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# Tropical Parasitic Infections in Individuals Infected With HIV

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**Abstract**
*Purpose of Review* Neglected tropical diseases share both geographic and socio-behavioral epidemiological risk factors with HIV infection. In this literature review, we describe interactions between parasitic diseases and HIV infection, with a focus on the impact of parasitic infections on HIV infection risk and disease progression, and the impact of HIV infection on clinical characteristics of tropical parasitic infections. We limit our review to tropical parasitic infections of the greatest public health burden, and exclude discussion of classic HIV-associated opportunistic infections that have been well reviewed elsewhere.
*Recent Findings* Tropical parasitic infections, HIV infection, and treatment with antiretroviral therapy alter host immunity, which can impact susceptibility, transmissibility, diagnosis, and severity of both HIV and parasitic infections. These relationships have a broad range of consequences, from putatively increasing susceptibility to HIV acquisition, as in the case of schistosomiasis, to decreasing risk of protozoal infections through pharmacokinetic interactions between antiretroviral therapy and antiparasitic agents, as in the case of malaria. However, despite this intimate interplay in pathophysiology and a broad overlap in epidemiology, there is a general paucity of data on the interactions between HIV and tropical parasitic infections, particularly in the era of widespread antiretroviral therapy availability.
*Summary* Additional data are needed to motivate clinical recommendations for detection and management of parasitic infections in HIV-infected individuals, and to consider the implications of and potential opportunity granted by HIV treatment programs on parasitic disease control.

**Keywords** HIV infection · Parasites · Malaria · Helminths · Neglected tropical diseases

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## Introduction

Endemic HIV infection and neglected tropical diseases share a broad geographical distribution: over 25 million people in sub-Saharan Africa are living with HIV, and over 500 million people in the same region are believed to be infected with neglected parasitic diseases, including hookworm, schistosomiasis, ascariasis, and trichuriasis [1]. The interplay between tropical parasitic disease, HIV, their treatments, and the human host have important implications for host immunity, inflammatory responses, disease acquisition risk and disease severity [2–4]. As the epidemiology of HIV has shifted from a routinely fatal disease to a chronic, manageable condition for those with access to antiretroviral therapy (ART), there is an important need to describe relevant interactions between HIV infection, ART, and co-endemic parasites.

In this review, we intend to summarize published literature on interactions between tropical parasitic infections and HIV, with attention to impacts of parasitic infections on HIV disease progression and to the associations between HIV infection and parasitic disease acquisition, severity, and management (Table 1). We exclude discussion of known opportunistic

**Table 1** Associations between parasitic infections and HIV susceptibility and disease progression, helminth infection severity and relevant drug-drug interactions

| Parasite | Helminth infection effect on HIV disease | HIV infection effect on helminth disease | Drug interactions [5, 6] | References |
|---|---|---|---|---|
| Hookworm | ↑ susceptibility (weak evidence) | ↓ severity | Increased albendazole concentrations with PIs, decreased concentrations with EFV/NVP | [7–12, 13••, 14–17, 18•, 19] |
| *Trichuris trichiura* | ↑ susceptibility (weak evidence) | – | Increased albendazole concentrations with PIs, decreased concentrations with EFV/NVP | [10, 19, 20] |
| *Strongyloides stercoralis* | – | ↑ susceptibility (weak evidence) | Increased ivermectin concentrations with PIs, decreased concentrations with EFV/NVP; increased potential for CNS toxicity or Mazzotti-like reaction | [21–23] |
| *Ascaris lumbricoides* | ↑ progression (weak evidence) | – | Increased albendazole concentrations with PIs, decreased concentrations with EFV/NVP | [14, 19, 20, 24–29] |
| *Wuchereria bancrofti* | ↑ susceptibility (weak evidence) | – | Limited data on DEC metabolism | [30–33, 34••, 35] |
| *Onchocerca volvulus* | ↑ progression (weak evidence) | ↑ severity | Limited data on DEC metabolism | [36–40] |
| *Loa loa* | – | – | Increased albendazole concentrations with PIs, decreased concentrations with EFV/NVP | [19, 20] |
| *Taenia solium* | – | – | Increased albendazole/praziquantel concentrations with PIs, decreased concentrations with EFV/NVP | [19, 20, 41–43] |
| *Echinococcus granulosis* | – | ↑ severity | Increased albendazole/mebendazole concentrations with PIs, decreased concentrations with EFV/NVP | [19, 20, 44–49] |
| *Schistosomiasis* | ↑ susceptibility<br>↑ progression | – | Increased praziquantel concentrations with PIs, decreased concentrations with EFV/NVP | [50–57] |
| Malaria | ↑ susceptibility<br>↑ progression | ↑ severity | Quinine, chloroquine, mefloquine, pyrimethamine-sulfadoxine, atovaquone-proguanil, doxycycline interactions with NVP, EFB, LPV/r, NFV, SQV/r; artemether-lumefantrine contraindicated with PIs | [4, 58–61] |
| *Leishmania spp.* | – | ↑ susceptibility | Paromycin and miltefosine may increase GI side effects with co-administration of RTV containing PIs; Sodium stibogluconate may exacerbate pancreatitis with DDL; potential additive bone marrow toxicity with AZT, may stimulate HIV-1 replication | [62–68] |
| Chagas disease | – | ↑ severity | Benznidazole/suramin/nifurtimox may increase peripheral neuropathy risk with DDL/D4T | [69, 70] |
| Sleeping sickness | ↑ (HIV-2 only, weak evidence) | ↑ severity | Pentamidine may increase pancreatitis with DDL; suramin may have additional nephrotoxicity with TDF; melarsoprol may increase CNS toxicity with EFV, nifurtimox may increase GI side effects with RTV containing PIs | [71–74] |

