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CHAPTER 139

Approach to the Patient with HIV and Coinfecting Tropical Infectious Diseases

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All … fall into one of two categories: infected with HIV or at risk for HIV infection (Mary E. Wilson[1])

INTRODUCTION

The morbidity, mortality, and social disruption due to the acquired immunodeficiency syndrome (AIDS) pandemic weigh disproportionately upon resource-poor areas of the tropics.[2] Consequently, the potential for interactions between human immunodeficiency virus (HIV) infection and other tropical infectious diseases is great.

Such interactions are marked by epidemiologic complexity. The AIDS pandemic is best described as the sum of discontinuous and overlapping epidemics of disease among populations of variable and varying risk (see Chapter 81). The predominant modes of transmission of HIV (perinatal, sexual, and parenteral) result in a bimodal distribution of disease, with peaks among young children and young adults. The risk of infection or disease due to tropical pathogens varies widely with differences in ecological, political, and socioeconomic conditions (including access to medical care); related specific host factors such as age of exposure, pregnancy, behavior, and nutrition; and host genetics. Disease due to a coinfecting pathogen may be due to primary infection, recurrent infection, or the reactivation of latent infection. For some pathogens, the risk factor responsible for the acquisition of HIV may also be the risk factor responsible for the acquisition of the coinfecting pathogen. As a consequence of this epidemiologic complexity, both the prevalence and the expression of coinfection are variable across ecological, economic, political, behavioral, and cultural divides.

EFFECTS OF HIV ON TROPICAL COINFECTIONS

Infection with HIV can influence the natural history of infection with other pathogens through: (1) facilitating infection; (2) altering the incidence of disease by increasing the ratio of disease to infection; (3) changing the presentation of disease; or (4) exacerbating the course of disease.[3] Such effects are primarily the result of the immunosuppression associated with HIV infection.

Abnormalities of immune function are found in essentially every cellular and functional compartment of the immune system in AIDS, although profound defects in cell-mediated immunity (CMI) appear to be of greatest clinical importance.[4] *In vitro* correlates include functional abnormalities of:

- CD4+ T cells, with progressive failure of proliferation, interleukin (IL)-2 and interferon-γ (IFN-γ) production,[5,6] dysregulated expression of molecules essential for T-cell/antigen presenting cell interactions;[6] abnormal activation-induced apoptosis,[7,8] preferential loss of Th17-polarized CD4+ T cells in the gastrointestinal (GI) tract;[9,10] and expansion of regulatory T cells that are potent inhibitors of immune responses both to self and to pathogens.[11,12]
- Monocyte/macrophages, with decreased chemotaxis and intracellular microbicidal activity and abnormal cytokine production.[4]
- Dendritic cells, with reduced ability to present antigen and activate T cells (along with efficient transfer of HIV infection to CD4+ T cells)[13] and with depletion of plasmacytoid dendritic cell populations.[14,15]
- CD8+ T cells, with decreased cytotoxic T-lymphocyte (CTL) function[4] and abnormal activation-induced apoptosis.[8]
- Natural killer (NK) cells, with decreased proliferation and IFN-γ production.[16]

Dysregulation of humoral immunity, marked by polyclonal B-cell activation, is also seen.[4] Functionally, abnormalities of CD4+ T-cell, macrophage, and dendritic cell function have been thought to be paramount to the suppression of CMI and the opportunistic infections (OIs) seen in patients with AIDS. In addition to direct effects of HIV infection, the immune system of HIV-infected people may also be compromised in clinically significant ways by profound nutritional and metabolic derangements (e.g., wasting or "slim disease"), therapeutic interventions (e.g., corticosteroids used for the treatment of *Pneumocystis* pneumonia), and immune abnormalities associated with secondary infections (e.g., suppression of CMI seen in visceral leishmaniasis (VL)).

The list of infectious diseases that are exacerbated by HIV coinfection[17] includes many that can be predicted from data demonstrating the important role of CMI in protection from the etiologic agent. Several pathogens for which immunity has been presumed to depend on CMI do not appear to be exacerbated by HIV coinfection, however. The HIV "experiment of nature" has caused a reexamination of the immunology of such "missing infections" in AIDS.[18]

HIV infection can also influence the therapeutic responses of patients with varied tropical infections. The ability to diagnose and monitor co-infection may be compromised by aberrant serologic responses, including false positives due to polyclonal B-cell activation, false negatives due to blunted antigen-specific antibody responses to newly acquired pathogens, and false serologic reversion after treatment in late HIV disease.[4] Diagnosis may also be hindered by unusual presentations of disease with coinfecting pathogens. Finally, a plethora of intercurrent pathologic conditions may lead to a dulling of Ockham's razor during disease evaluation in AIDS patients. A single pathogen, multiple pathogens, HIV infection, side effects of therapeutic drugs, or a combination of these may be responsible for the presenting complaints. Given the suboptimal response to the chemotherapy of many infections in the presence of profound immunosuppression, drugs may need to be given in greater numbers or for a longer duration. With many pathogens, in the absence of immune reconstitution resulting from highly active antiretroviral therapy (HAART), lifelong suppressive therapy is necessary. Drug therapy in the

HIV-infected patient may be complicated further by increased rates of drug allergy as well as by untoward drug interactions in the setting of polypharmacy.[19] Prophylaxis against coinfections may be compromised by substandard vaccination responses. Finally, the presence of HIV coinfection can complicate the public health consequences of tropical diseases. AIDS may increase the transmissibility of secondary infections and provide fertile soil for the development of drug resistance. Public health resources devoted to the AIDS pandemic may divert resources away from the control and prevention of other infectious diseases.

The presence of HIV coinfection can lead to disease of markedly greater incidence or severity (the standard definition of an OI)[17] with some tropical infectious diseases, such as leishmaniasis and American trypanosomiasis. Coinfection has also been demonstrated to have subtle effects on the course of disease with other tropical agents, such as *Schistosoma mansoni*. No robust alteration has been found in the natural history of many tropical infections, including most nematodes. With organisms in the latter groups, the current absence of evidence of significant effects of HIV on the expression of disease or the response to treatment should not be construed as strong evidence for the absence of such effects. Most research resources have been spent on understanding the clinical and epidemiologic manifestations of the HIV pandemic in industrialized countries, where tropical infectious diseases are under-represented. Where coinfections with HIV and endemic tropical diseases are marked by low prevalence, subtlety of interaction, diagnostic difficulty, or low research priority, the presence and significance of any interaction are likely to be missed. For example, despite the research priority among tropical infections accorded to malaria, the first significant interaction appreciated with HIV infection – the lack of a benefit of increasing parity in the control of malaria in pregnant women – was only discovered 15 years after the AIDS epidemic was recognized.[20] With less heavily studied pathogens, comparatively subtle interactions will likely emerge over time as research resources are appropriately directed.

Focusing on OIs may help to highlight some of the clearest data on the clinical expression of AIDS in the tropics. Of the more than 100 agents known to cause OIs in AIDS patients, several are classic tropical pathogens. These are mostly found among the intracellular protozoans, bacteria, and endemic fungi; there is a marked absence of metazoans. Overall, the clinical expression of AIDS in many resource-poor areas of the tropics appears to involve a different spectrum of OIs than those common in North America and Europe. In place of the high incidences of *Pneumocystis* pneumonia, disseminated *Mycobacterium avium*, and cytomegalovirus (CMV) found in the resource-rich north, the clinical expression of AIDS in much of the tropics has been marked by frequent tuberculosis (the most common serious AIDS OI in the world), chronic diarrhea, wasting, chronic fever without an obvious localizing source, and pulmonary disease.[21]

The contribution of predominantly tropical pathogens to these latter common syndromes is unclear, which illuminates the problems with much of the available data on HIV disease in the tropics. Understanding the spectrum of AIDS-associated OIs in any given area depends on the presence of adequate surveillance systems, which are often lacking in resource-poor regions of the tropics. In the presence of inadequate infra-structures, limited financial resources, and difficult access to medical care on the part of the socially disadvantaged, surveillance is likely to be sporadic and to involve mainly the sampling of subgroups of AIDS patients at late stages of disease.[20] Where resources are limited, diagnostic reporting is likely to be biased in favor of OIs that are inexpensive to diagnose (or misdiagnose).[20] Even the common impression that the progression of AIDS is more rapid in sub-Saharan Africa than in industrialized countries[22–25] rests on data that are less than robust.[26] A more rapid observed course (presumed due to a higher frequency and virulence of coinfection and problems of nutrition and access to medical care) may represent in large part a systematic bias in favor of later initial diagnosis of HIV infection and AIDS.[20,27] Conversely, it has been suggested that the burden of illness and mortality in early HIV disease (often unrecognized as such) due to high-grade pathogens, such as *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and the salmonellae, may rival that due to the OIs of late-stage AIDS in the tropics.[27,28]

HIV has shed light on many previously obscure human pathogens. Some, such as the enteric microsporidians, were unknown as agents of human disease prior to the AIDS epidemic. Others, such as *Cryptosporidium parvum*, were underappreciated as causes of disease in normal hosts until their prevalence in AIDS patients led to systematic study in normal hosts.

EFFECTS OF TROPICAL INFECTIONS ON HIV COINFECTION

There are theoretical and experimental reasons to believe that coinfection can significantly alter the course of HIV pathogenesis. The central role of ongoing viral replication in HIV pathogenesis is firmly established, and the set point concentration of plasma viremia correlates well with long-term clinical outcome.[29] It is presumed that any increases in viral replication have the potential for accelerating the course of disease. Efficient replication of HIV in $CD4^+$ T cells is dependent on cellular activation. Similarly, activation of macrophages and dendritic cells can stimulate HIV replication by increasing transcription factor binding to the HIV long terminal repeat region, enhancing transcription. Coinfecting pathogens can stimulate such immune cell activation either directly (e.g., stimulating signaling through Toll-like receptors[30] or upregulating transcription factor transactivation in coinfected immune cells) or indirectly (e.g., promoting the generation of proinflammatory cytokines or activating $CD4^+$ T cells as part of the adaptive immune response). Immune activation can also lead to upregulation of the expression of HIV coreceptors,[31] thereby facilitating the infection of fresh cells.

Immunologic responses to pathogens, as well as to purified vaccine antigens, clearly have the potential for enhancing the dynamic burden of HIV replication. *In vitro* studies with diverse pathogens have provided mechanistic support for this idea.[32–34] Experimental evidence has also suggested that immune activation-driven augmentation of the HIV viral burden can occur *in vivo*.[35–42] There is also circumstantial evidence that such immune activation may enhance HIV pathogenesis.[43,44] Both points remain somewhat controversial, however.[45] Whether immune activation-related increases in viral loads actually accelerate the pathogenesis of HIV may depend on whether the changes are transient (as with immunization or with treated acute infection) or chronic (as with untreated infection, or through a resetting of the set point of plasma viremia by a particular coinfection).[46]

Direct equation of immune activation with upregulation of HIV replication is simplistic, however. With $CD4^+$ T cells, the mechanism of activation appears to be critical to whether viral replication is induced or suppressed.[47–49] Furthermore, activation of proinflammatory cytokine production with positive effects on HIV replication goes hand in hand with activation of anti-inflammatory cytokine production, which can inhibit HIV replication. More generally, immune responses reliably induce counterregulatory responses that may well suppress HIV replication.[50,51] It thus should not be surprising that *in vitro* studies have provided mechanistic support for the ability of coinfecting pathogens to suppress HIV replication.[52–55] Indeed, whereas infection with some tropical pathogens (e.g., *Plasmodium falciparum*) has been shown to increase plasma HIV load, the overall effect of acute coinfection with some pathogens, including measles virus, dengue virus, and *Orientia tsutsugamushi*, may be a decrease in HIV viral load.[56–58] That said, measures of persistent immune activation, broadly taken, have been shown to correlate, independently of plasma viral load, with a steeper slope of $CD4^+$ T-cell depletion, disease progression, and mortality risk.[59,60] While the responsible mechanisms remain underdefined, coinfection may thus favor the progression HIV disease independently of effects on viral dynamics. In this context, the provocative finding that HIV infection leads to sustained systemic exposure to microbial products from the gut[61] (something that may well be abetted by tropical gut luminal and tissue pathogens) is potentially of special importance.

In addition to the viral sequelae of generalized immunologic activation, induction of specific alterations in the immunoregulatory environment of the host by ubiquitous tropical pathogens has been postulated to accelerate the course of HIV. Cross-regulating subsets of CD4+ T cells have been distinguished by their cytokine profiles and functional activities: Th1 cells (producing IFN-γ, among other cytokines) are important in classical macrophage activation, the development of CMI, and the generation of humoral responses involving complement-fixing antibody isotypes; Th2 cells (producing IL-4, IL-5, and IL-13, among other cytokines) are important in alternative macrophage activation, the generation of immunoglobulin E (IgE) responses, eosinophilia, mast cell responses, and atopy. The immunologic response to most helminthic parasites is dominated by Th2 cytokine production. Mouse models have shown that helminth-driven Th2 polarization can shift the immunologic response to heterologous antigens and pathogens from a Th1- to a Th2-dominant pattern, as well as significantly suppress CD8+ T-cell-mediated viral clearance.[62,63] Such responses have also been found to impair antigen-specific Th1 immune responses in both mice and humans.[62,64]

Chronic helminthic infections are widespread in the tropics. The resultant Th2 "priming" of the immune system may favor progression of HIV disease.[65] Several mechanisms have been postulated. First, a Th2-polarized immune system may directly suppress CD8+ T-cell-mediated anti-HIV responses.[63] Second, HIV appears to replicate preferentially in Th2 cells,[66] something that may well be due to increased expression of APOBEC3G, a cytidine deaminase with anti-HIV activity, in Th1 cells.[40,41] Third, T cells from HIV-seropositive people undergo abnormal activation-induced apoptosis,[7,8] which is thought to play a role in the depletion of both CD4+ and CD8+ T cells over time.[41] Th2 cytokines can amplify such activation-induced apoptosis.[67] Fourth, Th2 cytokines can upregulate HIV coreceptor expression by CD4+ T cells and monocyte/macrophages.[68] Of note, it has been demonstrated that peripheral blood cells from patients with intestinal helminth infection are more susceptible to in vitro infection with HIV than are cells from helminth-uninfected patients.[69,70] Fifth, diverse chronic helminth infections are associated with the development of strong immune counterregulatory responses, which may blunt heterologous anti-HIV immune responses.[43] Finally, both tissue trematodes (e.g., schistosomes) and luminal nematodes (e.g., geohelminths) are likely to have effects on gut mucosal permeability, something that may drive immune activation and disease progression by increasing systemic exposure to gut-derived microbial products.

There is thus clear biological plausibility for the hypothesis that endemic helminth coinfection can lead to acceleration of HIV disease course in the tropics. The hypothesis has been difficult to clearly address experimentally. An initial study in Ethiopia indicated that HIV viral load was significantly higher in individuals with various helminthic infections than in individuals without helminths, correlating positively with the parasite load as well as decreasing after elimination of the worms by antiparasitic treatment.[71] Subsequently, several similar studies from southern Africa failed to replicate these findings,[72,73] one study even reporting significant, transient increases in viral load after therapy for schistosomiasis.[45] A Cochrane Review[49] analyzed the only three randomized, controlled trials published to date on the effects of anthelminthic therapy on HIV disease progression in antiretroviral naïve patients: (1) a randomized trial of praziquantel for schistosomiasis, which found a significant benefit of treatment on plasma HIV-1 RNA load (a lack of an increase with treatment, compared with an increase in viral load in the absence of treatment), with a nonsignificant trend towards a beneficial effect on CD4+ counts in HIV-infected individuals;[50] (2) a randomized, double-blind, placebo-controlled, cross-over trial of diethylcarbamazine for bancroftian filariasis, which reported a decrease in plasma HIV-1 RNA load (and a nonsignificant trend towards a beneficial effect on CD4+ counts) with treatment;[51] and (3) a randomized, double-blind, placebo-controlled trial of albendazole for infection with diverse geohelminths (including hookworms, Ascaris, and Trichuris), which found a nonsignificant trend towards a beneficial effect of treatment on plasma HIV-1 RNA load, but a significant benefit of treatment on CD4+ T-cell counts, specifically in the subset of patients with Ascaris infection.[52] Pooling of data from

these three trials – a procedure that seems biologically tenuous – suggested significant (at least short-term) benefit of deworming on plasma HIV-1 mRNA load and CD4+ T-cell counts.[49] The overall hypothesis thus remains compelling. However, given the short-term follow-up, the variable biology and epidemiology of these different organisms, and the different interventions used in these trials, the clearest conclusions to be made are that more data on the subject are needed – something underscored by a recent alarming report that maternal helminth coinfection is associated with a significantly increased risk for mother-to-child transmission of HIV infection.[53]

Other effects of coinfection are perhaps more concrete. Tropical diseases may lead directly to an increased risk of infection with HIV. Treatment of the severe anemia induced by malaria has led to the HIV infection of countless children by transfusion.[74] Genital schistosomiasis, like other genital inflammatory conditions, appears to increase the efficiency of HIV transmission.[75]

CLINICAL SUSPICION OF COINFECTION

The basic biology of HIV; the progression, diagnosis, and treatment of HIV disease; and the epidemiology of HIV/AIDS in the tropics are discussed in Chapter 81. This chapter focuses on tropical infectious diseases that may be OIs in the HIV-infected patient. OIs that are common in the industrialized world are not discussed in depth unless there are compelling clinical or epidemiologic reasons for doing so. Multiple references are available that discuss these cosmopolitan OIs.[17,77–79] Further information on the specific organisms discussed here can be found in the cited pathogen-specific chapters.

The diagnostic, prophylactic, and therapeutic recommendations discussed here describe an approach to the HIV patient that is not limited by scarce medical resources. As such, like many strategies for dealing with HIV disease that have evolved in affluent industrialized countries (including high-technology diagnostics, and multidrug chemoprophylaxis), many of these recommendations may not easily be translated to resource-poor areas of the tropics.

PATHOGENS

Protozoan Infections

Malaria

Malaria (see Chapter 96) remains one of the most important infectious diseases in the world today.[55] Evidence from mouse and human studies suggests an important role for CD4+ T cells in protective immunity to blood-stage malaria. With large areas of shared endemicity, a medically significant interaction between HIV and malaria was thus expected and feared.[79] Initial studies were negative; falciparum malaria did not appear be an OI or to accelerate the progression of HIV disease.[80–84] However, follow-up studies have revealed complex bidirectional interactions between P. falciparum and HIV. (There remains little information about the interaction of HIV with P. vivax, P. malariae, P. ovale, or P. knowlesi.)

