HIV and Schistosoma spp. interactions: epidemiology and consequences for detection and prevention in the lake region of Tanzania

Colombe, S.

CHAPTER 1 – GENERAL INTRODUCTION

I. CONTEXT FOR THIS THESIS 10

*1) Epidemiology of HIV/***Schistosoma** *spp. co-infections and study site* 10

2) Genital schistosomiasis and its pathologies 10

3) Diagnosis of HIV and **Schistosoma** *spp. infection* 11

II. *SCHISTOSOMA* AND HIV CO-INFECTIONS: GAPS IN KNOWLEDGE 14

1) Effect of **Schistosoma** *spp. infection on HIV susceptibility and disease* 14

A. Effect of *Schistosoma* spp. on HIV susceptibility 16

B. Effect of *Schistosoma* spp. on HIV RNA viral load 16

C. Discrepancies in the results 17

2) Effect of HIV on **Schistosoma** *spp. infection* 21

A. Effect of HIV on praziquantel efficacy 23

B. Effect of HIV on egg excretion 23

I. CONTEXT FOR THIS THESIS

*1) Epidemiology of HIV/*Schistosoma *spp. co-infections and study site*

Approximately 36.7 million people are infected with HIV around the world while 218 million are infected with *Schistosoma* spp.[1, 2]. These infections overlap and an estimated 6 million individuals are HIV/*Schistosoma* spp. co-infected[3-5]. The majority of co-infections occur in Africa[4].

The coastline of Lake Victoria in East Africa too harbors both diseases[1, 2] and, due to common risk factors, such as occupation and socio-economic status[6, 7], is a site with a high level of co-infections. We have set our studies in the Lake Zone of Tanzania, the Tanzanian side of Lake Victoria. It comprises 6 regions and has a population of about 11.8 million inhabitants, representing one-fourth of the country's population[8, 9]. The Lake Zone is predominantly rural, with fast changing demographics regarding urbanization and the increased availability of healthcare[8, 9].

In East Africa, both *S. haematobium* and *S. mansoni* are found, with prevalences ranging from 1% to over 80% in the Lake Zone of Tanzania[10, 11]. The HIV prevalence in the Lake Zone of Tanzania varies between 3.6% and 7.4%[12]. In the context of the HIV/AIDS epidemic, co-infections typically exacerbate morbidity and mortality, as shown by studies looking at interactions between HIV and tuberculosis, cryptococcosis, hepatitis B virus, hepatitis C virus, and malaria[13, 14]. The immunodeficiency caused by chronic HIV infection increases the risk of co-infection with many pathogens[13, 14]. Moreover, administration of antiretroviral therapy (ART) does not always restore the pathogen-specific immune response to co-infections to normal levels[14]. We might thus expect HIV infection to increase morbidity associated with *Schistosoma* spp., and likely *vice versa*.

This thesis seeks to add to the current knowledge on HIV and *Schistosoma* spp. co-infections through new research questions and identification of gaps in the current methodology.

2) Genital schistosomiasis and its pathologies

S. haematobium most prominently affects the genitourinary system while *S. mansoni* affects the gastro-intestinal system[15]. Clinical manifestations of schistosomiasis are caused by the eggs laid by adult worms of the *Schistosoma* spp. that live in the vasculature. Eggs secrete proteolytic enzymes as they migrate through tissues en route to the lumen of the urinary bladder or intestine, where they are subsequently excreted in urine or stool[16]. When the eggs are sequestered in the uro-genital tract, the disease caused is called urogenital schistosomiasis, which is marked by inflammation, friability, and bleeding of the urinary and genital mucosa[17, 18]. Late-stage complications of urogenital schistosomiasis include bladder cancer and urinary tract obstruction with hydronephrosis[17, 18]. *S. mansoni* eggs can also be found in the urogenital tract, resulting in both species being able to cause urogenital schistosomiasis[19,20]. It is estimated that *S. mansoni* causes 1 case of urogenital

schistosomiasis for every 4 cases of urogenital schistosomiasis caused by *S. haematobium*[19, 20]. *S. mansoni* eggs most frequently cause disease in the lower intestine and the liver, leading to bloody diarrhea and liver periportal fibrosis. Advanced *S. mansoni* infection can lead to ascites, variceal hemorrhage, and death[15]. Differences in clinical diseases, diverse physical and immunologic effects of eggs in different tissues, and host characteristics all contribute to the observed differences in interactions between *Schistosoma* and HIV infections[19, 20].

Men and women are affected differently by genital schistosomiasis. In men, eggs are found at the highest frequency in the seminal vesicles with high egg per gram counts. Eggs are also found in the prostate, testes, and epididymis, thus affecting mostly internal organs[17, 20-22]. Genital lesions due to eggs sequestration and induced inflammation are less common in men than in women[17, 21, 23], and the burden of infection in men is not always proportional to the degree of inflammation [21]. In women, eggs are found both in the cervix and the vagina at high frequency, with high counts of eggs per gram in the vagina[22, 23]. Eggs can also sometimes be found in the ovaries, fallopian tubes, and uterus[23]. Sequestered eggs and their associated lesions in women are thus found in sites directly accessible during sexual contact[18].

Schistosoma eggs are highly immunogenic and lead to recruitment of immune cells including Th2 helper cells and macrophages that are preferential targets of HIV. Several studies on urogenital schistosomiasis in women found a variety of tissue reactions surrounding the ova associated with higher densities of genital mucosal CD4+ T lymphocytes (CD4), macrophages, and eosinophils compared with cervicovaginal mucosa without ova[24]. The cell modifications shown in women are likely to be similar in men[17]. In addition, increased levels of leukocytes as well as expression of IL-4, IL-6, IL-10, IFN-γ, and TNF-α have been found in semen of *S. haematobium*-positive men, which in return might induce accelerated replication of HIV[25].

3) Diagnosis of HIV and Schistosoma *spp. infection*

The Tanzanian national guidelines for HIV testing follow WHO recommendations. The standard procedure for diagnosis of HIV in our study population involves the use of rapid tests for antibody testing[26]. A positive screening test is followed by a second and different confirmatory rapid test. To determine when to initiate ART and monitor response to treatment and progression of the disease, CD4 counts were measured every 6 months until 2016[26]. Since 2016, monitoring guidelines changed as HIV RNA viral load quantification using PCR was implemented[27]. Before and at start of ART, CD4 counts are still measured, but anyone with HIV is started on ART regardless of their CD4 counts. After ART initiation, HIV RNA viral load testing is used to evaluate response to ART, with a first HIV RNA viral load test 6 months after initation. Routine testing is then implemented every 12 months if the patient is virally suppressed or every 3 months if the patient is not responding to treatment[27]. Where HIV RNA viral load monitoring is unavailable, clinical monitoring and CD4 monitoring are still in use[27]. Since 2016, HIV RNA viral load testing in the Lake Zone is performed at Bugando Medical Centre, the zonal referral hospital serving 15 million people in the Lake Zone. However, with small clinics progressively sending their samples for HIV

RNA testing further upscaling of HIV RNA viral load testing is needed to prevent back-log. Very little data on HIV RNA viral load was available before 2016. The progress in HIV testing and access to health care is described in **Chapter 2**.

Both CD4 counts and HIV RNA viral load change over the course of a natural HIV infection, and are predictors of the course of the HIV infection[28-30]. They vary proportionally as a higher HIV RNA viral load leads to a lower CD4 count due to the pathogenesis of the virus. The natural course of an HIV infection can be divided into three stages, all characterized by different slopes of decline/increase in CD4 counts and HIV RNA viral load: the primary infection, a latent stage, and AIDS[31]. For CD4 counts, significant declines in the systemic levels of CD4 cells occur in the first 2–8 weeks following HIV-1 infection[32]. CD4 counts then re-increase slightly to progressively decline again with an average yearly loss of approximately 60 CD4 cells/μl[33], (varying according to HIV type), during the latent stage of the disease. Over a period of years the decrease in CD4 counts leads to death from immune failure and opportunistic infection[34, 35]. After 8-12 years, without ART initiation, CD4 counts drop below 200 cells/μl making the patient susceptible to AIDS-defining opportunistic infections and neoplasms[36, 37]. The decline in the level of CD4 typically continues until reaching the null, but the decline is not seen in the small percentage of individuals who are long-term nonprogressors. Primary infection is also accompanied by a burst in HIV RNA viral load, mirroring viral replication[38-40]. Antiviral immune responses further lead to high declines in plasma viremia [41-43], which then stabilize. This steady-state HIV RNA viral load is called the viral load set point and is highly predictive of HIV transmission and progression to AIDS disease[44]. There is continuous viral replication during the latent stage as it is a clinical latency rather than a viral latency[45, 46]. At the end stage of the infection, HIV RNA viral loads peak again to virtually infinity. Disease progression is directly linked to HIV RNA viral load and to the extent of viral replication[44].

In the absence of ART, the natural course of HIV infection can vary widely with some HIV-positive individuals able to maintain high CD4 counts and/or suppressed HIV RNA viral load.

The current gold standard for diagnosis of active *Schistosoma* infection and detection of the species, as recommended by the WHO, is microscopy on urine or stool [2], via urine filtration or Kato Katz technique for stool. It is well recognized that egg excretion varies, depending on prevalence, time of the day, and worm burden[47-53], and that microscopy may be less sensitive than other diagnostic strategies including antigen testing and PCR[54]. In addition, it is tedious, needs an experienced microscopist, and ideally would require multiple sampling. An advantage of microscopy is the near-perfect specificity and the ability to differentiate between *Schistosoma* species, which is not possible with some of the other diagnostics.