SQV/*r* saquinavir/ritonavir, *NFV* nelfinavir, *LPV/r* lopinavir/ritonavir, *D4T* stavudine, *DDL* didanosine, *TDF* tenofovir disoproxil fumarate, *AZT* zidovudine, *EFV* efavirenz, *NVP* nevirapine, *PI* protease inhibitor

infections commonly studied in the developed world, such as toxoplasmosis, and gastrointestinal protozoa.

## Nematode Infections

### Hookworm

Human hookworm infection is caused by *Ancylostoma duodenale* in northern Africa and India, and by *Necator americanus* in most of the rest of the tropics including sub-Saharan Africa and Southeast Asia. It is a clinically significant infection in the tropics, where it may cause iron-deficiency anemia, and, in cases with high worm burdens, has been associated with malnutrition and cognitive deficits among children [75]. In pregnant women living with HIV, hookworm infection has been demonstrated to worsen anemia and increase the risk of maternal mortality [76–79]. There are 730 million people in the world living with hookworm infection, 130 million of whom are in sub-Saharan Africa [7, 80].

Estimates of HIV and hookworm co-infection vary by region but, in East Africa, have ranged from 2 to 28% among people living with HIV (PLWH) [24, 81–84].

Although incompletely described, the interactions between HIV and hookworm infections demonstrate the complex host-pathogen interplay at work in co-infections. An induced T helper (Th)-1 cell response is thought to be protective against HIV infection; however, as the disease progresses and CD4+ T cells are destroyed, a Th-2 response predominates and could theoretically be protective against hookworm infection [8]. However, depletion of T cells in advanced HIV may contribute to advancing parasitic disease through downregulation of IL-10 and TGF-β, which are known to play a beneficial role in hookworm infection [85]. Although supportive clinical data are sparse, a study of treatment-naive PLWH co-infected with tuberculosis (TB) found a lower prevalence of hookworm (12 vs 25%) and disease burden (49 vs 123 eggs/g of stool) in HIV-infected versus HIV-uninfected individuals, respectively [9]. Conversely, some evidence links hookworm infection to accelerated HIV disease progression through a favored Th2 immune response, consequent production of IL-10 and TGF-β, and expansion of T cell HIV virion targets [86, 87]. This relationship has been postulated to induce an increased HIV-1 RNA viral load in hookworm co-infected individuals [10].

This shift from a Th1- to a Th2-favored immune response [85, 88] may also increase susceptibility to other intracellular infections, such as tuberculosis and cryptococcosis. For example, HIV-uninfected children in Tanzania with hookworm infection were more likely to be co-infected with latent TB than those without hookworm [89]. This relationship was seen despite the known decreased sensitivity of interferon-γ-based latent tuberculosis tests seen in patients with helminthic infection [90]. Other studies have also demonstrated independent associations between helminth infection and tuberculosis risk [91–93].

Finally, interactions between hookworm infection and HIV infection also appear to play out at the gut epithelial-lumen interface. Both hookworm and HIV infection have been demonstrated to induce microbial translocation and resulting immune activation [94]. Although elevated, the Th2-mediated increases in IL-10 seen in hookworm infection may partially mitigate HIV-associated inflammation in those with co-infection [94, 95].

