Current Infectious Disease Reports (2019) 21:49
https://doi.org/10.1007/s11908-019-0703-8

HIV/AIDS (C YOON, SECTION EDITOR)

Tissue Parasites in HIV Infection

Eva H. Clark[1,2] · Jose A. Serpa[1]

Abstract

Purpose of Review The purpose of this review is to discuss the current knowledge of HIV and tissue parasite co-infection in the context of transmission enhancement, clinical characteristics, treatment, relapse, and clinical outcomes.

Recent Findings The pathophysiology and clinical sequelae of tissue parasites in people living with HIV (PLWH) have been well described for only a handful of organisms, primarily protozoa such as malaria and leishmaniasis. Available published data indicate that the interactions between HIV and tissue parasites are highly variable depending on the infecting organism and the degree of host immunosuppression. Some tissue parasites, such as *Schistosoma* species, are known to facilitate the transmission of HIV. Conversely, uncontrolled HIV infection can lead to the earlier and more severe presentation of a variety of tissue parasites and can make treatment more challenging.

Summary Although much investigation remains to be done to better understand the interactions between consequences of HIV and tissue parasite co-infection, it is important to disseminate the current knowledge on this topic to health care providers in order to prevent, treat, and control infections in PLWH.

Keywords Tissue parasite · HIV · AIDS · Infectious diseases · Tropical

Introduction

Parasitic diseases remain a major cause of morbidity and mortality worldwide, particularly in tropical, low-resource regions, which overwhelmingly include communities with high HIV prevalence. Both intestinal and tissue parasites frequently cause disease in people living with HIV (PLWH); however, in this article, we will focus on the parasitic organisms that most often cause disease by invading host tissues rather than those that primarily affect only the gastrointestinal tract. In addition, we will not include those parasitic infections native to the USA (e.g., toxoplasmosis) that are commonly seen in PLWH, as those diseases are reviewed in great detail elsewhere. Herein, we will discuss the current knowledge of HIV and tissue parasite co-infection in the context of transmission enhancement, clinical characteristics, treatment, relapse, and clinical outcomes.

This article is part of the Topical Collection on *HIV/AIDS*

✉ Eva H. Clark
eva.clark@bcm.edu

Jose A. Serpa
jaserpaa@bcm.edu

[1] Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, TX, USA

[2] Houston HSR&D Center for Innovations in Quality, Effectiveness and Safety (IQuEST), Baylor College of Medicine, Michael E. DeBakey VA Medical Center, 2450 Holcombe Blvd., Suite 01Y, Houston, TX 77021, USA

Protozoa

Malaria

The co-existence of malaria and HIV, particularly in sub-Saharan Africa, is a long-standing problem that has caused significant morbidity and mortality, leading to more than 2 million deaths annually [1]. PLWH have an increased risk of developing malaria as well as other non-malaria febrile illnesses [2]. The interaction between malaria and HIV leads to the activation of a complex immunologic cascade followed by numerous detrimental clinical effects, including decreased CD4 counts [3, 4], increased HIV viral load [5], and higher malaria parasitemia [6]. These sequelae in turn are associated with worse clinical outcomes and increased HIV transmission [7, 8]. PLWH in areas of stable malaria transmission typically

Published online: 16 November 2019

have more frequent infections with higher levels of parasitemia than HIV-negative individuals, while PLWH in areas of unstable malaria transmission have an increased risk for severe malaria infection and death. [9]

Malaria treatment failure is more common in PLWH, particularly those with low CD4 counts. HIV infection has been known to weaken the efficacy of anti-malarial treatment, increase adverse events, and select for parasites with drug-resistant mutations [10]. However, due to a paucity of data on the effect of HIV on malaria treatment, current guidelines recommend that PLWH should be treated for acute malaria infection just as their HIV-negative counterparts are, e.g., primarily with artemisinin-based combination therapies (ACTs) [9]. Particular attention should be focused on potential drug interactions between anti-retroviral therapy (ART) and anti-malarials [11]. An excellent resource for evaluating the possibility of any drug interaction with ART is the freely available web-based Liverpool HIV Drug Interactions tool [12].

Notably, many PLWH receive trimethoprim-sulfamethoxazole (TMP-SMX) for the prophylaxis of opportunistic infections, and this drug has been found to at least partially control malaria parasitemia, even in regions where malaria parasites have developed resistance to TMP-SMX. Discontinuing TMP-SMX prophylaxis in patients on ART has been shown to result in progressive increases in malaria parasitemia [13]. However, despite this likely benefit of TMP-SMX, it should not be used as a substitute for malaria treatment or prophylaxis. In addition, TMP-SMX should not be continued if sulfadoxine-pyrimethamine is chosen for anti-malarial treatment due to significant risk of adverse drug reactions. The World Health Organization (WHO) advises avoiding the use of several additional drug combinations, including the combination of artesunate and amodiaquine in patients who are being treated with efavirenz or zidovudine, as together these drugs can lead to significant neutropenia [9]. Hepatotoxicity is also common when efavirenz and amodiaquine are used concomitantly.

Pregnant women with HIV have an even higher incidence of malaria [14, 15], particularly in the setting of profound immunosuppression [16]. Co-infected mothers are more likely to transmit HIV via the placenta [17, 18], and co-infection during pregnancy increases the risk of adverse birth outcomes including intrauterine growth retardation, preterm delivery, and low birth weight [19]. Chemoprophylaxis for and treatment of malaria has the potential to significantly decrease the transmission of HIV from mother to child. Currently, the recommended strategies for the prevention of malaria during pregnancy include using insecticide-treated bed nets and intermittent preventive treatment (IPTp) [9]. Both sulfadoxine-pyrimethamine and mefloquine are considered appropriate choices for IPTp in pregnant women with HIV [20]. However, just as in any PLWH, the WHO recommends avoiding the use of IPTp with sulfadoxine-pyrimethamine in pregnant women with HIV who are also taking TMP-SMX for opportunistic infection chemoprophylaxis, due to the risk of adverse drug reactions. Regarding the use of mefloquine for IPTp, monthly mefloquine in addition to daily TMP-SMX was shown to reduce the risks of clinical malaria, malaria infection at delivery, and hospital admissions; however, it has been associated with increased maternal HIV viral load and mother-to-child transmission of HIV [21]. ACTs are effective for the treatment of malaria in pregnancy [22, 23], but there are limited data on their use in pregnant women living with HIV. 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 [24]. Several studies in HIV-negative pregnant women have shown that IPTp with DP is associated with a lower burden of malaria as compared with IPTp with sulfadoxine-pyrimethamine [25, 26]. These findings can likely be extrapolated to pregnant women with HIV, although, importantly, for pregnant women with HIV on TMP-SMX for opportunistic chemoprophylaxis, adding monthly DP to daily TMP-SMX has not been shown to reduce the risk of placental or maternal malaria or improve birth outcomes [27].

Finally, regarding PLWH who are planning travel to a malaria-endemic area, choice of malaria chemoprophylaxis should be based on avoiding significant drug interactions with the individual's ART as well as the malaria drug resistance patterns in the country to which travel is planned.

