**Coinfection with HIV and Tropical Infectious Diseases. II. Helminthic, Fungal, Bacterial, and Viral Pathogens**

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(See the article by Karp and Auwaerter on pages 1208–13)

The morbidity, mortality, and social disruption caused by the human immunodeficiency virus (HIV) pandemic continue to weigh disproportionately on resource-poor regions of the tropics. As a result, the potential for significant epidemiological, biological, and clinical interactions between HIV and other tropical pathogens is great. An overview of the available data on tropical helminths, fungi, bacteria, and viruses is provided here; interactions between HIV and tropical protozoa are covered in a related mini-review in this issue of *Clinical Infectious Diseases*. Special attention is given to evidence relevant to the hypothesis that helminth coinfection plays a particularly important role in accelerating the pace of HIV pathogenesis in the tropics.

Considerable experimental and theoretical attention has been given to interactions 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 in this issue, which discusses HIV and tropical protozoa [2], the focus here is on pathogens that cause disease of markedly greater incidence in the tropics, except for pathogens for which there is considerable published experience and research in the industrialized world (e.g., *Mycobacterium tuberculosis*). Interactions between HIV and tropical infectious agents are marked by considerable complexity; 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 [3].

There are reasons for believing that any coinfecting pathogen can accelerate the pace of HIV pathogenesis (as well as facilitate transmission) by augmenting viral replication, and there is clear evidence that some pathogens do just this. Efficient replication of HIV is dependent on cellular activation, which can be induced by coinfecting pathogens either directly (e.g., via toll-like receptor signaling) or indirectly (e.g., by inducing proinflammatory cytokines or by activation of CD4⁺ T cells as part of the adaptive immune response). Helminth coinfection, ubiquitous in low-income tropical countries, has received particular attention as a potential accelerator of the course of HIV disease. In addition to the potential viral sequelae of chronic immune activation, it has been hypothesized that helminth-associated Th2 polarization may play an important role in driving HIV pathogenesis through preferential replication of HIV in Th2 cells, amplification of lymphocyte apoptosis, and upregulation of HIV coreceptor expression. Indeed, peripheral blood cells from patients with filariasis and schistosomiasis are more susceptible to in vitro infection with HIV than are peripheral blood cells from helminth-uninfected individuals [4, 5]. However, the overall hypothesis remains unproven. An initial study from Ethiopia indicated that HIV viral load was significantly higher in helminth-infected individuals than in helminth-uninfected individuals, correlating positively with parasite load and decreasing after therapeutic worm elimination [6]. However, similar studies performed in southern Africa that examined far larger numbers of patients have generally [7–11] (if not always [12]) failed to replicate these findings; 1 study even reported transient increases in viral load in patients receiving therapy for schistosomiasis [10].

This is perhaps to be expected. Direct equation of immune activation with amplification of HIV replication is a bit simplistic. Replication can be induced or suppressed in activated
CD4+ T cells, depending on the mechanism of activation [13, 14]. In addition, activation of proinflammatory cytokine production with positive effects on HIV replication goes hand in hand with activation of antinflammatory cytokine production, which can inhibit HIV replication [15]. Thus, it should not be surprising that some tropical pathogens (e.g., *Plasmodium falciparum*) increase plasma HIV load, and other tropical pathogens (e.g., measles virus and dengue virus) may actually decrease plasma HIV load. More generally, immune responses reliably induce counter-regulatory responses that may well suppress HIV replication. The immune environment of chronic helminth infection appears to be an especially good inducer of such counter-regulatory responses [16, 17].

On the other hand, recent studies have indicated that immune activation, broadly taken, is associated with accelerated CD4+ T cell count depletion, disease progression, and risk of mortality, independent of plasma HIV load [18, 19]. Although the mechanistic links remain unclear, coinfection may thus favor disease progression independent of effects on viral replication. In this regard, the recent demonstration that chronic HIV infection is associated with sustained systemic exposure to gut-derived microbial products may be of special interest [20]. Both luminal (e.g., geohelminths) and tissue (e.g., *Schistosoma* species) helminths may further alter the functional permeability of the gut, driving immune activation and disease progression, independent of effects on viral load. It should also be noted that helminth co-infection has been associated with an increased risk for mother-to-child transmission of HIV infection [21]. There is a desperate need for more research on these issues.