Given the complex interplay between HIV infection and hookworm infection, the impact of empiric helminth treatment on HIV disease progression has been an important and controversial area of study. While it has been suggested that there are beneficial effects of anthelmintic therapy on viral load and CD4+ T cell concentration trajectories in ART-naïve STH co-infected individuals [11] others have found no such impact [12, 96]. Morawski et al. found that PLWH receiving ART were less likely to have hookworm co-infection. Additionally, those co-infected with hookworm had lower CD4+ T cell counts, and this effect was sustained up to 2 years after ART initiation [84]. A case-control study and two randomized controlled trials among ART- ineligible PLWH demonstrated no benefit of either empiric or targeted treatment with albendazole on CD4+ T cell count trajectories [13••, 14, 15]. Lankowski et al. studied CD4+ T cell recovery following anthelmintic treatment in PLWH initiating ART and found no immunologic benefit, although a sub-analysis restricted to women suggested a benefit of deworming [16]. Similarly, a randomized controlled trial of HIV-infected pregnant women on ART in Rwanda found a significant benefit in CD4+ T cell count change and HIV RNA viral load reduction 48 weeks after treatment, regardless of confirmed helminth co-infection [97]. However, in a double-blind, randomized, placebo-controlled trial of ART-naïve pregnant women in Uganda, there was no difference in HIV viral load after anthelmintic treatment [10]. In a meta-analysis of six studies on the subject, Sangare et al. did not demonstrate a significant benefit of deworming on markers of HIV-1 disease progression [17]. Another meta-analysis of eight observational and interventional trials analyzing the effect of anthelmintic treatment on HIV viral load and CD4+ T cell concentration found minimal impact of anthelmintic therapy on either CD4+ T cell concentration or viral load, whether treatment was empiric or for confirmed parasite infection [18•]. Of the eight studies included in this meta-analysis, two included PLWH who had initiated ART, and only one demonstrated a positive effect of anthelmintic chemotherapy on CD4+ T cell reconstitution [98]. Given the rapid expansion in ART availability in sub-Saharan Africa, further data that will elucidate these clinical questions in the current era of ART are required.

The World Health Organization (WHO) treatment recommendations for hookworm currently include presumptive treatment with 400 mg albendazole at a prevalence-dependent frequency for all at-risk persons (children, women of childbearing age, and adults with additional occupational exposures) [99]. There are no specific guidelines for treating hookworm in the setting of HIV infection, and thus, similar recommendations are presumed to apply for PLWH. However, there are important drug-drug interactions between HIV antiretroviral therapies and selected anthelmintic therapy, e.g., ritonavir-boosted protease inhibitors, which may decrease concentrations of albendazole [100] through induction of the CYP3A4 metabolic pathway (Table 1) [19, 20].

## Trichuriasis

*Trichuris trichiura*, or whipworm, is commonly asymptomatic but, in cases with a heavy worm burden, can cause dysentery and anemia, and has been associated with stunted growth [101, 102]. There are few data on interactions between whipworm and HIV infection, although in some regions, the prevalence of trichuriasis in PLWH has been reported to be up to 20% [25, 103, 104]. *Trichuris* infection has been associated with increased T cell activation (HLA DR+ CD38+) and

CD4+ CCR5 co-receptor expression, which may increase HIV susceptibility by increasing target effector cells [105]. Like hookworm infection, *Trichuris* infection has also been associated with a higher viral load in pregnant women living with HIV [10], likely due to T cell expansion promoting viral replication. Treatment for trichuriasis is either 400 mg albendazole for 3 days, 100 mg mebendazole twice a day for 3 days, or 200 mcg/kg/day for 3 days, and no alternate considerations have been made among PLWH.

## Strongyloidiasis

In healthy individuals, *Strongyloides stercoralis* infection is often characterized as a benign chronic infection. However, various forms of immunosuppression increase risk of a severe and potentially fatal disseminated disease [106–108], where the organism is present in organs outside the skin, GI tract, or lungs. Higher rates of strongyloidiasis have been reported in PLWH versus uninfected individuals in Ethiopia, Brazil, Thailand, and South India [109–112], although broader co-infection prevalence rates are not available in sub-Saharan Africa. Interestingly, disseminated disease appears to be exceptionally rare in HIV infection, including those with advanced disease [107]. Persistent anti-*Strongyloides* IgG in PLWH appears to maintain protection from disseminated strongyloidiasis, even at low CD4+ T cell concentrations [107]. Nonetheless, because of the overlapping geographic risk, and the indication for corticosteroids with multiple HIV-related syndromes (e.g., tuberculous meningitis, *Pneumocystis jiroveci* pneumonia, immune reconstitution inflammatory syndromes), empiric therapy for strongyloidiasis infection may be indicated for this patient population to prevent morbidity from disseminated infection.