Leishmaniasis

Leishmaniasis is a disease caused by a group of protozoa in the *Leishmania* genus that are traditionally transmitted by the bite of the sand fly [28], although these protozoa can also be transmitted via less common means such as blood transfusion and injection drug use (IDU). There are three standard classifications of leishmaniasis: cutaneous, mucocutaneous, and visceral (VL, also known as "kala-azar"). Cutaneous and mucocutaneous manifestations of the disease are more prevalent in Latin America than Asia and Africa. In contrast, VL is uncommon in Latin America (with the exception of Brazil) and very common in Asia and Africa. In practice, leishmaniasis encompasses a spectrum of diseases ranging from mild cutaneous ulcers that may not require treatment to widespread, mortal infections. The type and severity of leishmaniasis is determined by the species of *Leishmania* infecting the host; however, the strength of the host's immune system also plays a significant role in modulating the severity and duration of the disease. PLWH in endemic areas are at high risk of exposure to leishmaniasis, and in some countries up to 20% of individuals with VL are co-infected with HIV [29]. Mortality and relapse rates associated with leishmaniasis

remain elevated in co-infected individuals even in the ART era, likely because leishmaniasis affects the host's immune system in several different ways. For instance, one of the major surface molecules of *Leishmania* species is associated with upregulation of HIV replication in host immune cells, including monocytes and CD4 cells [30]. This in turn causes CD4 depression, which provides an ideal environment for primary infection with *Leishmania* or for reactivation of latent infection [31, 32].

Diagnosis of VL can be challenging in PLWH, and one of the reasons for this is that PLWH are less likely to present with symptoms typical of VL; only about 50% of co-infected individuals present with fever, splenomegaly, and hepatomegaly [32–34]. PLWH, particularly those with low CD4 counts, are more likely to have disseminated disease, and it is not uncommon to find unusual niduses of parasite multiplication in their gastrointestinal, respiratory, and central nervous systems [31, 33, 34]. Further confounding the diagnosis of VL in PLWH is that the humoral response to leishmaniasis is blunted in PLWH [35]. However, diagnosis via blood smear is often easier in PLWH than in their HIV-negative counterparts because disseminated disease is more common in PLWH [32, 36]. In practice, confirmation of the presence of parasites via spleen or bone marrow aspiration is still typically done in low-resource communities [29]. Although not often used in the clinical setting in leishmaniasis-endemic regions due to cost, PCR tests using whole blood can detect *Leishmania* in nearly 100% of co-infected patients [37, 38]. Rapid tests using finger prick blood samples to detect VL do exist but to date have been shown to have only moderate sensitivity; they may have some utility in treatment monitoring of co-infected patients [39].

Treatment for the various forms of leishmaniasis is usually guided by the species of the infecting organism and will not be discussed in detail here. However, regarding treatment of VL in PLWH, historically, co-infected individuals have been treated with pentavalent antimony plus paromomycin, or amphotericin B preparations [32, 36, 40]. It is important to note that leishmaniasis treatment side effects are more frequent and severe in PLWH, especially when they are treated with pentavalent antimony [33, 41]. The World Health Organization (WHO) now recommends monotherapy with liposomal amphotericin B when available. Toxicity of treatment is lower with liposomal amphotericin B for both PLWH and HIV-negative individuals [40]. A recent Ethiopian study evaluated the effectiveness of combination liposomal amphotericin B (total cumulative dose of 30 mg/kg) and oral miltefosine (100 mg/day for 28 days) to treat VL in PLWH and found promising results that support this regimen's use as first line therapy for co-infected patients [42].

The availability of ART has reduced VL incidence [43], although PLWH treated for VL continue to have higher initial treatment failure and subsequent relapse rates than their HIV-negative counterparts, particularly if their initial parasite load was high [44]. Supplementing ART with secondary antileishmanial prophylaxis has been shown to only achieve partial protection against relapses [45–47]. For instance, one study evaluated giving monthly intravenous pentamidine as secondary prophylaxis in PLWH for 12 months after their initial VL treatment and found that more than a third of patients relapsed within 2 years. Predictably, relapse rates were highest for those with a low baseline CD4 counts and a history of VL relapse. Importantly, patients with CD4 counts of more than 200 cells/mm^3 had no relapses 1 year after stopping pentamidine [48]. Other studies have supported the use of monthly liposomal amphotericin B (3 mg/kg/day every 21 days) as secondary prophylaxis to decrease relapse rates in co-infected patients [47].

African Trypanosomiasis (Sleeping Sickness)

Human African trypanosomiasis (HAT) is a disease of the nervous system that, in humans, is caused by two protozoa (*Trypanosoma brucei* [*T. b.*] *gambiense* and *T. b. rhodesiense*) transmitted by the tsetse fly (*Glossinia* genus). It occurs only in Africa and consists of two stages. In the first stage, the patient experiences fevers, headaches, arthralgias, and itching as the protozoa multiplies in subcutaneous tissues. This is followed by the second stage as the protozoa cross the blood-brain barrier and cause sleep cycle disturbances as well as other neurologic sequelae including behavior changes, confusion, sensory disturbances, and disequilibrium. Without treatment (ideally during the first stage), HAT is considered nearly uniformly fatal. Although HIV has diffused into HAT-endemic regions over the last several decades, most epidemiologic studies have shown no significant influence of the HIV epidemic on HAT prevalence [49–51]. Other than their overlapping epidemiology, the relationship between HIV and HAT has not been well studied, even though interaction between the two diseases is physiologically reasonable given the importance of cell-mediated immunity in the host response to HAT.

Treatment for HAT traditionally has been unsatisfying in all populations; however, the development of new drugs for this disease promises to make treatment easier and more effective [52]. At this time, PLWH are treated just as their HIV-negative counterparts are, although the few studies that have been done indicate that PLWH are more likely to relapse after treatment with eflornithine [53] and have significantly worse outcomes after treatment with melarsoprol [54]. Additional studies are needed to determine the best treatment strategies for co-infected patients, especially as the WHO works to eradicate HAT in the near future.

American Trypanosomiasis (Chagas Disease)

Trypanosoma cruzi is the protozoan etiologic agent of Chagas disease. Chagas disease is found only in Latin America and is traditionally transmitted to humans via the fecal matter of its

triatomine vector, although less frequently transmission by other means has been identified, such as by blood transfusion and organ donation or from mother to child via the placenta. *T. cruzi* infection is characterized by a short acute phase with high parasitemia followed by an asymptomatic chronic phase with low parasitemia. Decades after initial infection more than a third of individuals chronically infected with *T. cruzi* will develop either cardiomyopathy or typical GI manifestations such as mega colon and mega esophagus. Although the vast majority of chronically infected individuals are asymptomatic until these later sequelae develop, if the chronically infected individual becomes immunosuppressed, the parasite may reactivate, leading to high levels of parasitemia that can cause severe acute disease including meningoencephalitis and myocarditis [55, 56].

