-oncogenic and oncogenic human papillomavirus (HPV) serotypes can also be particularly aggressive in individuals living with HIV infection. For example, patients with HPV type 6 infection are prone to developing giant

condylomata which can become disfiguring. The vast majority of low-grade anogenital dysplasias affecting immunocompetent adolescents and adults caused by oncogenic HPV types 16 and 18 resolve spontaneously, largely due to the effector functions of an intact cellular immune response. Those who do develop persistent infection typically won't develop malignant changes for more than a decade. In contrast, individuals with HIV infection and AIDS can progress from low- to high-grade dysplasias to carcinoma in situ to cancer within 2 years or even less.

41.5.2 Other Complications

HIV infection is also associated with an increased risk of complications that can affect organ systems other than the immune system. Complications may include metabolic and endocrine changes, such as dyslipidemia, lipodystrophy, osteoporosis, and diabetes mellitus; malignancies, including Kaposi sarcoma, cervical cancer, anal cancer, central nervous system lymphoma, cardiovascular disease, and renal disease; and neurologic manifestations such as neuropathy or dementia. Individuals may also be at risk for other sexually transmitted infections. These risks and complications may stem from HIV infection, and the associated cellular immunodeficiency may represent adverse effects from ongoing treatment regimens or may be a direct consequence of ongoing risk behavior. Comprehensive care of HIV-infected individuals demands expertise in screening and managing a wide array of infectious and noninfectious complications [11].

41.6 HIV Prevention

Since the start of the AIDS pandemic, a tremendous amount has been learned about HIV transmission and prevention, yet thousands continue to be newly infected every day [48]. The HIV pandemic, like many others, occurs within a complex social environment where social norms can affect disease transmission. Examples include specific sexual practices such as receptive anal intercourse, patterns of sexual partnering involving multiple sexual partners, sex inequality, sexual networks, contraceptive choices, recreational use or abuse of substances that decrease sexual inhibitions, and a tenacious stigma that still seems to restrict access to health care for many high-risk and infected individuals [16, 49]. There are multiple dimensions to consider in HIV prevention. No single intervention has been shown to be highly effective by itself. Multiple intervention strategies are therefore necessary if there is any hope to control the pandemic [49].

The most effective intervention to reduce sexual transmission of HIV is effective antiretroviral therapy for infected individuals. It is also imperative to note the importance of using of barrier methods during sexual activity, such as condoms and dental dams, as they have been shown to decrease HIV transmission and acquisition by up to 90–95% when used consistently [50, 51]. Medical male circumcision is also an effective HIV prevention intervention in resource-poor settings [52]. Pre-exposure prophylaxis (PrEP) is a newer and emerging prevention strategy that can be used for individuals known to have a higher risk for HIV acquisition based on behavioral risk factors. PrEP currently refers to the use of the oral antiretroviral therapy combination, tenofovir plus emtricitabine (TDF-FTC), as a once-daily dose each day. This strategy has been shown to effectively reduce HIV acquisition by greater than 90% [53]. Finally, postexposure prophylaxis (PEP) is a strategy implemented for individuals who have a single, isolated high-risk exposure to HIV. In this strategy, a 28-day course of treatment with three antiretroviral drugs is started within 72 h of the exposure. Patients who present more than once with indications from PEP should be counseled on the availability of PrEP if appropriate to the circumstances [54].

A safe and effective HIV vaccine has remained elusive [48F]. Currently, there are multiple other potential prevention strategies that remain under investigation, including HIV vaccines and the use of vaginal and rectal microbicides that target different stages of the HIV life cycle.

41.7 Summary

Initial HIV infection is associated with an acute retroviral syndrome that can easily be mistaken clinically as a bout of infectious mononucleosis. HIV infection, unchecked, leads to a gradual and progressive cellular immunodeficiency. Many patients go undiagnosed until they develop unexplained wasting or an unusual opportunistic infection that is typically seen only in immunocompromised patients. Excellent diagnostic testing tools and highly effective treatment regimens for HIV infection have emerged and evolved since the virus was initially identified as the cause of AIDS in the early 1980s. The progress has allowed for tremendous improvements in the prognosis and quality of life for individuals infected with HIV. The life expectancy of individuals with HIV infection who are treated with ART now mirrors that of the general population [55]. While some populations continue to be at high risk for new acquisition of infection, the overall prevalence of HIV has decreased in all developed and most underdeveloped areas of the world. A cure for HIV remains elusive as challenges exist in targeting reservoirs or cells that remain hidden from host defense and therapeutic interventions. Hope for a "cure" for HIV infection was reenergized in 2009 when the "Berlin patient" was cured after receiving a stem cell transplant to treat a malignancy [56]. To date, no other individual has achieved a cure, but remarkable progress has been made in transforming HIV from a fatal infection into that of a chronic illness. The single instance of cure provided new insights and new enthusiasm to the field.