Although disseminated infection is uncommon in HIV, ART initiation in strongyloidiasis co-infection has been associated with an immune reconstitution-type syndrome [21, 22, 113, 114]. HIV infection has been rarely associated with other complications of strongyloidiasis infection [105, 108, 113, 115] including invasion of the CNS [114]. Moreover, while data are relatively sparse, HIV infection has been described as an independent risk factor for strongyloidiasis. Small studies in Ethiopia, Thailand, and India have all found estimated increased odds or prevalence of *S. stercoralis* infection among PLWH receiving ART [21–23]. Furthermore, one cross-sectional study in India exhibited a "dose-response" relationship between increasing infection rates and decreasing CD4+ T cell concentrations [22]. However, ART use does not appear to significantly affect the prevalence of *S. stercoralis* in PLWH [116]. Whether this is a true independent effect of HIV infection or another confounding risk factor (e.g., socioeconomic status or health system strengthening) remains unknown.

Strongyloidiasis does not appear to affect the progression of HIV disease, and comparable baseline HIV disease markers, CD4+ T cell concentration, and viral loads were observed in Strongyloides-infected versus uninfected individuals in PLWH [109, 112]. There are no specific recommendations on the timing of ART and/or anthelmintic dosing for PLWH co-infected with *Strongyloides*. Empiric treatment should be strongly considered in patients from endemic regions who have an indication for corticosteroid use and/or other immunosuppressive therapies. CDC treatment guidelines recommend a dose of ivermectin 200 ug/kg daily for 2 days, or until stool exams are persistently negative in hyper-infection syndrome [117]. Caution is advised in regions with co-prevalent strongyloidiasis and loiasis, because treatment with ivermectin can cause a fatal encephalopathy in those with the latter [117].

## Ascariasis

*Ascaris lumbricoides* is the most common soil-transmitted helminth infection of humans globally [7, 118]. *Ascaris* infection is often asymptomatic, but can be complicated by intestinal and biliary obstruction due to worm migration, especially in children [119].

HIV disease stage does not appear to predispose individuals to ascariasis [24] and a similar prevalence of *Ascaris* has been shown in PLWH compared to HIV-uninfected individuals [25, 26]. Although a decreased prevalence of all STH, including *Ascaris*, was reported in Brazil in an era of ART expansion compared to the pre-ART era [27], these findings have not been validated in other settings, and concomitant advances in hygiene and sanitation could be responsible.

*Ascaris* infections are characterized by a dominant Th2 response [120], which, as described previously, has been postulated to increase HIV susceptibility [105], although this has not been demonstrated by epidemiologic studies. There is evidence that untreated *Ascaris* infection can adversely affect HIV disease progression [28] through reduced production of Th1 cytokines [28, 121]. ART-naïve PLWH in southern Ethiopia treated for confirmed *Ascaris* infection had increases in CD4+ T cell concentrations at 15 weeks and at 6 months [29]. Similarly, a randomized trial found a significant improvement in CD4+ T cell concentrations among a subgroup of *Ascaris* and PLWH co-infection following treatment with albendazole compared to placebo [14]. The Center for Disease Control (CDC) recommends treating ascariasis with a single dose of 400 mg albendazole, with no treatment-specific guidelines for HIV-infected individuals [122].

## Filarial Diseases

### *Lymphatic Filariasis*

Lymphatic filariasis is caused most commonly by the filarial nematode *Wuchereria bancrofti*. It has been decreasing in

prevalence worldwide, largely due to elimination programs, but remains a significant public health problem in tropical regions [123]. In sub-Saharan Africa, an estimated 50 million people are infected with lymphatic filariasis [1, 124]. Prevalence of co-infection with HIV has been difficult to estimate, particularly in Asia and East Africa, where the disease burden is greatest [125]. Estimates from a study in Tanzania prior to mass treatment found an overall lymphatic filariasis prevalence of 25%, an HIV prevalence of 9%, and a co-infection prevalence of 42% in adults older than 18 years of age [30].