The epidemiology and immunobiology of P. falciparum are integral to this complexity. Severe disease and death due to P. falciparum occur in those lacking specific acquired immunity, something that only develops in the face of high rates of transmission and over time. With stable, heavy transmission, the greatest burden of disease occurs in young children, travelers, and pregnant women (the latter, for reasons discussed below); nonpregnant adults tend to be parasitemic in the absence of symptoms. With unstable or low transmission rates, the relationship between parasitemia and disease tends to be more direct, and the burden of disease falls more equally.[85] As might be expected, interactions between P. falciparum and HIV vary with malaria transmission dynamics.[86]

The first significant clinical effect of HIV on malaria was found in the setting of pregnancy in areas of high malarial endemicity. Despite age-dependent induction of immunity to severe disease in such areas, pregnant women have heightened vulnerablility to both asymptomatic and

symptomatic parasitemia;[87] the placental vasculature shields parasitized erythrocytes from the systemic immune response, allowing localized parasite replication. Placental parasitemia has been associated with low birth weight and increased infant mortality. Uteroplacental immune responses do restrict parasite replication, however, and the effectiveness of these responses increases in subsequent pregnancies under pressure of recurrent malarial exposure. Parity-acquired immunity to *P. falciparum* is delayed or impaired in the presence of HIV infection.[88,89] In turn, the beneficial effects (maternal, placental, and neonatal) of parity in the control of parasitemia during pregnancy are markedly attenuated in the face of HIV coinfection.[90–100] HIV infection is associated with increased rates and levels of peripheral and placental parasitemia, clinical malaria, and maternal anemia in pregnant women; and coinfection is associated with a higher risk of low birth weight, preterm birth, intrauterine growth retardation, and postnatal infant mortality. Although placental parasitemia is associated with increased placental HIV viral loads in coinfected patients,[90] it remains unclear as to whether this increases the risk of mother-to-child transmission of HIV. Conflicting results (enhancement, protection, and no effect) have all been published.[96,97,100] A World Health Organization (WHO) technical consultation has recommended that HIV-infected pregnant women at risk for malaria should use insecticide-treated bednets, along with (according to HIV stage) either intermittent preventive treatment with sulfadoxine/pyrimethamine (at higher doses than is recommended for nonpregnant populations) or daily trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis.[101,102]

In areas with unstable transmission of *P. falciparum*, HIV coinfection is a risk factor for severe malaria in both adults and young children.[101,103,104] In areas of heavy transmission, HIV infection is thought also to be a risk factor for severe malaria in children, although clear data are lacking.[105] In contrast, the presence of HIV coinfection seems to have only a modest impact on risk of parasitemia and clinical malaria in semi-immune adults in such areas. The risk does increase with decreasing CD4+ T-cell numbers, but the correlation is less strong than with other HIV-related OIs.[106–108]

As acquired immunity is important for therapeutic clearance of drug-resistant parasites, one might predict that HIV infection hinders the response to antimalarial therapy, particularly when suboptimal, in adults in areas of heavy transmission. Recent data support this.[109,110] HIV coinfection has also been found to be associated with an increased risk for reinfection after successful treatment for malaria.[111,112] Whether this is due to immunosuppression-associated compromise of immune responses to liver-stage parasites, or to an increased frequency of biting by *Anopheles* mosquitos in the presence of HIV-associated febrile diseases, is unclear.

Daily prophylaxis with TMP-SMX, recommended by WHO for all children and adults in sub-Saharan Africa with CD4+ T-cell counts <500/mm^3, led to a 95% decrease in febrile malaria episode frequency in a study in Uganda.[113] The fact that the addition of antiretroviral therapy was associated with a further >60% decrease in such episodes provides biological support for the link between HIV infection and vulnerability to disease with *P. falciparum*. The use of insecticide-treated bednets lowered the risk further.

HIV replication in peripheral blood cells is enhanced by exposure to *P. falciparum* antigens *in vitro*, in part through induction of TNF-α.[114] HIV-uninfected peripheral blood mononuclear cells challenged with malarial (sporozoite) extracts exhibit increased susceptiblity to HIV infection, and peripheral blood mononuclear cells from HIV-infected individuals exhibit higher levels of HIV replication after exposure to parasite antigens.[115] Increased HIV replication in dendritic cells has also been seen after *in vivo* infection with *P. chabaudi* of mice transgenic for the HIV genome.[116] As might therefore be expected, *P. falciparum* infection has been shown to be associated with increased HIV viral burden in peripheral as well as placental blood.[90,117] Malaria treatment has been associated with reductions in plasma HIV viral load, although the viral burden remained elevated compared to controls for the 4-week duration of the study.[117] Whether or not malaria-mediated increases in HIV replication accelerate the course of HIV disease remains to be determined.[118]

Pharmacological interactions between antiretrovirals and antimalarials have been recognized and studied *in vitro*.[119–121] A number of protease inhibitors (PIs) as well as the nonnucleoside reverse transcriptase inhibitors delaviradine and efavirenz inhibit hepatic cytochrome P450 enzymes. Principal effects are on the CYP3A4 isoform (with ritonavir being the most potent inhibitor), although the CYP2D6 isoform may also be affected.[122,123] Nevirapine and efavirenz cause secondary induction of CYP3A4, an effect of ritonavir and nelfinavir as well.[122] Most antimalarial agents are largely metabolized via P450 enzymes. Mefloquine appears to be no exception, although details remain poorly understood.[124] Proguanil and chloroquine metabolism appears to be largely by the CYP2C19 and CYP2D6 isoforms, respectively.[125–128] Chloroquine also undergoes appreciable renal excretion, whereas doxycycline largely avoids these pathways. However, it should be noted that these interactions are *in vitro* observations, and it is unknown whether these theoretical considerations have practical consequences *in vivo*. Published pharmacokinetic data suggest that: (1) there are no significant drug–drug interactions between nelfinavir or indinavir and mefloquine;[129] (2) ritonavir has minimal effects on mefloquine pharmacokinetics, whereas mefloquine suppresses ritonavir plasma levels;[130] and (3) atovaquone increases serum zidovudine (AZT) levels by approximately 30%, although AZT has no effect on the pharmacokinetics of atovaquone.[131] In summary, the actual pharmacokinetics are not easily predictable from theoretical considerations, and there is a paucity of data. Based on the current data, mefloquine, doxycycline, chloroquine, and malarone (atovaquone + proguanil) are likely to be safe and to retain efficacy for prophylaxis of sensitive strains of malaria.

Among other malaria treatment options, quinidine, quinine, and β-artemether (and possibly other artemesinin compounds) are all predominantly metabolized through CYP3A4 isoforms.[122] Large (more than threefold) increases in the area under the curve for quinidine are expected for ritonavir.[132] As a result, quinidine has been considered to be contraindicated for those on ritonavir,[132] and this likely applies to quinine as well. There are no actual clinical data, however. Whether there are clinically relevant effects of these PIs on the metabolism of artemisinin compounds (dependent at least in part on CYP3A4) remains unknown. Uncomplicated malaria can probably be safely treated with mefloquine (in regions of susceptible strains), or atovaquone/proguanil or artemesinins plus doxycyline. Use of quinine, quinidine, or artemisinin compounds remains essential for the parenteral therapy of severe chloroquine-resistant malaria. For those on ritonavir (and/or other PIs, delaviridine, or efavirenz), the normal loading dose of quinine or quinidine should probably be given, along with some reduction of the maintenance infusion dose. Obviously, careful monitoring needs to be done for the potentially fatal arrhythmic consequences of quinine/quinidine overdosage in this setting. Given the lack of data, however, underdosing may also be a potential problem. The "washout" period for the metabolic effects of ritonavir is thought to be 24–48 hours.

Recent WHO guidelines for malaria treatment recommend artemesinin-based combination therapy containing artemether and lumefantrine or artesunate and amodiaquine, mefloquine or sulfadoxine–pyrimethamine as first-line treatment for uncomplicated malaria.[133] In malaria-endemic regions, first-line treatment for HIV infection includes antiretroviral therapy containing efavirenz,[134] which has been found to elevate amodiaquine levels and half-life.[135–138] These findings raise concerns about the safety of the combination treatments in question. In addition, the rare occurrence of amodiaquine-related hepatotoxicity, along with reports of neutropenia in HIV-infected children treated with artesunate plus amodiaquine, are causes for concern.[139–141]

A higher incidence of allergic responses to sulfonamides makes pyrimethamine–sulfadoxine less attractive as a malaria therapy in HIV-seropositive patients, at least in North American populations.[142] Furthermore, Stevens–Johnson syndrome and related adverse mucocutaneous reactions to the long-acting sulfa compound, sulfadoxine, have contraindicated its use in malaria prophylaxis in developed countries.[143]

The presence of HIV infection alters the predictive value of fever in the empirical diagnosis of malaria. In areas with a high prevalence of both HIV and malaria, the common practice of empirically treating febrile

adults for malaria leads to gross overestimation and overtreatment of malaria.[108] Finally, treatment of severe anemia due to malaria is one of the most common reasons for blood transfusion in sub-Saharan Africa. Malaria thus provides an indirect but very important risk factor for the acquisition of HIV infection by children where the blood supply is not well screened for HIV.[144,145]

Babesiosis

A significant clinical interaction with HIV infection has been suggested for *Babesia microti* (see Chapter 97), raising the possibility that infection with other tropical babesial species may be a risk for AIDS patients. There are a handful of reported cases of *B. microti* infection in HIV-infected people.[135,136,146,147] Two occurred in splenectomized patients; in one, chronic low-level hemolysis due to *Babesia* prior to splenectomy was likely. Patients with intact spleens have presented with fevers of unknown origin in the face of CD4 counts less than 200/µL. Quinine plus clindamycin or atovaquone plus azithromycin both appear to have therapeutic efficacy in acute disease. In the face of HIV infection, chronic suppressive therapy appears to be indicated.[146] As with all vector-borne diseases, vector avoidance is the most efficient way to prevent disease. Significant interactions with HIV infection remain to be described for European bovine *Babesia* species (*B. bovis* and *B. divergens*) and the emerging agents of human babesiosis (WA1, CA1, MO1) in North America.

Leishmaniasis

With the exception of *Toxoplasma gondii*, *Leishmania* species (see Chapter 100) are the most common tissue protozoa causing OI in patients with AIDS. This is not surprising because CMI (in particular, Th1-mediated immune responses) is critical for protection from *Leishmania*, and competence of the Th1 axis of cellular response becomes increasingly compromised during the progression of HIV-related immunosuppression. *In vivo*, the overall loss of immunological control of parasite infection is reflected by often-aberrant manifestations of VL in AIDS, including peripheral parasitemia (found in more than 50%) and parasite dissemination to unusual body compartments.[148] An AIDS-related OI occurring at low CD4+ T-cell counts, leishmaniasis may be due either to primary infection or to the reactivation of clinically latent infection.[149,150] Although published data on the interaction of HIV and *Leishmania* focus largely on the effects of HIV on leishmanial infection and disease, there is also both *in vitro* and *in vivo* evidence that *Leishmania* can augment HIV replication.[151–153]

Leishmania normally require an arthropod vector, the sandfly, to move from its zoonotic cycle to human hosts. With certain species of *Leishmania* (*L. tropica* and *L. donovani*) and in some locations (e.g., Syria and India, respectively), an anthroponotic human-to-human cycle via the sandfly can exist. In situations in which intravenous drug use is practiced, transmission is simplified even further by direct person-to-person transfer via contaminated needles and syringes. Generally, however, leishmaniasis is a rural or periurban zoonosis.

The experience with VL complicating HIV/AIDS in Mediterranean countries indicates that many, perhaps most, of the leishmanial infections are acquired with HIV or after HIV infection has already occurred. The transmission of both agents that occurs by sharing of needles and syringes by intravenous drug users could theoretically be reduced by an aggressive program of education and provision of clean needles and syringes. An effective program of sandfly vector control will interrupt transmission from heavily infected human reservoirs to other humans as well as the more usual cycle of infected dogs to humans. Vector control is also the only way to prevent coinfection with *Leishmania* in those who acquire HIV sexually.

From the relatively high prevalence of latent leishmanial infection, it would appear that reactivation of latent infection could account for the increasing numbers of HIV–*Leishmania* coinfections; however, this concept is not always supported by epidemiologic evidence. A greater variability in zymodemes (enzyme markers) has been found in parasite isolates from HIV-infected than uninfected patients. In one series, five isolates were recovered from HIV-infected patients that had previously not been encountered in immunocompetent people with either VL or cutaneous leishmaniasis (CL).[154] The finding that certain strains of *Leishmania* typically causing cutaneous disease are being recovered from the bone marrow of coinfected patients could support either the primary or the reactivation hypothesis.[155] Normally, the age distribution of VL caused by *L. donovani* includes adults as well as children. In contrast, VL due to *L. infantum* affects children predominantly, often age 5 years or younger. In Spain, where intravenous drug use accounts for the majority of HIV–*Leishmania* coinfections, the age distribution of VL has been reversed, with most cases occurring in young adult males.[156] The fact that half of patients have demonstrable organisms in peripheral blood smears[157] and the fact that sandflies can readily be infected by feeding on coinfected patients[158] provide evidence for an additional anthroponotic cycle of transmission in this setting.[155] In summary, although reactivation of latent leishmanial infection is difficult to exclude, increasing evidence – in southern Europe, at least – favors primary infection by certain strains of *Leishmania* as the main mechanism for coinfection with HIV/AIDS.

With the spread of the HIV pandemic, there is increasing epidemiological overlap of areas in which HIV and leishmaniasis occur. Cases have been reported from approximately 40 countries, although the bulk of cases have been reported from southern Europe.[148–150,155,159,160] Of note, relatively few cases of American mucocutaneous leishmaniasis have been recognized in HIV-infected subjects.[161,162] The propensity for disseminated disease in the presence of HIV appears to be limited to certain species of *Leishmania*. The bulk of the information on VL complicating HIV infection involves *L. infantum* in the Mediterranean region. Presumably, the ability to visceralize under the influence of HIV also applies to *L. donovani* in southern Asia and Africa and to *L. chagasi* in Latin America; however, documentation for this is still somewhat meager, one of the possible reasons being the poor overlap between geographic distribution of leishmaniasis caused by these species and the distribution, as well as prevalence, of HIV infection. The species of *Leishmania* that cause CL have been implicated only rarely as OIs in HIV/AIDS. In one instance, *L. braziliensis* was recovered from the bone marrow of a patient with a CD4+ T-cell count of less than 10/µL,[163] but the main clinical picture in this case, as well as in others,[164–166] including a patient infected with *L. major*,[167] has been one of multiple cutaneous lesions resembling diffuse CL. Diffuse CL has also been reported as part of the immune reconstitution inflammatory syndrome (IRIS).[168,169]

A febrile illness of longer than 2 weeks' duration in an HIV-infected person with a lifetime history of travel to *Leishmania*-endemic regions of the world should raise suspicion of leishmaniasis complicating HIV infection. If the patient is an intravenous drug user, travel to southern Europe, especially Spain, France, and Italy, would be particularly pertinent. Clinical diagnosis of VL in *Leishmania*–HIV coinfected people may be difficult. Only 75% of HIV-infected patients, as opposed to 95% of non-HIV-infected patients, exhibit the characteristic clinical pattern, namely fever, splenomegaly, and hepatomegaly.[149,150,155,160,170] With increasing immunosuppression, clinically evident ectopic localization of parasites becomes common.[171] Gastrointestinal, laryngeal, pulmonary, and peritoneal involvement has been reported.[171–178] Single and multiple cutaneous forms and/or mucosal and mucocutaneous lesions have also been described in AIDS patients worldwide.[166,173,179]

In immunocompetent people, serological tests have been very useful in the diagnosis of VL because B-cell activation is prominent, with large amounts of both specific and nonspecific antibody being produced. In contrast, approximately 50% of coinfected patients lack detectable antibody levels.[142,149,150,170] The situation may be different in instances in which leishmanial infection precedes HIV infection and the impaired immune responses that ensue. Gradoni and associates[180] suggested that this type of serologic data could be used as an indicator of the sequence of acquisition of the two infections. Support for this concept is provided by a report from Ethiopia of seven cases of VL with HIV coinfection, all with highly elevated antileishmanial antibody titers.[181] All patients had lived for many years in a leishmaniasis-endemic area of Ethiopia.[181] The

recombinant antigen rK-39 appears to be highly sensitive and specific for immunodiagnosis of VL due to *L. donovani* and *L. chagasi* in patients without complicating HIV infection; however, the sensitivity of rK-39 for immunodiagnosis of cutaneous cases from Turkey was greatly reduced compared with most cases of VL.[182] The utility of rK-39-based diagnostics is not clear in HIV-seropositive people. The peripheral parasitemia displayed by many HIV-coinfected individuals allows the detection of parasites from the blood in approximately 50% of cases. Cultures and polymerase chain reaction (PCR) of buffy-coat preparations are positive in 70% and up to 100%, respectively.[149,150,183]

There is abundant evidence that successful treatment of leishmanial disease, regardless of the drugs used, ultimately requires intact CMI. The coinfected patient is the victim of a double insult to the immune system. VL is associated with antigen-specific T-cell unresponsiveness[184] and dysfunctional cytokine responses.[185] This situation is further compounded by the immunologic abnormalities associated with HIV infection.

Therapy for VL in the face of HIV coinfection remains controversial, largely due to a lack of firm data. The same drugs used for treatment of VL in normal hosts (including pentavalent antimonials and amphotericin B preparations) have utility in the treatment of coinfected patients, albeit with significantly less efficacy.[170] Amphotericin B is a conventional drug for all forms of leishmaniasis, including visceral disease. Liposomally encapsulated amphotericin has the theoretical advantage of being targeted to macrophages, host cells for leishmanial parasites. Between 40% and 65% of coinfected patients have initial parasitological cure after treatment with pentavalent antimonials, amphotericin B deoxycholate, or amphotericin B lipid complex.[170,186,187] Among these options, treatment with lipid formulations of amphotericin B appears to have similar efficacy, but less severe toxicity, than the other drugs. However, the experience with lipid formulations of amphotericin B in coinfected patients is limited. These lipid formulations are also quite expensive. Miltefosine, an oral agent that is safe and effective for the treatment of Indian patients with VL,[188] has shown promise in early compassionate-use treatments of VL in HIV-infected subjects.[189]

Even with initial cure, relapse is predictable, occurring in up to 80% of coinfected individuals within 1 year.[169,170,186,190,191] The optimal drug for secondary prophylaxis remains unclear. Pentamidine given once every 3 or 4 weeks[192] and liposome-encapsulated amphotericin every 2 weeks[193] or 3 weeks[191] have been used.