The interaction of HIV and *T. cruzi* has been extensively studied in endemic regions, particularly in Brazil, where *T. cruzi* reactivation has been recognized as a significant AIDS-associated opportunistic infection and is thought to occur in about 40% of co-infected individuals [57]. Although *T. cruzi* reactivation is most often diagnosed in individuals with CD4 counts less than 200 cells/mm^3, it has also been described in PLWH who have higher CD4 counts [58]. For unclear reasons, *T. cruzi* seems to particularly affect the central nervous system in PLWH [59–61], resulting in devastating consequences including acute fatal meningoencephalitis and granulomatous encephalitis [62–64]. Diagnosis of *T. cruzi* infection is traditionally confirmed by serologic tests, but in PLWH false-negative serologic tests commonly occur [57], likely due to their impaired ability to produce an adequate humoral response. Thus, suspicion for the disease must be higher in PLWH from endemic areas presenting with appropriate clinical findings. In these patients, *T. cruzi* is often found by tissue diagnosis, including cerebrospinal fluid examination. A rapid test that uses nanoparticles to quantify *T. cruzi* antigen in the urine is being developed for use as a correlate of *T. cruzi* parasitemia in co-infected patients [65].

Due to the possibility of severe complications resulting in high mortality, treatment with benznidazole should be started as soon as possible in co-infected individuals, even when patients are asymptomatic [57, 66]. Furthermore, some experts recommend monitoring for parasitemia via blood smear and/or PCR in PLWH known to be at risk for reactivation and who have CD4 counts less than 200 cells/mm^3 or uncontrolled HIV viral loads [57]. At this time, secondary prophylaxis for these patients is not recommended due to the significant side effects of the few available drugs with efficacy against *T. cruzi*. The role of immune reconstitution syndrome (IRIS) in exacerbation of *T. cruzi* disease has not been well characterized as of yet but is possible [67], thus PLWH from endemic areas should be evaluated for *T. cruzi* infection and treatment with benznidazole should be started prior to starting ART. PLWH should be closely monitored for symptoms characteristic of increased *T. cruzi* parasitemia after starting ART [65]. Treatment of co-infected women of childbearing age is doubly important as the rate of transmission of *T. cruzi* to fetuses via the placenta is likely higher in co-infected mothers, although, interestingly, in vivo studies of *T. cruzi*-infected placental cells has shown impaired HIV-1 replication in these cells [68], and pregnant women found to be *T. cruzi* positive cannot be treated until after delivery due to the toxic effects of benznidazole and nifurtimox on the fetus [69]. There remain many issues regarding *T. cruzi* infection in PLWH that would benefit from further study, including the specific host characteristics and physiologic mechanisms that lead to parasite reactivation and placental transmission, the effect of HIV control (or lack thereof) and starting ART on the likelihood of *T. cruzi* reactivation, and interactions between ART and drugs used for *T. cruzi* treatment, including new agents that are currently under development.

Nematodes (Roundworms)—Filaria

Onchocerciasis (River Blindness)

Onchocerciasis is caused by *Oncocerca volvulus*, a filarial nematode transmitted to humans via the bite of the blackfly (*Simulium* species). It primarily occurs in West Africa, although small foci of disease are found in parts of Brazil, Venezuela, and Yemen. Migration of *O. volvulus* microfilariae to various host tissues causes a range of symptoms including severe itching and skin disfiguration, but most significantly it often leads to visual impairment and permanent blindness.

HIV infection is common in the countries where *O. volvulus* is endemic, although the prevalence of onchocerciasis in PLWH does not seem to differ from that of HIV-negative individuals [70]. Little data has been collected describing the relationship between the two diseases. Regarding immunologic response to infection, PLWH have both impaired humoral responses to *O. volvulus* antigens [71] and decreased cellular immune responses when compared with HIV-negative individuals with *O. volvulus* infection [72]. In one case-control study of co-infected patients in Uganda, microfilariae density was found to be lower in PLWH as compared with HIV-negative individuals [70]. Even with lower levels of circulating microfilariae, skin disease caused by *O. volvulus* seems to be more severe in PLWH [73].

Diagnosis of *O. volvulus* infection is the same in PLWH as in HIV-negative individuals. The organism is typically identified via microscopy of skin snips in conjunction with examination of a timed blood smear to identify other filarial parasites that may be co-endemic. Treatment is also the same for PLWH and HIV-negative individuals. Ivermectin (150 mcg/kg orally) has been shown efficacious in co-infected patients [70], and mass treatment with ivermectin in areas with high prevalence of co-infection is safe [74]. Further investigation

will be necessary to elucidate the effect of these findings on *O. volvulus* transmission rates, disease progression, and the effect of therapy in co-infected individuals.

Loiasis (African Eye Worm)

Loa loa is another filarial nematode found primarily in Africa's rain forests. It is transmitted to humans via the deerfly (*Chrysops* species) and can cause a spectrum of disease ranging from no symptoms to nodular skin lesions to eye disease and, less commonly, pulmonary manifestations. The common name for this parasite, "African Eye Worm," developed because of the pathognomonic clinical presentation that occurs when the adult worm becomes visible as it passes under the patient's conjunctiva.

Both HIV and *L. loa* are highly endemic in Central and West Africa. Although little data has been published on this co-infection, HIV is generally thought to increase the severity of *L. loa* infection. One study suggested that immune regulation of *L. loa* infection is weakened in the setting of HIV co-infection by showing that plasma levels of *L. loa*-specific IgG3 and IgG4 antibodies are decreased in PLWH [75]. Treatment of PLWH with both ART and sulfamethoxazole-trimethoprim was shown to decrease the risk of *L. loa* infection in one study [76], suggesting that improvement in the robustness of the immune response and/or prophylaxis with anti-folate medications in endemic regions may prevent *L. loa* infection.

The diagnosis and treatment of *L. loa* can be challenging and has not been well studied in PLWH. When characteristic eye or skin manifestations are present, *L. loa* is usually identified macroscopically once it has been removed from the eye or from skin snips. Otherwise the diagnosis is typically made by daytime blood smear or *L. loa* serologic tests, although false negatives can occur in patients with low numbers of circulating microfilariae or decreased ability to produce a humoral response, as is characteristic of PLWH [75]. The decision to treat a patient infected with *L. loa* should be undertaken with care as significant side effects can occur in patients with high microfilariae burdens. The treatment of choice in endemic regions is diethylcarbamazine (DEC), which kills both the microfilariae and adult worms. Albendazole is often used in individuals who are not cured after multiple DEC administrations. It is unclear whether PLWH respond differently to traditional treatment than their HIV-negative counterparts.

Lymphatic Filariasis

Wuchereria bancrofti and *Brugia malayi* are the two mosquito-borne species of filaria that most often cause lymphatic filariasis, which is commonly known by many other names including "elephantiasis." These filaria preferentially affect the host's lymphatic system and infection can result in the pathologic enlargement of one or more gravity-dependent appendages (typically the legs). As with the other filarial diseases mentioned previously, regions where lymphatic filariasis is endemic often overlap with those of high HIV prevalence [77], and there is a paucity of data describing the effect of HIV infection on patients with lymphatic filariasis. Although one in vitro study found that HIV replication was significantly increased in the peripheral blood mononuclear cells of patients with untreated lymphatic filariasis [78], most studies had not found evidence for an interaction between HIV and *W. bancrofti* that altered the clinical course of either infection [79–81]. A more recent prospective observational study in Tanzania is the largest to date to study lymphatic filariasis in PLWH. Although the prevalence of lymphatic filariasis was similar in PLWH and their HIV-negative counterparts in this study, the authors found that individuals with lymphatic filariasis were much more likely to acquire HIV than those who did not have lymphatic filariasis [82]. In addition, they demonstrated a reduction in the prevalence of lymphatic filariasis as well as microfilariae burden in the study cohort after 2 years of mass drug treatment using albendazole and ivermectin. Mass drug administration was more effective in PLWH than in HIV-negative participants indicating that co-infection did not impair effectiveness of anti-filarial therapy [83].