**HELMINTHS**

**Trematodes.** There is no evidence that any trematode infection is more severe in HIV-infected persons. Subtle interactions have been explored in the context of schistosomiasis [22]. The CD4+ T cell–dependent granulomatous response to schistosome eggs is important for luminal migration of eggs in mouse models. Suppression of egg excretion efficiency has been found in HIV-coinfected patients with heavy *Schistosoma mansoni* or *Schistosoma haematobium* burdens, although the significance of this observation remains unclear [23]. Although praziquantel retains efficacy in the context of HIV coinfection when assessed by egg counts (at least when schistosome exposure precedes HIV infection) [24], it may be less effective at reducing the adult worm burden in coinfected patients [25]. Increased susceptibility to reinfection has also been observed [26]. Finally, female [27] (and, likely, male [28]) urogenital schistosomiasis due to *S. haematobium* increases the risk for HIV transmission. To date, the literature is lacking regarding significant interactions between HIV and intestinal, hepatic, or pulmonary trematodes.

**Cestodes.** Unusual manifestations of cestode infection have been reported in patients with AIDS, although the literature is not extensive. In the context of neurocysticercosis, the frequency of giant cysts and racemose forms of disease appears to be elevated in patients with cases complicating HIV infection [29]. Four cases of severe subcutaneous disease due to the larval form of *Taenia crassiceps* (a cestode whose definitive hosts are carnivores in North America and northern Eurasia) have been reported [30–33]. Because the only other reported human case was in an immunosuppressed patient, it appears likely that *T. crassiceps* causes opportunistic infection (OI) in patients with AIDS. Unusual, rapidly progressive hepatic alveolar echinococcal disease in a patient with AIDS has also been described [34]. Finally, an as yet uncharacterized cestode identified by ribosomal DNA analysis caused a lethally invasive abdominal mass in a patient with AIDS [35].

**NEMATODES**

**Strongyloides stercoralis.** The only nematode suspected of causing OI in the context of AIDS was *S. stercoralis*—the only nematode (apart from *Capillaria philippinensis*) that is capable of multiplying within human hosts. *S. stercoralis* hyperinfection syndrome was initially designated as an AIDS-related OI on the basis of experience in other immunosuppressed populations, particularly patients receiving corticosteroids [36]. Hyperinfection is the result of massive upregulation of the normal process of autoinfection, with the production of large numbers of larvae that disseminate widely. The clinical picture is dominated by gram-negative bacterial sepsis, meningitis, and/or pneumonia [36]. When it became apparent that hyperinfection syndrome was not encountered frequently in North American patients, it was removed from the list of AIDS-defining OIs. Because the syndrome has prominent clinical features and is generally fatal if untreated, it is unlikely that the association has escaped notice. Even in the few reported cases of HIV-related hyperinfection syndrome, the presence of hyperinfection is largely poorly documented. Unfortunately, confusion of gastrointestinal disease with hyperinfection syndrome is embedded in the literature. Although it is possible that severe strongyloidiasis complicates HIV infection more frequently in the tropics, this association is notably absent [37, 38]. A recent study has shed interesting light on the subject: HIV-related immunosuppression is associated, paradoxically, with suppression of the development of infectious larvae in the gut (which is necessary for autoinfection) [39]. This provides a likely explanation for anecdotal reports of immune reconstitution leading to hyperinfection syndrome [40]. More subtle interactions, such as increased gastrointestinal parasite burden or a slower response to therapy, may have been missed. It should also be noted that conditions that often cosegregate with HIV infection or AIDS are known to predispose to hyperinfection syndrome,
including steroid use, inanition, and coinfection with human T cell lymphotropic virus type 1 [41].

**Filaria.** Onchocerca volvulus coinfection has been studied in a large cohort, without finding significant epidemiological associations or any treatment differences with ivermectin in HIV-infected patients [42]. Onchocercal skin disease may be worse in patients with HIV infection [43], and 2 studies have suggested a significant association of lymphatic filariasis with HIV infection [21, 44]. The increased infectability of TH2-skewed CD4+ T cells may provide an explanation for this surprising finding, although an increased risk for HIV infection has not similarly been observed with other helminths.

