Coinfection with HIV and Tropical Infectious Diseases. I. Protozoal Pathogens

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(See the article by Karp and Auwaerter on pages 1214–20)

The brunt of the human immunodeficiency virus (HIV) pandemic has been borne disproportionately by resource-poor regions of the world, where tropical infectious diseases continue to hold greatest sway. As a result, our understanding of the epidemiological, biological, and clinical interactions between HIV and tropical pathogens has lagged, compared with our understanding of the interactions between HIV and pathogens that are common in the industrialized world. Because of the current rapid expansion of HIV care in the tropics, with increasing resources being made available, an overview of the available data is timely. Tropical protozoa are discussed here; other tropical pathogens are discussed in a related mini-review in this issue of Clinical Infectious Diseases.

Much has been learned about the relationship between HIV infection and neglected tropical infectious diseases since the topic was last reviewed in Clinical Infectious Diseases [1]. As in the related mini-review covering HIV and tropical nonprotozoal pathogens [2], the focus here is on microbial agents that cause disease of markedly greater incidence in the tropics, except for such agents for which prevalence in the industrialized world has led to considerable published experience and research. The “tropical” label is burdened with some misleading historical associations. Traditionally, the field of tropical medicine focused on diseases caused by protozoa, helminths, and arboviruses. The triumvirate of pathogens currently devastating the tropics—Plasmodium falciparum, HIV, and Mycobacterium tuberculosis—includes only 1 such pathogen. That said, for practical reasons, the emphasis here remains largely on traditional tropical pathogens; cosmopolitan pathogens that have significant prevalence in HIV-infected persons in the industrialized world will not be discussed here in any depth.

Several tropical pathogens lead to opportunistic infection (OI) in the context of HIV infection. Coinfection has more subtle effects on the course of disease due to other tropical agents. No HIV-related alterations in epidemiology, natural history, or therapeutic response have been identified in the case of many tropical pathogens, including most nematodes. This should not be construed as strong evidence for the absence of such effects. In regions where coinfection with HIV and endemic tropical diseases is marked by low prevalence, subtlety of interaction, diagnostic difficulty, or low research priority, the interactions are likely to be overlooked. It took 15 years for the first significant interaction between infection with the high-profile pathogen P. falciparum and infection with HIV to be demonstrated—a relative lack of benefit of increasing parity among pregnant women in the control of malaria [3].

The clinical expression of HIV infection and AIDS in much of the tropics is marked by a high prevalence of tuberculosis (the most common serious AIDS-related OI worldwide), chronic diarrhea, wasting, chronic fever without an obvious source, and pulmonary disease. The contribution of tropical pathogens to the latter syndromes remains unclear, which underscores the limitations of the available data. With limited resources and poor access to medical care, surveillance is likely to be sporadic, with biased sampling (namely, of patients in the late stages of AIDS). Furthermore, reporting will likely favor OIs that are inexpensive to diagnose or misdiagnose. Even the reasonable hypothesis that the progression of HIV disease is more rapid in sub-Saharan Africa than in industrialized countries is based on data that are less than robust and, perhaps,
also prejudiced by later initial diagnosis in impoverished settings. Conversely, the burden of illness and mortality associated with early HIV disease (often unrecognized as such) due to infection with bacteria, such as Streptococcus pneumoniae, Salmonella species, and M. tuberculosis, may rival that due to the OIs that occur during late-stage AIDS in the tropics.

There are abundant complexities to the interactions between HIV and tropical infectious agents. Either pathogen has the potential for altering the epidemiology, natural history, and/or response to therapy of the other. The topic has recently been reviewed in greater depth than is possible here [4].