Cestodes (Flatworms)—*Taenia solium* and Neurocysticercosis

The pork tapeworm, *Taenia solium*, is commonly found in tropical regions of the world. *T. solium* causes two different clinical entities in humans: intestinal taeniasis (adult worm dwelling in the gut) and cysticercosis (tissue invasion by the larval stage of the parasite). Cysticercosis occurs when the host unintentionally ingests embryonated *T. solium* eggs. Once in the host's gastrointestinal tract, the *T. solium* eggs develop into oncospheres that can penetrate the intestinal wall and travel to skeletal and heart muscles, and also the brain (neurocysticercosis). The clinical presentation of neurocysticercosis depends on the location of the cysts and host immune response. While some patients are asymptomatic at the time of diagnosis, those with symptoms typically present with headaches, seizures, and localized neurologic deficits.

The degree to which cysticercosis occurs in PLWH remains unclear. Even in countries where the prevalence of both diseases is high, there have been few reports of PLWH presenting with neurocysticercosis [84]. One Mexican study indicated that neurocysticercosis diagnosed by autopsy was actually less common in PLWH than in HIV-negative individuals [85]. It is possible that neurocysticercosis is underdiagnosed in PLWH as the less robust inflammatory response seen in PLWH with low CD4 counts may result in less manifestation of symptoms. PLWH with lower CD4 counts have been noted to present either asymptomatically or atypically (e.g., with giant and racemose cysts or with meningoencephalitis) [86–88].

Diagnosis of neurocysticercosis can be challenging in PLWH because of the multiple alternative etiologies of ring-enhancing brain lesions, including central nervous system (CNS) toxoplasmosis and CNS lymphoma. However, if such a patient is from a *T. solium*-endemic region and does not respond to 2 weeks of appropriate anti-*Toxoplasmosis* therapy, then empiric treatment for neurocysticercosis is usually warranted prior to resorting to brain biopsy [84, 87]. Treatment recommendations for neurocysticercosis do not differ for PLWH [89], although the pros and cons of starting ART in the setting of neurocysticercosis have not been well studied. At least one case report suggests that initiation of ART may result in activation of latent neurocysticercosis in the context of IRIS [90].

Trematodes (Flukes)—Schistosomiasis

Schistosomiasis is a parasitic disease that can be found in many tropical and subtropical regions, although it is most commonly seen in Africa and the Middle East. Human schistosomiasis is caused by five *Schistosoma* species: *Schistosoma mansoni*, *S. haematobium*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*. These organisms have complex life cycles that generally require the participation of freshwater snails. Human hosts are typically infected when they come into contact with freshwater containing *Schistosoma* cercariae, which are able to penetrate the host's skin and travel to the pelvic or gastrointestinal organs. Once there, adult *Schistosoma* worms lay hundreds of eggs daily that can cause inflammation as well as mucosal tears. Intestinal schistosomiasis, most often caused by *S. mansoni* and *S. japonicum*, can cause abdominal pain, diarrhea, and blood in the stool, followed by longer-term consequences such as anemia, hepatosplenomegaly, periportal fibrosis, and cirrhosis if untreated. Urogenital schistosomiasis, most often caused by *S. haematobium*, usually first manifests as hematuria, vaginal bleeding, and genital lesions. If untreated, the tissue inflammation caused by *Schistosoma* infection may lead to damage to the kidney, ureter, bladder, or prostate, and even bladder cancer and infertility in some cases.

The mucosal changes caused by *Schistosoma* infection are thought to increase the susceptibility of women and men who have sex with men to HIV infection [91, 92]. Indeed, several studies have shown not only that the prevalence of HIV is higher in *Schistosoma*-infected women [93, 94] but also that *Schistosoma* infection increases the likelihood of HIV acquisition in this population [95, 96]. A similar mechanism may make co-infected men more likely to acquire and transmit HIV. One study out of Madagascar demonstrated that men infected with *S. haematobium* had increased prostate and seminal vesicle inflammation, which could result in increased viral shedding into their semen [97]. PLWH, particularly those with lower CD4 counts, are probably also at higher risk for *Schistosoma* reinfection than their HIV-negative counterparts [98].

Diagnosis of schistosomiasis is more challenging in PLWH. Traditionally, the diagnosis is made by microscopic evaluation for *Schistosoma* eggs in urine or stool specimens. However, PLWH co-infected with *Schistosoma* seem to excrete fewer eggs and less blood into the urine/stool than their HIV-negative counterparts [99, 100]. Thus, PLWH from a schistosomiasis-endemic area presenting with suggestive symptoms should be treated empirically even if testing is negative. This is particularly important as *Schistosoma* treatment decreases the patient's likelihood of HIV transmission [96] and contributes to both decreased HIV viral load and increased CD4 count [101]. Praziquantel, the drug of choice for schistosomiasis, is effective in patients with *S. mansoni* or *S. haematobium*-HIV co-infection [100, 102].

Conclusions

As the HIV epidemic encompasses much of the tropical and subtropical world where parasitic infections are common, it is important to understand the impact and sequelae of co-infections. The interactions between HIV and tissue parasites are quite variable depending on the infecting organism and the degree of host immunosuppression. Some tissue parasites, such as *Schistosoma* species, are well known to facilitate the transmission of HIV. Conversely, uncontrolled HIV infection can lead to the earlier and more severe presentation of a variety of tissue parasites and can make treatment more challenging. A working knowledge of the epidemiology, pathophysiology, and diagnosis and treatment strategies for parasitic co-infections in PLWH may help to prevent and control these potentially devastating diseases.

Compliance with Ethical Standards

Conflict of Interest All authors declare 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 either of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. World Malaria Report. World Health Organization. 2017. http://www.who.int/malaria/publications/world-malaria-report-2017/report/en/. 2018. Accessed May 2019.

