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Preface

Infectious diseases have plagued humans since the earliest times of civilization. The early history of infectious diseases was marked by unpredictable, sudden outbreaks of epidemic proportion. By the middle of the 20th century, the introduction of antibiotics and the development of effective vaccines resulted in the control and prevention of many infectious diseases, especially in industrialized countries. Despite the fact that infections remain the leading cause of death worldwide, attention to infectious diseases diminished in the 1970s and 1980s as there was a shift in focus to chronic degenerative diseases. This complacency regarding the control and prevention of infectious diseases has been associated with outbreaks of disease and the emergence of new pathogens.

Emerging infectious diseases have been defined as those that newly appear in the population or have been known but are rapidly increasing in incidence or geographic distribution. New infectious diseases, frequently with unknown long-term impact, continue to be identified. Factors responsible for the emergence of infectious diseases are complex but include: ecologic changes in agriculture, economic development, climate, human behavior and demographics, travel and commerce, technology and industry, microbial adaptation and change and erosion of public health measures.

Old and new infections will occur in the future as they have in the past. Effective global surveillance efforts will be needed to blunt the emergence of such infections and to forestall epidemics and pandemics. Surveillance will need to be coupled with broad-based research efforts to devise new strategies for diagnosis, treatment, and prevention. It will also be necessary to develop new insights into microbial pathogenesis and genetics as well as host immune responses to these invading microbial pathogens.

In this atlas, six emerging infectious diseases (HIV-1, hepatitis C, respiratory viruses, tuberculosis, malaria and diarrheal disease) are reviewed in terms of evolving epidemiology, microbial pathogenesis, clinical features, and important approaches to diagnosis and management.

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Abbreviations

AASLD  American Association for Liver Diseases
AFB  acid-fast bacillus
AFP  alpha fetoprotein
AIDS  acquired immunodeficiency syndrome
ALT  alanine aminotransferase
ARDS  acute respiratory distress syndrome
AST  aspartate aminotransferase
BCG  Bacille Calmette–Guérin
CDAD  Clostridium difficile-associated disease
CDC (US)  Centers for Disease Control and Prevention
CIN  cervical intraepithelial neoplasia
CK  creatine kinase
CMV  cytomegalovirus
CNS  central nervous system
COPD  chronic obstructive pulmonary disease
CRP  C-reactive protein
CSF  cerebrospinal fluid
CT  computed tomography
DNA  deoxyribonucleic acid
DOTS  directly observed therapy, short course
EBV  Epstein–Barr virus
EIA  enzyme immunoassay
ELISA  enzyme-linked immunosorbent assay
ETEC  enterotoxigenic Escherichia coli
EVR  early virologic response
G6PD  glucose-6-phosphate dehydrogenase
GBS  Guillain–Barré syndrome
HAART  highly active antiretroviral therapy
HAI  hemagglutination-inhibition
HCC  hepatocellular carcinoma
HCV  hepatitis C virus
HIV  human immunodeficiency virus
hMPV  human metapneumovirus
HPV  human papilloma virus
HRCT  high resolution chest computed tomography
IBS  irritable bowel syndrome
IF  immunofluorescence
INH  isoniazid
IRIS  immune reconstitution inflammatory syndrome
KS  Kaposi’s sarcoma
LCR  ligase chain reaction
LDH  lactate dehydrogenase
LTBI  latent tuberculosis infection
MAI  Mycobacterium avium-intracellulare
MDR  multidrug resistant
MGIT  mycobacterial growth indicator tube
MRI  magnetic resonance imaging
NHL  non-Hodgkin’s lymphoma
NNRTI  non-nucleoside reverse transcriptase inhibitor
NRTI  nucleoside reverse transcriptase inhibitor
OC  opportunistic complications
OHL  oral hairy leukoplakia
PCNSL  primary CNS lymphoma
PCP  Pneumocystis jirovecii pneumonia
PCR  polymerase chain reaction
PGL  persistent generalized lymphadenopathy
PI  protease inhibitor
PML  progressive multifocal leukoencephalopathy
RBM  Roll Back Malaria (Program)
RIBA  recombinant immunoblot assay
RNA  ribonucleic acid
RSV  respiratory syncytial virus
RT-PCR  reverse transcriptase polymerase chain reaction
SARS-CoV  severe acute respiratory syndrome-associated coronavirus
SIL  squamous intraepithelial lesions
SP  sulfadoxine-pyrimethamine
STD  sexually transmitted disease
SVR  sustained virologic response
TB  tuberculosis
TST  tuberculin skin test
WHO  World Health Organization
Chapter 1

HIV and AIDS

Benigno Rodríguez, MD and Robert A Salata, MD, FACP, FIDSA

Introduction

The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981, when a cluster of cases of uncommon opportunistic infections and malignancies was reported among otherwise healthy men who had sex with men in San Francisco, Los Angeles, and New York. Alert clinicians and immunologists recognized the unusual infections as indicative of a profound cellular immunodeficiency, a notion promptly confirmed by a diversity of laboratory assays. Alternative routes of acquisition, including parenteral, perinatal, and transfusion-associated were quickly identified, and further reports that an indistinguishable illness had been known for decades in sub-Saharan Africa began to emerge. Subsequent developments occurred at a remarkably fast pace, unprecedented for a novel infectious disease: the retrovirus now known as human immunodeficiency virus (HIV) was identified as the causative agent within 2 years of the first case reports by independent groups in France, Bethesda, and San Francisco; a serological test became available shortly thereafter; the genome was fully sequenced in 1985; and the first clinically usable therapeutic compound, zidovudine, became commercially available in 1987. Since then, combinations of drugs that act at different stages of the virus’ life cycle (see below), known as highly active antiretroviral therapy (HAART) have proven capable of suppressing viral replication to extremely low levels, and to restore, at least partially, the impaired cellular immune function that is ultimately responsible for the increased susceptibility to opportunistic infections in AIDS patients.

The HIV pandemic, however, continues virtually unabated, having spread to every continent, and to all demographic groups throughout the world. Moreover, no curative treatment is available, and predictions for the time to development of an effective, widely available, preventive vaccine are measured in decades. Thus, HIV infection and AIDS remain major health problems that concern virtually every practicing clinician, and the complexity of their management can only be expected to increase in coming years. This chapter focuses mostly on the clinically relevant aspects of HIV infection and AIDS. Excellent reviews of the biology, immunology, and virology of HIV have been published elsewhere.

Etiology and pathogenesis

HIV-1 is the etiologic agent of the majority of AIDS cases worldwide. A closely related agent, HIV-2, also causes AIDS in parts of West Africa; sporadic cases occur elsewhere. Throughout the remainder of this chapter, ‘HIV’ is used to refer to HIV-1, unless otherwise indicated. HIV is a member of the lentiviridae family with a plus-stranded ribonucleic acid (RNA) genome that encodes structural, regulatory and accessory proteins, as well as the enzymatic activities; the genomic organization of HIV is shown in Fig. 1.1, and the structure of the infective viral particle is shown in Fig. 1.2.