**Fungi**

*Penicillium marneffei.* Disseminated infection with *P. marneffei*, a dimorphic fungus that is endemic to Southeast Asia and southern China, is an important OI in patients with CD4+ T cell counts <100 cells/mm³. The onset of symptoms is generally sudden and intense. Presentations commonly include fever (in 92% of patients), anemia (77%), weight loss (76%), and skin lesions (71%; characteristically, a generalized papular rash with central umbilication) [45]. Other frequent signs and symptoms include cough, generalized lymphadenopathy, hepaticomegaly, and diarrhea. Chest radiograph findings are frequently abnormal, with diffuse reticulonodular and/or localized alveolar infiltrates. A high index of suspicion is needed for diagnosis, including (outside of areas of endemcity) an appropriate travel history. The differential diagnosis includes tuberculosis (TB) and other endemic fungi. A lack of cutaneous findings, seen characteristically in the context of a syndrome primarily involving the liver, may hamper diagnosis [46]. Examination of Wright’s stained bone marrow, lymph node aspirate, or a skin biopsy specimen touch preparation can yield a presumptive diagnosis. Basophilic elliptic yeast-like organisms with central septation are characteristic of *P. marneffei*. Typical intracellular organisms may also be seen in routine blood smear specimens. In the study by Supparatpinyo et al. [45], definitive diagnosis was achieved by culture of blood (in 76% of patients), skin biopsy (90%), bone marrow (100%), and sputum (34%) samples. Diagnostic antigenemia tests that may prove to be valuable for rapid diagnosis have been developed. Quantitative urinary antigen measurement by EIA is especially promising. Of note, *P. marneffei* causes false-positive reactions in the Histoplasma capsulatum polysaccharide antigen immunoassay [47].

Mortality rates associated with *P. marneffei* infection are high in the absence of prompt treatment. Treatment with amphotericin B for 2 weeks, followed by itraconazole for 10 weeks, is safe and effective [48]. In patients with mild to moderate illness, primary therapy with itraconazole may be reasonable. Secondary prophylaxis is mandatory. Itraconazole is the drug of choice until sufficient immune reconstitution occurs [49, 50]. Itraconazole primary prophylaxis effectively prevents both penicilliosis and cryptococcosis if CD4+ T cell counts are <200 cells/mm³ [51].

**Paracoccidioides brasiliensis.** Paracoccidioidomycosis, the most common systemic mycosis in South America, occurs in 2 clinical forms in HIV-uninfected persons: an acute or subacute “juvenile” form and a chronic “adult” form. Juvenile disease, accounting for a small minority of cases, is marked by a rapid course with disseminated involvement of macrophages and lymphoid tissue and severe suppression of cellular immunity. Adult disease, accounting for the vast majority of cases, is a slowly progressive disease with prominent pulmonary manifestations, frequently accompanied by oral, nasopharyngeal, or cutaneous lesions, lymphadenopathy, and/or adrenal infiltration. Because cellular immunity is critical to host defense, paracoccidioidomycosis might be expected to be a prominent OI in South America. In fact, relatively few cases have been reported, despite the presumed wide prevalence of HIV coinfection in regions such as urban Brazil [52, 53]. Possible reasons for this include (1) use of trimethoprim-sulfamethoxazole prophylaxis for pneumocystis pneumonia; (2) use of ketoconazole for oropharyngeal candidiasis; (3) misdiagnosis as pneumocystis pneumonia, with a response to trimethoprim-sulfamethoxazole therapy; (4) lack of diagnosis; and/or (5) the presence of a particularly subtle interaction between these pathogens.

In HIV-infected persons, paracoccidioidomycosis presents primarily in the juvenile form, with prominent involvement of the reticuloendothelial system. However, pulmonary and oral mucosal involvement, more typical of the chronic form, often coexists [52, 53]. Although disseminated disease occurs in patients with a broad range of degrees of immunosuppression, such disease occurs more frequently in patients with CD4+ T cell counts <200 cells/mm³. Disease spans a wide spectrum, from indolent to rapidly progressive. Clinical manifestations include fever, weight loss, cough, dyspnea, generalized lymphadenopathy, hepatosplenomegaly, skin lesions, oral lesions (ulcerative and/or nodular), osteoarticular lesions, and meningitis. Direct examination or culture of skin, lymph node, bone marrow, CSF, or blood specimens may provide the diagnosis. Sputum specimens should be examined using potassium hydroxide, calcofluor white (a fluorescent stain that binds to chitin), or immunofluorescence. Serological studies have not been diagnostically helpful. No randomized clinical trials have been performed with any of the drugs commonly used for the treatment of *P. brasiliensis* infection, even in HIV-uninfected persons. That said, itraconazole is probably the drug of choice in HIV-uninfected persons [54]. Although amphotericin B and itraconazole may both have therapeutic roles to play in HIV-coinfected patients, amphotericin B should probably be used as initial treatment. Secondary suppressive therapy is necessary;
of HIV on published data on coinfection do not support a significant effect. Despite this, the meager experience and research on HIV-TB interactions in the industrialized world, TB will not be further considered here.