2. Molineaux L. Malaria and mortality: some epidemiological considerations. Ann Trop Med Parasitol. 1997;91(7):811–25. https://doi.org/10.1080/00034989760572.
3. French N, Nakiyingi J, Lugada E, Watera C, Whitworth JA, Gilks CF. Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. AIDS. 2001;15(7):899–906.
4. Jegede FE, Oyeyi TI, Abdulrahman SA, Mbah HA, Badru T, Agbakwuru C, et al. Effect of HIV and malaria parasites co-infection on immune-hematological profiles among patients attending anti-retroviral treatment (ART) clinic in Infectious Disease Hospital Kano, Nigeria. PLoS One. 2017;12(3):e0174233. https://doi.org/10.1371/journal.pone.0174233.
5. Hoffman IF, Jere CS, Taylor TE, Munthali P, Dyer JR, Wirima JJ, et al. The effect of plasmodium falciparum malaria on HIV-1 RNA blood plasma concentration. AIDS. 1999;13(4):487–94.
6. Okonkwo I, Ibadin M, Sadoh W, Omoigberale A. A study of malaria parasite density in HIV-1 positive under-fives in Benin City, Nigeria. J Trop Pediatr. 2018;64(4):289–96. https://doi.org/10.1093/tropej/fmx065.
7. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science. 2006;314(5805):1603–6. https://doi.org/10.1126/science.1132338.
8. Franke MF, Spiegelman D, Ezeamama A, Aboud S, Msamanga GI, Mehta S, et al. Malaria parasitemia and CD4 T cell count, viral load, and adverse HIV outcomes among HIV-infected pregnant women in Tanzania. Am J Trop Med Hyg. 2010;82(4):556–62. https://doi.org/10.4269/ajtmh.2010.09-0477.
9. Organization WH. Guidelines for the treatment of malaria. 3rd ed; 2015.
10.•• Flateau C, Le Loup G, Pialoux G. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. Lancet Infect Dis. 2011;11(7):541–56. https://doi.org/10.1016/S1473-3099(11)70031-7. **A comprehensive review of malaria in HIV infection**.
11. Seden K, Gibbons S, Marzolini C, Schapiro JM, Burger DM, Back DJ, et al. Development of an evidence evaluation and synthesis system for drug-drug interactions, and its application to a systematic review of HIV and malaria co-infection. PLoS One. 2017;12(3):e0173509. https://doi.org/10.1371/journal.pone.0173509.
12.•• HIV Drug Interaction Checker. University of Liverpool. https://www.hiv-druginteractions.org/checker. Accessed July 26, 2019. **The Liverpool HIV Drug Interaction Checker is an extremely up-to-date and useful tool for querying the interactions between any HIV drug and any other medication**.
13.• Ottichilo RK, Polyak CS, Guyah B, Singa B, Nyataya J, Yuhas K, et al. Malaria parasitemia and parasite density in antiretroviral-treated HIV-infected adults following discontinuation of cotrimoxazole prophylaxis. J Infect Dis. 2017;215(1):88–94. https://doi.org/10.1093/infdis/jiw495. **This reference describes a carefully-designed study describing the consequences of cotrimazole prophylaxis in PLWH in malaria-endemic areas**.
14. Bloland PB, Wirima JJ, Steketee RW, Chilima B, Hightower A, Breman JG. Maternal HIV infection and infant mortality in Malawi: evidence for increased mortality due to placental malaria infection. AIDS. 1995;9(7):721–6.
15. Verhoeff FH, Brabin BJ, Hart CA, Chimsuku L, Kazembe P, Broadhead RL. Increased prevalence of malaria in HIV-infected pregnant women and its implications for malaria control. Tropical Med Int Health. 1999;4(1):5–12.
16. Eki-Udoko FE, Sadoh AE, Ibadin MO, Omoigberale AI. Prevalence of congenital malaria in newborns of mothers co-infected with HIV and malaria in Benin city. Infect Dis (Lond). 2017;49(8):609–16. https://doi.org/10.1080/23744235.2017.1312667.
17. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, Serwadda D, Sewankambo N, Lutalo T, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. AIDS. 2003;17(17):2539–41. https://doi.org/10.1097/01.aids.0000096868.36052.29.
18. Mwapasa V, Rogerson SJ, Molyneux ME, Abrams ET, Kamwendo DD, Lema VM, et al. The effect of plasmodium falciparum malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. AIDS. 2004;18(7):1051–9.
19. Ayisi JG, van Eijk AM, ter Kuile FO, Kolczak MS, Otieno JA, Misore AO, et al. The effect of dual infection with HIV and malaria on pregnancy outcome in western Kenya. AIDS. 2003;17(4):585–94. https://doi.org/10.1097/01.aids.0000042977.95433.37.
20. Akinyotu O, Bello F, Abdus-Salam R, Arowojolu A. Comparative study of mefloquine and sulphadoxine-pyrimethamine for malaria prevention among pregnant women with HIV in Southwest Nigeria. Int J Gynaecol Obstet. 2018;142(2):194–200. https://doi.org/10.1002/ijgo.12516.
21. Gonzalez R, Desai M, Macete E, Ouma P, Kakolwa MA, Abdulla S, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. PLoS Med. 2014;11(9):e1001735. https://doi.org/10.1371/journal.pmed.1001735.
22. Piola P, Nabasumba C, Turyakira E, Dhorda M, Lindegardh N, Nyehangane D, et al. Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated plasmodium falciparum malaria: an open-label, randomised, non-inferiority trial. Lancet Infect Dis. 2010;10(11):762–9. https://doi.org/10.1016/S1473-3099(10)70202-4.
23. Rijken MJ, McGready R, Boel ME, Barends M, Proux S, Pimanpanarak M, et al. Dihydroartemisinin-piperaquine rescue treatment of multidrug-resistant plasmodium falciparum malaria in pregnancy: a preliminary report. Am J Trop Med Hyg. 2008;78(4):543–5.
24. White NJ. Intermittent presumptive treatment for malaria. PLoS Med. 2005;2(1):e3. https://doi.org/10.1371/journal.pmed.0020003.
25. Desai M, Gutman J, L'Lanziva A, Otieno K, Juma E, Kariuki S, et al. Intermittent screening and treatment or intermittent preventive treatment with dihydroartemisinin-piperaquine versus intermittent preventive treatment with sulfadoxine-pyrimethamine for the control of malaria during pregnancy in western Kenya: an open-label, three-group, randomised controlled superiority trial. Lancet. 2015;386(10012):2507–19. https://doi.org/10.1016/S0140-6736(15)00310-4.
26. Kakuru A, Jagannathan P, Muhindo MK, Natureeba P, Awori P, Nakalembe M, et al. Dihydroartemisinin-piperaquine for the prevention of malaria in pregnancy. N Engl J Med. 2016;374(10):928–39. https://doi.org/10.1056/NEJMoa1509150.
27.• Natureeba P, Kakuru A, Muhindo M, Ochieng T, Ategeka J, Koss CA, et al. Intermittent preventive treatment with dihydroartemisinin-piperaquine for the prevention of malaria among HIV-infected pregnant women. J Infect Dis. 2017;216(1):29–35. https://doi.org/10.1093/infdis/jix110. **This reference describes the most recent data on intermittent preventive treatment with dihydroartemisinin-piperaquine for the prevention of malaria in pregnant PLWH**.
28. Molina R, Gradoni L, Alvar J. HIV and the transmission of Leishmania. Ann Trop Med Parasitol. 2003;97(Suppl 1):29–45. https://doi.org/10.1179/000349803225002516.
29. Diro E, Lynen L, Ritmeijer K, Boelaert M, Hailu A, van Griensven J. Visceral Leishmaniasis and HIV coinfection in East Africa.

PLoS Negl Trop Dis. 2014;8(6):e2869. https://doi.org/10.1371/journal.pntd.0002869.