Although antibody-based tests exist and are cheap and easy to use for *Schistosoma* spp. testing[54], they do not allow differentiation of active versus past *Schistosoma* spp. infection and are therefore not often used in endemic settings. They do have a role in diagnosis of travelers who would not be expected to have been previously exposed to *Schistosoma* spp.

infection. Current PCR techniques detect active infection but are expensive and often do not distinguish between *Schistosoma* species[54, 55]. In addition, some of the PCRs described remain positive for a long time after clearance of the infection due to slow degradation of the sequestered eggs[56].

Schistosome antigen testing is increasingly accepted as a highly sensitive technique for diagnosis of *Schistosoma* spp., although it does not allow distinction between *Schistosoma* species[54]. Circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) are glycosaminoglycan-like carbohydrates produced in the gut of adult schistosome worms and regurgitated into the host bloodstream during active infection with any *Schistosoma* species (including veterinarian)[57]. They can be detected in the serum and urine of infected individuals, and the level of these antigens is proportional to the intensity of infection[54]. CAA and CCA levels rise and fall rapidly post-infection and post-treatment respectively[58-60, 61] and do not seem to present any circadian variability[61]. The CAA and CCA based tests have been optimized for improved sensitivity and use in the field and each have their specific application. User-friendliness and sensitivity of the CAA assay was initially improved utilizing the luminescent up-converting phosphor technology in combination with a lateral flow-based platform (UCP-LF)[62] as well as the introduction of a sample concentration method[63,64]. This genus specific test requires some basic laboratory equipment and includes a sample preparation step with incubation that permits sample concentration and ultimate sensitivity (single worm detection)[63, 64]. It can be used on blood-derived samples as well as urine and saliva. The UCP-LF assay for CAA detection has been adapted to a dry reagent format that allows convenient storage at ambient temperature and shipping without the need for a cold chain[65], and alternative methods are explored to make the sample preparation and concentration step more field applicable[66]. As CAA is extremely stable[52], this assay can also be applied on dried blood spot samples[67, 68]. For CCA detection, a commercial lateral flow based assay for rapid point-of-care testing on urine is available, POC-CCA (Rapid Medical Diagnostics, Pretoria, South-Africa). The test allows rapid identification of active infections, and is recommended for medium to high endemic *S. mansoni* settings[69].

II. *SCHISTOSOMA* AND HIV CO-INFECTIONS: GAPS IN KNOWLEDGE

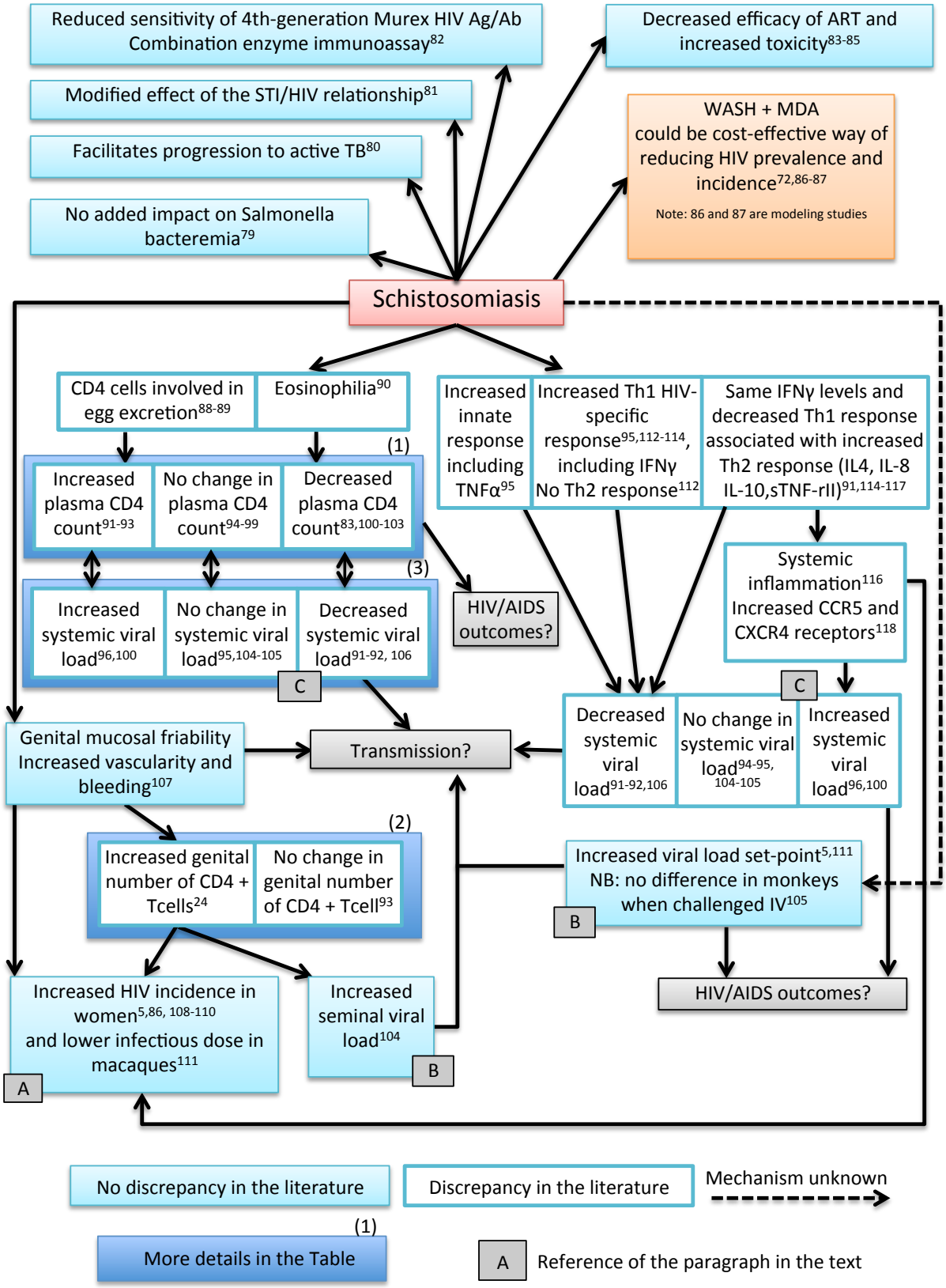
Despite multiple studies reporting interactions between infection with HIV and *Schistosoma* spp. in humans and macaques, little is still known about the processes and modalities of this co-infection. A systematic search on Pubmed for all scientific publications focusing on the epidemiology, immunology, and clinical aspect of HIV/*Schistosoma* spp. co-infections yielded only a total of 85 publications from 1985 to 2017. Of these, 10 were literature reviews, and 6 were case reports.

Several cross-sectional studies and mathematical models have reported a clear association between HIV and *Schistosoma* spp. infection in women but not in men[4, 70-78]. Other studies have explored specific directions of the relationship between HIV and *Schistosoma* spp., looking separately on the one hand at the effect of *Schistosoma* spp. on HIV susceptibility and disease, and on the other hand at the effect of HIV on *Schistosoma* spp. infection. The knowledge and gaps (at the start of the investigations presented in this thesis) on the epidemiology of HIV/*Schistosoma* spp. co-infections, and the immunological and mechanical processes behind it are summarized below.

1) Effect of Schistosoma *spp. infection on HIV susceptibility and disease*

The effect of *Schistosoma* spp. on HIV susceptibility and disease is described in **Figure 1**. Each arrow describes a plausible or reported causal pathway, starting from co-infection with *Schistosoma* spp. all the way to HIV susceptibility and disease. The pale blue boxes show findings for which either only one study was conducted, or for which there is agreement in the literature. The white boxes show discrepant findings. The parts of the graph indicated with capital letters are described in more details below. The dark blue boxes are detailed in **Table 1** below.

Figure 1 - Co-infection conceptual framework – Effect of Schistosoma spp. infection on HIV susceptibility and disease progression.



A. Effect of *Schistosoma* spp. on HIV susceptibility

One longitudinal study and several mathematical models indicated that *Schistosoma* spp. infection is a risk factor for HIV acquisition in women, but not in men[5, 86, 108, 109]. In addition, in macaques infected with *Schistosoma mansoni*, lower doses of simian HIV (sHIV) are required for infection[111]. Research on co-infections has so far been lacking longitudinal studies to confirm the relationship and define a link of causality. Only two longitudinal studies investigated the link of causality between *Schistosoma* spp. infection and HIV acquisition in humans [5,110]. One did not find any[110], while the other found a link of causality only when stratifying by sex[5]. Longitudinal studies thus need to be repeated and results should be confirmed in other settings for both species of *Schistosoma*.

B. Effect of *Schistosoma* spp. on HIV RNA viral load

In addition to demonstrating increased HIV susceptibility, one of the longitudinal studies in Tanzania also found increased HIV RNA viral load set-points in both men and women who were infected with *Schistosoma* spp. at time of HIV seroconversion[5]. *Schistosoma* spp. co-infection has also been associated with increased local seminal HIV RNA viral load[104] and increased systemic HIV RNA viral load in some studies[96, 100]. A similar effect of *S. mansoni* infection was also observed in macaque studies of sHIV[105].

