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

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CHAPTER 1 – GENERAL INTRODUCTION

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

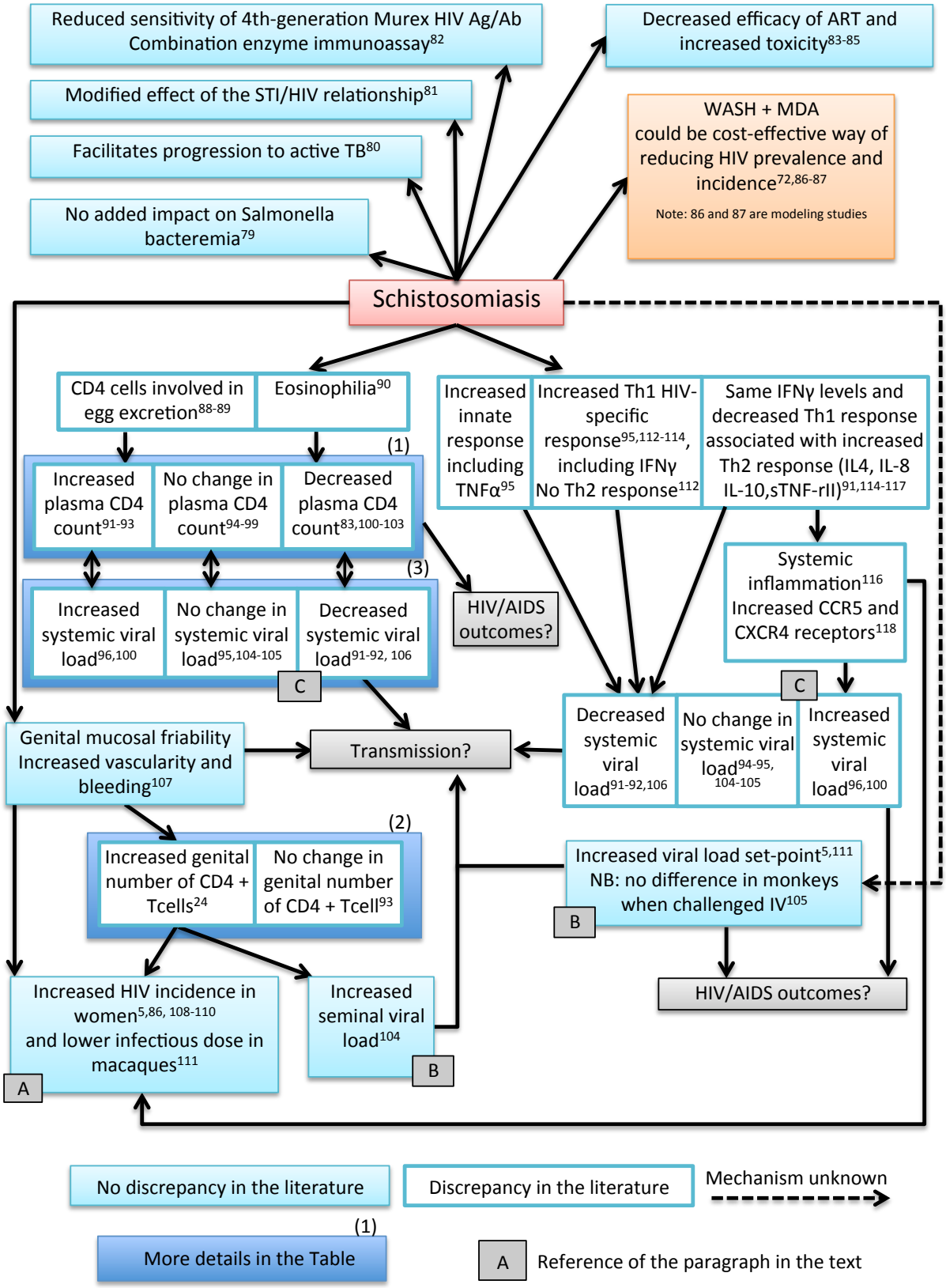
Despite multiple studies reporting interactions between infection with HIV and *Schistosoma* spp. in humans and macaques, little is still known about the processes and modalities of this co-infection. A systematic search on Pubmed for all scientific publications focusing on the epidemiology, immunology, 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

