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Tropical Diseases in HIV

Eva Clark, MD, PhD[*]
Jose A. Serpa, MD, MS

Address
[*]Department of Internal Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, TX, USA
Email: eva.clark@bcm.edu

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Abstract

Purpose of review With the rise of HIV, its impact on tropical infections has been undeniable. The presence of some tropical pathogens can facilitate the transmission of HIV, whereas untreated HIV infection can lead to the earlier and more severe presentation of a variety of tropical diseases and can make their treatment more challenging. Although the quality and availability of antiretroviral therapy has advanced significantly over the last two decades, it may not be readily available to all populations in low-resource regions.
Recent findings In addition, very little research has been done regarding drug interactions between antiretroviral therapy and medications used to treat tropical diseases.
Summary This article reviews existing data on coinfections of the most common tropical diseases and HIV, as well as current strategies for their treatment and control.

Introduction

The burden of parasitic, bacterial, fungal, and viral diseases in the tropics has uniformly increased in areas of elevated HIV prevalence. There are many ways in which the immunosuppression caused by HIV infection alters the natural history of tropical diseases. For instance, chronic infections such as schistosomiasis can increase the likelihood of HIV acquisition and transmission, while infections with organisms such as helminths and protozoa can accelerate the progression of HIV. Here we will review the available literature on the major tropical diseases presenting in HIV-infected patients and will identify conditions that would benefit from further investigation.

Nematodes

Soil-transmitted helminths

Soil-transmitted helminths (STHs) are endemic throughout the tropical regions of the world and affect all age groups. The most common STHs include *Ascaris* *lumbricoides* (roundworm), *Necator americanus* ("New World" hookworm), *Ancylostoma duodenale* ("Old World" hookworm), *Trichuris trichiura* (whipworm), and *Strongyloides stercoralis* (threadworm) [1]. The presentation of STH infections in HIV-infected individuals appears to be similar to that of their HIV-uninfected counterparts. Often STH infection is asymptomatic, although some STH infections such as hookworm are associated with anemia and growth stunting in children. Although *S. stercoralis* infection may be more likely to cause diarrhea in HIV-infected patients, they do not have an increased incidence of hyperinfection and dissemination syndromes, in contrast to individuals coinfected with HTLV-1 [2].

Some studies have demonstrated that patients with STH infections are more susceptible to HIV infection [3, 4]. Ten to 45% of HIV-infected individuals living in endemic regions have STH co-infection [4–6]. A recent Ugandan study found that 35% of HIV-infected individuals receiving ART tested positive for one or more STHs, mostly *N. americanus*, and almost 5% were infected with two or more STHs. In this study, HIV-infected individuals with hookworm had lower CD4 counts than their hookworm-negative counterparts [4]. There are several possible immunologic mechanisms that might explain this increased susceptibility. One of these is that an increased "type 2" (TH2) host immune response during helminth infection, such as the production of interleukin-4, may cause downregulation of "type 1" (TH1) responses, and subsequently, the individual may be more susceptible to viral infections, such as HIV [7]. Furthermore, HIV replicates preferentially in TH2 cells (CD4 T cells) and TH2 cells are abundant in immunocompetent individuals infected with helminths [8].

Regarding the effect of treating coinfected patients with antihelminth therapy, studies have yielded conflicting results. A Zambian study evaluated HIV-infected individuals both before and after antihelminth treatment and did not find an association between treatment of STH infections and reduction in viral load [9]. Subsequently, a larger Ugandan trial evaluated the effect of empiric STH treatment in HIV-infected individuals not receiving ART and found that CD4 count and HIV viral load did not differ between those treated with albendazole and praziquantel and those who did not receive antiparasitic treatment [10]. In contrast, an Ethiopian study evaluating STH-infected individuals prior to initiation of ART found that coinfected individuals had significantly higher CD4 counts 15 weeks and 6 months post-anti-helminth treatment [11]. Other studies with comparable design yielded similar results [10, 12].