Case Study

Case Examples

Case 1	Case 2
A 40-year-old woman presents in active to the obstetrics department of her local hospital. She has not had any prenatal care and admits to having two different sexual partners during the current pregnancy. She tested negative for HIV 2 years ago when she was pregnant with her first child. The patient has never required treatment for a sexually transmitted infection. She delivers a healthy male infant. Postdelivery, blood is collected for routine studies and a rapid HIV test. The rapid HIV test was reported positive later the same day	A 15-year-old female with a prior history of sexual abuse presents to the emergency department with 1 month of fatigue, a 15-pound weight loss, clear vaginal discharge, ulcerations around her labia majora, and headache. Her review of systems was positive for some nuchal rigidity and generalized abdominal pain but negative for photophobia and altered mental status. On physical examination, she had right lower and right upper quadrant abdominal tenderness. Her genital examination showed a clear vaginal discharge and several 1.5 cm ulcerations on her labia. Her neurological examination was normal. Laboratory test results were notable for an absolute lymphocyte count of 200 cells/mm^3 and mild elevations in serum hepatic transaminases. Diagnostic testing for HIV, EBV, hepatitis B and C, syphilis, HSV, gonorrhea, and chlamydia was collected. The patient was hospitalized for further management
Next steps: (1) maternal, a fourth-generation HIV antibody-antigen test was collected for confirmatory HIV testing	Next steps: The rapid HIV test and the HSV DNA PCR-based test were both reported to be positive. Confirmatory HIV testing was obtained. A lumbar puncture was performed. HSV DNA PCR and antigen-based testing for *Cryptococcus neoformans* were performed on the cerebrospinal fluid
Next steps: (2) infant, the newborn was considered a high-risk infant. Postexposure prophylaxis was administered using a three-drug regimen. Blood was collected from the infant to perform a qualitative HIV RNA PCR test	
Resolution: Confirmatory testing on the mother, a fourth-generation HIV antibody-antigen test was negative. Additionally, a qualitative HIV RNA PCR was negative on the infant. Once confirmatory tests performed on blood collected from the mother and infant were resulted as negative, the ARV medications were stopped	Resolution: Acyclovir therapy was started as treatment for HSV genital disease and possible aseptic meningitis. Cefoxitin and doxycycline were administered to treat suspected pelvic inflammatory disease. Fourth-generation HIV testing confirmed HIV infection, and ARV medications were prescribed after the cryptococcal antigen test on the cerebrospinal fluid was reported back as negative
Highlights: Rapid HIV antibody tests are very sensitive but may have a specificity of only 90%, depending on the method used, leading to a non-negligible rate of false-positive results. In most circumstances, it is appropriate to begin ARV treatment when maternal HIV rapid testing is positive while awaiting confirmatory test results	Highlights: Physical examination and/or laboratory findings that are consistent with a sexually transmitted infection (STI), such as genital HSV infection, should always prompt a careful investigation for other STIs. The physical examination finding of genital ulcerative disease suggestive of HSV infection did not explain the patient's recent weight loss or newly documented lymphopenia

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41.8 Exercises

Please refer to the supplementary information section for answers to these exercises.

1. A 23-year-old male presents with 2 weeks of low-grade fevers, fatigue, and myalgias. On physical examination, he is found to have pharyngeal erythema without exudate, a painful shallow ulcer on the right buccal mucosa, anterior and posterior cervical lymphadenopathy, and a fine erythematous macular rash on his upper chest. He notes that he has a new sexual partner with whom he is using condoms "90% of the time." He reports that he is sexually active with both men and women.

   Of the following, which do you think is the most likely diagnosis?

   A. Infectious mononucleosis
   B. Hodgkin's lymphoma
   C. Streptococcal pharyngitis
   D. Acute retroviral syndrome
   E. Syphilis

2. A rapid antigen test for group A streptococcal infection is negative. A complete blood count with differential shows mild leukopenia but is otherwise normal. A heterophile antibody test for infectious mononucleosis is negative. A rapid plasma regain test is negative. An HIV p24 antigen test is positive. You decide to confirm your diagnosis of acute HIV infection by requesting laboratory testing for the patient's CD4+ T-cell count and HIV viral load. What do you expect the results to look like?

   A. Normal CD4+ T-cell count, low viral load
   B. High CD4+ T-cell count, high viral load

C. Normal CD4+ T-cell count, high viral load
D. Low CD4+ T-cell count, low viral load

3. A 37-year-old man with a past history of syphilis has a positive HIV screening test. His last HIV test was negative 6 months ago. He is asymptomatic and reports that he has felt depressed at times regarding the new diagnosis. He has been sexually active with multiple male partners in the past but recently began a monogamous relationship with an HIV-negative male partner. The patient is worried about transmitting HIV to his new partner. The patient's laboratory evaluation reveals a CD4+ T-cell count of 632 cells/mm^3 and an HIV viral load of 32,000 copies/ml. When should he start ART?
   A. As soon as possible
   B. When his CD4+ T-cell count drops below 500 cells/mm^3
   C. When his CD4+ T-cell count drops below 350 cells/mm^3
   D. When his CD4+ T-cell count drops below 200 cells/mm^3

4. A 42-year-old Indian woman presents with generalized fatigue, fevers, night sweats, hemoptysis, and weight loss of 25 lbs over 6 months. A chest radiograph shows hilar adenopathy and a cavitary lesion in the upper lobe of the right lung. Sputum cultures are obtained and grow *Mycobacterium tuberculosis*. During the evaluation she is also found to be infected with HIV. Her CD4+ T-cell count is 32 cells/mm^3. Treatment for tuberculosis is initiated. ART with tenofovir alafenamide, emtricitabine, and dolutegravir is also prescribed. The woman's cough, fever, and night sweats initially improve; however, 4 weeks later, she again develops fevers, worsening cough, and shortness of breath. Repeat chest radiography shows new nodular opacities surrounding the cavitary lesion seen initially. The hilar lymphadenopathy appears somewhat more pronounced. Repeat sputum testing is negative for acid-fast bacilli (AFB) by smear and culture. What is the most likely cause of the patient's most recent symptoms?
   A. A drug interaction between two or more of her HIV and tuberculosis medications
   B. An immune inflammatory response syndrome
   C. Multidrug-resistant pulmonary tuberculosis with failed initial therapy
   D. Evolving adenocarcinoma of the lung

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