30. Bernier R, Barbeau B, Tremblay MJ, Olivier M. The lipophosphoglycan of Leishmania donovani up-regulates HIV-1 transcription in T cells through the nuclear factor-kappaB elements. J Immunol. 1998;160(6):2881–8.
31. Harms G, Feldmeier H. HIV infection and tropical parasitic diseases - deleterious interactions in both directions? Tropical Med Int Health. 2002;7(6):479–88.
32. Leishmania/HIV co-infection, south-western Europe, 1990–1998. Wkly Epidemiol Rec. 1999;74(44):365–75.
33. Alvar J, Canavate C, Gutierrez-Solar B, Jimenez M, Laguna F, Lopez-Velez R, et al. Leishmania and human immunodeficiency virus coinfection: the first 10 years. Clin Microbiol Rev. 1997;10(2):298–319.
34. Lopez-Velez R, Perez-Molina JA, Guerrero A, Baquero F, Villarrubia J, Escribano L, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfected with human immunodeficiency virus and Leishmania in an area of Madrid, Spain. Am J Trop Med Hyg. 1998;58(4):436–43.
35. ter Horst R, Tefera T, Assefa G, Ebrahim AZ, Davidson RN, Ritmeijer K. Field evaluation of rK39 test and direct agglutination test for diagnosis of visceral leishmaniasis in a population with high prevalence of human immunodeficiency virus in Ethiopia. Am J Trop Med Hyg. 2009;80(6):929–34.
36. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. Medicine (Baltimore). 2001;80(1):54–73.
37. Bossolasco S, Gaiera G, Olchini D, Gulletta M, Martello L, Bestetti A, et al. Real-time PCR assay for clinical management of human immunodeficiency virus-infected patients with visceral leishmaniasis. J Clin Microbiol. 2003;41(11):5080–4.
38. Pandey N, Siripattanapipong S, Leelayoova S, Manomat J, Mungthin M, Tan-Ariya P, et al. Detection of Leishmania DNA in saliva among patients with HIV/AIDS in Trang Province, southern Thailand. Acta Trop. 2018;185:294–300. https://doi.org/10.1016/j.actatropica.2018.06.006.
39. Vogt F, Mengesha B, Asmamaw H, Mekonnen T, Fikre H, Takele Y, et al. Antigen detection in urine for noninvasive diagnosis and treatment monitoring of visceral Leishmaniasis in human immunodeficiency virus coinfected patients: an exploratory analysis from Ethiopia. Am J Trop Med Hyg. 2018;99(4):957–66. https://doi.org/10.4269/ajtmh.18-0042.
40. Laguna F, Videla S, Jimenez-Mejias ME, Sirera G, Torre-Cisneros J, Ribera E, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. J Antimicrob Chemother. 2003;52(3):464–8. https://doi.org/10.1093/jac/dkg356.
41. Delgado J, Macias J, Pineda JA, Corzo JE, Gonzalez-Moreno MP, de la Rosa R, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. Am J Trop Med Hyg. 1999;61(5):766–9.
42.•• Diro E, Blesson S, Edwards T, Ritmeijer K, Fikre H, Admassu H, et al. A randomized trial of AmBisome monotherapy and AmBisome and miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients in Ethiopia. PLoS Negl Trop Dis. 2019;13(1):e0006988. https://doi.org/10.1371/journal.pntd.0006988. **This trial describes using IV Ambisome and oral miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients**.
43. Tumbarello M, Tacconelli E, Bertagnolio S, Cauda R. Highly active antiretroviral therapy decreases the incidence of visceral leishmaniasis in HIV-infected individuals. AIDS. 2000;14(18):2948–9.
44. Abongomera C, Diro E, Vogt F, Tsoumanis A, Mekonnen Z, Admassu H, et al. The risk and predictors of visceral Leishmaniasis relapse in human immunodeficiency virus-coinfected patients in Ethiopia: a retrospective cohort study. Clin Infect Dis. 2017;65(10):1703–10. https://doi.org/10.1093/cid/cix607.
45. Lopez-Velez R. The impact of highly active antiretroviral therapy (HAART) on visceral leishmaniasis in Spanish patients who are co-infected with HIV. Ann Trop Med Parasitol. 2003;97(Suppl 1):143–7. https://doi.org/10.1179/000349803225002615.
46. Villanueva JL, Alarcon A, Bernabeu-Wittel M, Cordero E, Prados D, Regordan C, et al. Prospective evaluation and follow-up of European patients with visceral leishmaniasis and HIV-1 coinfection in the era of highly active antiretroviral therapy. Eur J Clin Microbiol Infect Dis. 2000;19(10):798–801.
47. Lopez-Velez R, Videla S, Marquez M, Boix V, Jimenez-Mejias ME, Gorgolas M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. J Antimicrob Chemother. 2004;53(3):540–3. https://doi.org/10.1093/jac/dkh084.
48. Diro E, Ritmeijer K, Boelaert M, Alves F, Mohammed R, Abongomera C, et al. Long-term clinical outcomes in visceral Leishmaniasis/human immunodeficiency virus-coinfected patients during and after pentamidine secondary prophylaxis in Ethiopia: a single-arm clinical trial. Clin Infect Dis. 2018;66(3):444–51. https://doi.org/10.1093/cid/cix807.
49. Noireau F, Brun-Vezinet F, Larouze B, Nzoukoudi MY, Gouteux JP. Absence of relationship between human immunodeficiency virus 1 and sleeping sickness. Trans R Soc Trop Med Hyg. 1987;81(6):1000.
50. Louis JP, Moulia-Pelat JP, Jannin J, Asonganyi T, Hengy C, Trebucq A, et al. Absence of epidemiological inter-relations between HIV infection and African human trypanosomiasis in central Africa. Trop Med Parasitol. 1991;42(2):155.
51. Meda HA, Doua F, Laveissiere C, Miezan TW, Gaens E, Brattegaard K, et al. Human immunodeficiency virus infection and human African trypanosomiasis: a case-control study in cote d'Ivoire. Trans R Soc Trop Med Hyg. 1995;89(6):639–43.
52.•• Pelfrene E, Harvey Allchurch M, Ntamabyaliro N, Nambasa V, Ventura FV, Nagercoil N, et al. The European Medicines Agency's scientific opinion on oral fexinidazole for human African trypanosomiasis. PLoS Negl Trop Dis. 2019;13(6):e0007381. https://doi.org/10.1371/journal.pntd.0007381. **This reference describes a new and safer drug for the treatment of African trypanosomiasis, oral fexinidazole**.
53. Pepin J, Ethier L, Kazadi C, Milord F, Ryder R. The impact of human immunodeficiency virus infection on the epidemiology and treatment of Trypanosoma brucei gambiense sleeping sickness in Nioki. Zaire Am J Trop Med Hyg. 1992;47(2):133–40.
54. Blum J, Nkunku S, Burri C. Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Tropical Med Int Health. 2001;6(5):390–400.
55. Perez-Ramirez L, Barnabe C, Sartori AM, Ferreira MS, Tolezano JE, Nunes EV, et al. Clinical analysis and parasite genetic diversity in human immunodeficiency virus/Chagas' disease coinfections in Brazil. Am J Trop Med Hyg. 1999;61(2):198–206.
56.• Sartori AM, Neto JE, Nunes EV, Braz LM, Caiaffa-Filho HH, Oliveira Oda C Jr, et al. Trypanosoma cruzi parasitemia in chronic Chagas disease: comparison between human immunodeficiency virus (HIV)-positive and HIV-negative patients. J Infect Dis. 2002;186(6):872–5. https://doi.org/10.1086/342510. **A**

comparison of the differences between *Trypanosoma cruzi* parasitemia in PLWH and those without HIV