Filaria

Onchocerciasis (river blindness)

Onchocerciasis is caused by *Oncocerca volvulus* and occurs in West Africa as well as smaller areas of Brazil, Venezuela, Guatemala, Mexico, and Yemen. Although HIV infection is prevalent in regions where individuals are most affected by *O. volvulus*, there is little information available describing coinfected populations. In one case–control study of coinfected patients in Uganda, microfilaria density was found to be lower in HIV-infected as compared with HIV-uninfected patients [13]. The same study showed that the efficacy of treatment with ivermectin and the occurrence of side effects was similar between the two groups, even when comparing those with lower CD4 counts. Sentongo et al. demonstrated a decreased cellular immune responsiveness in coinfected individuals when compared with those with only *O. volvulus* infection [14]. Similarly, the antibody response to *O. volvulus* antigen has been shown to be decreased in HIV-infected individuals [15]. The impact of these findings on transmission rates or disease progression is unknown.

Loiasis (African eye worm)

Both HIV and *Loa loa* are highly endemic in Central and West Africa. HIV infection generally is thought to enhance *L. loa* disease; however, few studies have examined the interaction between these two infections. A recent study evaluating plasma levels of *L. loa*-specific antibodies found significantly decreased levels of IgG3 and IgG4, as well as a significant increase in IgE, in HIV-infected individuals compared with uninfected controls, implying a decrease in *L. loa* immune-mediated regulation [16].

Lymphatic filariasis

Human lymphatic filariasis is primarily caused by two species, *Wuchereria bancrofti* and *Brugia malayi*. In tropical sub-Saharan Africa, areas of intense filarial infections overlap with regions of high HIV prevalence [17]. Several studies have found no clear evidence for a clinical interaction between HIV and *W. bancrofti* infection [18–20]. In contrast, a study by Gopinath et al. revealed that in vitro HIV replication was significantly increased in peripheral blood mononuclear cells from patients with untreated lymphatic filariasis [21]. More recently, a prospective observational study in Tanzania found a significantly higher HIV incidence in lymphatic filariasis-positive individuals (1.91 cases per 100 person-years) than in lymphatic filariasis-negative individuals (0.80 cases per 100 person-years) [22].

Cestodes (flatworms)

Taenia solium and neurocysticercosis

Taenia solium, or the pork tapeworm, is broadly endemic in tropical areas of the world. If embryonated *T. solium* eggs or gravid proglottids are accidentally ingested, the *T. solium* eggs develop into oncospheres that can penetrate the intestinal wall and travel to the skeletal muscles, heart muscles, and even the brain to form cystic structures called cysticercoses. A Mexican autopsy study showed that neurocysticercosis was less common in HIV-infected individuals (1.1%) than in HIV-uninfected individuals (2.4%) [23]. In a study in South Africa, neurocysticercosis was found to be one of the most common causes of focal brain lesions presenting with neurological signs in HIV-infected patients [24].

Little is known about how HIV changes the natural history of *T. solium* infections, and the available studies exhibit conflicting results. Some have shown that patients with higher CD4 counts are more likely to develop symptomatic neurocysticercosis requiring treatment, while others indicate that patients with advanced HIV and lower CD4 counts present either asymptomatically or atypically (e.g., with giant and racemose cysts) [24–26]. At least two studies found no significant correlation between the presence of *T. solium* antibody and CD4 counts [27, 28]. A case report suggested that initiation of ART might be associated with activation of latent neurocysticercosis in the context of IRIS [29].

Echinococcal disease

Echinococcal parasites are endemic worldwide and, although infection is usually asymptomatic, hydatid cyst formation with resulting complications can occur. A depressed immune response may lead to both an increased susceptibility to and a more severe manifestation of hydatid disease [30, 31]. One study from Mozambique evaluating parasitic diseases in HIV-infected individuals showed a high prevalence of seropositivity to echinococcosis [27].