The fact that significant reductions in the incidence of AIDS-related VL were seen in southern Europe after the advent of HAART,[194,195] along with the fact that HAART-related immune reconstitution has allowed secondary prophylaxis for other OIs to be stopped, has raised hope that HAART will allow for safe discontinuance of secondary prophylaxis for VL.[196–198]

American Trypanosomiasis (Chagas Disease)

American trypanosomiasis (see Chapter 99), is a well-recognized OI in AIDS.[199] The causative organism, *Trypanosoma cruzi*, and its triatomine vector are widely distributed from the United States to Chile and Argentina. Because the cases of HIV-related Chagas disease reported to date largely represent reactivation of chronic infection during the course of HIV-induced immunosuppression and not primary infection in the face of AIDS (not surprising given the differing patterns of epidemiological risk for these infections: largely rural for *T. cruzi* and largely urban for HIV), this OI can be expected to appear outside these geographic bounds. It should be noted that activation of latent *T. cruzi* infection, as well as exacerbated primary infection (transmitted by blood transfusion), is also well described in the face of the iatrogenic immunosuppression used for solid-organ transplantation and therapy for hematological malignancies.

Clinical *T. cruzi* reactivation in the face of HIV coinfection appears to occur largely in those with CD4$^+$ T-cell counts less than 200/µL. Clinically, such reactivation most commonly involves the central nervous system (CNS).[199,200] *T. cruzi* was probably late in being recognized as an opportunistic pathogen in this setting because the most prominent

features of disease are similar to those of toxoplasmic meningoencephalitis. Enlargement of hemorrhagic foci can produce mass effects simulating brain tumors. Lesions are often multiple, with computed tomographic (CT) scans and magnetic resonance imaging (MRI) showing ring enhancement and preferential involvement of the white matter. Toxoplasmic encephalitis may coexist in the same patient.[201] The cerebrospinal fluid (CSF) findings include a slight pleocytosis, increased protein, slightly decreased glucose in some patients, and the presence of trypanosomes. Histologically, the brain lesions show necrotic foci with hemorrhage and infiltration of inflammatory cells. Amastigote forms of the parasite are abundant in glial cells and macrophages and only occasionally in neuronal cells. Myocarditis is a common autopsy finding in those dying of AIDS-related *T. cruzi* meningoencephalitis.[198] Such myocarditis is often clinically silent. Clinical manifestations, when present, involve arrhythmias and congestive heart failure.[199,202,203] Diagnosis of reactivated *T. cruzi* infection depends, first, on considering the possibility based on the geographic origin of the patient, and on an appreciation of the clinical picture. If neurologic signs are present, performing a CT scan or MRI is key.[204] The imaging pattern of CNS *T. cruzi* infection is indistinguishable from that of toxoplasmic encephalitis. Direct microscopic examination of centrifuged sediment of CSF will often show motile trypanosomes. If fever and other systemic signs are present, direct examination of the buffy coat from the microhematocrit tube may also show motile trypanosomes. Since serum antibodies to *T. cruzi* indicate previous infection with the parasite, this test is only useful for ruling out reactivated infection if it is negative. If other tests are inconclusive, biopsy of a brain lesion to demonstrate characteristic organisms can be done. PCR on blood or CSF requires research laboratory facilities.

Clinically, differentiating HIV-related reactivation of Chagas disease from chronic chagasic disease may be difficult. HIV-related reactivation is associated with high parasitemia, however, whereas the parasitemia of chronic disease is very low.[205] Indeed, even in the absence of overt, clinical reactivation, chronic Chagas disease is associated with a higher percentage and level of parasitemia in those coinfected with HIV (independent of CD4 count) than in HIV seronegatives.[206] The effects of coinfection appear to be bidirectional. HIV viral load has been documented to increase simultaneously with an asymptomatic increase in *T. cruzi* parasitemia, returning to baseline in the face of successful antiparasitic treatment.[207] Nifurtimox and benznidazole, both of which have moderate antitrypanosomal activity, are the standard drugs recommended for treatment of Chagas disease. However, there is not enough experience to evaluate the effectiveness of these drugs in the treatment of *T. cruzi* infections complicating HIV/AIDS, especially in cases with meningoencephalitis. No information is available on the penetration of nifurtimox and benznidazole into the CNS, and the survival time of reported cases of coinfection has been short. A patient reported by Nishioka and coworkers[208] survived for 92 days, with disappearance of trypanosomes from the blood and CSF as well as clearance of a brain lesion while being treated with benznidazole at a dose of 8 mg/kg/day for 80 days. Clinical improvement and reduction in size of a brain lesion were attributed to treatment with benznidazole plus, later, itraconazole and fluconazole in another patient with coinfection who survived for at least 6 months.[209] Itraconazole and ketoconazole have been used and are reported to have reduced parasitemia in one case each,[210] but both cases succumbed to HIV infection. Although there is no other reported experience with the use of itraconazole or fluconazole in the treatment of American trypanosomiasis in humans, itraconazole was reported to be very effective in experimental infections.[211] It has been recommended that treatment of *T. cruzi* infection in the setting of HIV be started early in the reactivation process, when parasitemia is detectable, but before irreversible end-organ damage has occurred.[207] Such a strategy would hinge on serological identification of those at risk, something indicated in all HIV-infected individuals with appreciable risk of *T. cruzi* infection. Although data are lacking, it should be noted that immunological reconstitution through HAART therapy is likely to provide considerable prophylactic and therapeutic benefit in this disease.

African Trypanosomiasis

No significant interactions between the agents of African trypanosomiasis (see Chapter 98) and HIV have been delineated. Although T-cell and macrophage responses are not thought to be important in the protective host response to trypanosomiasis, trypanosomiasis can suppress cellular immune responses, so a biologic interaction between the two is plausible. No significant epidemiologic association between *Trypansoma brucei gambiense* and HIV has been found.[212–215] Whether HIV alters the clinical course of either West or East African trypanosomiasis is unclear.[214] There is anecdotal evidence that HIV may complicate the therapy of West African trypanosomiasis, however. Of 18 patients treated with melarsoprol in a rural hospital in the Congo, all 14 HIV-negative patients recovered, whereas 3 of 4 HIV-positive patients died during treatment (likely due to treatment-related encephalopathy) and the fourth failed to respond to therapy.[216]

Other Trypanosomatids

In addition to the two genera, *Leishmania* and *Trypanosoma*, known to cause disease in humans, the Trypanosomatidae family includes other genera that parasitize other vertebrates, insects, and plants. There have been three reports of HIV-infected individuals presenting with symptoms typical of VL in which ultrastructural, isoenzyme, and/or kinetoplast DNA analyses of the isolated lesional parasites have indicated that the responsible organism actually belongs to one of these latter genera.[217] The strong implication is that HIV-related immunosuppression can render humans vulnerable to normally nonpathogenic lower trypanosomatids.

Toxoplasmosis

Toxoplasma gondii is a ubiquitous parasite of mammals throughout the world (see Chapter 103). Latent infection lasts for the lifetime of the host. Maintenance of latency is dependent on CMI responses. Reactivation of latent infection is common with increasing immunosuppression in AIDS. The principal manifestation of such reactivation, toxoplasmic encephalitis, is thus a common OI in AIDS patients throughout the world. The incidence of toxoplasmic encephalitis is proportional to the prevalence of latent infection in the population at risk of or with AIDS.[218] In the United States, the rate of latent infection varies between 10% and 40%; in Paris, the rate is 90%.[218] Acquisition of *Toxoplasma* infection is age-dependent, but there is wide variation in infection rates even over narrow geographic areas.[219,220] Prevalence rates in the tropics vary from 0% to 90%, with most measured communities falling in a broad middle range.[221–227]

In the United States, prior to the advent of HAART, one-third of *Toxoplasma*-seropositive AIDS patients developed toxoplasmic encephalitis in the absence of prophylaxis,[228] 90% of such cases were in patients with less than 200 CD4$^+$ T cells/μL, and 70% in those with less than 100 CD4 T cells/μL.[229] The prevalence of toxoplasmic encephalitis in AIDS patients in the tropics is unclear, but the burden is thought to be immense and underdiagnosed. Autopsy series that have included examination of the brain have suggested disease prevalence rates in late-stage AIDS patients of 15% in Abidjan, Côte d'Ivoire,[230] 25% in Mexico City,[231] and 36% in Kampala, Uganda.[232]

The presumptive diagnosis of toxoplasmic encephalitis is based on clinical presentation, positive *Toxoplasma* serologies, and characteristic neuroradiologic features.[233] A final clinical diagnosis is made based on the clinical and radiographic response to specific chemotherapy. Less common manifestations of toxoplasmosis in AIDS include pneumonia, retinochoroiditis, myocarditis, orchitis, and gastrointestinal involvement. Excellent reviews on *Toxoplasma* in AIDS provide information on the clinical management of this cosmopolitan OI.[17,76,78,234]

Five percent of toxoplasmic encephalitis occurs not as reactivation but as an acute infection.[228] Preventing the transmission of *T. gondii* to *Toxoplasma*-seronegative, HIV-infected people has two facets: (1) avoiding the ingestion of tissue cysts of other intermediate mammalian hosts (i.e., cooking meat well); and (2) avoiding the oocysts of the definitive host, the cat. Avoiding cat feces in and around dwellings is probably not sufficient because the oocysts are viable for up to 18 months in moist soil. Contamination of fresh vegetables may be a common method of human infection, and such foodstuffs should probably be washed well or cooked or both.

Primary prophylaxis (TMP-SMX is preferred)[235] should be taken by all *Toxoplasma*-seropositive HIV patients with a CD4$^+$ T-cell count less than 100/μL. It is safe to discontinue both primary and secondary prophylaxis after HAART-related immune reconstitution (sustained CD4$^+$ T-cell counts >200/μL).[76–78]

Free-Living Amebae

Free-living amebae of the *Acanthamoeba* and *Balamuthia* genera (see Chapter 101) are rare causes of opportunistic encephalitis and cutaneous disease in late-stage AIDS. Most case reports have been from the United States, but the worldwide environmental distribution of these ubiquitous protozoans and the fact that diagnosis is often postmortem suggest that underdiagnosis is widespread in the tropics and elsewhere. *Acanthamoeba* and *Balamuthia* have been isolated from soil, water (including tap water, bottled water, chlorinated pools, and natural sources of fresh and seawater), and air throughout the world.[236] The isolation of *Acanthamoeba* from the nasopharynx of healthy adults indicates that these organisms may be common constituents of normal flora.[237] Cellular immunity, along with antibody and complement, appears to be critical for protective immunity.[238] Invasive disease occurs in the immunocompromised and debilitated.[239] Occasionally, encephalitis with *Balamuthia mandrillaris* has occurred in apparently normal hosts.[240–242]

Granulomatous amebic encephalitis (GAE), a subacute to chronic disease of compromised hosts caused by multiple species of *Acanthamoeba* as well as *B. mandrillaris*, generally causes death in weeks to months. Clinical and pathologic data, along with animal models, suggest that the pathogenesis involves hematogenous dissemination to the brain from initial respiratory (or perhaps cutaneous) sites of infection.[239] Pathologic changes, in the form of necrotizing granulomatous inflammation, are found predominantly in the posterior neuraxis.

More than 20 cases of GAE, due to a variety of species, have been reported in AIDS patients.[239,243–253] Disseminated cutaneous disease (subacute granulomatous dermatitis) has been a feature of many of these cases and has preceded clinical cerebral involvement by weeks or months in some. Subacute granulomatous dermatitis has been the sole manifestation of invasive disease in some patients.[254–258] CD4$^+$ T-cell counts in HIV-infected individuals with GAE have been reported to be less than 250/μL (median, 24/μL) at the time of presentation. Where CD4 counts have not been reported, the histories reveal clinical evidence of late-stage AIDS.[236,239]

In AIDS patients, GAE is marked by a more rapid course (with death in 3–40 days)[239] and a paucity of well-formed granulomas in comparison to other hosts with the disease.[239,257] Symptomatic involvement of the nasopharynx, paranasal sinuses, or the skin prior to development of GAE is common in AIDS patients.[239,259] Cutaneous lesions are usually nodular, with subsequent enlargement, ulceration, and metastatic spread. Such lesions can be quite pleomorphic (pustules, plaques, eschars, and cellulitis), however, and have been confused with cat-scratch disease, cryptococcosis, sporotrichosis, bacillary angiomatosis, mycobacterial infections, and vasculitis.[239] The most common presentation of cerebral disease is that of fever and headache.[239,256] Focal neurologic deficits and profound changes in mental status are also frequent. Neuroradiologic findings mimic those of toxoplasmic encephalitis, with multiple enhancing mass lesions and surrounding edema. CSF findings are quite variable.[239,256]

A high index of suspicion and tissue or microbiologic diagnosis are key to the antemortem identification of GAE. Wet mounts of CSF are occasionally useful (perhaps less useful in *Balamuthia* infection).[259] CSF examination generally reveals lymphocytic pleocytosis with mild to severe elevation ($\geq$1000 mg/dL) of protein and normal or low glucose. Both

trophozoites and cysts can be found in tissue biopsies. Cysts have been mistaken for the sporangia of *Rhinosporidium* or *Prototheca* or for cryptococci; trophozoites have been mistaken for macrophages.[259] *Acanthamoeba* can be isolated by culture on *Escherichia coli*-seeded nonnutrient agar or in tissue culture medium.[239,256] Identification of species (and even differentiation of *Acanthamoeba* from *Balamuthia*) is not possible morphologically. Immunofluorescence techniques can differentiate *Acanthamoeba* to the group level in tissue section or with cultured organisms.

Treatment of disseminated disease due to these organisms is difficult in any host. No chemotherapeutic regimen is clearly efficacious. Miltefosine showed some efficacy in a recently reported case.[260] Other agents with possible clinical utility in combination therapy include pentamidine, 5-fluorocytosine, sulfamethazine, sulfadiazine, fluconazole, itraconazole, ketoconazole, macrolides, phenothiazines, and rifampin.[239,252,254,255,261] There may be value in testing clinical isolates for drug sensitivities. With isolated cerebral lesions, there may be a role for surgical excision.[253]

A case of primary amebic meningoencephalitis due to an apparently newly recognized ameba and not associated with thermally polluted water was reported in a patient with late-stage AIDS in Spain.[262,263]

Enteric Coccidiosis (*Isospora, Cryptosporidium*, and *Cyclospora*)

A trio of coccidian protozoa – *Isospora belli, Cryptosporidium* spp., and *Cyclospora* (*Eimeria*) *cayetanensis* – are all prominent causes of self-limited, small-bowel diarrhea in immunologically normal hosts as well as causes of chronic, severe disease in the face of HIV coinfection. All are cosmopolitan infections. Infection with a fourth organism, *Sarcocystis hominis*, responsible for both enteric and disseminated coccidioisis in humans, has been reported as a coinfecting organism in only a handful of cases with HIV infections.[264]

Cryptosporidium spp. (see Chapter 94)

In addition to the most common human pathogen within this genus, *C. hominis*, a variety of zoonotic species also infect humans, including *C. parvum, C. canis, C. felis, C. meleagridis*, and *C. muris*.[265–267] Zoonotic species may cause more severe human disease and may occur more commonly in immunocompromised people. Because of the high prevalence of disease and the lack of effective specific treatment, cryptosporidiosis is a particularly common and severe problem as an OI throughout the world. Chronic infection and disease are most frequent with CD4$^+$ T-cell counts less than 180/μL[268] and are associated with increased mortality.[269–271] The use of HAART therapy has led to a decreasing prevalence of cryptosporidial disease in HIV-infected individuals; however, rates of diarrhea in HIV-infected individuals associated with *Cryoptosporidium* spp. in developing countries remain high, up to 83% in symptomatic and 57% in asymptomatic individuals.[272–274]

Four clinical syndromes of cryptosporidial diarrheal disease in patients with AIDS have been limned: (1) chronic diarrhea (36%); (2) cholera-like disease (33%); (3) transient diarrhea (15%); and (4) relapsing illness (15%). The severe end of the spectrum is seen largely in those with CD4$^+$ T-cell counts less than 180/μL.[275,276] Less commonly, extraintestinal sites are secondarily involved, including biliary tract, stomach, pancreas, lung, paranasal sinuses, and middle ear.[275–278] Of these, biliary tract involvement (presenting with right upper-quadrant pain, nausea, vomiting, and fever) represents the most common, clinically important site, being found in up to one-fourth of patients with AIDS-related intestinal disease prior to the use of HAART.[279] Individuals with CD4$^+$ T-cell counts less than 50/μL are at a particular risk for development of symptomatic biliary disease.[279] No antimicrobial agent has demonstrable, consistent efficacy in HIV-related cryptosporidiosis. Immune reconstitution with HAART should be pursued,[280–283] along with supportive treatment with fluids, nutrition, and antimotility agents.[76–78]

Isospora belli (see Chapter 95)

Disease due to *Isospora* is less cosmopolitan than that due to *Cryptosporidium*, being most common in tropical and subtropical areas.[284] In some regions, it has been reported to be one of the most common parasitic etiologic agents of diarrhea in HIV-infected individuals, rivaling rates for *Cryptosporidium*.[285–287] Rates of infection have fallen dramatically with the introduction of HAART.[288] Isosporiasis usually presents with chronic watery diarrhea and weight loss, with or without vomiting, abdominal pain, and fever.[288] Invasion of gallbladder tissue, similar to that described with *Cryptosporidium*, has been described, along with disseminated involvement of mesenteric and tracheobronchial lymph nodes, in the setting of HIV coinfection.[289,290] Prominent tissue eosinophilia of the involved lamina propria is often present.[284] TMP-SMX provides effective therapy.[291] Pyrimethamine (with leucovorin) provides a second option.[292] Clinical response is usually rapid, but relapses are common. In the absence of immune reconstitution, suppressive therapy is indicated.[76–78]

Cyclospora cayetanensis (see Chapter 95)

The clinical picture of enteric infection with *C. cayetanensis* in AIDS appears to be similar to that due to other coccidia.[293] Biliary tract involvement – manifested as right upper-quadrant pain, elevated alkaline phosphatase, and thickened gallbladder by ultrasound – has also been described in *Cyclospora* infection.[294] Thus, all three human enteric coccidia are capable of invading the gallbladder. As with isosporiasis, cyclosporiasis in AIDS is treatable with TMP-SMX.[293] Follow-up suppressive therapy is indicated.[76–78]

Microsporidiosis

Microsporidia are intracellular protozoans that, due to HIV and AIDS, have emerged from their relative obscurity as pathogens of insects, fish, and laboratory animals to occupy a new role as important OIs of humans.[295] These cosmopolitan emerging pathogens of the immunosuppressed (including *Enterocytozoon bienusi, E.* (*Septata*) *intestinalis, E. cuniculi, E. hellem*, as well as pathogens from several other genera) are considered in Chapter 102.