If *Schistosoma* spp. co-infection impacts systemic and local seminal HIV RNA viral loads, then we would expect to see worse HIV-AIDS outcomes in co-infected individuals given the known worse outcomes with higher HIV plasma RNA viral loads[119]. Furthermore, we would expect an increased transmission to sexual partners (independent of the sexual partner *Schistosoma* spp. status)[119, 120]. Only one study, to our knowledge, has investigated the impact of *Schistosoma* spp. infections on HIV-related outcomes. This randomized trial looked at the effect of annual praziquantel (PZQ) treatment (25 mg/kg) on CD4 counts and death[97]. Treatment was given empirically, regardless of the infection status, and baseline estimate of prevalence of *Schistosoma* spp. in the treatment and control group were unknown. This study led to inconclusive results likely due to empiricality of treatment and the low prevalence of *S. mansoni* (about 2%) previously reported in the area[97, 121].

This thesis investigates the relationship between *Schistosoma* spp. infection at time of HIV seroconversion and HIV/AIDS outcomes as defined by death and CD4 counts in **Chapter 3**. We hypothesized that *Schistosoma* spp. infection at time of HIV seroconversion would lead to worse HIV-AIDS outcomes. In **Chapter 4**, we quantify the impact of *Schistosoma* spp. infection in HIV positive individuals on intra-marital transmission of HIV to a serodiscordant spouse. We hypothesized that *Schistosoma* spp. co-infection would lead to increased HIV-1 transmission to serodiscordant spouse. Both were retrospective longitudinal studies that used stored Dried Blood Spots (DBS) for the testing of *Schistosoma* spp..

C. Discrepancies in the results

There is discrepancy in the literature regarding the effect of *Schistosoma* spp. infection on systemic HIV RNA viral load and CD4 counts[5, 24, 83, 91-98, 100-104, 106], with studies documenting either higher or lower HIV RNA viral loads/CD4 counts, or no effects[5, 91, 92, 94-97, 100, 104, 106]. Most studies have studied the effect of *Schistosoma* spp. infection on systemic HIV RNA viral load or CD4 counts by treating co-infected individuals with PZQ and comparing baseline HIV RNA viral load and CD4 counts to post-treatment values[91, 92, 94, 97, 100, 104, 106]. The length between treatment and re-testing varies, leading to contradicting results, and studies showing transitory increase in HIV RNA viral load and decrease in CD4 counts after treatment[92, 94, 100, 106].

HIV RNA viral load and CD4 counts are markers of the virological and immunological aspects of the HIV/*Schistosoma* spp. relationship and tools for understanding HIV disease progression. Efforts to understand the reason behind those differences in reported HIV RNA viral loads and CD4 counts in relationship to *Schistosoma* spp. infections are crucial to define the interactions between HIV and *Schistosoma* spp. In the meantime, establishing uniform and replicable study designs and analysis methods would minimize confounding and allow comparability of the studies. In **Table 1**, we present the studies with conflicting results to highlight the differences and potential reasons for the findings. Duration of HIV infection, duration of *Schistosoma* spp. infection, duration of co-infection, age, sex, and ART intake are all potential confounders and effect modifiers[5, 28-30, 122-124] that are rarely studied in depth when looking at the epidemiology of HIV/*Schistosoma* spp. co-infections.

In **Chapter 5**, we seek to find an explanation to the discrepancies found regarding the effects of *Schistosoma* spp. on systemic HIV RNA viral load. We hypothesized that duration of HIV infection, which largely affects HIV RNA viral load[28-30] could have been a main confounder in past studies.

Table 1 - Relationship between *Schistosoma* infection and CD4 counts and HIV RNA viral loads.

Reference	Total sample size (% schisto)	Study type	Species	*Schistosoma* test	Population	ART	Findings in those with *Schistosoma* co-infections
(1) Plasma CD4 count							
91. Brown M et al., 2005. J Infect Dis	152 (100%)	-Longitudinal -Treatment with PZQ -3 follow ups, up to 5 months	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART not available at time of study	Increased plasma CD4 count
92. Elliott AM et al., 2003. Trans R Soc Trop Med Hyg	108 (26%)	-Longitudinal -Treatment with PZQ -2 follow-ups up to 4 months	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART Naive	Increased plasma CD4 count
93. Prodger JL et al., 2015. PLoS Negl Trop Dis	24 (50%)	Cross-sectional	*Sm*	Kato-Katz Urine-CCA	Human Adults Male only	NA	Increased plasma CD4 count
101. Kallestrup P et al.,2005. J Infect Dis	356 (75%)	Cross-sectional	All	Microscopy CAA	Human Adults Male and Female	ART not widely available at time of study	Decreased plasma CD4 count for *S. mansoni* No change in plasma CD4 count for *S. haematobium*
94. Brown M et al., 2004. J Infect Dis	401 (42.9%)	-Longitudinal -Treatment with PZQ -Only 1 follow-up at 6 months	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART naive	No change in plasma CD4 count
95. Obuku AE et al., 2016. AIDS Res Hum Retroviruses	34 (52.9%)	Cross-sectional	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART naive	No change in plasma CD4 count
97. Walson J et al., 2012. Lancet Infect Dis	877 (2%)	-Longitudinal study -Treatment with PZQ -Follow-up every 3 months, up to 24 months	All	Kato-Katz PCR	Human Adults Male and Female	Eligible participants did not meet criteria for ART initiation	No change in plasma CD4 count

98. Noormahomed EV et al., 2014. PLoS Negl Trop Dis	601 (23%)	Cross-sectional	All	Western Blot	Human Adults Male and Female	Taken into account as a confounder	No change in plasma CD4 count
100. Kallestrup P et al., 2005. J Infect Dis	227 (100%)	-Longitudinal -Treatment with PZQ -Only 1 follow-up at 3 months	All	Microscopy CAA	Human Adults Male and Female	ART not widely available at time of study	Decreased plasma CD4 count
83. Efraim L et al., 2013. J Acquir Immune Defic Syndr.	351 (27.6%)	Cross-sectional	All	Microscopy Urine CCA	Human Adults Male and Female	Immunologically failing on ART	Decreased plasma CD4 count
102. Mwinzi PN et al., 2004. Am J Trop Med Hyg.	81 (100%)	Cross-sectional	*Sm*	Kato Katz Liver ultrasound	Human Adults Male only	NA	Decreased plasma CD4 count
103. Sadlier CM et al., 2013. AIDS Res Ther	90 (7.7%)	Cross-sectional	All	ELISA	Human Adults Male and Female	NA	Decreased plasma CD4 count
(2) CD4 counts in genital tissue							
24. Jourdan PM et al., 2011. Am J Trop Med Hyg	61 (100%)	Cross-sectional	*Sh*	Microscopy	Human 15-49 yo Female only	NA	Increased number of CD4 count in cervical mucosa
93. Prodger JL et al., 2015. PLoS Negl Trop Dis	24 (50%)	Cross-sectional	*Sm*	Kato-Katz Urine-CCA	Human Adults Male only	NA	No change in number of CD4 count in penile foreskins
(3) Systemic HIV RNA viral load							
100. Kallestrup P et al., 2005. J Infect Dis	227 (100%)	-Longitudinal -Treatment with PZQ -Only 1 follow-up at 3 month	All	Microscopy CAA	Human Adults Male and Female	ART not widely available at time of study	Increased systemic HIV RNA viral load