Trematodes (flukes)

Schistosomiasis

More than 200 million people in the world are infected with one of five *Schistosoma* species: *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*. These organisms live in the host's pelvic and gastrointestinal venules and lay hundreds of eggs daily that migrate to the urogenital and gastrointestinal mucosa. These eggs can cause inflammation and breaks in the mucosa, which likely make women and men who have sex with men more susceptible to HIV transmission [32]. Downs et al. showed that women with *S. haematobium* infection were 4 times more likely to be HIV-infected than women without schistosomiasis, and women with *S. mansoni* were 6 times more likely to be HIV-infected [33, 34]. A more recent study by the same group demonstrated that schistosomiasis increases the likelihood of HIV acquisition in women and is associated with a higher HIV viral load at the time of HIV seroconversion [35]. A study in Madagascar demonstrated that infection with *S. haematobium* in men caused inflammation of the prostate and seminal vesicles, which theoretically may result in increased viral shedding into the semen of coinfected men [36]. Studies in macaques rectally infected with *S. mansoni* developed simian HIV infection at a dose 17 times lower than macaques without schistosomiasis [37, 38]. HIV infection could also affect reinfection with schistosomiasis. In a Kenyan cohort of individuals coinfected with HIV and *S. mansoni*, the time until reinfection with schistosomes was shorter than in HIV-uninfected individuals. The effect became more prominent in individuals with lower CD4 counts [39].

Regarding diagnosis of schistosomiasis, individuals, especially women, coinfected with some *Schistosoma* species and HIV have been found to excrete fewer eggs into stool and urine, indicating that stool/urine microscopy may not be the ideal way to diagnose infections in these patients [40]. One study showed that coinfected individuals not only excrete fewer eggs into the urine but also have less hematuria than HIV-uninfected individuals [41]. Praziquantel, the drug of choice for schistosomiasis, is effective in patients with *S. mansoni*– or *S. haematobium*–HIV coinfection [41, 42].

An interesting tangential development in the study of HIV–*Schistosoma* coinfection involves the efficacy of HIV vaccine candidates. In a recent mouse model study, investigators evaluated the ability of *S. mansoni* infection to alter

Table 1. Potential interaction between antimalarial medications and common antiretroviral drugs

		Anti-malarial drugs				
		Artemisinin	**Atovaquone**	**Chloroquine**	**Doxycycline**	**Lumefantrine**
NRTIs	Abacavir	–	–	–	–	–
	Emtricitabine	–	–	–	–	–
	Lamivudine	–	–	–	–	–
	TAF	–	–	–	–	–
	TDF	–	–	–	–	–
NNRTIs	Efavirenz	Decrease artemether level, long QT	Decrease atovaquone level, induction of glucuronidation by efavirenz	Long QT	–	Decrease lumefantrine level, long QT
	Etravirine	Decrease artemether level	Decrease atovaquone AUC	–	–	Decrease lumefantrine level
	Rilpivirine	Decrease rilpivirine level, long QT	–	Torsade de Pointes, tachycardia, long QT	–	Long QT
PIs	Atazanavir/cobicistat	Increase artemether level, decrease atazanavir level, long QT	Decrease atovaquone level	–	–	Increase lumefantrine level, long QT
	Darunavir/cobicistat	Increase artemether level, decrease cobicistat level, long QT	decrease atovaquone level	–	–	Increase lumefantrine level, long QT
	Ritonavir	Increase artemether level, decrease ritonavir level, long QT	Decrease atovaquone level	–	–	Increase lumefantrine level, decrease ritonavir level, long QT
Integrase inhibitors	Bictegravir	–	–	–	–	Decrease bictegravir level
	Dolutegravir	–	–	–	–	Decrease dolutegravir level
	Elvitegravir	Decrease elvitegravir level	–	–	–	Decrease elvitegravir level
	Raltegravir	–	–	–	–	–