Other Protozoa

Entamoeba histolytica

This intestinal parasite (see Chapter 92) was initially associated with HIV because of its high prevalence in men who have sex with men (MSM), and seroprevalance studies continue to indicate a high exposure rate in MSM, although the significance of this observation remains unclear.[296–299] Despite considerable evidence that immunity in amebiasis requires the participation of CMI, there is no evidence that patients with HIV infection or AIDS are more likely to develop invasive disease.[297]

Giardia lamblia

As with *E. histolytica*, a high prevalence of infection with *G. lamblia* (see Chapter 93) was found in the 1980s among MSM.[300] A study of MSM performed at that time revealed no increase in prevalence or severity of giardiasis in patients with AIDS.[301] Since then, no evidence has been found of a significant effect of HIV coinfection.[298] Although some studies have indicated a higher prevalence of giardiasis in HIV seropositives, this has not been a consistent finding.[302] Therapy of giardiasis in people with AIDS is usually successful. Some patients, immunocompromised as well as immunocompetent, are refractory to standard therapeutic regimens for giardiasis. It may well be that such refractoriness to standard therapy is found more commonly in the face of HIV coinfection.[303]

Blastocystis hominis

Controversy continues to exist as to the role of this organism as a cause of diarrheal disease in either immunocompetent patients or HIV-infected people.[302,304]

Balantidium coli

No information is available as to whether this organism can serve as an OI in HIV-infected people.

Helminthic Infections

Trematodes

There is no evidence that any trematode infection is more severe or difficult to treat in the face of HIV coinfection. More subtle interactions have been explored in schistosomiasis (see Chapter 122). A study of car washers working on the shores of Lake Victoria in Kenya, a population with a high intensity of exposure to *Schistosoma mansoni* and an HIV seroprevalence of approximately 30%, has provided insights into the bidirectional effects of coinfection.[305] The CD4$^+$ T-cell-dependent granulomatous response to schistosome eggs has been shown to be important in egg migration from venules to the lumen of the intestine in mouse models of disease.[306] As might thereby be expected, a significant suppression of egg excretion efficiency, controlled for the degree of infection, was found in *S. mansoni*-infected patients in the presence of HIV coinfection and low CD4$^+$ T-cell counts.[307] Although successful therapy of *S. mansoni* infection with praziquantel may depend on the host antibody response, praziquantel was efficacious in treating schistosomiasis in this HIV-infected cohort.[308] Given that schistosome infection likely preceded HIV infection in these individuals, whether praziquantel will have equal efficacy in individuals infected first with HIV remains an open question. In this context, a study from Kenya reported that treatment with a standard regimen of praziquantel in coinfected individuals resulted in normal kinetics of reduction in egg excretion, but a slower decline in serum levels of an adult worm antigen – interpreted to indicate less efficient killing of adult worms.[309] Notably, despite similar responses to therapy, individuals with HIV coinfection and low CD4$^+$ T-cell counts showed increased susceptibility to reinfection after therapy,[310] something that appeared to correlate with blunted immunological responses to successful drug therapy (and the resultant release of parasite antigens) in such individuals.[311] A study of HIV/*S. haematobium* coinfection in Zambia mirrored these findings: (1) coinfected individuals had lower egg excretion; and (2) praziquantel retained efficacy in the face of coinfection.[312] No alteration in resistance to reinfection with *S. haematobium* was seen in the face of HIV infection, but CD4$^+$ T-cell counts were not performed in this cohort that lacked clinically evident HIV disease. It thus remains possible that, as with *S. mansoni* infection, resistance to reinfection with *S. haematobium* is decreased with progression of HIV/AIDS.

As for the effects of schistosomiasis on HIV, both female and male urogenital schistosomiasis, like other inflammatory genital diseases, are thought to increase the risk for HIV transmission.[309,313–317] Schistosomiasis is also a prime example of a chronic tropical infection that has been postulated to enhance the pathogenesis of HIV. Schistosome infections act as powerful inducers of Th2 polarization and immune counterregulatory responses in both mice and humans.[309,318–320] Such infections are also likely to alter gut mucosal permeability and systemic exposure to gut-derived microbial products. As noted above, following on the heels of negative studies, a recent randomized trial of praziquantel for schistosomiasis found a significant benefit of treatment on plasma HIV-1 RNA load, along with a nonsignificant trend towards a beneficial effect on CD4$^+$ counts in HIV-infected individuals.[321]

The literature appears to be silent as to whether there are any significant interactions between pulmonary, hepatic, or intestinal trematodes and HIV.

Cestodes

A few unusual manifestations of cestode infection have been reported in AIDS patients. A rapidly expanding, invasive, and ultimately lethal abdominal mass in a patient with a CD4$^+$ T-cell count less than $100/\mu L$ was found, by ribosomal DNA amplification and sequencing, to be due to *Hymenolepis nana*.[322,323] Whether this represents merely the fortuitous concurrence of an unusual pathologic finding with dramatic improvements in diagnostic technology (previous rare cases in normal hosts having occurred in the absence of diagnosis) or the recognition of a new disease because its expression is facilitated or dependent on immunosuppression (AIDS patients serving as "sentinel chickens" for the population at large)

is unclear. The latter interpretation is favored by a previous similar case report of presumably disseminated cestode infection in the face of immunosuppression due to Hodgkin's disease and its therapy.[324]

Four cases of exuberant subcutaneous disease due to the larval form of *Taenia crassiceps* have been reported in AIDS patients.[325–328] Thus, HIV infection may be a risk for disease with this cestode. A case of hepatic alveolar echinococcal disease in a 6-year-old child with AIDS has been described.[329] Uncommon features of this case include the remarkably young age and hence short incubation period for disease and the complete lack of demonstrable parasite-specific humoral or cellular immune responses. The paucity of reported cases of hydatid disease in HIV-infected patients does not permit any conclusions about the biology or clinical course of coinfection.

Finally, several cases of neurocysticercosis have been reported in HIV-infected patients.[330] Most cases of coinfection have presented with multiple parenchymal lesions.[330] The frequency of giant cysts and racemose forms of disease is elevated in reported cases,[331] again perhaps a reflection of the role of CD4$^+$ T cells in tissue immunity to *T. solium*. Further clinical data on the interaction between HIV and cestode infections are awaited.

Nematodes

Strongyloides stercoralis

Strongyloides stercoralis (see Chapter 117) appeared to qualify as a potential OI because it is one of the two nematodes (apart from *Capillaria philippinensis*; coinfection not yet reported) capable of multiplying in human hosts, especially in immunocompromised subjects.

One way in which immunosuppression enhances *Strongyloides* infection is by permitting or stimulating an increased degree of the normal process of autoinfection.[332] In this process, first-stage rhabditiform larvae (L1) produced by the adult female worm in the upper small bowel are transformed into infective filariform larvae (L3) that can reinvade the colonic intestinal wall or the perianal or perineal areas. Massive upregulation of the autoinfective process results in the hyperinfection syndrome, with the development of many more adult worms, and the production of large numbers of larvae that disseminate to all organs. The clinical picture is dominated by Gram-negative bacterial sepsis, meningitis, and/or pneumonia. Hyperinfection is usually associated with immunosuppression, particularly the administration of corticosteroids.

Strongyloidiasis was initially designated as an AIDS OI based on the past record of *S. stercoralis* in causing hyperinfection in the immunosuppressed.[333] Five years later, when it became apparent that hyperinfection syndrome was not being encountered frequently in patients with AIDS, it was removed from the list of AIDS-defining OIs.[334] Given the low but appreciable rate (3.9%) of strongyloidiasis among men attending sexually transmitted disease clinics in New York City in 1981,[335] the AIDS epidemic in the United States should have provided some clinical evidence of any predisposition of AIDS patients to hyperinfection. This did not occur. The available evidence makes it extremely unlikely that misdiagnosis or underreporting are the relevant factors here; severe strongyloidiasis or hyperinfection syndrome has prominent clinical features and is often fatal if untreated, and it is not likely that the association would escape notice. Few cases of hyperinfection syndrome have been reported in the English-language literature.[336–345] Even among these cases, the presence of hyperinfection is poorly documented in many; and, all too frequently, there is confusion between severe GI disease and hyperinfection.[346]

Diagnosis (as opposed to suspicion) of hyperinfection syndrome depends on the demonstration of markedly increased numbers of filariform larvae in the stool or multiple such larvae in the sputum. The mere presence of filariform larvae in the sputum only indicates the existence of autoinfection. (It should also be noted that the presence of rhabditiform larvae in the sputum points to neither autoinfection nor hyperinfection but to the presence of adult female worms in the lung.)

It is possible that the frequency of severe strongyloidiasis complicating HIV infection is much higher in certain areas of the tropics where both infections are prevalent and medical facilities are lacking; however, an

absence of such an association has been noted from just such areas.[18] Petithory and Derouin[347] pointed out that clinical studies of AIDS patients in central Africa, where the prevalence of strongyloidiasis varies from 26% to 48%, did not mention extraintestinal strongyloidiasis. Similarly, a report from Brazil estimated a 1–2% prevalence of *Strongyloides* infection in the population of São Paulo, finding the parasite in 10% of 100 AIDS patients, who showed no evidence of systemic strongyloidiasis.[348] Similar results have been found in Zambia.[349,350] A survey of urban adults in Kinshasa detected *S. stercoralis* in 20% by intensive fecal examinations of single specimens, and estimated a 50% infection rate in the same population on the basis of positive serologies. There were no significant differences in infection rates in those seropositive or seronegative for HIV (F. Neva, unpublished observations).

Taken together, these data suggest that the presence and severity of clinical disease due to *S. stercoralis* are not significantly increased in patients with HIV infection or AIDS alone. A recent study has shed light on the subject.[351] Careful quantitation of the numbers and proportions of free-living adult worms and directly developing L3 larvae in stool cultures revealed a surprising negative correlation between CD4+ T-cell count and the development of infectious larvae in the gut, the latter process being necessary for autoinfection.[352]

More subtle interactions, such as an increased mean GI parasite burden or slower response to therapy, may have been missed. Also, some conditions that cosegregate with HIV/AIDS are known to predispose to the hyperinfection syndrome, including the use of steroids (given for *Pneumocystis* pneumonia and lymphoma in AIDS), inanition (seen in patients with chronic diarrhea, untreated oropharyngeal or esophageal candidiasis, and slim disease), and coinfection with human T-cell lymphotropic virus type I (HTLV-I; see Chapter 81). Strongyloidiasis is an important OI in individuals infected with HTLV-I, and *Strongyloides* infection has been suspected to be a cofactor in the development of acute T-cell leukemia and tropical spastic paraparesis in asymptomatic carriers of HTLV-I.[353,354] Notably, intravenous drug use is a risk factor for infection with both HTLV-I and HIV.

Other Geohelminths

Approximately one-third to one-half of the world's population is thought to be infected with a soil-transmitted geohelminth.[355,356] Apart from *S. stercoralis*, the heaviest public health burdens are posed by *Ascaris lumbricoides*, hookworm species, and *Trichuris trichuria*.[355] There are no published data indicating that infection or disease with any of these latter organisms is excerbated by HIV infection. Indeed, in the case of hookworm, while anemia is an independent risk factor for early death in HIV[357,358] and while hookworm infection can lead to anemia, the actual literature on hookworm infection in HIV has not revealed anything striking apart from the puzzling findings: (1) of a negative association between hookworm infection and HIV infection;[359] (2) of significantly higher CD4+ T cells counts in HIV-infected individuals with hookworm infection than those without hookworm infection;[360] and (3) of a significantly lower prevalence of, and mean intensity of, hookworm infection in those with pulmonary tuberculosis and HIV, than those with pulmonary tuberculosis without HIV.[361] What, if any, significance these observations have remains unclear.

On the other hand, for reasons discussed above, chronic/recurrent geohelminth infection has been suspect as a cofactor for HIV progression. Again, following the publication of conflicting studies, a recent randomized, double-blind, placebo-controlled trial of albendazole for infection with diverse geohelminths (including hookworm, *Ascaris,* and *Trichuris*) found a significant benefit of treatment on CD4+ T-cell counts – specifically in the face of *Ascaris* infection, not in those with the considerably more prevalent hookworm infection.[362] A nonsignificant trend towards a beneficial effect of treatment on plasma HIV-1 RNA load was also seen.[362] More data are needed on the subject.

Filariasis

Among the tissue-infecting filaria, the effect of HIV coinfection has been studied in a large cohort of patients with *Onchocerca volvulus* infection (see Chapter 106). No significant epidemiological association was found

between the two infections, nor was there any difference in the efficacy of ivermectin treatment in HIV-infected compared with uninfected patients.[363] Onchocercal skin disease may be worse in the face of HIV infection[364] and HIV-coinfected individuals have lower levels of antibodies to *O. volvulus*.[365]

In contrast, two studies have suggested a significant epidemiological association of lymphatic filariasis (see Chapter 104) with HIV infection.[366] The increased infectability of Th2-polarized CD4+ T cells may underlie this surprising finding – although a similarly increased risk for HIV infection has not been observed with infection with other helminths. As for the effect of lymphatic filariasis on HIV progression, a randomized, double-blind, placebo-controlled, cross-over trial of diethylcarbamazine for *Wuchereria bancrofti* infection reported a significant treatment-associated decrease in plasma HIV-1 RNA load, along with a nonsignificant trend towards a beneficial effect on CD4+ counts.[360]

Arthropods

Sarcoptes scabiei var. *hominis* stands alone among the arthropod and crustacean infestations of humans (see Chapter 124) as a cause of exacerbated disease in the presence of HIV. In normal hosts, scabies is usually manifest as a markedly pruritic, papular, and vesicular dermatitis, with pathognomonic burrows harboring gravid females. Excoriations, nodules, and eczematous or impetiginized plaques may also be found. Relatively few adult mites are normally present. Crusted scabies is seen in neurologically impaired or immunosuppressed patients. Pruritus is often absent or mild. Lesions consist of widespread hyperkeratotic, crusted, scaling, fissured plaques. The nails are frequently involved. Patients tend to be heavily infested, with thousands of adult mites (see Chapter 124). Crusted scabies has been reported as a complication of HIV infection. CD4+ T-cell counts in reported cases have been less than 500/μL.[367–369] Both typical and atypical presentations are seen, the latter including the "pruritus of AIDS," crusting with pruritus, pruritic papular dermatitis, and mimics of Darier's disease and psoriasis.[368] Secondary sepsis and death have been reported.[370] In the face of this clinical variability, the diagnosis of crusted scabies in HIV-seropositive people rests on appropriate clinical suspicion and the demonstration of heavy infestation by microscopic examination of skin scrapings. With such extraordinary mite loads, these patients are remarkably contagious.[371,372] Combination therapy with ivermectin 200 μg/kg and topical benzyl benzoate (or perhaps permethrin) appears to be the treatment of choice.[369,373] Single-dose ivermectin is also effective at preventing transmission in close contacts.

There is no evidence of transmission of HIV by arthropod vectors. Pruritic papular eruptions associated with HIV infection are common in sub-Saharan Africa. The etiology of these intensely pruritic lesions has been attributed to exaggerated immune responses to arthropod bites in HIV-infected individuals.

Fungal Infections

Penicillium marneffei

Disseminated infection with *P. marneffei*, a dimorphic fungus endemic to Southeast Asia and southern China (see Chapter 87), has emerged as an important OI in AIDS patients. It is the third most common OI in HIV disease in northern Thailand, after extrapulmonary tuberculosis and cryptococcal meningitis.[374–376] Infection with *P. marneffei* was a rare event before the arrival of the AIDS pandemic.[376] Since then, thousands of cases have been diagnosed, primarily in southern China, northern Thailand, Hong Kong, Taiwan, Malaysia, Vietnam, Singapore, Indonesia, and Myanmar.[376–380] The overwhelming majority of cases have been in AIDS patients, although normal hosts are also known to develop systemic disease with this fungus.[376,378,381] There is a pronounced intracountry variation in infection rates. In northern Thailand, up to one-fourth of AIDS patients suffer disease with it, whereas in southern Thailand the prevalence is 10-fold less.[380] It remains unresolved whether the human disease, penicilliosis, results from zoonotic or sapronotic transmission. The ecological reservoirs remain unknown despite more than a decade of

research. The organism has been isolated from the organs, feces, and burrows of three species of bamboo rats.[374] The geographic range of these rodents overlaps the previously mentioned known areas of endemicity for disease with *P. marneffei*[377–379] and suggests the likelihood that this fungus is also endemic in Laos, Cambodia, and Malaysia.[376] Whether bamboo rats are important reservoirs for human infection or just another natural host is unclear. There is no evidence of transmission between rats and humans. The seasonal distribution of the diagnosis of disseminated disease in AIDS patients suggests expansion of the reservoir during the rainy season.[377] Exposure to soil appears to be a key factor.[382]

The pathogenesis of penicilliosis is presumed, by analogy with other endemic systemic mycoses, to involve transmission by inhalation, with secondary systemic dissemination. Like *Histoplasma capsulatum*, *P. marneffei* is an intracellular parasite of macrophages.[378] Mouse models indicate that T cells play a central role in controlling infection.[383,384] In coinfected patients, disseminated disease is associated with CD4$^+$ T-cell counts less than $100/\mu$L.[376,385]

The largest clinical series of disseminated *P. marneffei* infection reported to date provided detailed information on 80 patients.[376] Symptom onset was generally sudden and intense. The most common presenting symptoms and signs were fever (92%), anemia (77%), weight loss (76%), and skin lesions (71%). Similar patterns of clinical symptoms have also been reported from other endemic regions.[386] Other frequent signs and symptoms included cough (49%), generalized lymphadenopathy (58%), hepatomegaly (51%), and diarrhea (31%). The most common cutaneous manifestation (87%) was a generalized papular rash with central umbilication that resembled the lesions of molluscum contagiosum. These were predominantly found on the face, scalp, and upper extremities but occurred throughout the body, including the palate. Other cutaneous lesions included papules without umbilication, a maculopapular rash, subcutaneous nodules, acne-like lesions, and folliculitis. Chest films were frequently abnormal, with diffuse reticulonodular or localized alveolar infiltrates the most common. The mean duration of illness prior to presentation in this study was 4 weeks.