The hallmark of HIV infection is depletion of CD4+ helper T lymphocytes, with ensuing loss of immune competence. Many other immune defects are evident as HIV disease progresses, however, and not all of them can be readily accounted for by the loss of help associated with
CD4+ T cell destruction. Among these, defects in B cell proliferation and antibody production, impaired cytotoxic lymphocytic responses, decreased dendritic cell number and function, and profound perturbations of the cytokine milieu have all been shown, particularly in advanced stages of HIV infection. The precise mechanism by which HIV infection leads to these wide-ranging defects is incompletely understood, although they are related to HIV replication, and can be partially corrected by effective antiretroviral therapy that suppresses plasma viremia to very low levels. The vital cycle of HIV is complex and includes multiple steps that can be targeted for therapeutic purposes. These steps are summarized in Fig. 1.3.

Active HIV replication is lytic to some, but not all infected cells. Because the predominant target of HIV is the CD4+ T cell, it has been proposed that direct destruction of these cells by HIV is the predominant mechanism of immunodeficiency in progressive HIV infection. More recent evidence, however, shows that the number and distribution of infected cells, the rate of CD4+ T cell turnover and the loss of large numbers of uninfected cells through indirect, or ‘bystander’, mechanisms do not support this model as the sole explanation for HIV-related immune deficiency. Moreover, studies in HIV-infected persons receiving clinical care show that the level of HIV viremia predicts poorly the subsequent rate of CD4+ T cell loss at the individual level, further highlighting that other, indirect mechanisms in effect lead to immunodeficiency in HIV infection. Uncontrolled immune activation is an additional feature of HIV infection that may underlie the CD4+ T cell loss and other immune derangements that eventually culminate in full-blown AIDS. Similarly, advanced HIV infection is associated with depletion of thymocytes and loss of thymic function, as well as impaired bone marrow activity, all of which limit the ability to restore the accelerated CD4+ T cell losses induced by HIV. The net result is a progressively increased susceptibility to a diversity of opportunistic complications that, in the era before the introduction of HAART, were almost invariably fatal within a short period after the initial diagnosis of AIDS.
Global epidemiology

Few human infections fit the description of an emerging disease better than HIV infection and AIDS. In the 25 years since its initial description, 75 million individuals worldwide have been infected with HIV, and the epidemic is now present throughout the world. The World Health Organization (WHO) estimates that, by the end of 2006, there were 39.5 million persons living with HIV/AIDS in the world, and 4.3 million acquired HIV in the previous year alone. Over 90% of these persons live in the developing world (62.5% in sub-Saharan Africa alone) and heterosexual intercourse is the route of acquisition in the vast majority of cases. Current estimates of the extent of the HIV epidemic worldwide are shown in Fig. 1.4.

In addition to the sheer number of cases, the HIV epidemic has changed dramatically over the past several years, leading to a truly re-emerging epidemiological pattern worldwide. Large epidemics are expanding rapidly in eastern Europe, Asia, and India, which is now the single country with the largest number of cases worldwide. Moreover, the proportion of cases occurring in women is increasing at an alarming pace. Close to 50% of all adults living with HIV/AIDS worldwide are women, and the proportion approaches 66% in parts of sub-Saharan Africa.

In the United States and western Europe, the introduction of HAART has produced dramatic reductions in HIV-related morbidity and mortality (Fig. 1.5), but trends in sex distribution are similar to those observed worldwide (Fig. 1.6). Furthermore, new cases are occurring disproportionately more often among minorities and disadvantaged populations, further changing the face of the epidemic.

**Fig. 1.3** Vital cycle of HIV and sites targeted by current anti-HIV medications. After HIV binds to its primary receptor, CD4 (1), the viral envelope undergoes a conformational change that facilitates binding to another cellular coreceptor, the most important of which are the chemokine receptors CCR5 and CXCR4 (2). Interaction with the coreceptor triggers further conformational changes in the envelope that bring the viral and cellular membranes into close proximity, thereby permitting their fusion (3) through insertion of the newly exposed fusion domain of the envelope protein gp41 into the host cell membrane. The HIV nucleocapsid then enters the cytoplasm, where the RNA genomic material of the virus is reverse transcribed into DNA (4) by the virally encoded reverse transcriptase. Next, the double-stranded viral DNA enters the nucleus, where it integrates into the host genome with the aid of the HIV-encoded enzyme integrase (5). The integrated proviral DNA is then transcribed into messenger RNA (6), which serves as the template for assembly of the main viral structural proteins (7). The protein complex is cleaved by a protease into functional segments (8), thus allowing assembly and budding of the new viral particles (9) to proceed.
Fig. 1.4 Global estimates of the HIV/AIDS epidemic at the end of 2006. (Adapted from UNAIDS and WHO, 2006 Report on the Global HIV epidemic, Geneva, UNAIDS, 2006.)

Fig. 1.5 Trends in annual rates of death due to the nine leading causes among persons 25–44 years old, USA, 1987–2004. HIV disease was the leading cause of death among person 25–44 years old in 1994 and 1995. With the introduction of HAART in 1995, the rank of HIV disease fell to 5th place from 1997 through 2000, and to 6th place in 2001 and 2002. The spike in the death rate due to homicide in 2001 resulted from the terrorist attack on September 11. (Adapted from CDC data.)

Fig. 1.6 Trends in the percentage distribution of deaths due to HIV disease by sex, USA, 1987–2004. The proportion of females among persons who died of HIV disease increased from 10% to 26% during this period, highlighting the increasing burden of disease among females in the US, as is the case in other countries. Because heterosexual transmission is emerging as the predominant mode of transmission, this trend can be expected to grow in the coming years. (Adapted from CDC data.)
Clinical manifestations

The clinical manifestations of HIV infection and AIDS are diverse and can affect virtually any organ system. The time to development of specific symptoms or syndromes varies considerably from person to person, and many cases remain asymptomatic for very prolonged periods. Nevertheless, HIV-related immunodeficiency develops in most cases as a predictable sequence of events, in which the massive depletion of CD4+ T cells that characterizes AIDS occurs only after a clinically silent interval. During this period, few clinical indications of HIV infection exist, despite vigorous viral replication in the lymphoid tissues and ongoing plasma viremia. This sequence of events is summarized in Fig. 1.7.

The first clinical manifestation of HIV infection may be a mononucleosis-like syndrome, termed acute retroviral syndrome, which occurs in over 50% of cases within 2–6 weeks of initial infection. Symptoms are nonspecific and may include fever, sore throat, lymph node enlargement, arthralgias, and headache and usually persist for several days to 3 weeks; in a significant proportion of symptomatic cases, the manifestations are severe enough to warrant medical attention. A maculopapular rash is common, as is nonspecific lymphadenopathy (Fig. 1.8), and some patients may present with self-limited aseptic meningitis, which manifests as cerebrospinal fluid (CSF) pleocytosis and isolation of HIV from CSF. In some cases, the acute retroviral syndrome may be accompanied by thrush or even opportunistic infections during the transient CD4+ T cell decline seen early in the disease course. Table 1.1 summarizes the most common clinical manifestations of acute retroviral syndrome. From the laboratory standpoint, the acute retroviral syndrome can be diagnosed on the basis of a negative HIV enzyme-linked immunosorbent assay (ELISA) and a positive antigen-based or HIV RNA test in a patient with risk factors.