	Anti-malarial drugs			
	Mefloquine	**Primaquine**	**Proguanil**	**Quinine**
NRTIs	–	–	–	–
	–	–	–	–
	–	–	–	–
	–	–	–	–
	–	–	–	–
NNRTIs	Decrease mefloquine level	–	Decrease proguanil level	Decrease quinine level, long QT
	Increase mefloquine level, long QT, seizures	–	Decrease proguanil level	Decrease quinine level
	–	–	–	Long QT
PIs	Decrease mefloquine level, long QT	–	Decrease proguanil level	Increase quinine level, long QT and PR, ventricular arrhythmias, CYP3A4
	Increase mefloquine level, long QT	–	Decrease proguanil level	Increase quinine level, long QT
	Decrease ritonavir level	–	–	Increase quinine level, long QT and PR
Integrase inhibitors	–	–	–	–
	–	–	–	–
	–	–	–	–
	–	–	–	–

Dash means no data available or not studied
NRTIs nucleoside/nucleotide reverse transcriptase inhibitors, *NNRTIs* non-nucleotide reverse transcriptase inhibitors, *PIs* protease inhibitors, *TAF* tenofovir alafenamide, *TDF* tenofovir disoproxil. En dash indicates no proven or potential drug–drug interactions

immune responses to three candidate HIV vaccines [43]. They found that chronic *S. mansoni* infection attenuates both HIV-specific T cell and antibody responses, although treatment of parasite infection may partially restore cellular but not antibody immunity.

Protozoa

Tissue Protozoa

Malaria

There are five species of malaria that are known to infect humans (*Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*). Malaria was estimated to cause nearly half a million deaths in 2016, with the highest morbidity and mortality in sub-Saharan Africa, where HIV prevalence is also highest [44]. Malaria and HIV both interact with the immune system, leading to complex activation of immune cells followed by tightly regulated production of cytokines and antibodies. Coinfected individuals typically have increased HIV viral load [45], decreased CD4 counts [46, 47], and higher parasitemia (at least in coinfected children under 5 years) [48], potentially worsening clinical outcomes and promoting HIV transmission [49, 50]. Recent data has indicated that coinfection has significant clinical consequences [51]. HIV contributes to more frequent and more severe malaria episodes [52], commonly manifested as anemia and cerebral malaria, and increased risk of congenital infection. One study found significantly more severe malaria and higher mortality in coinfected patients than in those with malaria alone [53].

HIV infection can also impair the efficacy of antimalarial treatment, increase adverse events, and select for parasites with drug-resistant mutations [54]. HIV-infected patients should be treated for acute malaria infection just as their HIV-uninfected counterparts are, though the prescriber should pay particular attention to potential drug interactions between ART and antimalarials (Table 1). Of note, many HIV-infected individuals receive trimethoprim-sulfamethoxazole (TMP-SMX) for opportunistic infection prophylaxis. This drug has been found to at least partially control malaria parasitemia, although it should not be used as a substitute for malaria treatment or prophylaxis. Ottichilo et al. recently observed that discontinuing TMP-SMX prophylaxis in patients on ART resulted in progressive increases in malaria parasitemia [55•].

Regarding HIV-positive travelers (including immigrants returning to malaria-endemic countries of origin after a prolonged absence), particular consideration should be paid to choosing appropriate antimalaria prophylaxis in the context of the individual's current HIV-regimen as well as the malaria drug resistance patterns in the country to which travel is planned. Table 1 includes potential interactions between antimalarial medications and common antiretroviral drugs.

Malaria in HIV-infected pregnant women

HIV-infected pregnant women have an increased incidence of malaria [56, 57]. Coinfection during pregnancy increases the risk of adverse birth outcomes, such as intrauterine growth retardation, preterm delivery, and reduction of birth weight [58]. In addition, coinfected mothers are more likely to transmit HIV via the placenta [59]. Mwapasa et al. observed a 2.5-fold higher plasma HIV viral load and a 2.4-fold higher placental HIV RNA concentration in HIV-infected women with placental malaria compared with those without placental malaria [60]. Eki-Udoko et al. found that congenital malaria was significantly higher in newborns of HIV-infected mothers than in those of HIV-uninfected mothers (34.6% and 22.2%, $p = 0.014$); profound immunosuppression (maternal CD4 count < 200 cell/mm^3) was significantly associated with congenital malaria in this study [61].