No association between lymphatic filariasis and HIV infection risk has been found in three studies in sub-Saharan Africa [30–32]. A single cross-sectional study demonstrated that lymphatic filariasis was correlated with HIV infection prevalence, but the results may have been confounded by age and gender [33]. The most compelling data of an association come from a cohort study in southwestern Tanzania, which demonstrated an increased risk of HIV acquisition in HIV-negative adults and adolescents with lymphatic filariasis compared to their parasite-free peers for up to 4 years of observation [34••]. The authors hypothesized that increased production of IL-4 and activated macrophages were responsible; however, more research into these relationships is needed [126, 127].

There is a mixed body of literature on the relationship between lymphatic filariasis infection, HIV disease stage, and response to antifilarial treatment. In a prospective case-control study of individuals with HIV and lymphatic filariasis co-infection, treatment with diethylcarbamazine (DEC) and albendazole did not appear to affect HIV disease indices 1 year after treatment, such as HIV-1 viral load and CD4+ T cell concentrations. Results were similar in a sub-analysis of ART-naïve individuals [32]. A cross-sectional study comparing cytokine profiles and HIV indices in PLWH with and without lymphatic filariasis observed no difference in HIV-1 viral load or CD4+ T cell percentage prior to treatment with DEC [128]. However, a double-blind, randomized controlled trial demonstrated that treatment of lymphatic filariasis with DEC in PLWH significantly reduces viral load [128]. A separate cross-sectional study of PLWH co-infected with lymphatic filariasis demonstrated that ART-treated individuals had a lower filarial load compared to ART-naïve individuals and the burden of filarial antigenemia also decreased with increasing duration of ART [31].

Interestingly, therapy against lymphatic filariasis may be more efficacious in PLWH. One study demonstrated significantly increased filarial-specific IgG3 in PLWH and significantly lower concentrations of IgG4, a biomarker of filarial infection, 12 weeks after lymphatic filariasis treatment compared to HIV-uninfected individuals [35]. The authors hypothesize that the increased levels of IgG3 were due to an initial HIV-induced Th1 response, while the reduction in IgG4 corresponded with circulating filarial antigen before and after treatment. Further research is required to determine if these results can offer insights into improving lymphatic filariasis therapy. Combination treatment with albendazole and ivermectin, an alternative regimen recommended by the WHO in select populations, appears to be as efficacious in reducing filarial burden in PLWH as it is in people without HIV infection [34••, 129]. One death due to "severe HIV infection" was reported in a randomized clinical trial demonstrating the efficacy of doxycycline over placebo through targeting of the *Wolbachia* endosymbiont, a finding which may require further investigation [130].

### *Onchocerciasis*

River blindness, caused by the filarial worm *Onchocerca volvulus*, is the second leading cause of infectious blindness worldwide [131]. Since neglected tropical diseases were included in the Millennium Development Goals in 2000, onchocerciasis eradication efforts have been successful in Colombia (2013), Ecuador (2014), Mexico (2015) [132], and Guatemala (2016) [133]. Onchocerciasis remains endemic in Uganda, Brazil, Ethiopia, Nigeria, Sudan, and Venezuela, where over 6.7 million PLWH reside [124]. HIV infection has been postulated to alter the presentation of *Onchocerca* infections, with worse dermatologic involvement among infected individuals [36]. Additionally, HIV infection has been shown to reduce antibody responses to onchocerciasis [37] potentially leading to slower clearance of filarial infection.

Onchocerciasis may alter immune responses to HIV infection. This was demonstrated in one in vitro study, where HIV viral replication increased after stimulation of PBMCs isolated from individuals with filarial infections, compared to parasite-free individuals [126]. However, in that same study, there was no difference in expression of proteins known to facilitate HIV infection such as CCR5 or CXCR4 co-receptors in those with and without prior filarial infection. Conversely, PBMCs from PLWH versus HIV-uninfected controls had an impaired specific response to onchocerciasis and were less efficient in producing interleukin (IL)-4 and IL-5, which are involved in the immune control of onchocerciasis [38]. These findings are consistent with the fact that a vigorous Th2 response is responsible for parasite death and may hasten resultant blindness [39, 40].

### *Loiasis*

*Loa loa*, the filarial eye worm, remains endemic in many West African countries. There are few studies of interactions between HIV and *Loa loa*. One study in Gabon demonstrated that PLWH taking trimethoprim-sulfamethoxazole prophylaxis were less likely to have *L. loa* co-infection [99]. Trimethoprim, which inhibits dihydrofolate reductase, an enzyme encoded in the *L. loa* genome, has been suggested as a potential target for drug therapy in various parasitic infections [134–136]. Future work is needed to assess if folate-inhibiting agents might

protect against *L. loa* and the mechanisms by which these agents may work.