The incubation period for disseminated disease is unclear, as is the percentage of patients whose disease is a result of reactivation of latent infection, as opposed to new infection or reinfection. The fact that reactivation with increasing immunosuppression occurs is supported by the several cases of disseminated disease reported from nonendemic areas in patients who had a distant history of travel to endemic areas.[385,387,388] Many such patients had spent little time in endemic areas, indicating that infection with *P. marneffei* can occur rapidly. The development of clinically active disease within weeks of exposure in endemic areas[389] and the reports of children with vertically transmitted HIV infection developing disease in the first months and years of life[390] demonstrate that primary infection can quickly lead to disseminated disease. Finally, the pronounced seasonal variation in disease incidence implies an important role for exogenous reinfection in the expression of disease in endemic areas.[377]

The mortality rate of patients with disseminated *P. marneffei* infection is very high in the absence of prompt treatment. Diagnosis depends on a high index of suspicion, including a careful history to assess residence or travel in an endemic area. The differential diagnosis includes tuberculosis, other endemic fungi, and cryptococcosis. Cutaneous lesions may mimic those of AIDS-related molluscum contagiosum, *H. capsulatum* and *Cryptococcus neoformans*. An absence of cutaneous lesions may retard diagnosis. In this regard, a characteristic syndrome of hepatic disease in the absence of skin lesions (fever, hepatomegaly, and markedly elevated serum alkaline phosphatase levels) should be noted.[391] A presumptive diagnosis can be made by the examination of a Wright's-stained bone marrow aspirate, lymph node aspirate, or touch preparations of skin biopsy specimens.[376,378,392] Intracellular and extracellular basophilic elliptic yeast-like organisms with central septation (as opposed to the budding of *H. capsulatum*) are characteristic. *P. marneffei* has characteristic cross-wall formations within macrophages, appearing as transverse cell walls separating individual conidia, which help in distinguishing it from other conidioform fungi. Indirect fluorescent antibody reagents have been developed that may prove useful for differentiating *P. marneffei* from *H.*

capsulatum and *C. neoformans* in tissue.[393] Characteristic intracellular organisms have been detected on routine blood smears.[394] In the series discussed above, definitive diagnosis was performed by culture of *P. marneffei* from blood (76%, even in the absence of routine lysis-centrifugation culture), skin biopsy (90%), bone marrow (100%), and sputum (34%). Diagnostic antigenemia tests that may prove valuable for rapid diagnosis have been developed.[395,396] Quantitation of urinary antigen by enzyme immunoassay is especially promising. High sensitivity and specificity were demonstrated in an area of high endemnicity.[397] Of note, *P. marneffei* infection is a known cause of false-positive reactions in the *H. capsulatum* polysaccharide antigen immunoassay, and also crossreacts with antisera raised against *Aspergillus* galactomannan.[374,398] Current serologic assays are unlikely to be helpful in the diagnosis of AIDS patients but, with improved sensitivity, may provide a useful index of infection.[393,399]

Amphotericin B, 0.6 mg/kg/day for 2 weeks, followed by itraconazole, 200 mg twice a day for 10 weeks, is safe and effective.[400] In mild to moderately ill patients, primary therapy with itraconazole may be reasonable. Voriconazole has also shown success in treatment of *P. marneffei* infections in HIV-infected travelers from nonendemic regions.[401] Secondary prophylaxis is mandatory, given relapse rates of 50% within 6 months in its absence.[402] A placebo-controlled, double-blind randomized trial showed that secondary prophylaxis with itraconazole (200 mg once daily) is safe and effective.[78,403] With immune reconstitution as a result of a successful response to HAART, discontinuation of secondary prophylaxis is probably safe.[404] A controlled, double-blind trial of primary prophylaxis with itraconazole (200 mg once daily) in Thai patients with AIDS and CD4$^+$ T-cell counts less than $200/\mu$L showed that the regimen was well tolerated and effective at preventing both cryptococcosis and penicilliosis.[405] No survival benefit was found, but the study was not powered to detect a survival advantage.[405]

Paracoccidioides brasiliensis

The dimorphic fungus, *P. brasiliensis,* is the cause of the most common systemic mycosis in Latin America (see Chapter 86). Two clinical forms are distinguished in normal hosts: an acute or subacute "juvenile" form and a chronic "adult" form. Acute, juvenile disease, occurring in children and young adults and accounting for a small minority of cases (3–5%), is marked by a rapid course, disseminated involvement of macrophages and lymphoid tissue, and severe suppression of CMI. Chronic, adult disease, accounting for the vast majority of cases, is a slowly progressive disease, predominantly of older men. In most patients, the primary clinical and pathologic manifestations are pulmonary, with nodular, infiltrative, or cavitary lesions progressing to fibrosis. Other frequent manifestations of adult disease include infiltrative and ulcerative mucosal lesions of the oro- and nasopharynx, polymorphic cutaneous lesions, lymphadenopathy, and adrenal infiltration. Most infections are subclinical. Long latency has clearly been demonstrated, with a mean of 15 years between leaving an endemic area and presentation.[406]

It is thought that CMI responses are critical to the host defense from disease with *P. brasiliensis*.[406,407] Clinical and experimental evidence indicates that paracoccidioidomycosis is associated with marked abnormalities of immune function, with suppression of CMI responses, polyclonal B-cell activation, and elevation of plasma IgE levels.[406–408] These immunologic perturbations are more common and severe in juvenile disease and are reversed with successful therapy.[406]

Given the immunology of paracoccidioidomycosis, one might expect it to be a prominent OI in South America and among HIV patients with a history of travel there. In fact, fewer than 100 cases have been reported, despite the presumed wide prevalence of infection or coinfection in areas such as urban Brazil.[409–414] Possible reasons for the low number of cases in HIV-seropositive patients include: (1) prophylaxis with TMP-SMX, which has activity against *P. brasiliensis*; (2) the use of ketoconazole for oropharyngeal candidiasis; (3) misdiagnosis as *Pneumocystis carinii* pneumonia, with a therapeutic response to TMP-SMX; (4) lack of diagnosis; and (5) the presence of a particularly subtle interaction between HIV and *Paracoccidioides brasiliensis*.[409,412]

Paracoccidioidomycosis in HIV-seropositive people has been primarily of the "acute" form; however, pulmonary and oral mucosal involvement, more typical of the "chronic" form, often coexists.[410] Although published reports have suggested that this disseminated disease may occur across a broad range of HIV-associated immunosuppression, CD4$^+$ T-cell counts less than 200/μL have been the reported norm.[410,411] More than one-third of patients with paracoccidioidomycosis have presented with another opportunistic coinfection, most frequently oral/esophageal candidiasis or tuberculosis.[410] Reported clinical presentations span a wide spectrum, from relatively indolent to rapidly progressive disease. Clinical manifestations have included prolonged fever, weight loss, cough, dyspnea, generalized lymphadenopathy, hepatosplenomegaly, skin lesions (localized or disseminated maculopapular, nodular, or ulcerative), oral lesions (ulcerative and/or nodular), osteoarticular lesions, and meningitis.[409,410]

Diagnosis in these patients was made by direct examination or culture of clinical specimens, including skin biopsies, lymph node aspirates or biopsies, bone marrow aspirates, CSF, or blood.[409,410] Sputum should also be examined using potassium hydroxide preparations, calcofluor stains, or immunofluorescence. The "pilot wheel" cell, consisting of numerous small buds surrounding the mother cell, is characteristic. Serologies have not been diagnostically helpful. PCR using primers for ITS1 region of the ribosomal gene has been found to be a highly sensitive and specific test that may prove to be useful as a diagnostic tool in the near future.[414]

Mortality in the reported cases of disease in HIV-seropositive people was 30%.[409] No randomized clinical trials have been performed with any of the drugs commonly used for the treatment of *P. brasiliensis* infection (sulfonamides, amphotericin B, ketoconazole, and itraconazole), even in normal hosts. Treatment recommendations are based on data from case series and comparison with historical controls.[412] However, the data are fairly compelling that itraconazole (100 mg/day) is the drug of choice in normal hosts.[406] Published reports of itraconazole treatment in the face of HIV coinfection are scant.[410,411] Although amphotericin B and itraconazole may both have therapeutic roles to play, amphotericin B should probably be used for initial treatment in HIV-coinfected patients. Trials with liposomal formulatins of amphotericin are awaited.[415] Lifelong suppressive therapy is necessary; itraconazole seems to be a reasonable choice.[415]

Histoplasma capsulatum var. duboisii

The endemic dimorphic fungus *H. capsulatum* var. *duboisii* is localized to western and central Africa and Madagascar (see Chapter 85). In normal hosts, it tends to cause chronic necrotizing cutaneous and skeletal infections. Disseminated disease is unusual. It may be an emerging OI in AIDS patients. A large retrospective case series, reporting on cases of HIV coinfected with *H. capsulatum* var. *duboisii* presenting to three referral centers in French Guiana, identified *H. capsulatum* infection as an AIDS-defining condition in 200 individuals, with 37% having coinfections with other AIDS-defining infections.[416] However, no increases in the incidence of African histoplasmosis were reported in a study from the People's Republic of the Congo (now Congo Republic) in the 1980s, despite a rapid increase in the AIDS-related incidence of cryptococcal disease.[417] Disease manifestations reported in reported coinfections suggest that AIDS patients are at risk of more severe, disseminated disease.[418–424] Diagnosis is typically by direct examination of clinical specimens and culture. Serodiagnostic tests are cross-reactive with *Aspergillus* and *Penicillium*.[425] The yeast form is larger and has a thicker wall than *H. capsulatum* var. *capsulatum*. Amphotericin B and itraconazole have therapeutic efficacy.[424] With the advent of HAART, there is increasing concern about emergence of *Histoplasma* and other invasive fungi as causes of IRIS.[424]

Sporothrix schenckii

The dimorphic fungus *S. schenckii* has a worldwide distribution, although most reports have been from tropical and subtropical areas of the Americas (see Chapter 90). The highest incidence of disease is thought to be in the highlands of Mexico and in southern Brazil. Recent reports from South Asia suggest high prevalence rates there as well.[426] Cutaneous and lymphocutaneous disease is most common. Extracutaneous involvement, including osteoarticular disease, pneumonia, and meningitis, has been described in both normal and immunosuppressed hosts. A handful of cases of severe, disseminated sporotrichosis in late-stage AIDS have been described.[427–430] Diffuse cutaneous involvement is the norm. Some patients have also presented with CNS, ocular, osteoarticular, splenic, bone marrow, and/or mucosal involvement. It appears likely that disseminated *Sporothrix* will become a more prominent OI in heavily endemic areas. The response to therapy (with amphotericin B, potassium iodide, itraconazole, ketoconazole, and 5-fluorocytosine) has been variable and problematic. Amphotericin B should probably be used for initial treatment, followed by lifelong suppressive therapy with itraconazole.[431]

Other Endemic, Systemic Mycoses

H. capsulatum, Blastomyces dermatitidis, and *Coccidioides immitis* are systemic mycoses endemic to the United States that cause AIDS-related OI. As such, they are not distinctly tropical diseases and have been covered in depth elsewhere.[76–78,432–434] The tropical extent of their respective areas of endemicity deserves brief mention, however.

H. capsulatum var. *capsulatum* (see Chapter 85) is found in distinct river basin systems worldwide between 45°N and 30°S of the equator.[432] Progressive disseminated histoplasmosis is common in AIDS patients in endemic areas.[432] In addition to the most prominent worldwide focus (the Ohio and Mississippi river valleys of the United States), cases have been reported from Central and South America, the Caribbean, Africa, Southeast Asia, and Europe.[435,436]

Disease caused by *B. dermatitidis* was originally named North American blastomycosis. It is now clear, however, that the distribution of this fungus is far more cosmopolitan (see Chapter 85). Blastomycosis has been reported in all the major regions of Africa, with a concentration in southern Africa. It is likely underreported.[437] Occasional cases have been reported from Central and South America, the Middle East, and India.[438] African strains of *B. dermatitidis* appear to be antigenically distinct from North American strains. The clinical spectrum likewise appears to be different in African cases, with prominent involvement of bone and chronic draining sinuses. Disseminated blastomycosis is an uncommon, late, frequently fatal OI in patients with AIDS in the United States.[439,440] Cases in Africa are to be expected in the future.

C. immitis is endemic to lower Sonoran life zones in the United States, Mexico, Guatemala, Honduras, Colombia, Venezuela, Bolivia, Paraguay, and Argentina (see Chapter 85). Coccidioidomycosis is a severe, often fatal disease in patients with AIDS and low CD4$^+$ T-cell counts.[434,441,442] Most have presented with diffuse or focal pulmonary disease; extrapulmonary dissemination is not uncommon. In some endemic areas, it is the third most common OI in AIDS patients.[434,441,442]

Cryptococcus neoformans

Cryptococcosis (see Chapter 85) is a common life-threatening fungal infection in AIDS patients.[443] Although *C. neoformans* can disseminate to any organ system in the face of HIV infection, meningitis is the most frequent manifestation. Other relatively common manifestations include pneumonia and cutaneous lesions. Occurring most commonly when CD4 counts fall well below 200/μL, cryptococcosis is a frequent presenting diagnosis in AIDS.[443] Excellent reviews on cryptococcosis in AIDS are available for detailed information on the clinical approach to this ubiquitous OI.[76–78,444,445]

C. neoformans is distributed globally. The distribution of cryptococcus as an OI in AIDS is global as well. Regional differences exist in the prevalence of disease as defined by clinical or autopsy series. The prevalence of cryptococcosis in AIDS patients in the United States was estimated to be 7–8% in the 1980s.[446] In Thailand, it is the second most common OI (after tuberculosis), with a prevalence of 13–44% in different clinical series.[20,447,448] In Africa, the case series prevalence has been variable, from 1% in Soweto, South Africa,[449] to 6–13% in Kinshasa (the former Zaire).[450–452] The prevalence in autopsy series has similarly varied from

3% in Abidjan (Côte d'Ivoire)[230] to 29% in Uganda.[232] Overall, the rates of disease in Africa appear to be higher than those in North America or Europe. Interestingly, a large retrospective case study in London found a significantly higher rate of extrapulmonary cryptococcal disease in Africans attending an HIV clinic than in non-Africans attending the same clinic.[453] Data from case series estimated the prevalence of cryptococcosis in Mexico to be 8–12%[454] and in Haiti 13%.[455] In Brazil, from 1980 to 2002, 6% of patients had cryptococcus as an AIDS-defining diagnosis.[456] Cryptococcal infections have been estimated to contribute to 10–30% of AID-related deaths in developing countries.[457]

C. neoformans exists in two varieties: *C. neoformans* var. *neoformans* and *C. neoformans* var. *gatti*. They inhabit different ecological niches, with *C. neoformans* var. *neoformans* being associated with soil contaminated with bird excrement and *C. neoformans* var. *gatti* having a unique, if poorly understood, association with the tree *Eucalyptus camaldulensis*.[458,459] With the completion of the genomic sequence of *C. neoformans*, enough differences have been found in the sequences of these two fungal subspecies for a proposal to raise *C. neoformans gatti* to its own species, *C. gatti*.[460] Whereas *C. gatti* has a predominantly tropical and subtropical distribution, *C. neoformans* occurs worldwide.[458,459] Of note, although cryptococcosis due to *C. gatti* occurs with some regularity in normal hosts in regions where this variety is endemic, cases of cryptococcosis in AIDS patients have been almost exclusively due to *C. neoformans*.[459,461]

Pneumocystis jirovecii

Throughout the world, there is almost universal serologic evidence of exposure by the age of 2 years to *P. jirovecii*[462] (see Chapter 91). The prevalence of antibodies to specific *P. jirovecii* antigens varies, however, suggesting exposure to antigenically different strains in different areas of the world,[463] which is mirrored by genetic studies revealing strain differences in this organism.[464] Prior to HAART, PCP (*Pneumocystis carinii* pneumonia, based on the prior terminology) occurred in 40–50% of patients in the United States and Europe with a CD4 count less than 100/μL per year, and in 60–80% of patients overall, in the absence of prophylaxis. PCP prevalence appears to be high among AIDS patients in Central and South America and in Asia.[465] Interestingly, however, the incidence of PCP in adult AIDS patients in Africa may be far lower than was seen in the pre-HAART era in industrialized countries.[465] Adult clinical series in Africa have shown prevalence rates of 0–22%.[449,455,466–469] Studies including bronchoscopy for diagnosis have described rates of 0–39% (the highest figures being obtained as a percentage of acid-fast bacillus-negative pneumonias).[455,466,470–472] Autopsy series have had rates of 0–11%.[231,468,473] The reasons for these lower rates are unclear. Possible explanations include less environmental exposure, exposure to differing strains, differences in host susceptibility, earlier deaths in tropical patients with AIDS due to exposure to more virulent organisms, diagnostic difficulties, and host-specific differences in susceptibility.[455,474] The existence of genetically and antigenically distinct human strains is likely; however, pediatric PCP rates in AIDS patients in Africa are quite similar to those in the industrial north.[465,475] Indeed, approximately one-third of HIV-infected infants in Africa die during the first year of life, and PCP is thought to be responsible for 30–50% of such deaths.[476,477] Demise from more virulent pathogens prior to clinical PCP may well occur in adults (and PCP does tend to occur early in the course of HIV disease in North American infants,[478] perhaps with initial exposure).[78] The high prevalence of cryptococcal disease in these same series, which is thought to occur at similar levels of immunosuppression, suggests that this is not the complete answer.[455] More recent studies from Africa, using bronchoscopy and improved microbiological identification, have yielded higher rates of PCP, so it is possible that lower rates in earlier studies may have represented reporting bias introduced by the use of suboptimal diagnostic techniques.[479,480]

The clinical presentation of PCP in the tropics appears to be similar to that in the industrial north.[472] Frequent coinfection with tuberculosis may obscure the diagnosis. Multiple reviews of the clinical approach to PCP in AIDS are available.[481–484]

Other Fungi

Other predominantly tropical fungi, such as the agents of maduromycosis, lobomycosis, rhinosporidiosis, and subcutaneous zygomycosis, may prove to cause OI in AIDS patients but do not appear to have been reported as such. Isolated case reports of infection due to a variety of unusual fungi in AIDS patients have been published (reviewed in references 485 and 486). Some may indeed prove to be OIs, even predominantly tropical OIs, but firm data are lacking. The common occurrence of superficial and invasive infections with *Candida* and the growing problem of *Aspergillus* infection in neutropenic long-term survivors of late-stage AIDS are beyond the scope of this chapter.