Because the risk of HIV transmission increases with higher HIV viral loads, adequate prophylaxis and treatment of malaria could potentially have an impact on the transmission of HIV from mother to child. Current strategies for the prevention of malaria during pregnancy include using insecticide-treated bed nets and intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine. For HIV-infected pregnant women taking daily TMP-SMX for prophylaxis, the World Health Organization (WHO) recommends avoiding the use of IPTp with sulfadoxine-pyrimethamine due to the risk of adverse drug reactions [62]. Monthly mefloquine as IPTp in addition to daily TMP-SMX reduced the risks of clinical malaria, malaria infection at delivery, and hospital admissions; however, it was associated with increased maternal HIV viral load and mother-to-child transmission of HIV [63]. Artemisinin-based combination therapies (ACTs) have been shown to be effective for the treatment of malaria in pregnancy [64, 65], but there are limited date on their use among HIV-infected women. The ACT dihydroartemisinin-piperaquine (DP) is currently recommended by the WHO for treatment of malaria in the second and third trimesters and is an especially attractive option for malaria prevention because it has a prolonged post-treatment prophylactic effect [66]. Several studies have shown that IPTp with DP is associated with a lower burden of malaria as compared with IPTp with sulfadoxine-pyrimethamine among HIV-uninfected pregnant women [67]. However, a recent study of HIV-infected pregnant women observed that adding monthly DP to daily TMP-SMX did not reduce the risk of placental or maternal malaria or improve birth outcomes [68•].

Leishmaniasis

Leishmaniasis is a protozoan parasite traditionally acquired via the bite of sand flies [69], and also more recently noted to be transmitted during injection drug use (IDU). Leishmania may cause a spectrum of diseases ranging from self-healing cutaneous ulcers to disseminated, fatal visceral infections. Cutaneous and mucocutaneous disease is typically seen in Latin America (the "New World") while visceral disease (VL) is more commonly found in Asia and Africa (the "Old World"). The type of manifestation and severity of disease depend mainly on the *Leishmania* species involved but also on the host's immune responsiveness. HIV-infected individuals are considered at high risk of developing leishmaniasis (or *Leishmania* reactivation as a manifestation of IRIS), and despite the introduction of ART, mortality rate and relapse rates are still high in coinfected individuals. Brazil, Ethiopia, and India appear to have the highest coinfection incidence. In Ethiopia, as many as 20% of individuals with VL are coinfected with HIV [70, 71].

Robust literature exists on the pathophysiology of the leishmaniasis–HIV interaction. The major surface protein of leishmania, a lipophosphoglycan, is associated with upregulation of HIV replication in monocytes and CD4 cells [72]. The CD4 depression caused by HIV provides a favorable environment for primary infection with *Leishmania* or for reactivation of latent infection. With depressed cellular immunity (defined as CD4 counts < 200 cells/mm^3), VL can manifest as an opportunistic infection, where parasite dissemination may occur [51, 73].

In coinfected individuals with visceral disease, only about half present with typical symptoms including fever, splenomegaly, and hepatomegaly [73–75]. Unusual localizations of parasite multiplication are common, and ulcers may be found in the gastrointestinal and respiratory tracts, in the CNS, and in the blood [51, 74, 75]. Diagnosis of VL is difficult in coinfected individuals. Few coinfected patients produce typical antibodies [76]. However, because spread of parasites into the circulation is more common in these patients, diagnosis via blood smear is more common than in their HIV-negative counterparts [73, 77] and PCR assays, although not widely available, can detect parasite DNA in up to 100% of coinfected patients [78, 79]. For VL diagnosis, invasive parasitological confirmation from spleen or bone marrow aspiration is still widely practiced in low-resource settings [71]. Rapid tests to detect VL have been evaluated in coinfected patients but have only moderate sensitivity and thus limited utility in monitoring during treatment [80].