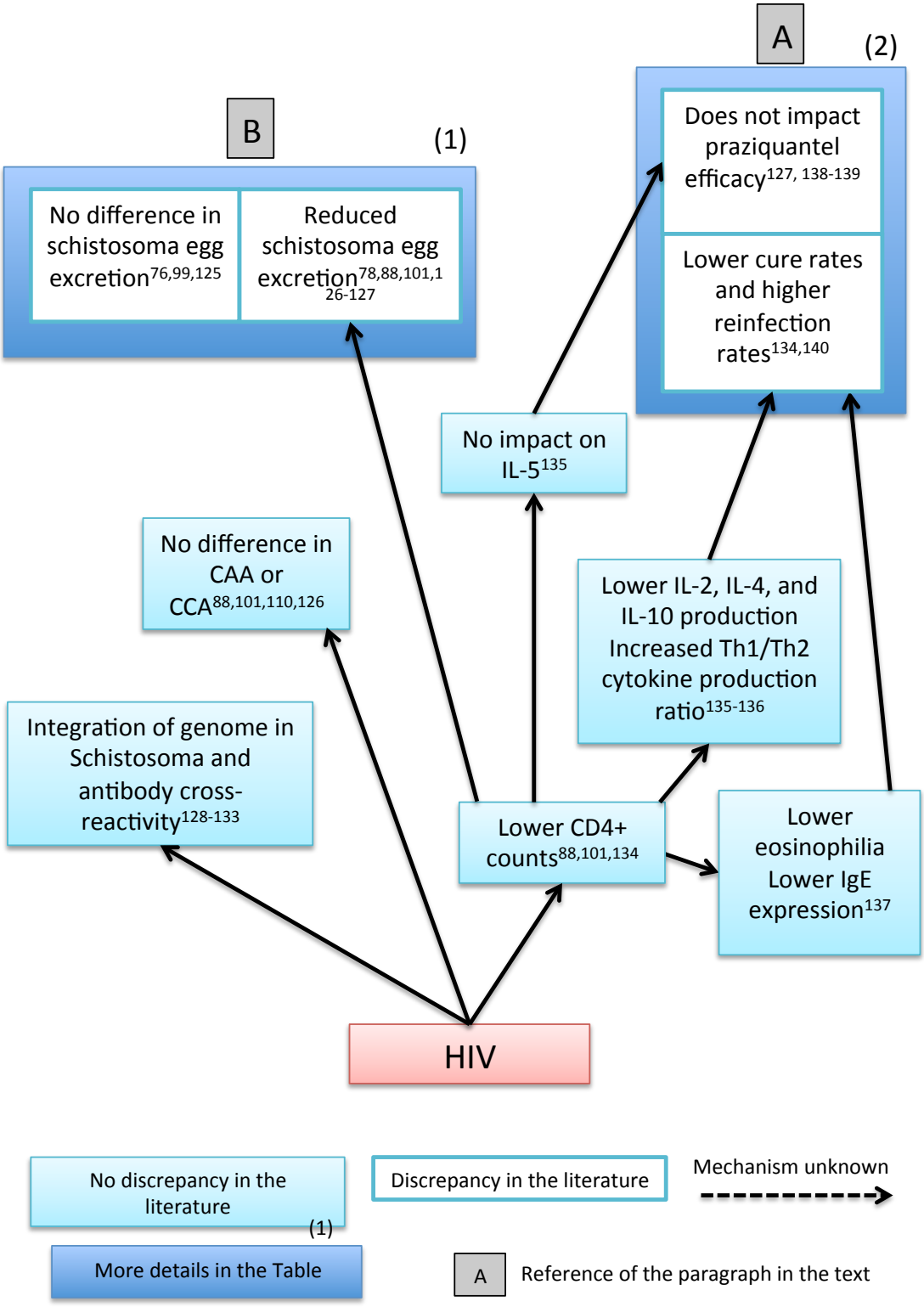
96. Sangare LR et al., 2011. Parasitology	4 articles	-Systematic literature review and meta-analysis	*Sm*	NA	Human Adults Male and Female	NA	Increased systemic HIV RNA viral load
104. Midzi N et al., 2017. Open Forum Infect Dis	18 (100%)	-Longitudinal -Treatment with PZQ -Only one follow-up	*Sh*	Microscopy	Human Adults Male only	Results stratified by ART	No change in systemic HIV RNA viral load
94. Brown M et al., 2004. J Infect Dis	418 (39.0%)	-Longitudinal -Treatment with PZQ -Only one follow-up at 6 months	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART naive	No change in systemic HIV RNA viral load
95. Obuku AE et al., 2016. AIDS Res Hum Retroviruses	34 (52.9%)	Cross-sectional	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART naive	No change in systemic HIV RNA viral load
105. Siddappa NB et al., 2011. PLoS Negl Trop Dis	15 (53.3%)	-Longitudinal -Follow ups, up to 20 weeks	*Sm*	NA	Macaques Adults Female only	NA	No change in systemic HIV RNA viral load
91. Brown M et al., 2005. J Infect Dis	119 (100%)	-Longitudinal -Treatment with PZQ -3 Follow ups, up to 5 months	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART not available at time of study	Decreased systemic HIV RNA viral load
92. Elliott AM et al., 2003. Trans R Soc Trop Med Hyg	108 (26%)	-Longitudinal -Treatment with PZQ -2 follow-ups up to 4 months	*Sm*	Kato-Katz CAA	Human Adults Male and Female	ART naive	Decreased systemic HIV RNA viral load
106. Lawn SD et al., 2000. AIDS	30 (100%)	-Longitudinal -Treatment with PZQ -Only one follow-up	*Sm*	Kato-Katz Plasma CCA	Human Adults Male only	NA	Decreased systemic HIV RNA viral load

schisto = *Schistosoma*
Sm = *S. mansoni*
Sh =*S. haematobium*
NA = Not available or not applicable

2) Effect of HIV on **Schistosoma** *spp. infection*

The effect of HIV on *Schistosoma* spp. infection is described in **Figure 2**. Each arrow describes a plausible or reported causal pathway. The diagram focuses on two aspects of the impact of HIV infection on *Schistosoma* spp.: section A illustrates the impact on PZQ efficacy and section B shows the impact on egg excretion. The pale blue boxes show findings for which either only one study was conducted, or for which there is agreement in the literature. The white boxes show discrepand findings. The parts of the graph indicated with capital letters are described in more details below. The dark blue boxes are detailed in **Table 2** below, providing additional information regarding several discrepant studies.

Figure 2 - Co-infection conceptual framework – Effect of HIV on *Schistosoma* spp. infection.



A. Effect of HIV on praziquantel efficacy

The role of HIV positivity on the efficacy of PZQ is unclear. Some studies have reported lower cure rates and higher rates of reinfection as measured by microscopy testing (egg detection)[134, 140] also in association with decreased immunity against *Schistosoma*[135-137]. Others have not been able to detect any effect[127, 138, 139]. PZQ treatment usually increases the Th2:Th1 ratio and the level of adult worm specific interleukins, including IL-2, IL-4, IL-5, and IL-10, leading to killing of adult worms and low chance of reinfection[141-144]. In addition, high levels of eosinophilia and of IgE expression are related to resistance against re-infection with schistosomes[142, 145, 146]. Contradictory, for HIV+ individuals, studies have shown that after treatment more Th1 cytokines are produced and IL-2, IL-4 and IL-10 production is decreased[135, 136]. This could explain the lower cure rates and higher reinfection rates seen in studies on co-infected individuals[134, 140]. CD4 declines in HIV+ individuals also lead to decreased ability to develop eosinophilia[137], and lower levels of IgE expression have also been observed[137], providing an additional (or alternative) explanation for the higher rates of reinfection with *Schistosoma* spp. observed in HIV+ individuals[134, 140].

The above indicated discrepancy could mirror the diverse effects of HIV infection on immune responses. It is also possible that it is linked to the fact that all studies have measured cure rates and rates of reinfection using egg microscopy which may lack sensitivity, is not a direct measure for worm burden, and might be affected by HIV infection.

B. Effect of HIV on egg excretion

Regarding the impact of HIV on *Schistosoma* spp. infection, there is no consensus as to whether *Schistosoma* spp. egg excretion is lowered in those with HIV infection as compared to those without[76, 78, 88, 99, 101, 126, 127]. Studies that looked at the circulating worm antigens in relation to HIV status indicated no relevant differences between the groups[88, 101, 110, 126].

In **Chapter 6**, we investigate the reasons for the discrepancies found regarding the impact of HIV infection on *Schistosoma* spp. excretion of eggs. Based on the difference in clinical disease in men and women, we hypothesized that sex would be a main confounder in the relationship between HIV status and *Schistosoma* spp. egg excretion.

Table 2 - Relationship between HIV infection and *Schistosoma* egg excretion and treatment.

Reference	Total sample size (% schisto)	Study type	Schisto species	Schisto test	Population	ART	Findings
(1) Egg excretion							
76. Mazigo HD et al., 2014. Parasit Vectors	1785 (47.8%)	Cross-sectional	*Sm*	Kato-Katz	Humans Adults Male and female	NA	No difference in egg excretion
99. Kleppa E et al., 2015. PLoS One	765 (20%)	Cross-sectional	*Sh*	Urine microscropy	Humans High-school students >16 yo Female only	Some on ART – not adjusted for	No difference in egg excretion
125. Olusegun AF et al., 2011. Oman Med J	2000 (0.3%)	Cross-sectional	*Sh*	Urine microscopy	Humans Adults Male and Female	NA	No difference in egg excretion
78. Sanya RE et al., 2015. Trop Med Int Health	1412 (57.2%)	Cross-sectional	*Sm*	Kato-Katz	Humans All ages >13 yo Male and Female	NA	Reduced egg excretion
101. Kallestrup P et al., 2005. J Infect Dis	1545 (43.4%)	Cross-sectional	All	Microscopy CAA	Humans Adults Male and Female	ART not widely available at time of study	Reduced egg excretion
126. Fontanet AL et al., 2000. Ann Trop Med Parasitol	1239 (31.4%)	Cross-sectional	*Sm*	Kato-Katz CAA	Humans 15-54 yo Male and Female	NA	Reduced egg excretion
88. Karanja DM et al., 1997. Am J Trop Med Hyg	53 (100%)	Cross-sectional	*Sm*	Microscopy CCA	Humans Adults Male only	NA	Reduced egg excretion