**MALARIA**

Because of large regions of shared endemicity, significant interactions between HIV and malaria were expected and feared. Although initial reports did not demonstrate interactions, complex bidirectional interactions between infection with *P. falciparum* and HIV have since been found [5, 6]. Part of the complexity relates to the epidemiology and immunobiology of malaria itself. *P. falciparum* causes severe disease and death largely among persons lacking specific acquired immunity. Such immunity is hard-won and only develops in the face of high rates of malaria transmission. In regions with stable, heavy transmission, the greatest burden of disease occurs in young children, pregnant women (vide infra), and travelers. Adults in such regions tend to be parasiticemic but asymptomatic. In regions with unstable or low transmission, the burden falls more equally on adults and children, and the relationship between parasitemia and disease is more direct [7]. Not unexpectedly, the interplay between HIV infection and malaria varies according to the dynamics of malaria transmission [5].

In regions with unstable transmission, HIV infection is a risk factor for severe malaria in both young children and adults [8–10]. HIV infection is presumably also a risk factor for severe malaria in young children in regions of heavy transmission, but firm data are lacking [5]. In contrast, HIV infection appears to only modestly increase the risk of parasitemia and clinical malaria in semi-immune adults in regions of holoendemicity. Although the risk increases with decreasing CD4+ T cell counts, malaria is less strongly associated with HIV-related immunosuppression than are other OIs [11–13].

Acquired immunity plays an important role in the clearance of drug-resistant parasites. HIV-associated immunosuppression would thus be predicted to affect the response to antimalarial therapy, especially when suboptimal, for adults in regions of holoendemicity. This appears to have been borne out by recent studies [6, 14]. HIV infection has also been associated with an increased risk of reinfection after successful treatment [15]. This may be a result of HIV-mediated weakening of immune responses to liver stage parasites. The additional possibility that *Anopheles* mosquitoes are more likely to bite those with HIV-related febrile illnesses should not be discounted. Of note, daily prophylaxis with trimethoprim-sulfamethoxazole, as recommended by the World Health Organization for all adults and children in sub-Saharan Africa with CD4+ T cell counts <500 cells/mm³, was associated with a 95% decrease in the frequency of febrile malaria episodes in a Ugandan study [16]. The further addition of antiretroviral therapy yielded an additional >60% decrease in the incidence of malaria-associated fever, supporting the link between HIV-related immunosuppression and vulnerability to *P. falciparum*. As might be expected, use of insecticide-treated bed nets decreased the risk further. What effect the broad use of trimethoprim-sulfamethoxazole in sub-Saharan Africa will have on the development of resistance to antifolate antimalarial drugs remains unclear. In addition, given the theoretical likelihood of significant metabolic interactions between anti-HIV and antimalarial drugs, the current lack of firm data on the subject is alarming [17, 18]. HIV infection alters the predictive value of fever in the empirical diagnosis of malaria; the common practice of empirically treating febrile adults for malaria likely leads to overestimation and overtreatment of malaria.

In regions of high malarial endemicity, the specific immunity that women of childbearing age have developed is compromised by pregnancy. Shielding of infected erythrocytes from the systemic immune response by the placental vasculature, in addition to expression of new antigens by placental parasites, allows local replication of *P. falciparum*. Local immunity constrains parasite replication, however, and the effectiveness of such local responses increases during subsequent pregnancies. The beneficial effects of parity are attenuated in the context of HIV infection. HIV infection is associated with increased incidence of peripheral and placental parasitemia, clinical malaria, and maternal anemia during pregnancy. Similarly, coinfection is associated with an increased risk of low birth weight, preterm birth, intrauterine growth retardation, and postnatal infant mortality [19]. It remains unclear whether malaria infection increases the risk of mother-to-child transmission of HIV infection; enhancement, protection, and no effect have all been published. A recent World Health Organization technical consultation recommended that HIV-infected pregnant women at risk for malaria should always be protected with insecticide-treated bed nets and should receive (according to stage of HIV infection) either intermittent preventive treatment with sulfadoxine-pyrimethamine or daily trimethoprim-sulfamethoxazole prophylaxis. The safety of the latter recommendation during pregnancy remains unclear [20].