After the acute retroviral syndrome, the majority of subsequent clinical manifestations are due to complications emerging from progressive immunodeficiency. These infections will be discussed according to the stage at which they characteristically present. It should be kept in mind, however, that while diseases that are typical of profound immunodeficiency rarely appear at earlier stages, those that occur with high CD4+ T cell counts can obviously also

![Fig. 1.7 Natural history of untreated HIV disease. Shortly after infection, viremia reaches extremely high levels, while CD4+ count decreases to levels that may be sufficient for the development of certain opportunistic complications. During this period, patients may experience the manifestations of the acute retroviral syndrome, and are highly infectious, thus making a high index of suspicion of paramount importance. After this initial phase, viremia decreases to a level (referred to as ‘set point’) at which it will remain, relatively constant, during the subsequent phase. At the same time, CD4+ T cell count rebounds, but does not return to pre-infection levels. A relatively asymptomatic period follows, during which there is ongoing viral replication and a slow but demonstrable decline in CD4+ T cell count. This phase ends years after infection with a precipitous fall in CD4+ T cell count and an exponential rise in plasma HIV RNA level, which heralds the beginning of AIDS. (Adapted from Fauci AS, Pantaleo G, Stanley S, et al. Immunopathic mechanisms of HIV infection. Ann Intern Med 1996;124:654.)](image-url)
Table 1.1 Clinical manifestations of acute retroviral syndrome

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>96</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>74</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>70</td>
</tr>
<tr>
<td>Rash</td>
<td>70</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>54</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>32</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>27</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>14</td>
</tr>
<tr>
<td>Thrush</td>
<td>12</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>12</td>
</tr>
</tbody>
</table>

(Data from Kahn JO, Walker BD. Human immunodeficiency Virus Type 1 infection. *N Engl J Med* 1998;339:33.)

Complications occurring with CD4+ T cell counts >500/mm³

Persistent generalized lymphadenopathy (PGL) can begin with the acute retroviral syndrome (Fig. 1.8), and is defined as two or more extrainguinal regions with lymphadenopathy persisting for at least 3–6 months in the absence of an alternative explanation. Up to 50–70% of HIV-infected patients may develop PGL, but PGL is not associated with adverse consequences in those individuals. Excluding a treatable etiology is critical, particularly with more localized lymphadenopathy. Some patients will experience constitutional symptoms (low-grade fevers, fatigue, and night sweats), diarrhea, or unexplained weight loss during the early stages of HIV infection; again, excluding other etiologies is imperative. Oral and vaginal candidiasis (Fig. 1.9) can also appear at all stages of HIV disease, although they increase in frequency as the CD4+ T cell count falls below 500 cells/mm³. Thrush presents as adherent, non-painful, off-white exudates that can be scraped off with a tongue depressor, leaving a denuded area of mucosa. Dermatomal herpes zoster (Fig. 1.10) is another frequent early manifestation; in more advanced stages, the presentation may involve multiple dermatomes, prolonged persistence of lesions, or systemic dissemination.

Table 1.2 US Centers for Disease Control 1993 revised classification system for HIV infection in adults and adolescents

<table>
<thead>
<tr>
<th>CD4+ T cell category</th>
<th>Clinical category</th>
<th>Category B: symptoms, non-AIDS-defining¹</th>
<th>Category C: AIDS-defining conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1: ≥500 cells/mm³</td>
<td>Category A: asymptomatic, PGL or acute viral syndrome</td>
<td>A1</td>
<td>B1</td>
</tr>
<tr>
<td>Category 2: 200–499 cells/mm³</td>
<td></td>
<td>A2</td>
<td>B2</td>
</tr>
<tr>
<td>Category 3: &lt;200 cells/mm³</td>
<td></td>
<td>A3</td>
<td>B3</td>
</tr>
</tbody>
</table>

Patients can be classified according to CD4+ T cell count and spectrum of clinical manifestations; increasing categories represent increasing degrees of immunodeficiency, although this classification was primarily created for surveillance purposes.

PGL: persistent generalized lymphadenopathy.

¹Conditions in this category include, but are not limited to, bacillary angiomatosis; thrush; persistent or refractory vaginal candidiasis; moderate to severe cervical dysplasia and cervical carcinoma in situ; constitutional symptoms including chronic diarrhea; oral hairy leukoplakia; recurrent or multidermatomal herpes zoster; idiopathic thrombocytopenic purpura; listeriosis; pelvic inflammatory disease; peripheral neuropathy.
Fig. 1.8 Maculopapular rash consistent with acute HIV infection.

Fig. 1.9 Mucosal candidiasis in moderately advanced HIV infection. A: Thrush (oropharyngeal candidiasis). Typical white exudates that can be removed with a tongue depressor are seen covering the oral mucosa. B: Vaginal candidiasis. The similarity of the exudates covering the vaginal wall is obvious. (A: courtesy of Dr S Silverman, CDC; B: courtesy of CDC.)

Fig. 1.10A, B Multidermatomal herpes zoster (shingles) in a patient with advanced HIV infection and incomplete CD4+ T cell replenishment after highly active antiretroviral therapy. Note the characteristic erythematous-vesicular rash that does not cross the midline and involves several dermatomes. Some of the lesions have begun to crust, while others (e.g. on the upper arm) are in a pustular phase.
Complications occurring with CD4+ T cell counts 200–500/mm³

Oral hairy leukoplakia (OHL) is the main differential diagnosis for oral candidiasis, as it also presents as a white, raised lesion of the oral mucosa (Fig. 1.11). OHL, however, typically presents on the lateral margin of the tongue and cannot be scraped off easily. Worldwide, the most common complication at this stage is tuberculosis (TB), both in pulmonary and extrapulmonary forms. TB can occur at any stage of HIV disease, however, and its clinical presentation relates to the CD4+ T cell count; thus, ‘typical’ cavitary forms are more commonly seen at early stages (Fig. 1.12), whereas more diffuse pulmonary and extrapulmonary forms become more frequent as the immunodeficiency progresses (Fig. 1.13). Kaposi’s sarcoma (KS) is a vascular neoplastic disorder characteristically seen in homosexual men that presents as red-purple nodules involving the skin and/or mucous membranes (Fig. 1.14); visceral involvement also occurs (Fig. 1.15), particularly with more advanced stages of disease.