Most coinfected individuals respond to treatment with pentavalent antimony or amphotericin B preparations [73, 77, 81]. However, treatment side effects are significantly more frequent and pronounced in these patients, especially when treated with pentavalent antimony [74, 82]. Toxicity of treatment is lower with liposomal amphotericin B for both HIV-infected and uninfected patients [81]. Overall, relapses occur in 25 to 80% of coinfected individuals [75, 82]. A recent Ethiopian study evaluated the initial effectiveness of a combination of liposomal amphotericin B and oral miltefosine to treat VL in coinfected patients and found promising results, with an initial cure rate of over 80% and parasitological failure rate of 3.5% [83].

The availability of ART has significantly reduced the incidence of VL [84], although HIV-infected patients treated for VL have higher initial treatment failure and relapse rates than their HIV-uninfected counterparts, especially if their initial parasite load was high [85]. Even if ART is combined with secondary antileishmanial prophylaxis, only partial protection against relapses is achieved [86–88]. A recent Ethiopian trial evaluated treatment with 12 months of pentamidine as secondary prophylaxis and found a 2-year relapse rate of almost 37%. Relapse rate was highest for those with a history of VL relapse and low baseline CD4 count. Of note, patients with CD4 counts > 200 cells/mm^3 had no relapses 1 year after stopping therapy [89]. In addition, patients receiving liposomal amphotericin B every 21 days seem to relapse less often than those receiving no prophylaxis [88].

African trypanosomiasis (sleeping sickness)

Sleeping sickness occurs only in Africa and is caused by two related protozoa (*Trypanosoma brucei* [*T. b.*] *gambiense* and *T. b. rhodesiense*) that are transmitted by the tsetse fly. Several relatively recent epidemiological studies found no major impact of HIV on African trypanosomiasis [90–92]; however, an older study observed that HIV-infected patients were more likely to relapse after treatment with eflornithine [93]. Similarly, in a study of 18 patients treated with melarsoprol for CNS trypanosomiasis, the four HIV-infected patients that were included either died or had an unfavorable outcome, whereas the 14 HIV-uninfected patients completely recovered [94]. Further studies are needed to determine the best treatment strategies for coinfected patients.

American trypanosomiasis (Chagas disease)

Chagas disease is caused by *Trypanosoma cruzi*, a parasite that only exists in Latin America, and, in immunocompetent hosts, is characterized by an acute phase with high *T. cruzi* parasitemia followed by a chronic phase with low parasitemia. Dormant *T. cruzi* infection can be reactivated if an individual becomes immunocompromised, and this often leads to high parasitemia [95, 96]. CNS involvement seems to occur more frequently in individuals coinfected with HIV compared with immunocompetent hosts [97–99]. Acute fatal meningoencephalitis, space-occupying lesions, and granulomatous encephalitis have been described [100–102]. Due to the possibility of severe complications, treatment with benznidazole should be started as soon as possible in coinfected individuals, even when patients are asymptomatic [103].

Bacteria

Buruli ulcer

Buruli ulcer is a necrotizing infection of skin and subcutaneous tissue caused by *Mycobacterium ulcerans*. This disease is most common in West and Central Africa, which are also regions of high HIV prevalence. Although coinfections are common, most published studies are small and show conflicting results on whether HIV infection is a risk factor for Buruli ulcer [104–106]. A relatively recent study from Cameroon found that the HIV prevalence in individuals with Buruli ulcers was 3–4 times higher than the estimated regional prevalence (36% compared with 8% in women, and 17% compared with 5% in men) [107]. The clinical presentation of coinfected patients also seems to be more severe than that of their HIV-uninfected counterparts. Several studies have found that HIV-infected individuals present with multiple lesions more often than HIV-uninfected patients, and the main lesion size appears to increase with decreasing CD4 counts [107–109]. For HIV-infected and uninfected patients, surgical debridement is the cornerstone of treatment for large ulcers while antibiotic therapy is effective for smaller lesions.