With regard to the effects of malaria on HIV infection, *P. falciparum* infection is associated with an increased viral burden in peripheral and placental blood. Malaria-driven increases in HIV replication may well accelerate the course of HIV disease, which in turn could facilitate the sexual transmission of HIV.
infection. Although these are vitally important issues, definitive data are lacking. Finally, treatment of severe anemia due to malaria is a common indication for blood transfusion. As a result, malaria is an important risk factor for the acquisition of HIV infection by children in regions where the blood supply is not well screened [21].

BABESIOSIS

Intraerythrocytic protozoa of the genus Babesia parasitize numerous vertebrates, predominantly in tropical and subtropical regions. Human disease has mostly been reported from temperate zones. Severe disease has been described in HIV-infected patients with one of the temperate species causing malaria-like disease in humans, raising the possibility that tropical species present a risk for patients with AIDS and providing the rationale for discussion here. Severe, persistent, and/or recrudescent Babesia microti parasitemia has occurred in immunosuppressed HIV-infected patients with intact spleens. Longer duration of therapy appears to be indicated, with close monitoring for relapse. Quinine, clindamycin, doxycycline, and azithromycin all can be used; combination therapy may be necessary.

LEISHMANIASIS

After toxoplasmosis, leishmaniasis is the most common tissue protozoan OI in patients with AIDS. The bulk of the reported data involves visceral leishmaniasis (VL) due to Leishmania infantum in the Mediterranean region. With the spread of the HIV pandemic, there is growing recognition of HIV-related VL due to Leishmania donovani in southern Asia and Africa and to Leishmania chagasi in South America [22].

Occurring in patients with low CD4+ T cell counts (generally <200 cells/mm³), HIV-related VL may occur because of primary infection or reactivation of clinically latent infection. A febrile illness lasting >2 weeks in an HIV-infected person with any history of residence or travel in regions of endemicity should raise clinical suspicion of VL. Although the basic clinical features of VL in HIV-infected patients mirror those in immunocompetent hosts (e.g., fever, weight loss, hepatosplenomegaly, and pancytopenia), aberrant manifestations of disease are often seen, including peripheral parasitemia (found in >50% of patients) and clinically evident ectopic parasites. Serosal, mucosal, and cutaneous involvement, including gastrointestinal, laryngeal, and pulmonary disease, have all been reported.

For immunocompetent persons, tests for antileishmanial antibodies have great use for diagnosing VL. In contrast, ~50% of coinfected patients lack detectable antibody levels. The situation may be different when leishmanial infection precedes HIV infection and subsequent impaired immune responses. Direct demonstration of organisms in blood or affected tissue samples is generally not difficult once the diagnosis has been considered. Among persons with AIDS, culture and PCR of buffy coat preparations yielded positive results for 55%–88% and 82%–98% of patients, respectively [23].

Successful treatment of leishmaniasis requires cellular immunity, regardless of the drugs used. The optimal therapy for VL in the context of HIV coinfection remains controversial. The same drugs used for treatment in HIV-uninfected hosts (including pentavalent antimonials and amphotericin B) can be used, albeit with significantly less efficacy [24]. Initially, 40%–65% of coinfected patients experience parasitological cure with treatment with pentavalent antimonials, amphotericin B deoxycholate, or amphotericin B lipid complex. The oral agent miltefosine also shows promise [25]. Secondary prophylaxis is essential. Both pentamidine and liposomal amphotericin therapies have been used; miltefosine therapy may well provide a practical alternative. The significant reduction in cases of AIDS-related VL seen in southern Europe after the advent of HAART has raised hope that immune reconstitution will allow successful cessation of secondary prophylaxis. The specific immunological and virological responses that are necessary for terminating secondary prophylaxis remain undetermined.

Despite a wider geographic distribution than VL, there are relatively few reports of coinfection with Leishmania species causing cutaneous leishmaniasis. As might be expected, the emerging clinical picture is one of difficult-to-treat, recurrent disease. Cutaneous dissemination is often seen; visceral dissemination has also been reported.