Recurrent bacterial pneumonia (most often due to *Streptococcus pneumoniae*) and other serious bacterial infections are common during this stage, and their

---

**Fig. 1.11** Oral hairy leukoplakia. This lesion is associated with Epstein–Barr infection of the keratinized epithelium of the tongue and the buccal mucosa, and can be distinguished from oral candidiasis by the characteristic location on the lateral surface of the tongue, its resistance to scraping with a tongue depressor and its failure to respond to antifungal therapy. OHL can be seen at relatively early stages of HIV disease, but its prevalence increases with decreasing CD4+ T cell counts. (Courtesy of Dr S Silverman, DDS.)

---

**Fig. 1.12** Cavitary pulmonary tuberculosis in a Ugandan patient with AIDS. This person was not known to be HIV infected when he presented to the TB clinic complaining of subacute respiratory symptoms, fevers, and diaphoresis. Note the characteristic right upper lobe location of the lesion, and the air–fluid level, indicative of a cavitating lesion in that location. At the time of this visit, the patient’s CD4+ T cell count was approximately 400 cell/mm³.
Fig. 1.13 Tuberculosis in advanced AIDS. A: Pleural tuberculosis. This massive pleural effusion resolved completely after anti-TB treatment. B: Tuberculous adenitis. This mass (arrows) can easily be mistaken for a neoplasia, leading to unnecessary interventions. C: Miliary tuberculosis in a patient with advanced AIDS. Note the finely micronodular infiltrate involving virtually all the pulmonary parenchyma. CD4+ T cell count at the time of diagnosis was <5 cells/mm³. (A and B courtesy of Dr R Kalayjian.)
frequency increases with progressive immunodeficiency. The risk of bacterial pneumonia is up to 100-fold greater in HIV infection. Other encapsulated organisms such as *Haemophilus influenzae* and highly virulent pathogens such as *Pseudomonas aeruginosa* are also more common in HIV-infected patients. Pneumococcal pneumonia typically presents with a similar clinical picture to that in HIV-negative patients (Fig. 1.16, 1.17), but mortality is increased in HIV-infected patients, particularly with advanced disease, when atypical presentations including subtle interstitial infiltrates and a protracted course reminiscent of *Pneumocystis jirovecii* can be seen. Concomitant bacteremia is especially common in this setting, making blood cultures an important part of the diagnostic evaluation. Nodular and cavitary lesions, in addition to mycobacterial and fungal disease, should raise suspicion for less common bacterial pulmonary pathogens including *Nocardia* species (Fig. 1.18) and *Rhodococcus equi*, particularly in the setting of clinical manifestations in other organ systems (Fig. 1.19).

HIV-infected women have an increased risk of squamous intraepithelial lesions (SIL) and cervical intraepithelial neoplasia (CIN), both of which are related to human papilloma virus (HPV) infection, and are often the first HIV-related symptom in HIV-positive women in the developed world (Fig. 1.20). Progression of SIL has been associated with declining CD4+ T cell counts; thus, regular screening for cervical lesions is especially important for HIV-infected women, in particular those with advanced disease. Condylomata acuminata are also often diagnosed at this stage, and tend to become more exuberant with disease progression (Fig. 1.21).

**Fig. 1.14** KS of the skin in a patient with advanced AIDS. KS is an avascular neoplastic disorder caused by human herpes simplex virus-8 (HHV-8), also known as KS-associated HSV. Cutaneous lesions often resolve with HAART, but more effective and better tolerated forms of chemotherapy have recently become available for treatment of the more extensive and invasive forms of the disease.

**Fig. 1.15** Visceral KS. Note the bronchial thickening apparent in this chest radiograph (arrow). While cutaneous KS can and often does present at intermediately advanced stages of HIV disease, extensive visceral involvement is more characteristic of advanced disease. Pulmonary KS can present as hemoptysis, sometimes massive, and can frequently be diagnosed by bronchoscopy, during which typical lesions are often seen and can be readily biopsied. Other frequent radiologic findings include nodules, hilar adenopathy and large pleural effusions. (Courtesy of Dr R Kalayjian.)
Fig. 1.16 Pneumococcal pneumonia in a patient with AIDS. Note the lobar consolidation with air bronchograms, indistinguishable from the expected presentation in an HIV-negative person. (Courtesy of Dr R Kalayjian.)

Fig. 1.17 Sputum Gram stain of the patient in Fig. 1.16. Abundant polymorphonuclear cells and Gram-positive diplococci in chains, some with visible capsule, are seen. (Courtesy of Dr R Kalayjian.)

Fig. 1.18 Nocardia pulmonary infection in an HIV-infected patient. There is marked right-sided hilar adenopathy with pulmonary nodules in that area. (Courtesy of Dr R Kalayjian.)

Fig. 1.19 CT of the brain of the patient in Fig. 1.18. There are multiple discrete focal masses consistent with Nocardia abscesses. Markedly immunosuppressed patients, including patients with AIDS, are at increased risk of disseminated Nocardia infections, such as in this case. The relatively rarity of Nocardia-related complications in HIV infection is likely due to the partially protective effect of cotrimoxazole, used for prophylaxis of Pneumocystis jiroveci pneumonia. (Courtesy of Dr R Kalayjian.)
Complications occurring with CD4+ T cell counts 100–200/mm³

In the pre-HAART era, *Pneumocystis jirovecii* pneumonia (PCP) was the most common AIDS-defining complication in industrialized countries, and it remains an important entity today among patients who are not aware of their HIV status or who are poorly compliant with treatment (*Figs. 1.20, 1.21*). Patients typically present with a subacute course of progressive exertional dyspnea, dry cough, chest pain, and fever. Severe hypoxemia is a poor prognostic marker, and in-hospital mortality from respiratory failure remains high, despite a decreasing incidence since 1990. Other complications include the development of thin-walled cysts (*Fig. 1.22*) and pneumothoraces (*Fig. 1.23*). Less commonly, disseminated infection may occur (*Fig. 1.24*). Neurologic complications also become prominent at this stage. Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by the polyomavirus JC that affects almost exclusively the central nervous system (CNS) white matter (*Fig. 1.25*). Patients present most commonly with focal neurologic symptoms including limb palsies, mental status changes, ataxia, and neuroophthalmological disorders. Imaging shows non-enhancing, hyperintense lesions in the subcortical white matter, typically without mass effect or edema (*Fig. 1.26*). HIV encephalopathy, also known as AIDS dementia complex, occurs in up to 15% of AIDS patients, and can manifest with a diversity of cognitive, behavioral and motor symptoms, including gait and coordination disturbances. The diagnosis of HIV encephalopathy requires exclusion of other, treatable conditions; imaging typically shows subcortical atrophy with or without white matter changes (*Fig. 1.27*). Several other neurologic syndromes can present at various stages of HIV infection; *Fig. 1.30* shows the relation of these syndromes to the degree of immunodeficiency.
Fig. 1.22 *Pneumocystis jirovecii* pneumonia. The perihilar distribution of the patchy, predominantly interstitial infiltrate that spares the apices and the absence of a pleural effusion despite extensive parenchymal disease are characteristic. (Courtesy of Dr R Kalayjian.)