127. Mwanakasale V et al., 2003. Am J Trop Med Hyg	507 (100%)	Cross-sectional	*Sh*	Urine microscopy	Humans 10-55 yo Male and Female	NA	Reduced egg excretion
(2) Praziquantel efficacy							
127. Mwanakasale V et al., 2003. Am J Trop Med Hyg	507 (100%) at baseline	-Longitudinal study -Treatment with PZQ -3 follow-ups up to 12 months	*Sh*	Urine microscopy	Humans 10-55 yo Male and Female	NA	No difference in PZQ efficacy
138. Mazigo HD et al., 2014. Infect Dis Poverty	555 (100%)	-Longitudinal study -Treatment with PZQ -Only one follow-up 12 weeks post-treatment	*Sm*	Kato-Katz	Humans Adults Male and Female	ART Naive	No difference in PZQ efficacy
139. Karanja DM et al., 1998. Am J Trop Med Hyg 59: 307-11.	47 (100%)	-Longitudinal study -Treatment with PZQ -Two follow-ups, up to 6 months	*Sm*	Microscopy CCA	Humans Adults Male only	NA	No difference in PZQ efficacy
140. Kallestrup P et al., 2006. Clin Infect Dis	287 (100%)	-Longitudinal -Treatment with PZQ -3 follow ups up to 12 months	All	Microscopy	Humans Adults Male and Female	ART not widely available	Lower PZQ efficacy
134. Karanja DM et al., 2002. Lancet	107 (100%)	-Longitudinal -Treatment with PZQ -Follow-ups every 2 months for at least 1 year	*Sm*	Microscopy	Humans Adults >17yo Male only	NA	Lower PZQ efficacy

Schisto = *Schistosoma*
Sm = *S. mansoni*
Sh = *S. haematobium*
NA = Not available or not applicable

SUMMARY

- 6 million individuals are HIV/*Schistosoma* spp. co-infected
- There is a clear association between *Schistosoma* spp. and HIV
- Being *Schistosoma* spp. infected increases a woman's risk of HIV acquisition
- A lot is still unknown or poorly understood about HIV/*Schistosoma* spp. co-infections
- Longitudinal studies, controlling for sex, age, and duration of HIV infection are missing

Questions that this thesis is trying to answer:

✓ Why is there so much discrepancy in the data?

✓ Is there an impact of *Schistosoma* spp. co-infection on HIV/AIDS outcomes?

✓ Is there an impact of *Schistosoma* spp. co-infection on HIV transmission?

- Thesis studies were conducted in the Lake Zone of Tanzania

REFERENCES

1. WHO. HIV/AIDS Fact Sheet. 2018. Available at: http://www.who.int/en/news-room/fact-sheets/detail/hiv-aids Accessed on December 8th 2017.
2. WHO. Schistosomiasis Fact Sheet. 2018. Available at: http://www.who.int/en/news-room/fact-sheets/detail/schistosomiasis Accessed on December 8th 2017.
3. UNAIDS. Fact sheet - Latest statistics on the status of the AIDS epidemic. 2016 Available at: http://www.unaids.org/en/resources/fact-sheet. Accessed on December 8th 2017.
4. Ndeffo Mbah ML, Poolman EM, Drain PK, Coffee MP, Werf MJ, Galvani AP. HIV and Schistosoma haematobium prevalences correlate in sub-Saharan Africa. Trop Med Int Health. 2013; 18(10), 1174-1179.
5. 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.
6. King CH. Parasites and poverty: the case of schistosomiasis. Acta Trop 2010; 113: 95–104.
7. Bruun B, Aagaard-Hansen J, for the UNICEF, UNDP, World Bank, WHO Special Programme for Research and Training in Tropical Diseases. The social context of schistosomiasis and its control: an introduction and annotated bibliography. Geneva: World Health Organization, 2008.
8. The United Republic of Tanzania. Migration and Urbanization Report 2015. 2012 Population and Housing Census.
9. The United Republic of Tanzania. National AIDS Control Program. CTC2 database. Available at http://www.nacp.go.tz/site/downloads. Accessed on December 8th 2017.
10. Mazigo HD, Nuwaha F, Kinung'hi SM, Morona D, de Moira AP, Wilson S, et al. Epidemiology and control of human schistosomiasis in Tanzania. Parasit Vectors. 2012; 5:274. doi:10.1186/1756-3305-5-274.
11. Downs JA, de Dood CJ, Dee HE, McGeehan M, Khan H, Marenga A, Adel PE, Faustine E, Issarow B, Kisanga EF, Kisigo GA, Ngahyolerwa S, Zahoro F, Miyaye D, Magawa RG, Mngara J, Lee MH, Corstjens P, van Dam GJ, Fitzgerald DW, 2017. Schistosomiasis and Human Immunodeficiency Virus in Men in Tanzania. Am J Trop Med Hyg. 2017; 96: 856-862.
12. Ministry of Health Zanzibar, National Bureau of Statistics Dar es Salaam, Office of Chief Government Statitician Zanzibar, ICF, USAID, UNICEF, UNFPA. Tanzania Demographic and Health Survey and Malaria Indicator Survey (TDHS-MIS) 2011-12. Dar es Salaam, Tanzania, Rockville, Maryl USA. 2016. doi:10.1017/CBO9781107415324.004.
13. Co-infection: new battlegrounds in HIV/AIDS. Lancet Infect Dis. 2013; 13(7):559.
14. Chang CC, Crane M, Zhou J, et al. HIV and co-infections. Immunological reviews. 2013;254(1):114-142. doi:10.1111/imr.12063.
15. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. Lancet. 2006;368(9541):1106–18.
16. Mandell GL, Bennett JE, Dolin R. Principles and Practice of Infectious Diseases, 6 edn. Churchill Livingstone; 2005.
17. Stecher CW, Kallestrup P, Kjetland EF, Vennervald B, Petersen E. Considering treatment of male genital schistosomiasis as a tool for future HIV prevention: a systematic review. Int J Public Health. 2015;60(7):839-48. doi:10.1007/s00038-015-0714-7.
18. Kjetland EF, Leutscher PDC, Ndhlovu PD. A review of female genital schistosomiasis. Trends Parasitol. 2012;28(2):58-65. doi:10.1016/j.pt.2011.10.008.
19. Feldmeier H, Daccal RC, Martins MJ, Soares V, Martins R. Genital Manifestations of Schistosomiasis Mansoni in Women: Important but Neglected. Mem Inst Oswaldo Cruz. 1998;93 Suppl 1:127-33. doi:10.1590/S0074-02761998000700018.
20. Cheever AW, Kamel IA, Elwi AM, Mosimann JE, Danner R. Schistosoma mansoni and S. haematobium infections in Egypt. II. Quantitative parasitological findings at necropsy. Am J Trop Med Hyg. 1977;26(4):702-16. doi:10.4269/ajtmh.1977.26.702.
21. Gelfand M, Ross CM, Blair DM, Castle WM, Weber MC. Schistosomiasis of the male pelvic organs. Severity of infection as determined by digestion of tissue and histologic methods in 300 cadavers. Am J Trop Med Hyg. 1970;19(5):779-84.
22. Edington GM, Nwabuebo I, Junaid TA. The pathology of schistosomiasis in Ibadan, Nigeria with special reference to the appendix, brain, pancreas and genital organs.Trans R Soc Trop Med Hyg. 1975; 69(1):153-6.

23. Gelfand M, Ross MD, Blair DM, Weber MC. Distribution and extent of schistosomiasis in female pelvic organs, with special reference to the genital tract, as determined at autopsy. Am J Trop Med Hyg. 1971; 20(6):846-9.
24. Jourdan PM, Holmen SD, Gundersen SG, Roald B, Kjetland EF. HIV target cells in Schistosoma haematobium-infected female genital mucosa. Am J Trop Med Hyg. 2001;85: 1060-4.
25. Leutscher PD, Pedersen M, Raharisolo C, Jensen JS, Hoffmann S, Lisse I, et al (2005) Increased prevalence of leukocytes and elevated cytokine levels in semen from Schistosoma haematobium-infected individuals. J Infect Dis. 2005;191(10):1639–1647. doi:10.1086/429334.
26. The United Republic of Tanzania. Ministry of Health. National guidelines for the clinical management of HIV and AIDS. National AIDS Control Programme 2nd ed. 2005 Apr.
27. The United Republic of Tanzania. Ministry of Health and Social Welfare. National guidelines for the management of HIV and AIDS. National AIDS Control Programme 5th ed. 2015 May.
28. Modjarrad K, Chamot E, Vermund SH. Impact of small reductions in plasma HIV RNA levels on the risk of heterosexual transmission and disease progression. AIDS. 2008;22(16): 2179.
29. Patrikar S, Basannar DR, Bhatti VK, Kotwal A, Gupta RM, Grewal RS. Rate of decline in CD4 count in HIV patients not on antiretroviral therapy. Med J Armed Forces India. 2014;70(2): 134-138.
30. Arnaout RA, Lloyd AL, O'Brien TR, Goedert JJ, Leonard JM, Nowak MA. A simple relationship between viral load and survival time in HIV-1 infection. Proc Natl Acad Sci.1999;96(20): 11549-11553.
31. Coffin JM, Hughes SH, Varmus HE. . Course of Infection with HIV and SIV. In Retroviruses. Cold Spring Harbor Laboratory Press; 1997. Available from: https://www.ncbi.nlm.nih.gov/books/NBK19374/.
32. Gaines H, von Sydow MA, von Stedingk LV, Biberfeld G, Bottiger B, Hansson LO, et al. Immunological changes in primary HIV-1 infection. AIDS. 1990;4:995–999.
33. Lang W, Perkins H, Anderson RE, Royce R, Jewell N, Winkelstein WJr. Patterns of T lymphocyte changes with human immunodeficiency virus infection: From seroconversion to the development of AIDS. J. Acquired Immune Defic. Syndr. 1989;2:63–69.
34. Haynes BF, Pantaleo G, Fauci AS. Toward an understanding of the correlates of protective immunity to HIV-1 infection. Science. 1996;271:324–328.
35. Pantaleo G, Fauci AS. New concepts in the immunopathogenesis of HIV infection. Annu Rev Microbiol. 1996;50:825–854.
36. Moss AR, Bacchetti P. Natural history of HIV infection. AIDS. 1989;3:55–61.
37. Lemp GF, Payne SF, Rutherford GW, Hessol NA, Winkelstein WJr, Wiley JA, et al. Projections of AIDS morbidity and mortality in San Francisco. J Am Med Assoc. 1990b;263:1497–1501.
38. Clark SJ, Saag MS, Decker WD, Campbell-Hill S, Roberson JL, Veldkamp PJ, et al. High titers of cytopathic virus in plasma of patients with symptomatic primary HIV-1 infection. N Engl J Med. 1991;324:954–960.
39. Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. N Engl J Med. 1991;324:961–964.
40. Tindall B, Cooper DA. Primary HIV infection: Host responses and intervention strategies. AIDS. 1991;5:1–14.
41. Ho DD, Sarngadharan MG, Resnick L, diMarzo Veronese F, Rota TR, Hirsch MS. Primary human T-lymphotropic virus type III infection. Ann Intern Med. 1985;103:880–883.
42. Cooper DA, Imrie AA, Penny R. Antibody response to human immunodeficiency virus after primary infection. J Infect Dis. 1987;155:1113–1118.
43. Gaines H, Sonnerborg A, Czajkowski J, Chiodi F, Fenyo EM, von Sydow M, et al. Antibody response in primary human immunodeficiency virus infection. Lancet. 1987;I:1249–1253.
44. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and $CD4^{+}$lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med. 1997;126:946–954.
45. Piatak MJr, Saag MS, Yang LC, Clark SJ, Kappes JC, Luk KC, et al. High levels of HIV-1 in plasma during all stages of infection determined by competitive PCR. Science. 1993;259:1749–1754.
46. Pantaleo G, Graziosi C, Demarest JF, Butini L, Montroni M, Fox CH, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature. 1993c;362:355–358.