57. Almeida EA, Ramos Junior AN, Correia D, Shikanai-Yasuda MA. Co-infection Trypanosoma cruzi/HIV: systematic review (1980-2010). Rev Soc Bras Med Trop. 2011;44(6):762–70.
58. Nishioka Sde A, Ferreira MS, Rocha A, Burgarelli MK, Silva AM, Duarte MI, et al. Reactivation of Chagas' disease successfully treated with benznidazole in a patient with acquired immunodeficiency syndrome. Mem Inst Oswaldo Cruz. 1993;88(3):493–6. https://doi.org/10.1590/s0074-02761993000300022.
59.• Ferreira MS, Nishioka Sde A, Silvestre MT, Borges AS, Nunes-Araujo FR, Rocha A. Reactivation of Chagas' disease in patients with AIDS: report of three new cases and review of the literature. Clin Infect Dis. 1997;25(6):1397–400. **This reference describes reactivation of *Trypanosoma cruzi* infection in PLWH with low CD4 counts**.
60. Pacheco RS, Ferreira MS, Machado MI, Brito CM, Pires MQ, Da-Cruz AM, et al. Chagas' disease and HIV co-infection: genotypic characterization of the Trypanosoma cruzi strain. Mem Inst Oswaldo Cruz. 1998;93(2):165–9.
61. Yasukawa K, Patel SM, Flash CA, Stager CE, Goodman JC, Woc-Colburn L. Trypanosoma cruzi meningoencephalitis in a patient with acquired immunodeficiency syndrome. Am J Trop Med Hyg. 2014;91(1):84–5. https://doi.org/10.4269/ajtmh.14-0058.
62. Ferreira MS, Nishioka Sde A, Rocha A, Silva AM, Ferreira RG, Olivier W, et al. Acute fatal Trypanosoma cruzi meningoencephalitis in a human immunodeficiency virus-positive hemophiliac patient. Am J Trop Med Hyg. 1991;45(6):723–7.
63. Cohen JE, Tsai EC, Ginsberg HJ, Godes J. Pseudotumoral chagasic meningoencephalitis as the first manifestation of acquired immunodeficiency syndrome. Surg Neurol. 1998;49(3):324–7.
64. Di Lorenzo GA, Pagano MA, Taratuto AL, Garau ML, Meli FJ, Pomsztein MD. Chagasic granulomatous encephalitis in immunosuppressed patients. Computed tomography and magnetic resonance imaging findings. J Neuroimaging. 1996;6(2):94–7.
65. Castro-Sesquen YE, Gilman RH, Mejia C, Clark DE, Choi J, Reimer-McAtee MJ, et al. Use of a Chagas urine nanoparticle test (Chunap) to correlate with parasitemia levels in *T. cruzi*/HIV co-infected patients. PLoS Negl Trop Dis. 2016;10(2):e0004407. https://doi.org/10.1371/journal.pntd.0004407.
66. Sartori AM, Caiaffa-Filho HH, Bezerra RC, Do SGC, Lopes MH, Shikanai-Yasuda MA. Exacerbation of HIV viral load simultaneous with asymptomatic reactivation of chronic Chagas' disease. Am J Trop Med Hyg. 2002;67(5):521–523.
67. Sartori AM, Ibrahim KY, Nunes Westphalen EV, Braz LM, Oliveira OC Jr, Gakiya E, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. Ann Trop Med Parasitol. 2007;101(1):31–50. https://doi.org/10.1179/136485907X154629.
68. Dolcini GL, Solana ME, Andreani G, Celentano AM, Parodi LM, Donato AM, et al. Trypanosoma cruzi (Chagas' disease agent) reduces HIV-1 replication in human placenta. Retrovirology. 2008;5:53–13. https://doi.org/10.1186/1742-4690-5-53.
69. Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). Hum Exp Toxicol. 2006;25(8):471–9. https://doi.org/10.1191/0960327106het653oa.
70. Fischer P, Kipp W, Kabwa P, Buttner DW. Onchocerciasis and human immunodeficiency virus in western Uganda: prevalences and treatment with ivermectin. Am J Trop Med Hyg. 1995;53(2):171–8.
71. Tawill SA, Gallin M, Erttmann KD, Kipp W, Bamuhiiga J, Buttner DW. Impaired antibody responses and loss of reactivity to Onchocerca volvulus antigens by HIV-seropositive onchocerciasis patients. Trans R Soc Trop Med Hyg. 1996;90(1):85–9.
72. Sentongo E, Rubaale T, Buttner DW, Brattig NW. T cell responses in coinfection with Onchocerca volvulus and the human immunodeficiency virus type 1. Parasite Immunol. 1998;20(9):431–9.
73. Kipp W, Bamuhiiga J, Rubaale T. Simulium neavei-transmitted onchocerciasis: HIV infection increases severity of onchocercal skin disease in a small sample of patients. Trans R Soc Trop Med Hyg. 2003;97(3):310–1. https://doi.org/10.1016/s0035-9203(03)90157-x.
74. Kipp W, Bamhuhiiga J, Rubaale T, Kabagambe G. Adverse reactions to the ivermectin treatment of onchocerciasis patients: does infection with the human immunodeficiency virus play a role? Ann Trop Med Parasitol. 2005;99(4):395–402. https://doi.org/10.1179/136485905X36262.
75. Njambe Priso GD, Lissom A, Ngu LN, Nji NN, Tchadji JC, Tchouangueu TF, et al. Filaria specific antibody response profiling in plasma from anti-retroviral naive Loa loa microfilaraemic HIV-1 infected people. BMC Infect Dis. 2018;18(1):160–11. https://doi.org/10.1186/s12879-018-3072-2.
76. Janssen S, Hermans S, Knap M, Moekotte A, Rossatanga EG, Adegnika AA, et al. Impact of anti-retroviral treatment and cotrimoxazole prophylaxis on helminth infections in HIV-infected patients in Lambarene. Gabon PLoS Negl Trop Dis. 2015;9(5):e0003769. https://doi.org/10.1371/journal.pntd.0003769.
77. Hunt NH, Grau GE. Cytokines: accelerators and brakes in the pathogenesis of cerebral malaria. Trends Immunol. 2003;24(9):491–9.
78.• Gopinath R, Ostrowski M, Justement SJ, Fauci AS, Nutman TB. Filarial infections increase susceptibility to human immunodeficiency virus infection in peripheral blood mononuclear cells in vitro. J Infect Dis. 2000;182(6):1804–8. https://doi.org/10.1086/317623. **This reference presents data that supports the increased susceptibility of individuals with filarial infections to acquisition of HIV**.
79. Nielsen NO, Friis H, Magnussen P, Krarup H, Magesa S, Simonsen PE. Co-infection with subclinical HIV and Wuchereria bancrofti, and the role of malaria and hookworms, in adult Tanzanians: infection intensities, CD4/CD8 counts and cytokine responses. Trans R Soc Trop Med Hyg. 2007;101(6):602–12. https://doi.org/10.1016/j.trstmh.2007.02.009.
80. Talaat KR, Kumarasamy N, Swaminathan S, Gopinath R, Nutman TB. Filarial/human immunodeficiency virus coinfection in urban southern India. Am J Trop Med Hyg. 2008;79(4):558–60.
81. Tafatatha T, Taegtmeyer M, Ngwira B, Phiri A, Kondowe M, Piston W, et al. Human immunodeficiency virus, antiretroviral therapy and markers of lymphatic Filariasis infection: a cross-sectional study in rural northern Malawi. PLoS Negl Trop Dis. 2015;9(6):e0003825. https://doi.org/10.1371/journal.pntd.0003825.
82. Kroidl I, Saathoff E, Maganga L, Makunde WH, Hoerauf A, Geldmacher C, et al. Effect of Wuchereria bancrofti infection on HIV incidence in Southwest Tanzania: a prospective cohort study. Lancet. 2016;388(10054):1912–20. https://doi.org/10.1016/S0140-6736(16)31252-1.
83. Kroidl I, Saathof E, Maganga L, Clowes P, Maboko L, Hoerauf A, et al. Prevalence of lymphatic filariasis and treatment effectiveness of albendazole/ ivermectin in individuals with HIV co-infection in Southwest-Tanzania. PLoS Negl Trop Dis. 2016;10(4):e0004618. https://doi.org/10.1371/journal.pntd.0004618.
84. Modi M, Mochan A, Modi G. Management of HIV-associated focal brain lesions in developing countries. QJM. 2004;97(7):413–21. https://doi.org/10.1093/qjmed/hch080.
85. Jessurun J, Barron-Rodriguez LP, Fernandez-Tinoco G, Hernandez-Avila M. The prevalence of invasive amebiasis is not increased in patients with AIDS. AIDS. 1992;6(3):307–9.