AMERICAN TRYPANOSOMIASIS

Chagas disease is a well-recognized OI associated with AIDS [26]. To date, the cases reported largely represent reactivation of chronic infection (not primary infection), which is expected because of the differing patterns of epidemiological risk for these infections; Trypanosoma cruzi infection occurs primarily in rural regions, and HIV infection occurs primarily in urban regions. Clinical reactivation generally occurs in persons with CD4+ T cell counts <200 cells/mm³ and most commonly involves the CNS. Lesions are often multiple, with preferential involvement of the white matter. Hemorrhagic foci can produce mass effects simulating brain tumors. Histologically, brain lesions exhibit necrosis, hemorrhage, and inflammatory infiltrates. Amastigote forms of the parasite are abundant in glial cells and macrophages. Myocarditis is a common autopsy finding in persons who have died of meningoencephalitis. Such myocarditis is often clinically silent. When present, clinical manifestations include arrhythmias and congestive heart failure.

Diagnosis depends primarily on considering the possibility of infection on the basis of geographic origin. If neurologic signs are present, imaging is key, but findings can be indistinguishable from toxoplasmic encephalitis, which may coexist. CSF findings include mild pleocytosis, increased protein levels,
and slightly decreased glucose concentrations in some patients. Motile trypanosomes may be visible on direct microscopic examination of centrifuged sediment, securing the diagnosis. If fever and other systemic signs are present, direct examination of the buffy coat may also reveal motile trypanosomes. Blood culture and xenodiagnosis are of considerable use; the latter is generally unavailable outside of regions of endemcity. PCR currently requires research laboratory facilities. *T. cruzi* serologies are only useful for ruling out reactivated infection. If tests are inconclusive, lesional biopsy may be performed. Clinical differentiation of HIV-related reactivation from chronic chagasic disease may be difficult. HIV-related reactivation is associated with high levels of parasitemia; however, parasitemia associated with chronic disease is very low. Indeed, even in the absence of clinical reactivation, chronic Chagas disease is generally associated with higher rates of parasitemia among patients coinfected with HIV than among HIV-seronegative persons [27].

There is not enough experience to evaluate the effectiveness of therapy with nifurtimox or benznidazole in HIV-coinfected patients, especially in persons with meningoencephalitis. No information is available on the penetration of these drugs into patients, treated with melarsoprol in a rural Congolese hospital, all 14 HIV-negative patients recovered, whereas 3 of 4 HIV-infected patients died during treatment, likely from treatment-related encephalopathy; the fourth patient did not respond to therapy [28].

In addition to human parasites of the genera *Leishmania* and *Trypanosoma*, the family of *Trypanosomatidae* includes genera that parasitize vertebrates, insects, and plants. There have been a few reports of HIV-infected individuals presenting with the clinical picture of VL, in whom analysis of lesional parasites has indicated that the responsible organisms actually belong to one of these latter genera [29]. Thus, it is likely that HIV-related immunosuppression can render humans vulnerable to normally nonpathogenic, lower trypanosomatids.

**OTHER TRYPANOSOMATIDS**

It is unclear whether HIV infection alters the epidemiology or clinical course of either West or East African trypanosomiasis. Anecdotal evidence exists that HIV infection may complicate the therapy of West African trypanosomiasis. Among 18 patients treated with melarsoprol in a rural Congolese hospital, all 14 HIV-negative patients recovered, whereas 3 of 4 HIV-infected patients died during treatment, likely from treatment-related encephalopathy; the fourth patient did not respond to therapy [28].

**FREE-LIVING AMOEBAE**

*Acanthamoeba* and *Balamuthia* species appear to be rare causes of opportunistic encephalitis, sinusitis, and cutaneous disease in patients with late-stage AIDS [30]. Most case reports have been from the United States, but the worldwide distribution of these ubiquitous protozoa and the fact that diagnosis is often post mortem suggest that underdiagnosis is widespread in the tropics. Granulomatous amebic encephalitis is a subacute to chronic disease of compromised hosts, generally causing death in weeks to months. Pathologic changes are found normally in the posterior neuraxis, mainly as necrotizing granulomatous inflammation. In patients with AIDS, granulomatous amebic encephalitis is marked by a more rapid course of disease and a paucity of well-formed granulomas. Patients with cerebral disease usually present with fever, headache, focal neurologic deficits, and mental status changes. Symptomatic involvement of sinuses or skin prior to the development of clinical granulomatous amebic encephalitis is common. Disseminated cutaneous disease has been involved in many reported cases and has been the sole manifestation of invasive disease in some patients. Cutaneous lesions, which can be quite pleomorphic, are usually nodular and may subsequently enlarge with ulceration and metastatic spread.