## Cesetodes

### Taeniasis

Neurocysticercosis is believed to be responsible for approximately 30% of epilepsy cases in sub-Saharan Africa, affecting between 760,000 and 2,460,000 people in the region [137]. HIV infection can complicate the diagnosis of neurocysticercosis as the differential diagnosis of intracerebral lesions is broad in PLWH and serologic assays are less sensitive in cerebrospinal fluid [138]. While a handful of published cases describe ART-related IRIS exacerbating neurocysticercosis infections, there is insufficient evidence to support this as a common phenomenon [41]. However, there are suggestions that HIV-related immune dysregulation influences clinical manifestations of neurocysticercosis. Cerebral inflammation in response to cystic rupture is partially dependent on Th1-mediated immune responses, which require active CD4+ T cell populations [41, 42]. Similarly, Th1-mediated immune activity prevents multi-cyst infection. Th2 responses, which are more vigorous as CD4+ T cells are depleted, have been associated with subclinical multi-cyst neurocysticercosis [43].

A combination of albendazole, praziquantel, and corticosteroids, which is informed by clinical severity, cyst viability, cyst location, and cyst number, is the standard of care for treatment of neurocysticercosis [139, 140]. Some have suggested that treatment thresholds for neurocysticercosis should be lowered among PLWH [140, 141]. As in all conditions requiring prolonged steroid use, careful attention to the risk for *Pneumocystis jiroveci* pneumonia, disseminated *Strongyloides*, active tuberculosis, hepatitis B virus reactivation, and other diseases with reactivation potential should be considered.

### Echinococcosis

Few cases of echinococcosis and HIV co-infection have been reported. A single case series of four patients suggested that advanced HIV disease might increase the risk of more rapid cyst development and growth [44]. As previously discussed, advanced HIV infection is believed to result in a Th2-dominant immune response. This Th2 milieu is hypothesized to create a more suitable host environment for *Echinococcus* growth [45]. For example, T cell lines from individuals infected with inactive cysts have been shown to have an exclusively Th1 immune response ex vivo when stimulated by sheep hydatid fluid and antigen B, whereas patients with active cystic disease showed a mixed Th1/Th2 response [142]. These data suggest that the HIV-induced Th2 imbalance may promote active cystic growth of the *Echinococcus* helminth. Other reports of *Echinococcus granulosus* infection in PLWH indicate that extra-hepatic disease might be more common in this population [46–49]. However, a review article in South Africa did not show a statistically significant difference in the prevalence of disseminated cystic echinococcosis in HIV infected verses uninfected adults [143].

## Trematodes

### Schistosomiasis

Human schistosomiasis is caused by the trematodes *Schistosoma haematobium*, *Schistosoma mansoni, Schistosoma japonicum*, and *Schistosoma mekongi,* and affects 240 million people worldwide mostly in tropical and subtropical regions [144]. Schistosomiasis can remain asymptomatic for decades, but can progress to a chronic sclerosing condition with hepatic or genitourinary involvement if untreated. Urogenital schistosomiasis, caused by *S. haematobium*, manifests as hematuria, fibrosis of the bladder and ureters, and, eventually, bladder cancer. Women with urogenital schistosomiasis may have genital lesions, vaginal bleeding, and dyspareunia. Some studies have suggested that urogenital schistosomiasis is a risk factor for HIV infection, and that the treatment and/or prevention of *Schistosoma* infections can potentially aid in HIV disease control [50]. Evidence supporting this theory includes findings of increased concentrations of HIV target cells surrounding *S. mansoni* parasites in vaginal tissue [51], and a resulting increased vascularization of the vagina and cervix in females with urogenital schistosomiasis [52]. Females with urogenital schistosomiasis have also been hypothesized to have higher HIV transmission rates due to compromised vaginal epithelial tissue and increased HIV target cells [53]. A case-control study from Uganda showed no difference in HIV acquisition between 50 people in a fishing community with HIV seroconversion and 150 people without seroconversion. Equal percentages in both groups had evidence of *Schistosoma mansoni* before HIV seroconversion suggesting that the effect, if present, is minimal [145••]. This study included almost equal numbers of men and women and it is possible that an effect would have been recognized in a predominantly female population, especially in settings with a higher prevalence of *S. haematobium* as opposed to *S. mansoni,* where genital lesions are more likely to be present. A recent (completed but unpublished) clinical trial in Uganda seeks to test the impact that *Schistosoma* infection and treatment may have on HIV susceptibility (ClinicalTrials.gov: NCT02878564).