86. Delobel P, Signate A, El Guedj M, Couppie P, Gueye M, Smadja D, et al. Unusual form of neurocysticercosis associated with HIV infection. Eur J Neurol. 2004;11(1):55–8.
87.•• Prasad S, MacGregor RR, Tebas P, Rodriguez LB, Bustos JA, White AC Jr. Management of potential neurocysticercosis in patients with HIV infection. Clin Infect Dis. 2006;42(4):e30–4. https://doi.org/10.1086/499359. **This reference describes the management of neurocysticercosis in PLWH**.
88. Foyaca-Sibat H, Cowan LD, Carabin H, Targonska I, Anwary MA, Serrano-Ocana G, et al. Accuracy of serological testing for the diagnosis of prevalent neurocysticercosis in outpatients with epilepsy, Eastern Cape Province. South Africa PLoS Negl Trop Dis. 2009;3(12):e562. https://doi.org/10.1371/journal.pntd.0000562.
89.•• White AC Jr, Coyle CM, Rajshekhar V, Singh G, Hauser WA, Mohanty A, et al. Diagnosis and treatment of Neurocysticercosis: 2017 clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2018;98(4):945–66. https://doi.org/10.4269/ajtmh.18-88751. **The recently updated clinical practice guidelines for the management of neurocysticercosis**.
90. Serpa JA, Moran A, Goodman JC, Giordano TP, White AC Jr. Neurocysticercosis in the HIV era: a case report and review of the literature. Am J Trop Med Hyg. 2007;77(1):113–7.
91. Secor WE. The effects of schistosomiasis on HIV/AIDS infection, progression and transmission. Curr Opin HIV AIDS. 2012;7(3):254–9. https://doi.org/10.1097/COH.0b013e328351b9e3.
92. Siddappa NB, Hemashettar G, Shanmuganathan V, Semenya AA, Sweeney ED, Paul KS, et al. Schistosoma mansoni enhances host susceptibility to mucosal but not intravenous challenge by R5 clade C SHIV. PLoS Negl Trop Dis. 2011;5(8):e1270. https://doi.org/10.1371/journal.pntd.0001270.
93. Downs JA, Mguta C, Kaatano GM, Mitchell KB, Bang H, Simplice H, et al. Urogenital schistosomiasis in women of reproductive age in Tanzania's Lake Victoria region. Am J Trop Med Hyg. 2011;84(3):364–9. https://doi.org/10.4269/ajtmh.2011.10-0585.
94. Downs JA, van Dam GJ, Changalucha JM, Corstjens PL, Peck RN, de Dood CJ, et al. Association of schistosomiasis and HIV infection in Tanzania. Am J Trop Med Hyg. 2012;87(5):868–73. https://doi.org/10.4269/ajtmh.2012.12-0395.
95. Downs JA, Dupnik KM, van Dam GJ, Urassa M, Lutonja P, Kornelis D, et al. Effects of schistosomiasis on susceptibility to HIV-1 infection and HIV-1 viral load at HIV-1 seroconversion: a nested case-control study. PLoS Negl Trop Dis. 2017;11(9):e0005968. https://doi.org/10.1371/journal.pntd.0005968.
96. Wall KM, Kilembe W, Vwalika B, Dinh C, Livingston P, Lee YM, et al. Schistosomiasis is associated with incident HIV transmission and death in Zambia. PLoS Negl Trop Dis. 2018;12(12):e0006902. https://doi.org/10.1371/journal.pntd.0006902.
97. Leutscher P, Ramarokoto CE, Reimert C, Feldmeier H, Esterre P, Vennervald BJ. Community-based study of genital schistosomiasis in men from Madagascar. Lancet. 2000;355(9198):117–8. https://doi.org/10.1016/S0140-6736(99)04856-4.
98. Karanja DM, Hightower AW, Colley DG, Mwinzi PN, Galil K, Andove J, et al. Resistance to reinfection with Schistosoma mansoni in occupationally exposed adults and effect of HIV-1 co-infection on susceptibility to schistosomiasis: a longitudinal study. Lancet. 2002;360(9333):592–6. https://doi.org/10.1016/S0140-6736(02)09781-7.
99.• Colombe S, Lee MH, Masikini PJ, van Lieshout L, de Dood CJ, Hoekstra PT, et al. Decreased sensitivity of Schistosoma sp. egg microscopy in women and HIV-infected individuals. Am J Trop Med Hyg. 2018;98(4):1159–64. https://doi.org/10.4269/ajtmh.17-0790. **This reference describes the difficulties in diagnosing schistosomiasis in PLWH**.
100. Mwanakasale V, Vounatsou P, Sukwa TY, Ziba M, Ernest A, Tanner M. Interactions between Schistosoma haematobium and human immunodeficiency virus type 1: the effects of coinfection on treatment outcomes in rural Zambia. Am J Trop Med Hyg. 2003;69(4):420–8.
101. Kallestrup P, Zinyama R, Gomo E, Butterworth AE, Mudenge B, van Dam GJ, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: effect of treatment of schistosomiasis on CD4 cell count and plasma HIV-1 RNA load. J Infect Dis. 2005;192(11):1956–61. https://doi.org/10.1086/497696.
102. Karanja DM, Boyer AE, Strand M, Colley DG, Nahlen BL, Ouma JH, et al. Studies on schistosomiasis in western Kenya: II. Efficacy of praziquantel for treatment of schistosomiasis in persons coinfected with human immunodeficiency virus-1. Am J Trop Med Hyg. 1998;59(2):307–11.