47. Doehring E, Feldmeier H, Daffalla AA. Day-to-day variation and circadian rhythm of egg excretion in urinary schistosomiasis in the Sudan. Ann Trop Med Parasitol. 1983;77: 587-94.
48. Birrie H, Medhin G, Erko B. Variability of egg excretion in Schistosoma mansoni infection in Ethiopia: a case report. East Afr Med J. 1994;71: 545-7.
49. Agnew A, Fulford AJ, Mwanje MT, Gachuhi K, Gutsmann V, Krijger FW, et al. Age-dependent reduction of schistosome fecundity in Schistosoma haematobium but not Schistosoma mansoni infections in humans. Am J Trop Med Hyg. 1996;55: 338-43.
50. Bethony J, Williams JT, Blangero J, Kloos H, Gazzinelli A, Soares-Filho B, et al. Additive host genetic factors influence fecal egg excretion rates during Schistosoma mansoni infection in a rural area in Brazil. Am J Trop Med Hyg. 2002;67: 336-43.
51. De Vlas SJ, Gryseels B, Van Oortmarssen GJ, Polderman AM, Habbema JDF. A pocket chart to estimate true Schistosoma mansoni prevalences. Parasitol Today. 1993;9(8):306-307.
52. Van Lieshout L, Polderman AM, Deelder AM. Immunodiagnosis of schistosomiasis by determination of the circulating antigens CAA and CCA, in particular in individuals with recent or light infections. Acta Trop. 2000;77(1): 69-80.
53. Doenhoff MJ, Chiodini PL, Hamilton JV. Specific and sensitive diagnosis of schistosome infection: can it be done with antibodies? Trends Parasitol. 2004;20: 35-9.
54. Utzinger J, Becker SL, van Lieshout L, van Dam GJ, Knopp S. New diagnostic tools in schistosomiasis. Clin Microbial Infect. 2015; 21(6), 529-542.
55. Meurs L, Brienen E, Mbow N, Ochola EA, Mboup S, Karanja DMS, et al. Is PCR the Next Reference Standard for the Diagnosis of Schistosoma in Stool? A Comparison with Microscopy in Senegal and Kenya. PLoS Negl Trop Dis. 2015 Jul; 9(7): e0003959. doi: 10.1371/journal.pntd.0003959.
56. Wichmann D, Poppert S, Von Thien H, et al. Prospective European-wide multicentre study on a blood based real-time PCR for the diagnosis of acute schistosomiasis. BMC Infect Dis. 2013;13:55. doi:10.1186/1471-2334-13-55.
57. de Water R, Fransen JA, Deelder AM. Ultrastructural localization of the circulating anodic antigen in the digestive tract of Schistosoma mansoni using monoclonal antibodies in an immunogold labeling procedure. Am J Trop Med Hyg. 1986;35(3):549–58.
58. van Dam GJ, Bogitsh BJ, van Zeyl RJ, Rotmans JP, Deelder AM. Schistosoma mansoni: in vitro and in vivo excretion of CAA and CCA by developing schistosomula and adult worms. J Parasitol. 1996;82(4):557–64.
59. de Jonge N, De Caluw P, Hilberath GW, Krijger FW, Polderman AM, Deelder AM. Circulating anodic antigen levels in serum before and after chemotherapy with praziquantel in schistosomiasis mansoni. Trans R Soc Trop Med Hyg. 1989;83(3):368–72.
60. van Lieshout L, de Jonge N, Bassily S, Mansour MM, Deelder AM. Assessment of cure in schistosomiasis patients after chemotherapy with praziquantel by quantitation of circulating anodic antigen (CAA) in urine. Am J Trop Med Hyg. 1991;44(3):323–8.
61. van Lieshout L, De Jonge N, Mansour MM, Bassily S, Krijger FW, Deelder AM. Circulating cathodic antigen levels in serum and urine of schistosomiasis patients before and after chemotherapy with praziquantel. Trans R Soc Trop Med Hyg. 1993;87(3):311-2.
62. Corstjens PL, van Lieshout L, Zuiderwijk M, Kornelis D, Tanke HJ, Deelder AM, et al. Up-converting phosphor technology-based lateral flow assay for detection of Schistosoma circulating anodic antigen in serum. J Clin Microbiol. 2008;46(1): 171-176.
63. Corstjens PLAM, De Dood CJ, Kornelis D, Fat EM, Wilson RA, Kariuki TM, et al. Tools for diagnosis, monitoring and screening of Schistosoma infections utilizing lateral-flow based assays and upconverting phosphor labels. Parasitology. 2014;141(14):1841-1855. doi:10.1017/S0031182014000626.
64. Corstjens PL, Nyakundi RK, de Dood CJ, Kariuki TM, Ochola EA, Karanja DM, et al. Improved sensitivity of the urine CAA lateral-flow assay for diagnosing active Schistosoma infections by using larger sample volumes. Parasit Vectors. 2015;8(1): 241.
65. van Dam GJ, Claudia J, Lewis M, Deelder AM, van Lieshout L, Tanke HJ, et al. A robust dry reagent lateral flow assay for diagnosis of active schistosomiasis by detection of Schistosoma circulating anodic antigen. Exp Parasitol. 2013;135(2): 274-282.