Fig. 1.23 Microscopic specimens from cases of *Pneumocystis jirovecii* pneumonia. A: Characteristic appearance of the organism on a silver stain of a bronchoalveolar lavage specimen from a patient with AIDS. Although the organism is relatively large and has a complex life-cycle reminiscent of that of certain protozoans, analyses of ribosomal RNA unequivocally place *Pneumocystis jirovecii* as a fungus. It does not respond to conventional antifungal agents, however, but it does to antimicrobial agents active against some protozoans, such as sulfas, atovaquone, clindamycin, and primaquine. B: Histologic specimen of a lung biopsy from a patient with PCP. The frothy, proteinaceous material in the alveolar space is characteristic, and experimented pathologists can confidently recognize a case of PCP based on this finding even before special stains showing the microorganism are available. (Courtesy of Dr R Kalayjian.)

Fig. 1.24 Thin-walled cysts in a patient with *Pneumocystis jirovecii* pneumonia. These lesions can grow to reach the proportion of true bullae. Pneumothorax (Fig. 1.25) may result from rupture of one of these cysts. (Courtesy of Dr R Kalayjian.)

Fig. 1.25 Pneumothorax.
Fig. 1.25 Spontaneous pneumothorax in a patient with *Pneumocystis jirovecii* pneumonia. The collapsed lung on the left can be seen as a faint outline next to the heart (arrows). Note also the lack of vascular markings on the left side. (Courtesy of Dr R Kalayjian.)

Fig. 1.26 Disseminated *Pneumocystis jirovecii* infection in a patient with advanced AIDS. A: Splenic lesions in a patient with profound AIDS-related immunodeficiency. B: *Pneumocystis* choroiditis. The lesions appear as white–yellow irregular patches. The eye is one of the sites where lesions can be seen in these uncommon cases, but bone marrow, liver, lymph node, and small bowel involvement have also been reported. The ocular lesion is characteristically a posterior choroiditis without vitreal inflammation, as illustrated in this image. Prophylaxis with aerolized pentamine is a risk factor for disseminated disease, due to the low proportion of the drug that enters the systemic circulation.

Fig. 1.27 Autopsy specimen from a case of progressive multifocal leukoencephalopathy. Note the location of the lesion involving exclusively the white matter. (Courtesy of Dr R Kalayjian.)
Fig. 1.28 Progressive multifocal leukoencephalopathy in a patient with AIDS. The location of the lesions (bright white areas, similar in intensity to CSF in the ventricles) in the subcortical white matter and the absence of a mass effect are characteristic. With the introduction of HAART, cases of ‘inflammatory’ PML have been described, in which the lesions enhance with magnetic contrast medium and can be surrounded by edema. This is considered a form of immune reconstitution syndrome. (Courtesy of Dr R Kalayjian.)

Fig. 1.29 AIDS dementia complex. There is extensive subcortical atrophy, with compensatory ex vacuo hydrocephalus, as well as non-specific white matter changes. (Courtesy of Dr R Kalayjian.)

<table>
<thead>
<tr>
<th>CD4+ T cell count</th>
<th>Seroconversion</th>
<th>&gt;500/mm³</th>
<th>200–500/mm³</th>
<th>&lt;200/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Aseptic meningitis</td>
<td>Chronic meningitis</td>
<td>AIDS dementia</td>
<td>Vacuolar myelopathy</td>
</tr>
<tr>
<td></td>
<td>Mononeuritis (e.g. facial palsy)</td>
<td>Inflammatory demyelinating polyneuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNS</td>
<td>Chronic meningitis</td>
<td>Mononeuropathy multiplex</td>
<td>Distal sensorypolyneuropathy</td>
<td>Myopathy</td>
</tr>
</tbody>
</table>

Fig. 1.30 Timing of different neurologic complications of HIV infection according to the degree of CD4+ T cell loss. Up to 50% of persons with HIV infection will experience neurologic symptoms throughout the course of the disease, and up to 80% of autopsies on HIV-infected persons show evidence of central nervous system involvement.
Complications occurring with CD4+ T cell counts <100/mm³

With advanced HIV disease, focal brain masses, mostly due to either *Toxoplasma* encephalitis or primary CNS lymphoma (PCNSL) begin to emerge. Both present with a subacute course ranging from weeks to 1–2 months, during which headache, mental status changes, lethargy, and various focal neurologic deficits can occur. Seizures are common with both diseases; fever is more frequent with *Toxoplasma* encephalitis. On magnetic resonance imaging (MRI), both present as space-occupying lesions with surrounding edema and ring-like enhancement after contrast (Figs. 1.31, 1.32). *Toxoplasma* lesions are more commonly multiple, and are characteristically located at the corticomedullary junction, in the white matter, or in the basal ganglia. PCNSL is less frequently multilesional, and more often involves the periventricular white matter, the cortex, or the corpus callosum. The two can be indistinguishable, however, but the patient’s *Toxoplasma* antibody status and history of exposure to prophylactic agents can help in the differential diagnosis (Table 1.3).

In patients with extremely low CD4+ T cell counts, *Toxoplasma* can also cause disseminated disease, with pulmonary and multisystemic involvement (Figs. 1.33, 1.34); the prognosis in these cases is usually poor. An

### Table 1.3 Probability of having *Toxoplasma* encephalitis among HIV-infected patients presenting with focal brain lesions accompanied by mass effect, according to *Toxoplasma* serologic status and exposure to prophylactic agents with activity against *Toxoplasma*

<table>
<thead>
<tr>
<th>Toxoplasma antibody</th>
<th>Receiving Toxoplasma prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Yes (%)</td>
</tr>
<tr>
<td></td>
<td>No (%)</td>
</tr>
<tr>
<td>Positive</td>
<td>59</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>87</td>
</tr>
</tbody>
</table>

The radiological pattern, although suggestive, has limited or no value for differential diagnosis in this setting, and the actual antibody titers are similarly not informative. As seen from the table, serologic status is particularly helpful with a negative result, which should always decrease the suspicion for *Toxoplasma* encephalitis considerably, regardless of prophylaxis history. (Data from Antinori A, Ammassari A, De Luca A, *et al.* Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology* 1997;48:687–694.)

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Fig. 1.31 *Toxoplasma* encephalitis. Note the multiple lesions, their annular shape, and the significant mass effect and vasogenic edema around them. In the United States, *Toxoplasma* was the most common cause of focal brain lesions in HIV-infected patients during the early phase of the HIV epidemic, but it has become a much less common complication with the widespread use of prophylaxis and combination antiretroviral therapy. (Courtesy of Dr R Kalayjian.)
Fig. 1.32 PCNSL in an AIDS patient. The periventricular location, single lesion, and marked perilesional edema with compression of adjacent structures are all highly suggestive of PCNSL, but are not sufficiently specific to differentiate this mass from those caused by *Toxoplasma* infection. Compare with Fig. 1.31. Virtually all PCNSL in HIV infection are positive for Epstein–Barr virus, and most occur at very low CD4+ T cell count levels. (Courtesy of Dr R Kalayjian.)