A high index of suspicion is key to antemortem diagnosis. Neuroradiologic findings mimic those associated with toxoplasmic encephalitis, with multiple enhancing mass lesions and surrounding edema. CSF findings are variable; wet mounts are occasionally useful. Both trophozoites and cysts can be found in tissue biopsy specimens but can be difficult to identify. *Acanthamoeba* species can be isolated by culture on *Escherichia coli*-seeded nonnutrient agar or in tissue culture media. No chemotherapeutic regimen is clearly efficacious for the treatment of disseminated disease. Agents with possible efficacy if used in combination include pentamidine, 5-fluorocytosine, sulfamethazine, sulfadiazine, fluconazole, itraconazole, ketoconazole, macrolides, phenothiazines, and rifampin. Testing isolates for drug susceptibility may be of value. In the context of isolated cerebral lesions, there may be a role for surgical excision.

Although primary amebic encephalitis due to the thermophile *Naegleria fowleri* has not been reported as a complication of HIV infection, a case of primary amebic encephalitis due to an apparently novel ameba that was not associated with thermally polluted water has been reported in a patient with late-stage AIDS [31, 32].

**MICROSPORIDIA**

Previously known as pathogens in insects, fish, and laboratory animals, *Microsporidia* species are intracellular protozoa that have emerged as important OIs in humans. Although *Microsporidia* species cause considerable disease in patients with AIDS
in the tropics, there is abundant experience with these cosmopolitan pathogens of immunosuppressed persons in industrialized countries; they will not be considered further here.

ENTERIC PROTOZOA

No significant effect of HIV coinfection on infection with Giardia lamblia has clearly been documented. Some immunocompetent and immunocompromised patients are refractory to standard therapeutic regimens. It may well be that such persistence is more common in the context of HIV infection [33].

In spite of evidence that protective immunity to Entamoeba histolytica requires cellular immunity, there is little evidence that patients with HIV infection or AIDS are more likely to develop invasive disease. Although several reports have suggested that Entamoeba seropositivity, intestinal colonization, and/or invasive disease are more prevalent among HIV-infected persons than among HIV-uninfected persons in East Asia (not a finding in other regions), the most likely explanation for this is the elevated local amebic colonization rate, specifically in men who have sex with men, as opposed to a biological effect of HIV infection.

A trio of coccidian protozoa—Isospora belli, Cryptosporidium species, and Cyclospora cayetanensis—are all causes of chronic, severe diarrheal disease in the context of HIV coinfection. There is considerable experience with HIV-related cryptosporidiosis and isosporiasis in the developed world. The clinical picture of HIV-related Cy. cayetanensis infection is similar, including the ability to involve the biliary tract. As with isosporiasis, trimethoprim-sulfamethoxazole provides effective therapy [34]. Relapses are common. In the absence of immune reconstitution, suppressive therapy is indicated. Infection with a fourth coccidian, Sarcocystis hominis, which is responsible for enteric and disseminated coccidiosis in humans, does not appear to have been reported in HIV-infected individuals.

No information is available with regard to whether Balantidium coli is a cause of OI in the context of HIV infection. Whether Blastocystis hominis causes diarrheal disease in either immunocompetent patients or in HIV-infected persons remains controversial. That said, some studies have found a higher incidence of B. hominis carriage in patients with AIDS who have diarrhea than in HIV-uninfected patients with diarrhea [35]. B. hominis is cosmopolitan, with no particular association with the tropics.

Acknowledgments

We thank F. Neva and R. Colebunders for helpful discussions.


References