66. Markwalter C, Corstjens P, Mammoser C, Camps G, van Dam G, Wright D. Poly(amidoamine)-coated magnetic particles for enhanced detection of Schistosoma circulating anodic antigen in endemic urine samples. Analyst. 2018;144(1):212-219. doi: 10.1039/c8an00941d.
67. Jamaly S, Chihani T, Deelder AM, Gabone R, Nilsson LA, Ouchterlony O. Polypropylene fibre web, a new matrix for sampling blood for immunodiagnosis of schistosomiasis. Trans R Soc Trop Med Hyg. 1997;91(4):412–5.
68. Downs JA, Corstjens PLAM, Mngara J, Lutonja P, Isingo R, Urassa M, et al. Correlation of Serum and Dried Blood Spot Results for Quantitation of Schistosoma Circulating Anodic Antigen: a Proof of Principle. Acta trop. 2015;150:59-63. doi:10.1016/j.actatropica.2015.06.026.
69. van Dam GJ, Wichers JH, Ferreira TMF, Ghati D, van Amerongen A, Deelder AM. Diagnosis of schistosomiasis by reagent strip test for detection of circulating cathodic antigen. J Clin Microb. 2004;42:5458–5461. doi: 10.1128/JCM.42.12.5458-5461.2004.
70. Biggar MJ, Johnson BK, Oster C, Sarin PS, Ocheng D, Tukei P, et al. Regional variation in prevalence of antibody against human T-lymphotropic virus types I and II in Kenya, East Africa. Int J Cancer. 1985; 35(6):763-767.
71. Biggar MJ, Melbye M, Sarin PS, Kestens L, Sarin PS, Bodner AJ, et al. ELISA HTLV retrovirus antibody reactivity associated with malaria and immune complexes in healthy Africans. Lancet. 1985;2(8454):520-523.
72. Brodish PH, Singh K. Association Between Schistosoma haematobium Exposure and Human Immunodeficiency Virus Infection Among Females in Mozambique. Am J Trop Med Hyg. 2016;94:1040-4.
73. de Lima e Costa MF, Proietti FA, Paulino UH, Antunes CM, Guimaraes MD, Rocha RS, et al. Absence of cross-reactivity between Schistosoma mansoni infection and human immunodeficiency virus (HIV). Trans R Soc Trop Med Hyg. 1988;82: 262.
74. 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: 868-73.
75. Kjetland EF, Ndhlovu PD, Gomo E, Mduluza T, Midzi N, Gwanzura L, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. AIDS. 2006;20: 593-600.
76. Mazigo HD, Dunne DW, Wilson S, Kinung'hi SM, Pinot de Moira A, Jones FM, et al. Co-infection with Schistosoma mansoni and Human Immunodeficiency Virus-1 (HIV-1) among residents of fishing villages of north-western Tanzania. Parasit Vectors. 2014;7: 587.
77. Ndhlovu PD, Mduluza T, Kjetland EF, Midzi N, Nyanga L, Gundersen SG, et al. Prevalence of urinary schistosomiasis and HIV in females living in a rural community of Zimbabwe: does age matter? Trans R Soc Trop Med Hyg. 2007;101: 433-8.
78. Sanya RE, Muhangi L, Nampijja M, Nannozi V, Nakawungu PK, Abayo E, et al. Schistosoma mansoni and HIV infection in a Ugandan population with high HIV and helminth prevalence. Trop Med Int Health. 2015;20:1201-1208.
79. Gordon MA, Zijlstra EE, Naus CW, Visser LG, Molyneux ME, van Lieshout L. Schistosomiasis does not contribute to death or recurrence of nontyphoid Salmonella bacteremia in human immunodeficiency virus-infected Malawian adults. Clin Infect Dis. 2003;37: e177-9.
80. Brown M, Miiro G, Nkurunziza P, Watera C, Quigley MA, Dunne DW, et al. Schistosoma mansoni, nematode infections, and progression to active tuberculosis among HIV-1-infected Ugandans. Am J Trop Med Hyg. 2006;74: 819-25.
81. Kjetland EF, Hegertun IE, Baay MF, Onsrud M, Ndhlovu PD, Taylor M. Genital schistosomiasis and its unacknowledged role on HIV transmission in the STD intervention studies. Int J STD AIDS. 2014;25:705-15.
82. Everett DB, Baisely KJ, McNerney R, Hambleton I, Chirwa T, Ross DA, et al. Association of schistosomiasis with false-positive HIV test results in an African adolescent population. J Clin Microbiol. 2010;48: 1570-7.
83. Efraim L, Peck RN, Kalluvya SE, Kabangila R, Mazigo HD, Mpondo B, et al. Schistosomiasis and impaired response to antiretroviral therapy among HIV-infected patients in Tanzania. J Acquir Immune Defic Syndr. 2013;e153-6.
84. Downs JA, Msango L, Kalluvya SE, Kidenya BR, Kabangila R, Peck RN. Renal dysfunction and schistosomiasis among HIV-infected patients starting antiretroviral therapy in Mwanza, Tanzania. AIDS. 2015;29: 2532-3.

85. Marti AI, Colombe S, Masikini PJ, Kalluvya SE, Smart LR, Wajanga BM, et al. Increased hepatotoxicity among HIV-infected adults co-infected with Schistosoma mansoni in Tanzania: A cross-sectional study. PLoS Negl Trop Dis. 2017;11:e0005867.
86. Ndeffo Mbah ML, Kjetland EF, Atkins KE, Poolman EM, Orenstein EW, Meyers LA, et al. Cost-effectiveness of a community-based intervention for reducing the transmission of Schistosoma haematobium and HIV in Africa. Proc Natl Acad Sci USA. 2013;110: 7952-7.
87. Ndeffo Mbah ML Poolman EM, Atkins KE, Orenstein EW, Meyers LA, Townsend JP, et al. 2013. Potential Cost-Effectiveness of Schistosomiasis Treatment for Reducing HIV Transmission in Africa – The Case of Zimbabwean Women. PLoS Negl Trop Dis. 2013;7(8):e2346. doi:10.1371/journal.pntd.0002346.
88. Karanja DM, Colley DG, Nahlen BL, Ouma JH, Secor WE. Studies on schistosomiasis in western Kenya: I. Evidence for immune-facilitated excretion of schistosome eggs from patients with Schistosoma mansoni and human immunodeficiency virus coinfections. Am J Trop Med Hyg. 1997;56: 515-21.
89. Muok EM, Simiyu EW, Ochola EA, Ng'ang'a ZW, Secor WE, Karanja DM et al. Association between CD4+ T-lymphocyte counts and fecal excretion of Schistosoma mansoni eggs in patients coinfected with S. mansoni and human immunodeficiency virus before and after initiation of antiretroviral therapy. Am J Trop Med Hyg. 2013;89: 42-5.
90. Smith C, Smith H, Seaton RA, Fox R. Seroprevalence of schistosomiasis in African patients infected with HIV. HIV Med. 2008;9: 436-9.
91. Brown M, Mawa PA, Joseph S, Bukusuba J, Watera C, Whitworth JA, et al. Treatment of Schistosoma mansoni infection increases helminth-specific type 2 cytokine responses and HIV-1 loads in coinfected Ugandan adults. J Infect Dis. 2005;191:1648-57.
92. Elliott AM, Mawa PA, Joseph S, Namujju PB, Kizza M, Nakiyingi JS, et al. Associations between helminth infection and CD4+ T cell count, viral load and cytokine responses in HIV-1-infected Ugandan adults. Trans R Soc Trop Med Hyg. 2003;97:103-8.
93. Prodger JL, Ssemaganda A, Ssetaala A, Kitandwe PK, Muyanja E, Mpendo J, et al. Schistosoma mansoni Infection in Ugandan Men Is Associated with Increased Abundance and Function of HIV Target Cells in Blood, but Not the Foreskin: A Cross-sectional Study. PLoS Negl Trop Dis. 2015;9:e0004067.
94. Brown M, Kizza M, Watera C, Quigley MA, Rowland S, Hughes P, et al. Helminth infection is not associated with faster progression of HIV disease in coinfected adults in Uganda. J Infect Dis. 2004;190:1869-79.
95. Obuku AE, Asiki G, Abaasa A, Ssonko I, Harari A, van Dam GJ, et al. Effect of Schistosoma mansoni Infection on Innate and HIV-1-Specific T-Cell Immune Responses in HIV-1-Infected Ugandan Fisher Folk. AIDS Res Hum Retroviruses. 2016;32:668-75.
96. Sangare LR, Herrin BR, John-Stewart G, Walson JL. Species-specific treatment effects of helminth/HIV-1 co-infection: a systematic review and meta-analysis. Parasitology. 2011;138:1546-58.
97. Walson J, Singa B, Sangare L, Naulikha J, Piper B, Richardson B, et al. Empiric deworming to delay HIV disease progression in adults with HIV who are ineligible for initiation of antiretroviral treatment (the HEAT study): a multi-site, randomised trial. Lancet Infect Dis. 2012;12:925-32.
98. Noormahomed EV, Nhacupe N, Mascaro-Lazcano C, Mauaie MN, Buene T, Funzamo CA, et al. A cross-sectional serological study of cysticercosis, schistosomiasis, toxocariasis and echinococcosis in HIV-1 infected people in Beira, Mozambique. PLoS Negl Trop Dis. 2014;8:e3121.
99. Kleppa E, Klinge KF, Galaphaththi-Arachchige HN, Holmen SD, Lillebo K, Onsrud M, et al. Schistosoma haematobium infection and CD4+ T-cell levels: a cross-sectional study of young South African women. PLoS One. 2015;10:e0119326.
100. 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;192:1956-61.
101. Kallestrup P, Zinyama R, Gomo E, Butterworth AE, van Dam GJ, Erikstrup C, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: implications of coinfection for excretion of eggs. J Infect Dis. 2005; 191:1311-20.