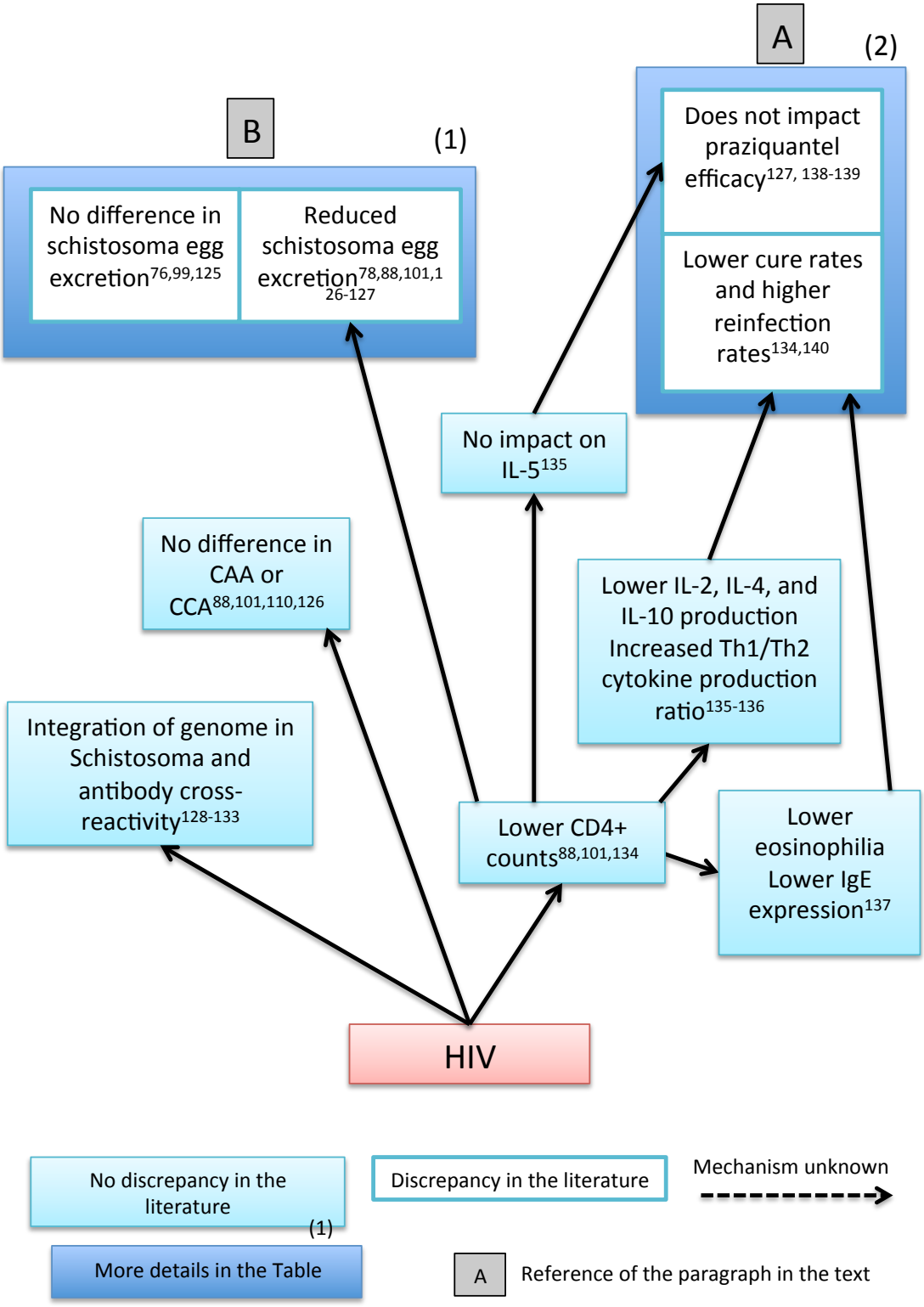
96. Sangare LR et al., 2011. Parasitology	4 articles	-Systematic literature review and meta-analysis	*Sm*	NA	Human Adults Male and Female	NA	Increased systemic HIV RNA viral load
104. Midzi N et al., 2017. Open Forum Infect Dis	18 (100%)	-Longitudinal -Treatment with PZQ -Only one follow-up	*Sh*	Microscopy	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

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