BACTERIAL INFECTIONS

Mycobacterial Infections

Mycobacterium tuberculosis

Approximately one-third of those living with HIV worldwide are coinfected with *M. tuberculosis* (see Chapter 35). In developing countries, 50% of patients with HIV infection will develop active TB; in contrast, in the United States, only 4% of patients with AIDS have had TB.[2,487] In some countries in sub-Saharan Africa, more than 70% of TB patients are HIV-seropositive. TB is the leading cause of death among people with HIV infection, accounting for one-third of AIDS deaths worldwide.[488] The introduction of HAART has decreased death and OIs such as TB by 60–90% among people living with HIV worldwide in affluent countries;[489] in developing countries, however, HAART still remains available only to a minority of those who need it.

Mycobacterium avium

The *M. avium* complex (MAC) (see Chapter 35) consists of multiple serovars of two *Mycobacterium* species, *M. avium* and *M. intracellulare*. MAC bacteria are ubiquitous, with organisms commonly being isolated from soil, natural sources of water, tap water, and domestic and wild animals worldwide.[490,491] Most MAC isolates from AIDS patients are *M. avium*; more than 90% are of serovars 1, 4, and 8.[492,493] Disseminated disease due to *M. avium* is the most common systemic bacterial infection in AIDS patients in the industrial north, occurring in up to 43% of AIDS patients in the United States.[494,495] Disease occurs almost exclusively in those with CD4$^+$ T-cell counts less than 100/μL, most frequently in those with CD4$^+$ T-cell counts less than 50/μL.[495] The pathogenesis of disseminated *M. avium* infection in AIDS is thought to involve primary infection (or reinfection) as opposed to reactivation, with initial colonization of the respiratory or GI tracts followed by widespread dissemination.[496–498] Systemic disease is marked by high-grade mycobacteremia (almost exclusively in monocytes) and impressive tissue burdens of bacteria.[499]

The remarkable feature of *M. avium* in the tropics is the apparent virtual absence of disseminated disease in AIDS patients in many areas, predominantly in sub-Saharan Africa. None of 95 blood cultures from severely ill patients with advanced AIDS in Uganda were positive for *M. avium*, nor were any of 165 mycobacterial sputum cultures from HIV-seropositive and seronegative patients at the same hospital found to be positive for *M. avium*.[500,501] None of 202 blood cultures from HIV-positive adult inpatients in Côte d'Ivoire grew *M. avium* (whereas 4% grew *M. tuberculosis*).[502] None of more than 200 diagnostic lymph node biopsies in HIV-seropositive African patients had histology characteristic of disseminated *M. avium* infection.[232] Intestinal biopsies from 98 Ugandan, Zairian, and Zambian patients with chronic HIV-related enteropathy yielded histology suggestive of *M. avium* infection in only 1 patient.[349,503,504] Autopsies on 78 HIV-seropositive children in Côte d'Ivoire revealed no evidence of *M. avium* infection, whereas autopsies on 247 adult HIV patients in Côte d'Ivoire revealed a 3% prevalence of pathologic changes "indicative of atypical mycobacteriosis."[230] In contrast, 3 of 48 (6%) patients hospitalized in Kenya with late-stage HIV disease had *M. avium* bacteremia.[505] Clinical and autopsy series from Mexico have revealed a prevalence of disseminated

disease due to *M. avium* of 4–6%,[231,506] whereas 18% of 125 hospitalized patients with AIDS in Brazil had *M. avium* cultured from bone marrow.[507] Few data are available from India and Southeast Asia. One study from East Asia showed patterns of MAC infection similar to those seen in the west, with ~55% of mycobacteremias being identified as due to MAC.[508]

The reasons for the apparent absence of disseminated disease due to *M. avium* in areas of the tropics are unclear. As with the decreased prevalence of PCP, many explanations have been proposed, including less exposure, exposure to less pathogenic variants, differences in host susceptibility, greater acquired immunity to mycobacteria, earlier death by more virulent pathogens, and diagnostic difficulties. Overall exposure to MAC organisms is likely to be similar. Environmental isolation of MAC occurs with similar or greater frequency in Congo and Uganda than in the United States[491,501] and skin test surveys suggest a similar frequency of exposure to MAC in economically developed and developing countries.[509] Piped water systems in the United States and Europe have a higher frequency of MAC isolation, however, and economic conditions may lead to greater exposure to MAC-containing droplets via showerheads in economically developed countries;[490,491,510] such differences, however, are unlikely to lead to an essentially total absence of disease in countries such as Uganda. Exposure to different *M. avium* serovars or strains may well be important. Data on serotyping of African clinical strains are scarce. Preliminary data suggest that African clinical isolates are distinguishable from European and American isolates by restriction fragment length polymorphism analysis.[511] The possibility of underlying genetic differences in host susceptibility is belied by the similar rates of disseminated *M. avium* infection as a presenting diagnosis in African and non-African AIDS patients in a London clinic.[453] Greater acquired immunity to mycobacterial disease through bacille Calmette–Guérin (BCG) vaccination[512] or prior infection with *M. tuberculosis* may exist, but the reported BCG coverage (50%) and purified protein derivative (PPD) reactivity (82%) in Uganda seem unlikely to explain the lack of any disseminated MAC disease.[501] Earlier death due to a greater environmental presence of, or greater latent infection with, more virulent pathogens may occur. This is unlikely to be the entire explanation because patients in many of the previously mentioned studies had clinical late-stage AIDS. Finally, the design of several of the previous studies makes the assertion that the central problem is one of a lack of diagnostic sophistication untenable. Further data from Africa are needed to this puzzling pattern of infections with MAC.

Mycobacterium leprae

The causative agent of leprosy (see Chapter 37) is an incredibly slow-growing parasite of macrophages. For comparative purposes, it may be useful to recall that *Leishmania*, which infects similar cells, is a prominent opportunistic pathogen for patients with HIV infection. The importance of CMI in leprosy and leishmaniasis was emphasized by Turk and Bryceson[513] in their detailed comparison of skin lesions and histopathology of both diseases. Moreover, the immunopathology of both infections is very similar. In view of the widespread prevalence of leprosy in the tropics and subtropics, the immunosuppressive effects of HIV/AIDS on leprosy would be expected to become readily apparent, but there is little or no evidence of this interaction. In fact, in a comprehensive analysis of the possible interaction between HIV/AIDS and leprosy, Lucas concluded that leprosy appears to be another "missing infection in AIDS."[18]

Several studies have examined positive serology for HIV in newly diagnosed leprosy cases. One report from a rural hospital in Zambia found a higher prevalence of reactors compared with blood donors and surgical patients (6 of 18 versus 9 of 105), but the numbers were small and the controls were not adequately matched.[514] A larger study of HIV seroprevalence in northwest Tanzania of 93 new leprosy cases compared with more than 4000 controls found that the presence of HIV antibody was significantly associated with multibacillary disease.[515] The fact that this association was based on only 5 HIV-positive cases with multibacillary disease illustrates the complexity of epidemiologic analysis in a disease such as leprosy. Another comparison of seropositivity for HIV was carried out among 189 new cases of leprosy matched for age, sex, and district of residence with 481 controls in Uganda. No significant difference in overall positive rates was found (12% in cases versus 18% in controls), but again, positive HIV reactions were more frequent among multibacillary cases.[516] A different clinical association was noted in Zambia in leprosy patients with active neuritis, which suggested that HIV-positive cases had poorer recovery of nerve function than controls after treatment with steroids.[517]

A factor that should be considered in evaluating reports of HIV/AIDS in leprosy patients is the greater likelihood of false-positive serologic reactions. One or more positive bands to HIV antigens in Western blots were commonly found in several hundred sera from northern India in the absence of positive enzyme-linked immunosorbent assays (ELISAs).[518] Another report claimed that 3 of 75 (4%) sera from Indonesia and 6 of 100 (6%) sera from Somalia gave positive HIV ELISAs but negative Western blots.[519] These were attributed to leprosy.

Published epidemiological data show neither an increased HIV prevalence among leprosy cases nor a higher rate of HIV among individuals infected with *M. leprae*. Further, there appears to be no striking evidence that HIV infection has an adverse effect on the course of leprosy nor any clear alteration in the clinical spectrum of leprosy among coinfected patients;[520] although some suggest that immune-mediated reactions that complicate leprosy occur at a higher frequency in coinfected patients,[521,522] several of the above reports suggest the possibility that multibacillary disease may develop more readily with coinfection. However, there are several features of leprosy that may tend to obscure an interaction with HIV infection. Both infections are chronic and slow in their progression, so it may simply take more time to recognize an influence of one on the other. Leprosy is predominantly a rural infection; HIV/AIDS is more urban. Patients with AIDS in the tropics may not survive long enough to display interactions with leprosy. Finally, patients in the early stages of leprosy have relatively subtle clinical manifestations with which physicians in the urban environment may not be familiar. Therefore, there may be more going on out there than we realize. Leprosy has now been reported presenting as immune reconstitution disease among patients commencing HAART.[523]

Other Nontuberculous *Mycobacteria*

Disease due to *M. genavense* (see Chapter 35) mimics that due to *M. avium*, causing disseminated disease in AIDS patients with very low CD4+ T-cell counts (mean, <50/μL). Pathogenesis appears to involve initial GI colonization followed by dissemination.[524,525] The important environmental reservoirs are unclear, but pet birds can have extensive GI tract involvement. The organism may also be present in tap water.[526] The geographic range of disease is only beginning to be defined. Cases have been reported from North America, Europe, and Australia.[524] The most common presenting symptoms and signs are fever, weight loss, abdominal pain, chronic diarrhea, lymphadenopathy, hepatosplenomegaly, "pseudo-Whipple's disease," and anemia.[524,527,528] Imaging of the spleen may suggest splenic abscesses;[529] diffuse nodular infiltrates may be seen in the lung.[530] Pathologically, involved organs are filled with histiocytes that are packed with acid-fast bacilli. The diagnosis can be established by the isolation of *M. genavense* from normally sterile sites (blood, bone marrow, lymph node, and spleen). Specific diagnosis is confounded by the fastidious growth requirements of the organism. Primary isolation on solid media is difficult, and growth in liquid broth may have only 50% sensitivity. Definitive identification demands PCR techniques.[524] The clear implication is that a significant percentage of cases ascribed to disseminated *M. avium* are likely due to *M. genavense*.[527] Data on treatment are all retrospective, but therapy appears to be associated both with improvement in symptoms and with survival. Multidrug regimens that include clarithromycin appear to be associated with the best clinical responses.[531,532] Like other nontuberculous mycobacteria, *M. genovense* has also been reported to declare itself during IRIS.[533]

Before the AIDS pandemic, *M. kansasii* was known primarily as a cause of chronic pulmonary disease, resembling TB, in lungs with

underlying damage. *M. kansasii* is second to MAC among nontuberculous mycobacteria as a cause of disease in HIV-infected patients in the United States.[534] Although *M. kansasii* has been reported as a cause of pulmonary disease in most areas of the world, most case reports of HIV coinfection are from North America and Europe. However, coinfection may be especially prevalent in the gold mines of the Transvaal in South Africa.[535] In HIV-infected individuals, disease due to *M. kansasii* and *M. tuberculosis* has very similar clinical and radiological characteristics.[536,537] A major difference (with epidemiological and prognostic implications) is that *M. kansasii* disease tends to occur later in the course of HIV infection. The mean CD4$^+$ T-cell count at the time of presentation is approximately 50–60/μL;[536–539] 60–90% present with pulmonary disease alone and 20–35% with disseminated disease.[539,540] The incidence in industrialized countries has plummeted in the HAART era.[541] With all nontuberculous mycobacteria, differentiation between colonization, contamination, and disease can be problematic. Mere colonization of the respiratory tract with *M. kansasii* appears to be infrequent in AIDS patients, however. All pulmonary isolates should be taken seriously.[538,540] Despite relative *in vitro* resistance to isoniazid,[541] the recommended therapy is isoniazid, rifampin, and ethambutol. Therapy clearly alters survival in patients with pulmonary disease.[539,540,542] Disseminated disease has a particularly poor prognosis.

M. malmoense is an uncommon cause of pulmonary disease resembling tuberculosis. The environmental reservoir is unknown. Person-to-person transmission has never been documented. Multisystem disease with bacteremia has rarely occurred in the presence of profound immunosuppression, including several patients with AIDS and low CD4$^+$ T-cell counts. Pulmonary and GI disease, along with bacteremia, is usual.[543,544] *In vitro* susceptibility testing does not correlate well with clinical response.[545] The best regimen for pulmonary disease in the nonimmunosuppressed patient appears to be isoniazid, rifampin, and ethambutol.[545] Optimal therapy in AIDS patients is unclear.

M. haemophilum causes localized lymphadenitis in immunologically healthy children and cutaneous, osteoarticular, and, more rarely, pulmonary or disseminated disease in immunocompromised patients. Several cases have been reported in AIDS patients.[546–551] Cutaneous lesions include furuncles, abscesses, papules, vesicles, and deep ulcers. Such lesions are usually diffuse, most often on the extremities. Culture (at 30–32°C) demands supplementation of media with an iron source. *In vitro* susceptibility data and scattered clinical reports suggest that rifampin plus ciprofloxacin is reasonable empirical therapy. Other agents with good activity include amikacin, ciprofloxacin, and clarithromycin.[548] The environmental source and mode of infection are unclear.

Several other mycobacteria have been demonstrated or suspected to cause opportunistic disease in AIDS patients, including *M. fortuitum* (primary pulmonary disease,[552] disseminated disease,[553] cervical lymphadenitis,[553] and meningitis),[554] *M. marinum* (cutaneous and disseminated disease),[555,556] *M. celatum* (pulmonary and disseminated disease),[557,558] *M. xenopi* (disseminated disease, pulmonary disease, and pulmonary colonization),[559–561] *M. gordonae* (pulmonary, cutaneous, and disseminated disease),[562–564] *M. scrofulaceum* (disseminated disease),[565] *M. bovis* (disseminated disease), and *M. simiae* (disseminated disease).[566–568] Although a smattering of case reports have suggested that HIV does not exacerbate disease due to *M. ulcerans*, the causative agent of Buruli ulcer[569] (see Chapter 36), a recent case report has called this into question.[570]

Spirochetal Infections

Along with other genital inflammatory diseases, syphilis (see Chapter 138) has been implicated as a cofactor in HIV transmission. Many case reports have suggested that HIV infection can alter the course of disease with *Treponema pallidum*. In the presence of concurrent HIV infection, syphilis has been thought to: (1) progress more frequently and rapidly to neurosyphilis;[571,572] (2) lead to an increased incidence of meningitic manifestations of neurosyphilis;[573] (3) lead to an increased frequency of "malignant secondary syphilis" with ulcerating lesions and prominent systemic symptoms;[574] and (4) be less amenable to successful therapy with standard regimens as assessed by clinical or serologic measures (including a lack of appropriate nontreponemal titer reduction or a serologic relapse).[575–580] Higher rates of serological failure continue to be reported in the post-HAART era, but it has become clear that effective suppression of HIV viremia clearly increases the rates of serological responses to standard therapy.[581–584] Concerns about effectiveness of standard therapy for syphilis in HIV-positive individuals, based largely on case reports and retrospective studies, were amplified by the disconcerting finding of *T. pallidum* invasion of the CNS in early syphilis in HIV-infected patients. Such early invasion of the CNS occurs equally frequently in HIV-seropositive and seronegative people, however,[585] and the above "atypical" courses of syphilis were well-known in the pre-AIDS era. Knowledge of the actual frequency and relative significance of such events awaited well-designed prospective studies. Three studies now provide evidence that the clinical presentation and clinical and serologic responses to treatment of syphilis may not be appreciably altered by HIV coinfection.[586–588] A major caveat of these studies is that the mean level of immunosuppression in the patients in these studies, as assessed by CD4$^+$ T-cell counts, was not severe. Furthermore, the number of patients involved was relatively small. Thus, the clinical course of syphilis in the face of severe HIV-induced immunosuppression may in fact be exacerbated, and the response to conventional therapy may lead to the infrequent occurrence of serious adverse treatment outcomes.[588] The clinical approach to the HIV patient infected with this cosmopolitan sexually transmitted disease has been thoroughly discussed elsewhere[76–78,589,590] and will likely continue to evolve.