102. Mwinzi PN, Karanja DM, Kareko I, Magak PW, Orago AS, Colley DG, et al. Short report: Evaluation of hepatic fibrosis in persons co-infected with Schistosoma mansoni and human immunodeficiency virus 1. Am J Trop Med Hyg. 2004; 71:783-6.
103. Sadlier CM, Brown A, Lambert JS, Sheehan G, Mallon PW. Seroprevalence of Schistosomiasis and Strongyloides infection in HIV-infected patients from endemic areas attending a European infectious diseases clinic. AIDS Res Ther. 2013; 10:23.
104. Midzi N, Mduluza T, Mudenge B, Foldager L, Leutscher PDC. Decrease in Seminal HIV-1 RNA Load After Praziquantel Treatment of Urogenital Schistosomiasis Coinfection in HIV-Positive Men-An Observational Study. Open Forum Infect Dis. 2017; 4:ofx199.
105. 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:e1270.
106. Lawn SD, Karanja DM, Mwinzia P, Andove J, Colley DG, Folks TM, et al. The effect of treatment of schistosomiasis on blood plasma HIV-1 RNA concentration in coinfected individuals. AIDS. 2000; 14:2437-43.
107. Mbabazi PS, Andan O, Fitzgerald DW, Chitsulo L, Engels D, Downs JA. Examining the relationship between urogenital schistosomiasis and HIV infection. PLoS Negl Trop Dis. 2011; 5:e1396.
108. Ndeffo Mbah ML, Gilbert JA, Galvani AP. Evaluating the potential impact of mass praziquantel administration for HIV prevention in Schistosoma haematobium high-risk communities. Epidemics. 2014; 7:22-7.
109. Mushayabasa S, Bhunu CP. Modeling schistosomiasis and HIV/AIDS codynamics. Comput Math Methods Med. 2011;2011:846174.
110. Ssetaala A, Nakiyingi-Miiro J, Asiki G, Kyakuwa N, Mpendo J, Van Dam GJ, et al. Schistosoma mansoni and HIV acquisition in fishing communities of Lake Victoria, Uganda: a nested case-control study. Trop Med Int Health. 2015;20:1190-1195.
111. Chenine AL, Shai-Kobiler E, Steele LN, Ong H, Augostini P, Song R, et al. Acute Schistosoma mansoni infection increases susceptibility to systemic SHIV clade C infection in rhesus macaques after mucosal virus exposure. PLoS Negl Trop Dis. 2008;2:e265.
112. Bui CT, Shollenberger LM, Paterson Y, Harn DA. Schistosoma mansoni soluble egg antigens enhance Listeria monocytogenes vector HIV-1 vaccine induction of cytotoxic T cells. Clin Vaccine Immunol. 2014;21:1232-9.
113. Bui CT, Shollenberger LM, Paterson Y, Harn DA. Schistosoma mansoni soluble egg antigens enhance T cell responses to a newly identified HIV-1 Gag H-2b epitope. Clin Vaccine Immunol. 2015;22:193-9.
114. McElroy MD, Elrefaei M, Jones N, Ssali F, Mugyenyi P, Barugahare B, et al. Coinfection with Schistosoma mansoni is associated with decreased HIV-specific cytolysis and increased IL-10 production. J Immunol. 2005;174: 5119-23.
115. Ayash-Rashkovsky M, Chenine AL, Steele LN, Lee SJ, Song R, Ong H, et al. Coinfection with Schistosoma mansoni reactivates viremia in rhesus macaques with chronic simian-human immunodeficiency virus clade C infection. Infect Immun. 2007;75:1751-6.
116. Erikstrup C, Kallestrup P, Zinyama-Gutsire RB, Gomo E, van Dam GJ, Deelder AM, et al. Schistosomiasis and infection with human immunodeficiency virus 1 in rural Zimbabwe: systemic inflammation during co-infection and after treatment for schistosomiasis. Am J Trop Med Hyg. 2008; 79:331-7.
117. Chenine AL, Buckley KA, Li PL, Rasmussen RA, Ong H, Jiang S, et al. Schistosoma mansoni infection promotes SHIV clade C replication in rhesus macaques. AIDS. 2005;19:1793-7.
118. Secor WE, Shah A, Mwinzi PM, Ndenga BA, Watta CO, Karanja DM. Increased density of human immunodeficiency virus type 1 coreceptors CCR5 and CXCR4 on the surfaces of CD4(+) T cells and monocytes of patients with Schistosoma mansoni infection. Infect Immun. 2003;71:6668-71.
119. Mellors JW, Rinaldo Jr CR, Gupta P, White RM. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science. 1996;272(5265):1167-70.
120. Hughes JP, Baeten JM, Lingappa JR, Magaret AS, Wald A, De Bruyn G, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1–serodiscordant couples. J Inf Dis. 2012; 205(3):358-365.

121. Walson JL, Otieno PA, Mbuchi M, Richardson BA, Lohman-Payne B, Macharia SW, et al. Albendazole treatment of HIV-1 and helminth co-infection: a randomized, double-blind, placebo-controlled trial. AIDS. 2008;22: 1601–09.
122. Kestens L, Seddiki N, Bohjanen PR. Immunopathogenesis of immune reconstitution disease in HIV patients responding to antiretroviral therapy. Curr Opin HIV AIDS. 2008;3(4):419-424. doi:10.1097/COH.0b013e328302ebbb.
123. Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. HIV Viral Load Response to Antiretroviral Therapy According to the Baseline CD4 Cell Count and Viral Load. JAMA. 2001;286(20):2560-7.
124. Colley DG, Secor WE. Immunology of human schistosomiasis. Parasite Immunol. 2014;36(8):347-357. doi:10.1111/pim.12087.
125. Olusegun AF, Ehis OC, Richard O. Proportion of Urinary Schistosomiasis among HIV-Infected Subjects in Benin City, Nigeria. Oman Med J. 2011;26:175-7.
126. Fontanet AL, Woldemichael T, Sahlu T, van Dam GJ, Messele T, Rinke de Wit T, et al. Epidemiology of HIV and Schistosoma mansoni infections among sugar-estate residents in Ethiopia. Ann Trop Med Parasitol. 2000;94: 145-55.
127. 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;69:420-8.
128. Khalife J, Grzych JM, Pierce R, Ameisen JC, Schacht AM, Gras-Masse H, et al. Immunological crossreactivity between the human immunodeficiency virus type 1 virion infectivity factor and a 170-kD surface antigen of Schistosoma mansoni. J Exp Med. 1990;172:1001-4.
129. Chacin de Bonilla L. Schistosoma mansoni and human immunodeficiency virus: new research avenues. Invest Clin. 1991;32:1-2.
130. Khalife J, Pierce RJ, Godin C, Capron A. Molecular characterization of two Schistosoma mansoni proteins sharing common motifs with the vif protein of HIV-1. Parasitology. 1994;108(5):533-42.
131. Suttiprapa S, Rinaldi G, Tsai IJ, Mann VH, Dubrovsky L, Yan HB, et al. HIV-1 Integrates Widely throughout the Genome of the Human Blood Fluke Schistosoma mansoni. PLoS Pathog. 2016;12:e1005931.
132. Mello MA, Mascarenhas RE, Ferraro GA, Harn D, Galvao-Castro M, Bou-Habib DC. Inhibition of HIV-1 infection by monoclonal antibodies to carbohydrates of Schistosoma mansoni. Med Microbiol Immunol. 2005;194: 61-5.
133. Shollenberger LM, Bui CT, Paterson Y, Nyhoff L, Harn DA. HIV-1 vaccine-specific responses induced by Listeria vector vaccines are maintained in mice subsequently infected with a model helminth parasite, Schistosoma mansoni. Vaccine. 2013;31:5651-8.
134. 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;360:592-6.
135. Joseph S, Jones FM, Laidlaw ME, Mohamed G, Mawa PA, Namujju PB, et al. Impairment of the Schistosoma mansoni-specific immune responses elicited by treatment with praziquantel in Ugandans with HIV-1 coinfection. J Infect Dis. 2004;190:613-8.
136. Mwinzi PN, Karanja DM, Colley DG, Orago AS, Secor WE. Cellular immune responses of schistosomiasis patients are altered by human immunodeficiency virus type 1 coinfection. J Infect Dis. 2001;184:488-96.
137.Ganley-Leal LM, Mwinzi PN, Cetre-Sossah CB, Andove J, Hightower AW, Karanja DM, et al. Correlation between eosinophils and protection against reinfection with Schistosoma mansoni and the effect of human immunodeficiency virus type 1 coinfection in humans. Infect Immun. 2006;74:2169-76.
138. Mazigo HD, Dunne DW, Kinung'hi SM, Nuwaha F. Praziquantel efficacy against Schistosoma mansoni among HIV-1 infected and uninfected adults living in fishing villages along Lake Victoria, Northwest Tanzania. Infect Dis Poverty. 2014;3:47.
139. 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;59:307-11.

140. Kallestrup P, Zinyama R, Gomo E, Butterworth AE, van Dam GJ, Gerstoft J, et al. Schistosomiasis and HIV in rural Zimbabwe: efficacy of treatment of schistosomiasis in individuals with HIV coinfection. Clin Infect Dis. 2006;42:1781-9.
141. Dunne D, Mountford A. Resistance to infection in humans and animal models. In: Mahmoud AAF, editor. Schistosomiasis. London: Imperial College Press; 2001. pp. 133–211.
142. Grogan JL, Kremsner PG, van Dam AM, Metzger W, Mordmüller B, Deelder AM, et al. Anti-schistosome IgG4 and IgE responses are affected differentially by chemotherapy in children versus adults. J Infect Dis. 1996;173(5):1242-7.
143. Grogan JL, Kremsner PG, Deelder AM, Yazdanbakhsh M. Elevated proliferation and interleukin-4 release from CD4++ cells after chemotherapy in human Schistosoma haematobium infection. Eur J Immunol. 1996;26(6):1365-70.
144. Joseph S, Jones FM, Walter K, Fulford AJ, Kimani G, Mwatha JK, et al. Increases in human T helper 2 cytokine responses to Schistosoma mansoni worm and worm tegument antigens induced by treatment with praziquantel. J Infect Dis. 2004;190(4):835-42.
145. Dunne DW, Butterworth AE, Fulford AJ, Ouma JH, Sturrock RF. Human IgE responses to Schistosoma mansoni and resistance to reinfection. Mem Inst Oswaldo Cruz. 1992; 87 Suppl 4:99-103.
146. Butterworth AE, Capron M, Cordingley JS, Dalton PR, Dunne DW, Kariuki HC, et al. Immunity after treatment of human schistosomiasis mansoni. II. Identification of resistant individuals, and analysis of their immune responses. Trans R Soc Trop Med Hyg. 1985; 79(3):393-408.