Some studies have found reduced worm burdens in those with co-infection compared to those without HIV infection [146]. Other studies have hypothesized that the life cycle of

the worm is dependent on a T cell response which is diminished during HIV infection. However, egg expulsion also appears to be dependent on T cell-mediated pathways, and could explain the decreased egg expulsion in PLWH. Egg retention does not appear to alter disease severity [147]. However, ecologic studies have suggested that regions with high prevalence of both HIV and schistosomiasis also have a high prevalence of renal dysfunction [2, 3]. A case-control study of children living with HIV and their uninfected siblings demonstrated schistosomiasis as an independent correlate of renal dysfunction [148].

Finally, there is evidence that schistosomiasis infection can accelerate HIV disease progression and hamper HIV treatment responses [149], as demonstrated by longer time to viral load suppression and reduced CD4+ T cell expansion following ART initiation [54, 55]. Although immediate treatment of schistosomiasis did not improve viral suppression in a randomized controlled trial comparing early versus delayed praziquantel therapy among PLWH receiving ART, those randomized to delayed praziquantel had higher viral loads and lower CD4+ T cell concentrations after 3 months of observation [56]. This effect has been attributed to increasing Th2 activity in response to treatment with praziquantel and worm killing [55–57]. There are no HIV-specific related treatment recommendations for schistosomiasis, and 40–60 mg/kg of praziquantel, depending on the species, is typically recommended [150].

## Protozoa

### Malaria

Globally, malaria prevalence and fatalities have decreased by 18 and 37%, respectively, since 2000 [151]. However, malaria remains an important public health issue due to its high associated mortality among children, and the recurrence of drug resistance to newer artemisinin-based therapies [152]. PLWH have a higher burden of malaria and, when infected, could have more severe anemia [4] and worse outcomes [58, 59]. Malaria infection also appears to increase HIV target cell expansion and consequentially increases HIV viral replication in ART-naïve, PCP-prophylaxis-naïve individuals [60, 61].

A randomized controlled trial of cotrimoxazole prophylaxis in children infected with HIV demonstrated a protective effect against malaria, compared to HIV-uninfected children not on prophylaxis [153]. Similar studies confirmed a protective effect of cotrimoxazole prophylaxis, and that the effect was no longer present after discontinuation [154, 155]. There is also mounting interest in the use of boosted protease inhibitors in the prevention of malaria in endemic areas, through improved pharmacokinetics of antimalarial drugs [156–161]. A randomized controlled trial in Uganda confirmed that protease inhibitor-based ART, compared to non-nucleoside-based regimens, was associated with a decreased incidence of malaria, and that this benefit was related to prolonged duration of therapeutic lumefantrine drug levels [162]. Partially based on these findings, WHO HIV guidelines recommend cotrimoxazole prophylaxis in all PLWH in malaria-endemic areas, and boosted protease inhibitors as first-line antiretroviral therapy in infants and children with HIV [163].

### Leishmaniasis

The three principal clinical manifestations of leishmaniasis include cutaneous, mucocutaneous, and visceral syndromes, which are caused by over 20 different *Leishmania spp.* In east Africa, 40% of patients with visceral leishmaniasis are co-infected with HIV [164]. Although leishmaniasis is typically transmitted by the sand fly vector, *Leishmania* transmission has been observed through needle sharing in PLWH [165]. There are many HIV-specific clinical features of *Leishmania* infection, and the visceral manifestation is considered an opportunistic infection [62, 63]. PLWH appear to be at risk for diffuse cutaneous leishmaniasis, treatment-resistant disease, and recurrent infections [64, 65], but also appear to more commonly have asymptomatic disease [66]. Atypical manifestations seen in PLWH, especially those with advanced immunosuppression, include the absence of the classic triad of fever, hepatomegaly, and splenomegaly, and the presence of amastigotes in atypical tissues including gastrointestinal tract, skin, tonsils, and lung [166]. Although HIV infection has been shown to significantly increase the risk for death from visceral leishmaniasis [67, 167], ART appears to be protective against leishmaniasis among PLWH [66] and likely reduces rates of relapse [68]. Specifically, protease inhibitors might have direct activity against the parasite, although more research is needed [164, 168]. Alternatively, prophylaxis for visceral leishmaniasis relapse in PLWH with monthly infusions of pentamidine has demonstrated preliminary success by reducing relapse-free survival from 50 to 100% in historical controls to 29% [169•].