Leprosy

Leprosy remains endemic in distinct portions of the tropical world, where leprosy–HIV coinfections are not uncommon. HIV infection does not seem to increase susceptibility to leprosy, although leprosy commonly presents as a manifestation of IRIS after initiating ART in HIV-infected individuals living in endemic regions. Available evidence indicates that coinfected individuals tend to develop milder forms of the disease [110, 111]. Some studies report a higher prevalence of tuberculoid forms and a higher occurrence of reactions and neuritis in coinfected patients [112]. Leprosy treatment is the same for HIV-infected and HIV-uninfected individuals, although a review is needed of potential drug interactions with certain antiretroviral medications.

Viruses

Retroviruses

HTLV1-1

Of the four types of human T cell lymphotropic virus (HTLV), HTLV-1 is the most clinically significant. It is associated with diseases like adult T cell leukemia and tropical spastic paraparesis (TSP; also known as HTLV-1-associated myelopathy or HAM). HTLV and HIV share the same routes of transmission and the same tropism for T cells. Coinfection likely occurs more often than is reported as routine testing for HTLV is uncommon. It is estimated that rates of HTLV-1 coinfections in HIV-infected individuals are 100 to 500 times greater than in general population. There are some geographic areas where up to 20% of HIV-infected individuals may be coinfected with HTLV-1, particularly in South America, the Caribbean, and Africa [113].

Regarding the interaction between the two infections, HIV appears to up-regulate HTLV-1 expression, leading to a higher risk of HTLV-1-associated diseases, such as TSP/HAM and adult T cell leukemia. Only small studies exist to date, but several suggest that coinfection is associated with faster clinical progression to AIDS and a shorter survival time. Coinfection may stimulate HIV replication by causing increased production of specific host cell proteins [114]. Another study concluded that, although coinfection was associated with higher CD4 counts, it also is associated with higher WHO HIV disease stage [115]. A Brazilian case–control study evaluating 198 HIV-infected patients including 63 who were coinfected with HTLV-1 found that coinfected patients had a shorter mean survival [113]. Similarly, a small study in French Guiana found an increased risk of death for coinfected patients [116]. In contrast, Beilke et al. found no significant differences in progression to AIDS, presence of opportunistic infections, or death in coinfected individuals [117].

Flaviviruses

The clinically important flaviviruses are dengue, yellow fever, Japanese encephalitis, St. Louis encephalitis, tick-borne encephalitis, West Nile, and Zika viruses. Most flaviviruses are naturally found in animal reservoirs and are transmitted to humans via infected mosquitos or ticks. Transmission also can occur through transfusion or transplantation of infected tissue. Flaviviruses and HIV have similar areas of endemicity in many parts of the world, although only a few studies have been done to evaluate the impact of their coinfection.

Most of the published literature on HIV–dengue coinfection consists of case reports and case series [118–121]. These reports indicate that the majority of coinfected individuals present with mild symptoms, although some can have severe outcomes [122•]. Dengue virus infection may influence the clinical profile and immune response in HIV patients [123].

The recent epidemic of Zika virus in South America has raised new concerns about HIV–Zika coinfections and life-threatening sequelae [124]. At this time, it is unclear whether HIV infection increases susceptibility to Zika virus infection or whether Zika could worsen HIV disease control, especially during pregnancy, but studies are ongoing.

Currently, there are only two flaviviruses that are vaccine preventable: the yellow fever virus and the Japanese encephalitis virus. In immunocompetent individuals, the live attenuated 17D strain yellow fever vaccine has a short-term seroconversion rate of up to 99% and is thought to be an effective preventive measure [125]. It is only recommended for asymptomatic HIV-infected individuals who have CD4 counts > 200 cells/mm^3 because it is a live vaccine that potentially poses a risk of life-threatening neurotropic and viscerotropic sequelae [126]. A recent study evaluated the long-term immune response of HIV-infected patients to the yellow fever vaccine and found that a robust and prolonged response was achievable in individuals with good control of HIV at the time of vaccination [127].

Compliance with Ethical Standards

Conflict of Interest
Eva Clark declares that she has no conflict of interest. Jose A. Serpa declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- • Of importance

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