Fig. 1.33 *Toxoplasma* pneumonitis in a patient with AIDS. There are subtle interstitial infiltrates that are out of proportion with the severity of the clinical picture, most likely as a consequence of the limited ability of these very advanced patients to mount a vigorous inflammatory response. Pulmonary involvement is almost invariably a reflection of systemic dissemination, and patients with this form of invasive *Toxoplasma* infection often present with a sepsis-like syndrome, with high fevers and hypotension. The prognosis is poor. (Courtesy of Dr R Kalayjian.)

Fig. 1.34 *Toxoplasma* tachyzoites (arrow) in lung tissue in an AIDS patient with pulmonary toxoplasmosis. (Courtesy of Dr R Kalayjian.)
additional important location for *Toxoplasma* complications is the eye, where it can infrequently cause a necrotizing chorioretinitis, commonly accompanied by vitreous inflammation (Fig. 1.35). Other causes of retinal disease in HIV infection include varicella-zoster, syphilis, and HIV itself, but cytomegalovirus (CMV) is by far the most common cause of retinitis. Active CMV retinitis presents with extensive exudates and hemorrhages following a vascular pattern and marked vitreal inflammation (Fig. 1.36). CMV retinitis can be sight-threatening, and can lead to acute retinal detachments with sudden loss of vision. In the CNS, CMV causes a form of encephalitis with periventricular inflammation that can be seen on MRI (Figs. 1.37–1.39); other sites of CMV pathology in AIDS patients include the gastrointestinal tract, lungs, spinal cord, and disseminated disease.

**Fig. 1.35** *Toxoplasma* chorioretinitis. Note the discrete, rounded necrotizing lesions and the vitreous haze, indicative of vitreal inflammation. (Courtesy of Dr R Kalayjian.)

**Fig. 1.36** Cytomegalovirus retinitis. There are confluent white exudates along vascular paths, with several areas of hemorrhage. Patients with this type of complication complain of progressive loss of visual acuity, blurry vision, ocular discomfort, and ‘floaters’. Symptoms are often unilateral initially, but eventual involvement of both eyes is common. CMV retinitis has become less frequent with the advent of HAART.
**Fig. 1.37** Cytomegalovirus ventriculoencephalitis. Marked periventricular enhancement is seen in this MRI study in a patient with AIDS. The clinical presentation can mimic that of HIV encephalopathy, but tends to have a more acute course. Concomitant focal lesions and extraneural CMV involvement are commonly present. Detection of CMV DNA in the CSF helps to establish the diagnosis. (Courtesy of Dr R Kalayjian.)

**Fig. 1.38** Autopsy specimen in a case of cytomegalovirus encephalitis. Note the inflammatory and necrotizing changes in and around the ventricles. (Courtesy of Dr R Kalayjian.)

**Fig. 1.39** Histologic findings in cytomegalovirus encephalitis. There are cells with CMV inclusions, that give them the almost pathognomonic appearance of ‘owl’s eyes’ (arrow). (Courtesy of Dr R Kalayjian.)
Fungal disease is also prominent in late HIV disease. *Candida* esophagitis ([Fig. 1.40](#)) is a common cause of dysphagia in these patients. The frequency of cryptococcal disease also rises dramatically at very low CD4+ T cell counts. Cryptococcal meningitis ([Fig. 1.41](#)) is one of the most common manifestations, but pulmonary syndromes ([Fig. 1.42](#)), focal neurologic disease ([Fig. 1.43](#)) and disseminated infection can also occur. In endemic areas, infection with the dimorphic fungus *Histoplasma capsulatum* can be a significant problem; in addition to pulmonary disease ([Fig. 1.44](#)), systemic forms can be seen in AIDS patients ([Fig. 1.45](#)). Atypical mycobacteria, especially *Mycobacterium avium-intracellulare* (MAI) complex ([Fig. 1.46](#)), become a major source of morbidity and mortality when CD4+ T cell counts drop below 50 cells/mm³.

Chronic, intractable diarrhea is common at this stage. The coccidian parasites *Cryptosporidium parvum* ([Fig. 1.47](#)) and *Isospora belli* and those in the phylum *Microsporidia* are frequently responsible, but mixed infections are often present. Other causes of gastrointestinal symptoms, sometimes severe, include CMV colitis and enteritis, MAI intestinal involvement, and dysbacteriosis. In the era of HAART, many cases of chronic diarrhea in advanced AIDS patients do not have an identifiable cause; HIV itself is known to infect certain cellular populations in the gastrointestinal epithelium and can be directly responsible for some of these cases. Malignancies have become an increasingly prominent cause of morbidity and mortality in AIDS patients, as the use of HAART has increased survival and the HIV-infected population, at least in the developed world, becomes older. Non-Hodgkin's lymphoma (NHL) ([Fig. 1.48](#)) is 100–1,000 times more common in HIV-infected than in HIV-negative persons. NHL can occur at any level of CD4+ T cell depletion, but its aggressiveness and prognosis are worse in advanced stages of the disease. In addition to primary CNS locations (discussed above, see [Fig. 1.32](#)), AIDS-related NHL is more often extranodal than in the general population. Hepatocarcinoma related to hepatitis B or C coinfection and invasive cervical carcinoma are other examples of important neoplastic complications of HIV infection.

**Fig. 1.40** *Candida* esophagitis in a patient with AIDS. The white exudates overlaying an erythematous mucosa are characteristic. Oropharyngeal candidiasis (thrush) is a common manifestation of early HIV disease, but involvement of the esophagus, as seen here, typically occurs only with lower CD4+ T cell counts: *Candida* esophagitis is one of the most frequent causes of dysphagia in this setting; many experienced clinicians treat empirically with antifungals when a patient with AIDS presents with thrush and dysphagia, pursuing endoscopic studies only if there is no or incomplete clinical response. Other causes of dysphagia and esophageal pain in this setting include CMV, HSV, and aphthous ulcers. (Courtesy of Dr J Conklin, UCLA.)
Systemic cryptococcosis in a patient with AIDS. This patient had <50 CD4+ T cells/mm³ when he presented with a 3-week history of fever and headaches. On exam he was lethargic, and had multiple cutaneous papular lesions with central umbilication on the face and extremities. CSF and blood cultures both yielded *Cryptococcus neoformans*. 

**A:** Yeast cells on an India ink stain of the CSF. **B:** Cutaneous lesions resemble those of moluscum contagiosum, a viral disease that is also common in AIDS patients.