There is little or no evidence of a significant interaction between Mycobacterium leprae and HIV [56]. HIV infection does not appear to be more common in patients with clinical leprosy, nor does the clinical spectrum of disease appear to be significantly altered by HIV infection or AIDS. However, the evidence is not extensive, and the reported data are limited in quality. Coinfection may lead to a higher incidence of erythema nodosum leprosum and recurrent reversal reactions. HAART-associated immune reconstitution has been associated with triggering of injurious inflammatory reactions.

The prevalence and mortality associated with TB in the tropics far surpasses that in temperate zones. Indeed, TB is the leading cause of death among people with HIV infection worldwide [57]. However, because of the extensive published experience and research on HIV-TB interactions in the industrialized world, TB will not be further considered here.

A cause of systemic disease worldwide, Brucella species are facultative intracellular parasites of macrophages. Cellular immunity is important in host resistance. Despite this, the meager published data on coinfection do not support a significant effect of HIV on Brucella infection.

Similarly, melioidosis, which is endemic in Southeast Asia, does not appear to behave as an AIDS-related OI. Despite impressions that cell-mediated immunity is important for protection against Burkholderia pseudomallei infection, the data are compelling; neither increased rates nor increased severity of disease are apparent among patients with HIV infection [58].

BACTERIA

There are several predominant tropical fungi, including the agents of maduromycosis, lobomycosis, rhinosporidiosis, and subcutaneous zygomycosis, which may prove to cause OI in patients with AIDS. However, this has not yet been reported.

VIRUSES

Hemorrhagic fever viruses and arboviruses. None of the viruses that, along with parasites, formed the traditional focus of the Anglo-American specialty of tropical medicine have been reported to be uniquely prevalent, severe, or unusual among HIV-infected individuals. In particular, no significant interactions have been well documented between HIV and bunyaviruses, hantaviruses, phleboviruses, arenaviruses, alphaviruses, or filoviruses. This may, of course, in part be because of insufficient experience with coinfection. Among the flavirviruses, case series have suggested the possibility that, with regard to St. Louis encephalitis virus, the ratio of disease to infection (although not the course of symptomatic disease) is worsened by HIV infection. There are insufficient data to know whether HIV infection alters the course of infection with yellow fever virus, dengue virus, or West Nile virus. Interestingly, genetic data indicate that the HIV coreceptor CCR5 mediates resistance to symptomatic infection with West Nile virus [59].

With regard to the live attenuated yellow fever vaccine, there are theoretical risks of vaccine-induced encephalitis and viscerotropic disease in immunodeficient persons [60]. Small published series involving travelers have suggested safety and variable efficacy of the 17D yellow fever vaccine in HIV-seropositive persons without severe immunosuppression. World Health Organization recommendations advise vaccine use in asymptomatic HIV-seropositive individuals. The Advisory Committee on Immunization Practices recommends that HIV-infected persons without AIDS or other symptomatic manifestations of HIV infection who have laboratory-confirmed HIV infection alter the course of infection with yellow fever virus, dengue virus, or West Nile virus. Interestingly, genetic data indicate that the HIV coreceptor CCR5 mediates resistance to symptomatic infection with West Nile virus [59]. With regard to the live attenuated yellow fever vaccine, there are theoretical risks of vaccine-induced encephalitis and viscerotropic disease in immunodeficient persons [60]. Small published series involving travelers have suggested safety and variable efficacy of the 17D yellow fever vaccine in HIV-seropositive persons without severe immunosuppression. World Health Organization recommendations advise vaccine use in asymptomatic HIV-seropositive individuals. The Advisory Committee on Immunization Practices recommends that HIV-infected persons without AIDS or other symptomatic manifestations of HIV infection who have laboratory-confirmed HIV infection who have laboratory-confirmed HIV infection alter the course of infection with yellow fever virus, dengue virus, or West Nile virus. Interestingly, genetic data indicate that the HIV coreceptor CCR5 mediates resistance to symptomatic infection with West Nile virus [59].

Measles virus. Measles virus is associated with an annual mortality rate in the tropics that far exceeds the annual mortality rate associated with “traditional” tropical disease viruses. Similar to HIV disease, measles is accompanied by immune abnormalities that are responsible for the increased susceptibility to secondary infections that accounts for much of the associated mortality. Measles is itself exacerbated in the presence of HIV coinfection [62, 63]. Coinfected patients also have a higher risk for prolonged shedding of measles virus [64]. Prevention is key. Postexposure prophylaxis with intramuscular immunoglobulin is recommended by the Advisory Committee on Immunization Practices for symptomatic HIV-infected persons.


67. Moss WJ, Cutts F, Griffin DE. Implications of the human immuno-
68. HIV-infected children should be immunized against measles. World Health Forum 1989; 10:288.