Whether HIV infection has a deleterious effect on the course of the nonvenereal, endemic treponematoses (see Chapter 43) is unknown, but such an effect has been postulated by analogy with syphilis.[591] No effects of HIV on concurrent infection with the *Borrelia* species that cause relapsing fever have been reported (see Chapter 44). Whether Lyme disease follows an unusual course in HIV-infected people is unclear.[592,593] Finally, initial observations suggest that leptospirosis (see Chapter 45) runs a similar course in patients coinfected with HIV.[594,595]

Rickettsial and Ehrlichial Infections

Among the Rickettsiae and related organisms, only infections with *Coxiella burnetii*, the etiologic agent of Q fever (see Chapter 53) and *Ehrlichia* spp. have been reported to be exacerbated by concurrent HIV infection. Notably, these pathogens are obligate intracellular parasites of monocyte/macrophages. *C. burnetii* lives and multiplies in the phagolysosomes of monocyte/macrophages, and host defense appears to depend on specific T-cell activation of the microbicidal effector functions of infected cells.[596,597] Case series have suggested that patients with immunocompromise due to a variety of causes (including leukemia, Hodgkin's disease, bone marrow and renal transplantation, and alcoholism) are more susceptible to both symptomatic acute and relapsing or chronic disease with *C. burnetii*.[598–600] While the rationale for expecting more frequent or serious disease in the HIV-infected patient is clear, supporting data are sparse. A study from southern France demonstrated a threefold higher prevalence of antibodies to *C. burnetii* in HIV-seropositive people.[601] This suggestion of an increased rate of transmission in HIV-infected people has not been found in other seroprevalence studies from Paris, Spain, or the Central African Republic.[602–604] Given the differential prevalence of risk factors for the acquisition of HIV infection between the studies, the contradictory data strongly suggest that *C. burnetii* can be bloodborne and that intravenous drug use is a risk for its transmission. Two studies from southern Europe have further suggested that HIV infection leads to a higher disease-to-infection ratio with *C. burnetii*.[601,605] A retrospective serologic study of 520 patients with acute Q fever from an area of Spain with a high incidence of both HIV and *C. burnetii* infection revealed no overrepresentation of HIV-infected people, however, with endocarditis being a common presentation.[604,606,607] The clinical features of Q fever do not appear to vary between HIV-infected and uninfected hosts.[601,603–605] However, definitive statements await prospective studies in severely immunosuppressed AIDS patients.

Human monocytic ehrlichiosis (HME), caused by the tick-borne agent *Ehrlichia chaffeensis*, is an acute febrile illness associated with leukopenia, thrombocytopenia, and hepatic enzyme abnormalities (see Chapter 52). While most reports of infection with *E. chaffeensis* have been from the United States, a report of infection in Mali supports a much wider distribution of disease, however.[608] HME appears to be an AIDS-related OI.[608–611] Reported hospitalized cases have had a high rate of complications and a mortality of approximately 30%[609] (compared with an estimated case-fatality rate for HME in the absence of HIV of <3%).[612] Patients with fatal disease had CD4+ T-cell counts less than 200/μL; in patients with less than 100/μL, the mortality rate was more than 50%. Of 8 reported cases of disease caused by *E. ewingii*, a related tick-borne agent, 7 occurred in patients with immune deficiencies, including 4 with HIV infection.[609,612] The suspicion is thus strong that *E. ewingii* is an opportunistic pathogen in the setting of HIV infection.[613] No cases of infection with the tick-borne agent of human granulocytic ehrlichiosis[614] in the face of HIV infection appear to have been reported.

There is no evidence implicating any of the spotted fever or typhus group of Rickettsiae as having a clinically significant interaction with HIV. A prospective study on scrub typhus (due to *Orientia* (formerly *Rickettsia*) *tsutsugamush*) revealed no increase in clinical severity at time of presentation in HIV-infected patients with a median CD4+ T-cell count of 70/μL.[615] Interestingly, rickettsemia occurred significantly less often in the HIV-seropositive patients. Neither the relative prevalence of infection nor the response to treatment was addressed in this study. Of interest, acute infection with *O. tsutsugamushi* has been associated with decreased plasma HIV viral load.[56]

Bacterial Infections

Brucella

A cause of systemic disease worldwide, *Brucella* species are facultative intracellular parasites that infect and multiply in macrophages (see Chapter 40). CMI responses, particularly the activation of monocyte/macrophages by antigen-specific T cells, are important in host resistance. Despite this, the meager published data on coinfection do not support a significant effect of HIV on infection with *Brucella* and, in fact, prior to the AIDS pandemic, only 2 cases of brucellosis in immunocompromised hosts (hairy cell leukemia and IgM deficiency) had been reported.[616,617] A retrospective seroprevalence study found no significant association between *Brucella* serology and HIV serology in a cohort of female sex workers in Kenya.[618] The clinical course of brucellosis in the 18 reported cases with concurrent HIV infection was not outside the spectrum of disease seen in normal hosts.[618–622]

Burkholderia pseudomallei

Melioidosis (see Chapter 33) does not appear to behave as an AIDS-related OI. The disease is endemic in Southeast Asia, particularly in northern Thailand, where the prevalence of AIDS is high. However, only one case of fatal, recrudescent, bacteremic disease in an HIV-seropositive person has been reported, and another study in the same region failed to note any difference in severity of illness in 8 HIV infected individuals compared to HIV-uninfected subjects.[66,623] Clinical series from Thailand are silent with regard to the presence of melioidosis in AIDS patients,[447,448,624,625,626] and a 10-year study of bloodstream infections in a hospital in northern Thailand reported a similar proportion of *B. pseudomallei* isolates in HIV-infected and uninfected patients.[627]

Enteric Bacteria

Several enteric bacterial infections have been reported to cause disease of greater severity, invasiveness, chronicity, or recurrence in the presence of HIV coinfection.[628–630] Enterotoxigenic *Escherichia coli* has not been described as causing more severe disease in HIV-seropositive patients, but *Shigella* species, *Salmonella*, *Campylobacter*, and *Listeria monocytogenes* have all been implicated as causes of more severe or relapsing disease in the presence of HIV. Data from the tropics on enteric bacterial pathogens are scant. Studies of slim disease (enteropathic AIDS) have not revealed an enteric bacterial cause in most cases.[349,503,504] The prevalence of certain enteric pathogens such as *Campylobacter*, *Vibrio*, and enteropathogenic *E. coli* in the tropics has not been accurately assessed because their detection requires the use of special media and experienced laboratory personnel. In the case of less fastidious organisms that are easier to detect, such as *Salmonella* spp., the phenomenon of bacteremia with nontyphoid organisms has been noted in tropical Africa.[27,249,628] Since bacteremia with *Shigella* spp. probably occurs more commonly in patients with HIV disease,[631] this association may be expected to occur in the tropics as well. There is no reported evidence to suggest that cholera is altered in the presence of HIV, although the gastric secretory failure that occurs commonly in AIDS may lead to a greater susceptibility to infection with *Vibrio cholerae*.[632,633] It should be noted that, although the live oral cholera vaccine is considered to be contraindicated in people with HIV infection by the US Public Health Service (USPHS)–Infectious Diseases Society of America (IDSA) working group,[235] it has been shown to be safe and immunogenic in HIV-infected adults in Mali.[634]

Other Bacteria

Although data on HIV infection and epidemic meningococcal meningitis have not provided evidence for a significant interaction,[635] studies suggest that HIV infection may be a risk factor for sporadic meningococcal disease.[636,637] Interactions between HIV and *Bacillus anthracis* or *Yersinia pestis* have not been reported. The globally endemic *Bartonella* species, *B. henselae* and *B. quintana* (see Chapter 39), cause acute and persistent bacteremia as well as localized tissue infection (including bacillary angiomatosis, bacillary peliosis, microscopic abscess formation, and lymphadenitis), primarily in AIDS patients and other immunocompromised people.[55,638–641] The closely related species *B. bacilliformis*, which is geographically restricted to Andean river valleys, causes a similar spectrum of disease (including acute and persistent bacteremia and hemangiomatous nodules resembling those seen in bacillary angiomatosis) in immunologically normal hosts (see Chapter 39). Cases of coinfection with HIV and *B. bacilliformis* do not appear to have been reported.

Viral Infections

Hemorrhagic Fever Viruses, Arboviruses, and Others

No significant interactions have been well documented between HIV and bunyaviruses, hantaviruses, phleboviruses, arenaviruses, alphaviruses, or filoviruses. In part, of course, this may be a function of a lack of sufficient experience with coinfection with these agents. Among the flaviviruses, two uncontrolled series of patients with St Louis encephalitis in Texas have suggested the possibility that the ratio of disease to infection, but not the course of symptomatic disease, is worsened in the presence of HIV infection.[642,643] There are insufficient data to determine whether HIV alters the course of yellow fever (no case reports; 20–50% mortality in the absence of coinfection),[644] West Nile virus infection (a handful of case reports; interestingly, genetic data implicate CCR5, the HIV coreceptor, in resistance to symptomatic West Nile virus infection),[645] or dengue infection (a handful of case reports;[646] interestingly, one report suggests that dengue fever, like acute measles and scrub typhus, may lead to a reversible suppression of HIV replication).[647]

Should the live-attenuated yellow fever vaccine be given to those infected with HIV? There are theoretical risks of vaccine-induced encephalitis and/or hepatic damage due to prolonged viremia in the immunodeficient.[644] A handful of cases of postvaccinial encephalitis or multiple-organ failure (yellow fever vaccine-associated viscerotropic disease) have been reported in presumably immunocompetent patients (against a denominator of approximately 400 million people vaccinated).[644] Of note, 4 of 23 vaccinees who developed yellow fever vaccine-associated viscerotropic disease had undergone thymectomy for thymomas, raising the concern that T-cell deficiency may be a risk factor.[648]

A single case has also been reported of fatal myeloencephalitis after vaccination in a Thai man with asymptomatic HIV infection, albeit a low CD4^{+} T-cell count and a high viral load.[649] Approximately 100 asymptomatic HIV-seropositive US military personnel received yellow fever vaccination prior to the introduction of routine HIV screening; no adverse effects were detected (R. Redfield, personal communication, 1997). Small published series of travelers have suggested safety and variable efficacy of the 17D yellow fever vaccine in HIV seropositives without severe immunosuppression,[650–652] a concept bolstered by retrospective analysis of 102 patients in the Swiss HIV Cohort Study who received yellow fever vaccine.[653] As might be expected, the latter study noted reduced vaccine immunogenicity and a more rapid decline in titers of neutralizing antibody in those with HIV infection. The immunogenicity of yellow fever vaccination has also been noted to be severely reduced, again in the absence of significant adverse events, in HIV-infected children in Côte d'Ivoire.[654] WHO recommendations are to use yellow fever vaccine in HIV-seropositive patients who are asymptomatic; it remains a part of the WHO EPI.[655] Pending further studies, yellow fever vaccine is not recommended for symptomatic HIV-infected patients by WHO.[655] The ACIP recommends that HIV-infected people without AIDS or other symptomatic manifestations of HIV infection, who have laboratory-established verification of adequate immune function, and who cannot avoid potential exposure to yellow fever be offered the choice of vaccination.[656,657] As genetic evidence has implicated disruption of the CCR5/RANTES axis in a previously healthy, HIV-uninfected vaccinee who developed viscerotropic disease after vaccination,[658] it would be prudent to avoid such vaccination in patients receiving CCR5 antagonists.[659] Given apparent reduced vaccination efficiency, neutralizing antibody titers should probably be measured prior to travel. If travel requirements (as opposed to actual risk of infection) are the only reason for vaccination of an asymptomatic HIV-infected person, a vaccination waiver letter (not accepted at some borders) should be obtained.[657] For all travelers, avoidance of areas of transmission and, if travel to such areas is essential, conscientiously avoiding mosquito exposure is prudent.

Measles Virus

Measles virus (see Chapter 54) causes an annual mortality in the tropics far in excess of that due to the "traditional" tropical disease viruses. In fact, until quite recently[660] the worldwide yearly mortality due to measles was rivaled among single pathogens only by falciparum malaria, TB, and AIDS. This mortality is predominantly in sub-Saharan Africa. Similar to AIDS, infection with measles virus is accompanied by marked abnormalities of CMI that contribute to the increased susceptibility to secondary infections that account for much of the morbidity and mortality of the disease.[661]

Measles is exacerbated in the presence of HIV coinfection.[662] The mortality rate in North American case series and reports of measles in HIV-positive children and adults has been 40%, far higher than the usual 0.1% case fatality rate seen in the United States.[663–673] Although the presentation of disease has been normal in many, up to 40% have had no rash. In these reports, giant cell pneumonitis has been the principal complication and the prime cause of death, although fatal subacute measles encephalitis has also been described. CD4^{+} T-cell counts have not been reported in many of these cases, but where they have been reported they have generally been less than 500/μL. Such case reports and series are obviously likely to be biased toward the severe end of the spectrum of disease, however.

Four substantial studies have investigated HIV–measles coinfection in sub-Saharan Africa.[662,674–676] A study of children hospitalized with measles in Kinshasa showed similar mortality rates among HIV-seropositive (31.3%) and -seronegative (28%) children.[674] The fact that only severely ill patients, with complications, were hospitalized likely obviated the ability to detect differential mortality in this study. An initial study of children with measles in Lusaka revealed a significantly higher mortality rate in HIV seropositives (28%) than seronegatives (8.3%).[675] A second prospective study in hospitalized children in Lusaka that distinguished between HIV infection and HIV seropositivity found few differences in the clinical presentation, complications, or mortality of HIV-infected compared to -uninfected children with measles.[676] However, enrollment was based on a clinical diagnosis of measles, which would be expected to minimize the ability to detect differences in clinical presentation; there was a bias against enrollment of critically ill children and those dying soon after admission; and there was significantly greater mortality among HIV-infected compared with -uninfected children among those with clinically diagnosed as opposed to confirmed measles.[676] Early death prior to mounting diagnostic measles IgM titers in the face of severe immunosuppression was suspected to be confounding. Indeed, extension of enrollment in this study revealed that HIV coinfection led to a more than two-fold increase in measles mortality.[662] Other positive findings in these studies included a higher proportion of HIV infection among children hospitalized with measles than expected from (maternal) population prevalence rates, a greater proportion of coinfected patients hospitalized with measles younger than the age of 9 months, and a longer duration of illness before hospitalization and longer hospitalization in coinfected children.[676] Follow-up studies have shown that coinfected patients have a higher risk (90.9% vs. 52.8%) for prolonged (30–61 days after rash onset) shedding of measles virus;[677] and that *in vivo* HIV replication is suppressed during acute measles.[678]

No therapies have been rigorously studied. Vitamin A, which has been shown to be protective in severe measles in malnourished children,[679] may be of benefit, especially given the marginal nutritional status of many with HIV infection. Ribavirin has been shown to reduce the severity of measles in normal hosts.[680] Reports of its use in HIV-positive patients with measles pneumonitis have suggested some efficacy, although rigorous data are lacking.[665,666,668,669,672] Intravenous use is probably most effective. Intravenous immunoglobulin (IVIG) may also be of benefit.[666]

Given the severity of measles in HIV patients, prevention is key. Postexposure prophylaxis with intramuscular immunoglobulin attenuates disease in normal hosts. It is recommended by the ACIP[681] in symptomatic HIV patients (and in those with CD4^{+} T-cell counts <200/μL) regardless of measles serostatus, but it may have limited efficacy in these and other immunosuppressed patients.[669,682] The recommended dose is 0.5 mL/kg (15 mL maximum), given intramuscularly within 6 (or, better, 3) days. Such postexposure prophylaxis is also recommended by the American Academy of Pediatrics (AAP) for all HIV-infected children and adolescents, and for all children of unclear infection status born to HIV-infected women, regardless of measles immunization status or degree of immunosuppression.[683] Preexposure prophylaxis with monthly IVIG has been advocated for HIV-positive children with documented measles vaccine nonresponsiveness during community outbreaks of measles,[669] but this is not likely to be an economically viable option in the resource-poor areas of the tropics where measles is heavily endemic.

Vaccination remains the principal strategy for preventing measles in HIV-infected people. In normal hosts, the protective efficacy of measles vaccination is greater than 95%.[684] Vaccination efficacy data in HIV-seropositive people is lacking, but seroconversion data are available. In adults with HIV infection, there appears to be no waning of measles antibody titers with increasing immunosuppression.[685–687] Unfortunately, there are no clear data on the response to vaccination in those adults who lack antibodies to measles.[688] In children, the situation is different. HIV-infected infants have lower rates of seroconversion after measles vaccination, generate lower titers of antibody on seroconversion, and have a high rate of secondary vaccine failure, with antibody titers that decrease with time and with increasing immunosuppression.[689] In the absence of HAART-related immune reconstitution[690] responses to second doses of vaccine in the face of immune suppression are generally poor.[691]

There is likely benefit to vaccinating early (at 6–9 months of age), both because of lower levels of passively transferred antibodies in infants born to HIV-infected mothers,[692] and because of there being less HIV-related immunosuppression at this early age.[5] While this immunization strategy is clearly immunogenic, a greater percentage of HIV-infected (compared to HIV-uninfected) infants still remain measles-susceptible.[693]

Safety concerns have obviously been of great importance in the use of this live-attenuated vaccine in HIV patients. The use of measles vaccine had appeared to be quite safe in HIV-infected children and adults,[694] although two reports have emphasized the need for some caution. A 20-year-old man with no HIV-related symptoms but a CD4$^+$ T-cell count "too few to enumerate" received a second dose of measles vaccine prior to entry into college. One year after vaccination, he developed progressive, vaccine-associated measles pneumonitis.[695] A study of the effect of HIV on measles mortality in 356 children hospitalized with measles in Lusaka, Zambia, is also troubling.[675] Previous studies have suggested that when prior measles vaccination does not prevent disease, it can reduce the severity of infection.[674] In HIV-seronegative boys hospitalized for measles, prior measles vaccination did lead to a significantly lower case-fatality rate.[675] Although case fatality rates were not significantly lower in vaccinated HIV-seropositive boys or HIV-seronegative girls than in their unvaccinated controls, there was a trend toward a lower case fatality rate in the vaccinees. Surprisingly, however, the case fatality rate was higher in measles-vaccinated than in unvaccinated HIV-seropositive girls. Although this did not reach statistical significance, it is reminiscent of the experience with the high-titered Edmonston–Zagreb (EZ) vaccine. Use of high-titered EZ vaccine at less than 9 months of age was associated with a delayed excess mortality in several study sites.[696–698] This occurred exclusively in female infants for reasons that remain unclear. It is notable that in the Zambian study noted previously, the highest mortality was seen in the youngest, vaccinated HIV-seropositive girls. However, in regions where there is measles transmission, risk–benefit analysis clearly favors measles immunization of all children regardless of HIV status.[691] In regions where measles transmission does not occur and where immune status can be monitored, withholding of measles vaccine from HIV-infected children with severe immune compromise is wise.[691] WHO recommends measles vaccination for all children in developing countries regardless of HIV infection or symptom status because of the high risk and severity of measles in general in such countries.[693,699]

In the United States, the USPHS–IDSA working group and the Advisory Committee on Immunization Practice (ACIP) recommend measles vaccination for HIV-infected people according to the schedule and conditions for normal hosts if they are not severely immunocompromised.[17,56] In addition, the risks and benefits of vaccination or immunoglobulin prophylaxis should be weighed in severely immunocompromised patients who are at increased risk due to travel or outbreaks.[17] AAP recommendations for HIV-infected infants to young adults in the United States include:

- No immunization in the face of severe immunosuppression.
- Use of the measles–mumps–rubella (MMR) vaccine at 12 months of age, with a second dose given as soon as 28 days after the first dose.
- With measles transmission in the community, vaccination of infants as young as 6 months old with MMR or monovalent measles vaccine, and revaccination with MMR at 12 months.
- Vaccination of all measles-susceptible household members of an HIV-infected person.
- Use of immunoglobulin prophylaxis as noted previously.[683]

Few data are available on other paramyxoviruses in AIDS. With respiratory syncytial virus infection, pneumonia may be more common with bronchiolitis with wheezing, and viral carriage may also be prolonged.[700–703] Copathogens may occur more frequently than in normal hosts.[701] As for metapneumovirus infection, emerging data suggest higher rates of hospitalization, bacterial coinfection and mortality in HIV-coinfected infants.[704]

Rabies

Most human rabies (see Chapter 79) occurs in tropical countries where canine rabies is still endemic. The presentation of rabies does not appear to be altered by HIV infection.[705] HIV-infected, immunosuppressed children and adults clearly have substandard responses to rabies vaccination, however.[706–708] WHO recommendations for postexposure prophylaxis in the face of HIV infection include mandatory use of rabies immunoglobulin, use of intramuscular vaccine, and monitoring of neutralizing antibody titers.[709] Revaccination may be necessary. Even multiple-site, double-dose postexposure vaccination has led to poor responses in the face of HIV coinfection in the presence of immunosuppression.[708]

Poliomyelitis

There is no evidence that HIV infection alters the outcome of infection with poliovirus (see Chapter 60). It has been estimated that more than 500 000 HIV-infected children have received live oral polio vaccine (OPV).[691] Only two cases of vaccine-associated paralytic poliomyelitis in HIV-infected children have been reported.[691] If there is greater risk of vaccine-associated disease in the face of HIV infection, the attributable risk is thought to be very low and OPV remains part of the WHO expanded program of immunization for all children.[691] ACIP recommendations have replaced oral polio vaccine with inactivated polio vaccine for all vaccinees in the United States.[710]

Other Enteric Viruses

Chronic diarrhea is a common problem in AIDS patients throughout the world. Although no definite pathogenic role has been ascribed to enteric viruses (small round structured viruses, enteric adenoviruses, and coronaviruses) in AIDS-related diarrhea in either North America or Africa,[711,712] there are some preliminary data suggesting greater disease severity in children coinfected with HIV and astroviruses[712] and an association of picobirnaviruses with diarrhea in HIV-coinfected patients.[713] In noncholera-endemic areas of the tropics, rotavirus is probably the principal cause of diarrheal deaths in HIV-uninfected infants.[714] Rotavirus diarrhea does not appear to be an opportunistic pathogen in children with HIV coinfection. In a large study in Malawi, no differences in the severity of rotavirus gastroenteritis were found between HIV-infected and uninfected children. Interestingly, rotavirus was less frequently detected in HIV-infected children with gastroenteritis. Despite equal resolution of clinical disease, however, the frequency of death after hospital discharge was significantly greater in coinfected children.[715]

Hepatitis Viruses

Infection with hepatitis A virus (HAV) (see Chapter 64) occurs worldwide. In resource-poor countries, especially in the tropics, HAV is hyperendemic, and exposure is essentially universal by the age of 10 years. Virtually all adults are immune. HIV/HAV coinfection appears to be associated with a higher HAV serum viral load, a longer duration of viremia, and lower elevations in serum alanine aminotransferase levels[716] but a similar disease course.[716–718] Vaccination against HAV is safe in HIV-infected patients.[719–721] Efficacy wanes with increasing immunosuppression.[720,721] The CDC, the National Institutes of Health (NIH), and the HIV Medicine Association (HIVMA) of IDSA recommendations are to vaccinate: (1) those with chronic liver disease, MSM, and intravenous drug users; and (2) hepatitis A-susceptible, HIV-infected persons with risk factors for HAV infection.[710]

Infection with hepatitis E virus (HEV) (see Chapter 64) is more localized, with sporadic and epidemic disease being reported in Mexico; North and West Africa; the Middle East; and South, Southeast, and East Asia. Clinical disease occurs in both adults and children. Data are not clear as to whether HEV has a significant interaction with HIV.

With the cosmopolitan hepatitis viruses that are capable of causing chronic disease, however, several potentially important interactions with HIV have been described. The prevalence of coinfection is furthered by the fact that these viruses share routes of transmission with HIV. For hepatitis B virus (HBV) (see Chapter 66), CMI responses are thought to be important both for the resolution of acute disease and for the production of hepatic inflammation in chronic disease. HIV infection has been reported to lead to: (1) at least a threefold increase in risk of the development of a chronic HBV carrier state (with an inverse correlation with the CD4 count), without a significant change in the severity of acute disease; (2) potential reactivation of quiescent HBV infection; (3) increased HBV

replication and decreased inflammation in those with[722,723] or without[724] chronic hepatitis; (4) decreased response to HBV vaccination;[725] (5) loss of HBV antibody over time;[725,726] and (6) increased rates of cirrhosis, and liver-related mortality, and increased risk of hepatocellular carcinoma.[727,728]

Vaccination against HBV has reasonable efficacy in HIV-seropositive populations. Interestingly, however, the highest reported rate of development of chronic carrier status in adults (56–80%) occurred in HIV-infected people who were vaccinated at the same time that they developed HBV infection.[729] HBV does not appear to have a significant effect on the clinical course of HIV infection.[730]

Coinfection with hepatitis C virus (HCV) (see Chapter 65) and HIV is associated with reduced likelihood of spontaneuous clearance, an increase in HCV viral set point, increased risk of cirrhosis, and reduced likelihood of a successful response to treatment.[731] In the HAART era, HCV-induced liver disease has become a leading cause of mortality in HIV-infected persons. Whether HCV infection has a significant effect on the natural history of HIV infection or the response to HAART remains controversial.[732–736] Maternal HCV infection appears to be associated with an increased risk of HIV vertical transmission.[737]

The data on hepatitis D virus (HDV) are more meager. HDV replication may be prolonged or reactivated in the presence of HIV coinfection.[738,739]

Herpesviruses (see Chapter 56)

As in the industrial world, herpes zoster is quite common in adult AIDS patients in the tropics. A history of shingles is reported by more than 10% of AIDS patients in Africa.[740] In areas of Africa with HIV high seroprevalence, the positive predictive value of a history of shingles for HIV infection is greater than 90%.[740] As elsewhere, zoster tends to develop early in HIV disease; recurrence is common.[740,741]

Chronic genital herpes simplex lesions are common throughout the world in patients with sexually transmitted HIV infection. CMV infection is ubiquitous in most of the tropics.[742] The reported incidence of severe disease due to CMV in AIDS in Africa and Asia (although not Latin America and the Caribbean) has lagged behind that of the industrial north, however, likely because of greater mortality at earlier stages of disease.[743,744] The natural history, diagnosis, and therapy of disease due to coinfection with these cosmopolitan herpesviruses have been discussed elsewhere.[745–747]

Endemic (central Africa), AIDS-related, "classic," and post-transplant Kaposi's sarcoma are all closely associated with human herpesvirus 8 (HHV-8).[748] In the AIDS era, Kaposi's sarcoma has become one of the leading malignancies in areas of sub-Saharan Africa.[749]

Other Viruses

The single case report of severe acute respiratory syndrome coronavirus infection in the face of HIV coinfection was within the described clinical spectrum of this newly emerging virus.[750]

Prevention of Opportunistic Infections

The CDC/NIH/HIVMA/IDSA working group has updated guidelines for preventing OIs in HIV-infected people.[17,78] Several factors were weighed for the generation of these evidence-based recommendations: (1) disease incidence; (2) disease severity in terms of morbidity and mortality; (3) the level of immunosuppression at which disease is most likely to occur; (4) the feasibility, efficacy, and cost of preventive measures; (5) the impact of intervention on quality of life; (6) toxicities, drug interactions, and the potential for drug resistance; and (7) the quality of the evidence supporting each recommendation.[17] The prevention of each OI was evaluated from the standpoint of prevention of exposure, prevention of the first episode of disease (primary prophylaxis), prevention of disease recurrence (secondary prophylaxis), and discontinuance of prophylaxis in those whose CD4+ T-cell counts have risen in response to HAART.[17] These guidelines address specific recommendations for 29 pathogens that

interact with HIV, including five pathogens in the tropics, including malaria, penicilliosis, leishmaniasis, Chagas disease, and isosporiasis.[17]

Specific recommendations for prevention of exposure were made for several agents, including *Toxoplasma gondii*, *Cryptosporidium parvum*, *Mycobacterium tuberculosis*, bacterial enteric agents, *Bartonella*, herpes simplex virus (HSV), varicella-zoster virus (VZV), CMV, HHV-8, human papillomavirus, and HCV.[17,78] For adults and adolescents, primary prophylaxis is strongly recommended as a standard of care for *Pneumocystis jirovecii* (daily TMP-SMX (160/800 mg) or thrice-weekly TMP-SMX (320/1600 mg)), *M. tuberculosis* (with tuberculin skin test reactivity, a positive IFN-γ release assay test or contact with a case of active tuberculosis isoniazid daily or twice weekly for 9 months, with pyridoxine to prevent peripheral neuropathy), *T. gondii* (daily or three times weekly TMP-SMX (320/1600 mg); recommended alternative is dapsone–pyrimethamine plus leucovorin), MAC (azithromycin or clarithromycin), and VZV (live attenuated varicella vaccine with exposure to chickenpox or shingles in patients without a history of such, or with negative serologies for VZV and CD4 count ≥200). Primary prophylaxis (vaccination) against HBV, HAV, influenza virus, and *Streptococcus pneumoniae* was generally recommended. Although evidence exists for efficacy, it was not considered sufficiently robust to recommend primary prophylaxis routinely against *Cryptococcus neoformans*, *H. capsulatum*, *Coccidioides immitis*, CMV, or bacterial infection (in the face of neutropenia). For two of these agents (*P. jirovecii* and *M. avium*), primary prophylaxis has been shown to confer a survival benefit.[751–753]

Secondary prophylaxis was strongly recommended as the standard of care for *P. jirovecii*, *T. gondii*, MAC, CMV, *Cryptococcus neoformans*, *H. capsulatum*, *Coccidioides immitis*, and nontyphi *Salmonella* species. Such prophylaxis was recommended for HSV and *Candida* only if subsequent episodes are frequent or severe.[17] With respect to OIs in tropical regions, secondary prophylaxis was recommended for malaria (with drug regimens tailored to specific regions, depending on rates of resistance to commonly used antimalarials), *Penicillium marneffei* (itraconazole), visceral leishmaniasis (amphotericin B lipid complex), Chagas disease (benznidazole for latent disease) and *Isospora belli* (TMP-SMX).[17]

For children and adolescents[78] primary prophylaxis was strongly recommended as a standard of care for *Pneumocystis jirovecii* (TMP-SMX), malaria (mefloquine or atovaquone–proguanil), *M. tuberculosis* (isoniazid or rifampin), MAC (clarithromycin or azithromycin), and VZV (VZIG); generally recommended for *T. gondii* (TMP-SMX), VZV (immunization in the absence of immunosuppression), and influenza virus; and recommended only in unusual circumstances for invasive bacterial infection (hypogammaglobulinemia), *Cryptococcus neoformans* (severe immunosuppression), *H. capsulatum* (severe immunosuppression, endemic geographic area), and CMV (CMV antibody positivity and severe immunosuppression).[78] Primary prophylaxis was also addressed through review of the recommendations for routine immunization schedules in HIV-infected children. In addition to standard schedules for immunization against HBV, HAV, polio, *H. influenzae* type b, diphtheria, tetanus, and pertussis, altered schedules for vaccination against *Streptococcus pneumoniae* (heptavalent pneumococcal conjugate vaccine beginning at 2 months, followed by 23-valent pneumococcal polysaccharide vaccine at 2 years), influenza (yearly), measles–mumps–rubella (no administration to severely immunosuppressed children), and VZV (administration only to asymptomatic, nonimmunosuppressed children) were reviewed.

Recommendations for secondary prophylaxis in children were similar to recommendations for adults.[17,78] The list of pathogens included *P. jirovecii* (TMP-SMX), *T. gondii* (sulfadiazine plus pyrimethamine plus leucovorin), MAC (clarithromycin plus ethambutol ± rifabutin), *Coccidioides* spp. and *Cryptococcus neoformans* (fluconazole), *Histoplasma capsulatum* (itraconazole), *Microsporidia* spp. (albendazole), CMV (ganciclovir), *Bartonella* spp. (doxycycline), *Candida* (fluconazole), and HSV (acyclovir), with the addition of a recommendation for use of TMP-SMX or IVIG to prevent invasive bacterial infection in the presence of more than two such infections in a 1-year period.[78]

These recommendations are likely to find broad applicability in the industrial world, where the OI spectrum, health care priorities, and

available prevention options are similar. The applicability to much of the tropics is less clear, however, given differing spectra of OIs, differences in antibiotic resistance patterns, and differences in sociocultural acceptability or feasibility of preventive measures. Limits in the availability of health care resources (including not just an inability to support the cost of many prevention regimens but also an inability to diagnose HIV disease early enough for preventive measures to be effective, to stage the degree of HIV-associated immunosuppression reliably, and to diagnose OIs definitively) also directly influence the range of prevention options and priorities. It should also be noted that, compared with HAART (or prevention of HIV infection), the benefit of OI prevention in reducing HIV-related morbidity and mortality may be somewhat modest.[754] Adequate global provision of HAART represents an ongoing, immense challenge, however, and wide implementation of simple, cheap, effective OI prevention strategies provides an opportunity to reduce morbidity and mortality rapidly and widely.[744]

In 1996, Kaplan and colleagues argued that effective research on OI prevention strategies in the tropics will require an integrated approach, including the area-specific determination of OI spectra, determination of environmental reservoirs of opportunistic pathogens and feasible ways to reduce exposure, assessment of immuno- and chemoprophylaxis against such pathogens, and improvement in the ability to identify and inexpensively stage HIV infection.[20] Since then, data on the efficacy of some OI prevention strategies in resource-poor countries of the tropics have accrued.

First, as noted previously, primary preventive therapy against TB with isoniazid has been shown be effective in HIV-infected individuals, regardless of tuberculin status.[744,755,756] WHO and UNAIDS recommendations are for primary preventive therapy to be given to PPD-positive, HIV-infected individuals who do not have active tuberculosis.[757] In settings where it may not be feasible to do PPD testing, primary preventive therapy should be considered for those living in populations with an estimated prevalence of infection >30%, health care workers, household contacts of TB patients, prisoners, miners, and other groups at high risk of acquisition or transmission of TB.[758]

Second, TMP-SMX – a cheap, widely available antibiotic with activity against a plethora of OIs (including PCP, nontyphoid salmonellosis, pneumococcal disease, and toxoplasmosis) and malaria – has been shown to reduce morbidity and mortality in HIV-infected adults[759–763] and children.[475,764–766] WHO/UNAIDS recommendations are that TMP-SMX be used for prophylaxis in adults and children living with HIV/AIDS in Africa as a minimum package of care.[766] WHO/UNAIDS/UNICEF recommends that such prophylaxis should be offered to adults (defined as those >13 years old) with symptomatic HIV disease, those who are asymptomatic with a CD4 count of 500/μL or less (or total lymphocyte equivalent), and pregnant women after the first trimester.[766] All HIV-exposed children (born to HIV-infected mothers) should get TMP-SMX from the age of 4–6 weeks, as should any child identified as HIV-infected with any clinical signs or symptoms suggestive of HIV, regardless of age or CD4+

T-cell count.[766] It is further recommended that TMP-SMX be discontinued: (1) in HIV-exposed children only once HIV infection has confidently been excluded (and the mother is no longer breastfeeding); (2) in HIV-infected children on antiretroviral therapy when evidence of immune restoration has occurred; and (3) in those with severe cutaneous, renal, hepatic, or hematological toxicity.[767] It has been noted that such mass prophylaxis strategies entail some yet-to-be quantified risks, principally of increasing rates of drug-resistant bacteria and malaria.[768] Studies in Kenya have reported a modest increase in rates of drug-resistant enteric bacteria, without a significant increase in rates of drug-resistant malaria in these settings.[763,769]

Third, a large, randomized, double-blind, placebo-controlled trial of the 23-valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults showed no protective effect (with invasive pneumococcal disease as the primary endpoint).[770] Surprisingly, increased rates of pneumococcal disease were seen in vaccine recipients. The potential mechanism remains unclear; not surprisingly, the study remains controversial. The Strategic Advisory Group of Experts of the WHO has recommended that the licensed 7-serotype conjugate vaccine (PCV-7), already used in developed countries, be introduced in countries where HIV is a significant cause of mortality and in populations with a high prevalence of other underlying conditions that increase the risk of pneumococcal disease, such as sickle cell disease.[771] The PCV-7 vaccine can be easily integrated into routine vaccination schedules, with the possibility of being administered at the same time as other vaccines in infant immunization programs.[771]

Fourth, among the specifically tropical OIs, a controlled, double-blind trial of primary prophylaxis with itraconazole in Thailand showed efficacy in preventing penicilliosis (and cryptococcosis), a second study demonstrating efficacy in secondary prophylaxis.[772,773] As a result, daily itraconazole is recommended for secondary prophylaxis by the CDC/IDSA.[17] Recent studies of secondary prophylaxis in visceral leishmaniasis have found that treatment with antileishmanial drugs, including liposomal amphotericin and stibogluconate, reduced relapse rates by 30–40%.[774–777] However, in the absence of head-to-head comparison of drugs, no particular regimen can be recommended.[17] There are little or no data available on the prophylaxis of other tropical OIs, such as American trypanosomiasis, although the utility of avoiding exposures to the vectors of the agents of these diseases should be clear.

More generally, certain options for preventing or reducing exposure to opportunistic pathogens are likely to be broadly useful, including avoiding unboiled water, raw or undercooked foods and unpasteurized milk to prevent enteric bacterial and protozoan infections as well as *T. gondii* exposure, and avoiding contact with patients with TB, for example, in patient care settings. Avoiding exposure to the opportunistic agents of disseminated fungal disease is likely to be impractical in most settings.

Issues pertinent to the HIV-infected traveler are considered in Chapter 126.

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