Severe cryptococcal pneumonia. The portal of entry for *Cryptococcus* is almost always the respiratory tract, and pulmonary manifestations can occur even in immunocompetent hosts. Severe progressive disease, however, is largely confined to profoundly immunocompromised persons. In this case, the presentation was in the form of necrotizing pneumonia with cavitation of the right upper lobe, mimicking pulmonary tuberculosis. Compare with **Fig. 1.12**. (Courtesy of Dr R Kalayjian.)
Fig. 1.43 Cryptococcoma of the CNS in an AIDS patient. While CNS involvement in cryptococcal disease is most frequently in the form of subacute meningitis, focal lesions, as seen in this case, can occur particularly with advanced immunosuppression. These lesions can produce focal findings and seizures; in some cases, they can expand and become clinically more apparent with immune recovery after HAART. (Courtesy of Dr R Kalayjian.)

Fig. 1.44 Chest radiograph (detail) of an AIDS patient with histoplasmosis. Several pulmonary nodules (arrows) can be seen. Although Histoplasma capsulatum is a ubiquitous fungus, there are areas of increased endemicity throughout the world. In the United States, the valleys of the Ohio, Mississippi, and St Lawrence rivers are the most important. The organism grows best in soils with high nitrogen content, especially those contaminated with bird manure or bat droppings. (Courtesy of Dr R Kalayjian.)

Fig. 1.45 Disseminated histoplasmosis. Many yeast forms of Histoplasma capsulatum can be seen in this peripheral blood smear from a patient with HIV. While Histoplasma can cause severe disease in both immunocompromised and immunocompetent hosts, depending on the size of the inoculum, immunocompromised hosts are much more susceptible to disseminated forms.
Fig. 1.46 Lymph node biopsy in a case of MAI. Large numbers of acid-fast bacilli, seen here as clumps of red elongated forms, are present throughout the node parenchyma. In AIDS patients, disseminated MAI infection is a late and often terminal complication that presents as an insidious, debilitating febrile illness accompanied by severe wasting, liver enzyme abnormalities, and various systemic symptoms. The organism can often be isolated from blood cultures in these patients. (Courtesy of Dr E Ewing, CDC.)

Fig. 1.47 Cryptosporidium parvum in the gallbladder epithelium of a patient with AIDS. Cryptosporidium is a common parasite of animals, and can cause self-limiting diarrheal disease in immunocompetent humans, sometimes in epidemic form. In AIDS patients with very low CD4+ T cell counts, however, it is associated with a protracted, copious diarrhea that is often intractable. The biliary tree is a frequent location of Cryptosporidium replication, and can be associated with cholangitis and other local complications. Cryptosporidium has become infrequent as a cause of AIDS-related chronic diarrhea with the introduction of HAART. (Courtesy of Dr E Ewing, CDC.)

Fig. 1.48 NHL in a patient with AIDS. There is a large pulmonary mass in the right parahilar region, which was confirmed by biopsy to correspond to NHL. While recent large-scale epidemiologic studies have confirmed that the incidence of AIDS-related NHL is declining since the introduction of HAART, the rate at which it is doing so is the slowest of all opportunistic complications. Histologically, most cases are large B cell or Burkitt's lymphomas. Up to 60% of non-CNS lymphomas and virtually all primary CNS lymphomas in HIV infection are EBV-positive. A unique clinical form, primary effusion lymphoma, occurs almost exclusively in HIV-infected patients and is associated with HHV-8, the etiologic agent of KS. Primary effusion lymphoma presents with large pleural or peritoneal effusions in the absence of identifiable masses or bone marrow involvement. (Courtesy of Dr R Kalayjian.)
Management

As discussed above, HAART has dramatically altered the natural course of HIV disease in industrialized countries, resulting in a precipitous decrease in AIDS-related complications and deaths (see Fig. 1.5). All currently approved antiretroviral agents target HIV’s reverse transcriptase, protease, or fusion, but new agents are being introduced that work at other stages of the virus’ life cycle (see Fig. 1.3). Currently approved drugs for treatment of HIV are listed in Table 1.4. Large clinical trials have established the superiority of combinations of antiretroviral agents over single agents for the management of HIV; currently recommended regimens are summarized in Table 1.5. Both the CD4+ T cell count and the plasma HIV RNA level predict the likelihood of progression to AIDS and death in HIV-infected patients, and this remains true in the era of HAART (Fig. 1.49); recent data, however, suggest that the HIV RNA level may be less helpful in deciding the timing of initiation of HAART. Moreover, the presence of clinical complications remains the most important criterion. Table 1.6 shows current recommendations for initiation of HAART. At least as important as HAART in reducing the morbidity and mortality of HIV infection has been the routine use of prophylactic antimicrobials to prevent the most common opportunistic complications (OC); current recommendations for OC prophylaxis are shown in Table 1.7.

With increasing numbers of patients receiving HAART, the limitations of these treatments have become apparent. Many antiretroviral agents have significant toxicities that

Table 1.4 Currently approved antiretroviral agents

<table>
<thead>
<tr>
<th>NRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Amprenavir</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Darunavir</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Fosamprenavir</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Lopinavir</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td></td>
<td>Ritonavir</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>hard gel</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>tablet</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Tipranavir</td>
</tr>
</tbody>
</table>

Fusion inhibitor
Enfuvirtide

NRTI: nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor

Fig. 1.49 Prognosis according to CD4+ cell count and viral load in the pre-HAART and HAART eras. The bars represent the probability of progression to AIDS or death according to CD4+ T cell count and plasma HIV RNA level before the HAART era (top) or at the time of initiation of HAART (bottom). (Adapted from Egger A, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002;360:119–29.)
### Table 1.5 Preferred regimens for HIV-infected patients beginning antiretroviral treatment

<table>
<thead>
<tr>
<th>Preferred components</th>
<th>Column A components</th>
<th>Plus</th>
<th>Column B components</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>Efavirenz</td>
<td></td>
<td>Tenofovir/emtricitabine (co-formulated)</td>
</tr>
<tr>
<td>Or</td>
<td>Zidovudine/lamivudine (co-formulated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI</td>
<td>Atazanavir + ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir + ritonavir (BID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir (co-formulated, BID)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative to preferred components</th>
<th>NNRTI</th>
<th>Abacavir/lamivudine (co-formulated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nevirapine</td>
<td>Or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Didanosine + (emtricitabine or lamivudine)</td>
</tr>
<tr>
<td>PI</td>
<td>Atazanavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir + ritonavir (QD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lopinavir/ritonavir (co-formulated, QD)</td>
<td></td>
</tr>
</tbody>
</table>

A regimen is constructed by selecting one component from column A (either an NNRTI or a PI) and one option from column B.