Although the cutaneous and mucocutaneous forms are diagnosed with biopsy and pathology, visceral forms can be challenging to diagnose, and serologic tests may have a lower sensitivity in PLWH due to a lack of a humoral immune response [62, 170]. Treatment for visceral and severe cutaneous forms of leishmaniasis involves liposomal or standard amphotericin B. However, in many areas where amphotericin B is not available, pentavalent antimony is still recommended. Although resistance to liposomal amphotericin B has been reported in HIV infection [171], there is insufficient evidence to warrant alternate recommendations for PLWH. Many recommendations include secondary prophylaxis until immune reconstitution, as defined by a CD4+ T cell concentration > 250 cells/mcL [172–174]. The FDA recently approved

miltefosine for all types of leishmaniasis, which was well tolerated in a small ($n$ = 5) study among PLWH [175].

### Trypanosomiasis

Chagas disease, caused by the protozoan parasite *Trypanosoma cruzi*, is an infection characterized by acute and chronic phases, ultimately leading to cardiomyopathy and, less commonly, esophageal dilatation in 10–30% of untreated patients [176, 177]. Reactivated Chagas disease is considered an AIDS-defining illness in Brazil [178, 179]. PLWH are more likely to have detectable parasitemia on peripheral blood smears in chronic Chagas infection than HIV-uninfected individuals [69], and there are reports of higher mortality due to chronic Chagas disease with cardiac involvement in PLWH [70]. To our knowledge, there are no reports of Chagas and HIV-related IRIS upon ART initiation. As in leishmaniasis, there is some evidence that protease inhibitors may have direct activity against trypanosomes. Nelfinavir and lopinavir may target aspartic peptidases and proteasomes of *T. cruzi* [156, 180]. Treatment for Chagas disease is typically recommended for younger patients, those with acute infection and those without significant cardiomyopathy, with benznidazole and nifurtimox as preferred agents [181, 182]. In contrast, treatment of chronic disease in those with advanced cardiomyopathy remains controversial [183]. No HIV-specific treatment recommendations are currently available.

Sleeping sickness is caused by the *Trypanosoma brucei rhodesiense* (East African Sleeping Sickness) protozoa in southern and eastern Africa and *Trypanosoma brucei gambiense* (West African Sleeping Sickness) in western and central Africa. The majority of cases are due to *T. brucei gambiense* and were reported in the Democratic Republic of the Congo (DRC). Infection is characterized in two stages: the first stage involves the blood and lymph nodes, and the second stage is characterized by the invasion of the central nervous system [184]. Data describing associations between African Sleeping Sickness and HIV infection are sparse. Some research has recommended that serology-based HIV testing should be avoided until after treatment of trypanosomiasis because false-positive HIV tests are reportedly more common during active infection [185]. HIV infection did not impact outcomes in individuals with second-stage sleeping sickness in Tanzania [71]. Early clinical studies in Zaire (presently DRC) prior to ART availability suggested that although HIV did not increase the risk factor of Sleeping Sickness acquisition, it was associated with trypanosomiasis treatment failure [72, 73]. Some evidence has also suggested that African Sleeping Sickness may predispose individuals to HIV-2 infection and additionally lower CD4+ T cell concentrations [74]. Treatment for East African Sleeping Sickness involves suramin for early-stage disease and melarsoprol (preferably co-administered with corticosteroids) for those with central nervous system involvement. In regions where onchocerciasis is endemic, additional caution should be used before administration of suramin. For West African Sleeping Sickness, treatment includes either monotherapy with pentamidine for 7–10 days for first-stage disease or intravenous eflornithine for 2 weeks with or without nifurtimox for infections with CNS involvement [186]. Neither disease has HIV-specific guidelines for treatment.

## Conclusion

Both HIV infection and parasitic infections are common in tropical regions and cause significant morbidity and mortality. Despite this, associations between HIV and most neglected tropical infections remain understudied, and poorly understood, and opportunities for integrated care are potentially overlooked [187]. As HIV increasingly becomes a prevalent, chronic condition, additional attention to the interplay between the two is warranted, particularly regarding preventing transmission of HIV infection, ensuring optimal long-term health of PLWH and strengthening efforts to eradicate and control neglected infections [188].

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**Compliance with Ethical Standards**

**Conflict of Interest** Emily Evans and Mark Siedner declare that they have no conflict of interest.

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- •• Of major importance

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