BID: twice a day; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; QD: once a day.
limit the ability of many patients to adhere to prescribed regimens. Certain nucleoside reverse transcriptase inhibitors (NRTIs), such as abacavir, and most non-nucleoside reverse transcriptase inhibitors (NNRTIs) can cause hypersensitivity reactions; several protease inhibitors (PIs) cause diarrhea and other gastrointestinal and hepatobiliary side-effects; certain NRTIs can cause anemia and bone marrow inhibition; the PIs indinavir and atazanavir produce indirect hyperbilirubinemia. Beyond these acute side-effects, several antiretrovirals are associated with chronic metabolic disturbances, including lipid abnormalities, fat distribution changes (Figs. 1.50, 1.51), mitochondrial toxicity, and hyperlactatemia. Additionally, exposure to antiretroviral agents leads to rapid selection of HIV mutants that are resistant to the effect of those agents. Several techniques are currently available that allow for detection of those mutants and help predict the alternative agents that may be active in a subsequent regimen. Recommendations for HIV resistance testing are shown in Table 1.8, and suggested regimens for salvage after failure of various initial regimens are shown in Table 1.9.

### Table 1.6 Recommendations for initiation of antiretroviral therapy in HIV-infected patients

<table>
<thead>
<tr>
<th>Clinical category</th>
<th>CD4+ cell count</th>
<th>Plasma HIV RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;200/mm³</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200–350/mm³</td>
<td>Any value</td>
<td>Offer treatment following full discussion of risks/benefits</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;350/mm³</td>
<td>&gt;100,000</td>
<td>Defer therapy in most cases; some clinicians will treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;350/mm³</td>
<td>&lt;100,000</td>
<td>Defer therapy</td>
</tr>
</tbody>
</table>

### Table 1.7 Guidelines for prophylaxis against selected opportunistic infections in HIV-infected patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication</th>
<th>First choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jiroveci</td>
<td>CD4+ T cell count &lt;200/mm³</td>
<td>Cotrimoxazole, 1 double-strength tablet qd</td>
<td>Dapsone, 100 mg qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Atovaquone, 1500 mg qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pentamidine, aerosolized, 300 mg q mo</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>TST (t) reaction &gt;5 mm, or prior positive TST without treatment, or contact with case of active tuberculosis</td>
<td>Isoniazid, 300 mg po, plus pyridoxine, 50 mg qd, x 9 mo</td>
<td>Rifampin, 600 mg, and pyrazinamide, 800 mg, qd x 2 mo</td>
</tr>
<tr>
<td>Isoniazid-sensitive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>IgG antibody to Toxoplasma and CD4 count &gt;100/mm³</td>
<td>Cotrimoxazole, 1 double-strength tablet qd</td>
<td>Dapsone, 50 mg po qd, plus pyrimethimine, 50 mg po q wk</td>
</tr>
<tr>
<td>Mycobacterium avium-intracellulare</td>
<td>CD4+ T cell count &lt;50/mm³</td>
<td>Azithromycin, 1200 mg q wk</td>
<td>Clarithromycin, 500 mg po bid</td>
</tr>
</tbody>
</table>
Fig. 1.50 Lipodystrophy, fat wasting. This patient had a history of non-Hodgkin’s lymphoma, which responded satisfactorily to treatment, and had an optimal response to HAART, with CD4+ T cell counts within normal levels. However, she developed marked body fat redistribution, which became disturbing enough for her to decide to interrupt HAART for almost 1 year. This image shows the loss of subcutaneous fat in the lower extremities, leading to the ‘masculine’ appearance due to the prominence of muscles and superficial blood vessels. Note the difference from AIDS wasting, in which muscle mass is also severely lost.

Fig. 1.51 Lipodystrophy, fat redistribution (same patient as in Fig. 1.50). This image shows the enlarged abdominal girth secondary to central fat accumulation, typical of lipodystrophy syndromes. Unlike usual obesity, in lipodystrophy the fat accumulation occurs intra-abdominally, as demonstrated by CAT scans and other imaging techniques. Several antiretroviral agents are associated with lipodystrophy, lipoatrophy and other metabolic syndromes; some of the most common culprits include the thymidine analogs stavudine and zidovudine and several protease inhibitors.

Table 1.8 Clinical circumstances in which HIV resistance testing is currently recommended

<table>
<thead>
<tr>
<th>Clinical setting/recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure during combination antiretroviral therapy</td>
<td>Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated</td>
</tr>
<tr>
<td>Suboptimal suppression of viral load after antiretroviral therapy initiation</td>
<td>Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated</td>
</tr>
<tr>
<td>Acute HIV infection, if decision is made to initiate therapy</td>
<td>Determine if drug-resistant virus was transmitted to help design an initial regimen or to change regimen accordingly (if therapy was initiated prior to test results)</td>
</tr>
<tr>
<td>Chronic HIV infection before therapy initiation</td>
<td>Available assays might not detect minor drug-resistant species. However, should consider if significant probability that patient was infected with drug-resistant virus (i.e. if the patient is thought to have been infected by a person receiving antiretroviral drugs)</td>
</tr>
</tbody>
</table>

Both genotypic and phenotypic HIV resistance tests are currently available. Interpretation of these tests is complex, and the criteria for HIV susceptibility to the various antiretrovirals are in permanent flux; therefore, seeking expert advice is usually recommended when managing patients with resistant viruses.
Conclusions

• HIV infection is one of the most explosive and widespread emerging infectious diseases in the recent history of mankind, having affected tens of millions of persons within 20 years of the beginning of the pandemic. The majority of cases continue to occur in the developing world.

• The pathogenesis of CD4+ T cell loss and other immune defects in HIV is incompletely understood, but it likely involves indirect mechanisms beyond the direct cytopathic effect of the virus. Non-specific immune activation is a prominent feature of HIV infection that is associated with disease progression.

• Many of the complications of HIV and AIDS tend to occur at specific stages of disease progression. The clinical presentation of these complications tends to become more atypical and severe with more advanced degrees of immunodeficiency.

• HAART has dramatically reduced the morbidity and mortality of AIDS, and should be offered to all patients with symptoms or advanced immunosuppression. Effective HAART regimens consist of combinations of antiretroviral agents, typically belonging to at least two different classes.

• Prophylactic antimicrobials can significantly reduce the morbidity of HIV infection. Specific prophylactic agents are recommended for different stages of HIV disease.

• Despite its extraordinary success, HAART is associated with severe toxicities and long-term metabolic complications, as well as with the emergence of resistant HIV strains, which limit its effectiveness in many patients.

Further reading


The current recommendations for antiretroviral treatment in the US, this document contains many useful tables that summarize the characteristics of all currently approved antiretrovirals.


A pivotal observational study that helped demonstrate the importance of CD4+ T cell level in determining the outcome of combination antiretroviral therapy.

Guidelines for preventing opportunistic infections among

The current recommendations for prophylaxis against opportunistic infections in HIV-infected patients. This document also contains current knowledge on criteria to discontinue prophylaxis after HAART-induced immune reconstitution.


An extremely useful document outlining the current guidelines for treatment of the various opportunistic complications of HAART, including side-effects, drug-drug and drug-food interactions, and dosing of drugs used to treat opportunistic infections in the presence of renal insufficiency.


Review of current concepts on the clinical use and techniques of antiretroviral drug resistance testing for HIV infection.


A classical paper that first showed the dramatic effect of HAART on HIV-related mortality.