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

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CHAPTER 7 – SUMMARIZING DISCUSSION

I. INITIAL COMPREHENSION ON *SCHISTOSOMA* SPP. AND HIV INTERACTIONS

There is a need to better understand the epidemiology of HIV and *Schistosoma* spp. co-infections, the consequences of one disease on the public health interventions targeting the other, the confounders in the interaction, and the ways to alleviate the combined burden to improve quality of life. The 2013 Global Burden of Disease Study estimated that schistosomiasis alone causes 2.6 million Disability-Adjusted Life Years (DALYs) lost annually, while HIV infection alone causes 66.7 million DALYs[1]. These numbers do not include the combined impact of co-infections. This thesis aimed at increasing the knowledge about HIV/*Schistosoma* spp. co-infections, as well as defining gaps in the past research methodology to improve future research and improve comparisons and advance accurateness of conclusions.

The studies described in this manuscript were conducted among the Tanzanian population of the Lake Zone, where regular HIV surveillance is conducted and where both *S. mansoni* and *S. haematobium* are present. *S. haematobium* and *S. mansoni* are thought to modify HIV epidemiology through both local and systemic modifications. *S. haematobium* eggs, as well as *S. mansoni* eggs to a lesser extent, can be found in the urogenital tract. They cause urogenital schistosomiasis, which is marked by inflammation, friability, and bleeding of the urinary and genital mucosa[2, 3]. Men and women are affected differently by genital schistosomiasis as genital lesions due to eggs' sequestration and induced inflammation are less common in men than in women[2, 4, 5]. In addition, sequestered eggs and their associated lesions in women are found in sites directly accessible during sexual contact[3], which is not the case for men[2, 4]. *Schistosoma* eggs are highly immunogenic and lead to recruitment of immune cells, including CD4+ T-cells (CD4 counts), that are preferential targets of HIV[2]. In addition, *Schistosoma* spp. infection is typically thought to increase the Th2 immune response and lower the Th1 immune response, which causes increased levels of interleukines that may induce accelerated replication of HIV[6].

Both HIV testing and *Schistosoma* spp. testing are important to take into account when comparing studies looking at the interaction between both infections. 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[7] and since 2016, HIV RNA viral load quantification using PCR has been in place to evaluate response to ART[8]. 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[9-11].

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. It is less sensitive than other diagnostic strategies but has a near-perfect specificity and allows to differentiate between the infecting *Schistosoma* species if both urine and stool are provided. Schistosome antigen testing has been improved over the years to reach a high sensitivity and specificity for diagnosis of *Schistosoma* genus, although it does not allow distinction between *Schistosoma*

species[12]. Circulating anodic antigen (CAA) and circulating cathodic antigen (CCA) can be detected either in the serum or in the urine of infected individuals, meaning the testing only requires one biological matrix to identify infection, and the level of these antigens is proportional to the intensity of infection[12]. The CAA and CCA based tests have been optimized for use in the field and CAA testing has been improved to be able to use dried blood spot samples for testing[13]. Current PCR techniques detect active infection but are expensive and often do not distinguish between *Schistosoma* species[12].

There is a clear association between *Schistosoma* spp. and HIV in women in the literature[14-18], and being infected with *Schistosoma* spp. increases the risk of HIV acquisition for women but not for men[19-22]. This is thought to be due to the difference in clinical urogenital schistosomiasis in men and women as mentioned above.

However there is still a lot unknown or poorly understood about HIV/*Schistosoma* spp. co-infections. Past 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. Most studies have looked at the effect of co-infections (in a cross-sectional way), while some have looked at the impact of *Schistosoma* spp. infection at time of HIV infection on HIV progression. There is still a lot of discrepancy in the literature regarding the role of *Schistosoma* spp. co-infection on HIV-RNA viral loads and CD4 counts, and regarding the role of HIV co-infection on *Schistosoma* spp. egg excretion. Based on schistosomiasis clinical differences between men and women, as well as differences in CD4 counts and HIV RNA viral load both between individuals and over the course of HIV infection, we would expect both sex and duration of HIV infection to be a main confounder in the relationship between HIV status and *Schistosoma* spp. infection.

The discussion will focus first on the conceptual framework presented in the introduction and the specific ways in which this thesis has strengthened our understanding of HIV/*Schistosoma* spp. co-infections. Then it will focus on the importance of taking into account HIV/*Schistosoma* spp. co-infections for prevention and diagnosis of both diseases, and finally it will indicate key limitations of most studies and recapitulate the questions that still remain to be answered.

II. REVISITING THE INITIAL CONCEPTUAL FRAMEWORK: WHAT GAPS DID WE FILL?

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

Studies had shown that co-infection with *Schistosoma* spp. increased HIV RNA viral load and viral load set point in humans[19, 23-25], as well as replication and reactivation of sHIV in macaques[26, 27]. As a result, it had been hypothesized for years that co-infection with *Schistosoma* spp. would hasten progression to HIV/AIDS outcomes and would increase transmission[28, 29]. Yet, to confirm these two assumptions, one needs longitudinal HIV/*Schistosoma* spp. co-infections studies. Ours were the first to try to answer these topics. The studies were built on the unique opportunity to have access to regular HIV testing results among a cohort of about 30,000 people over a period of 10 years and to be able to test the stored Dried Blood Spots (DBS) for the presence of *Schistosoma* spp. derived antigen indicating active infection at the time of DBS collection. The study results did not support the longstanding hypotheses but indicated the opposite (**Chapter 3 & 4**), explained in detail below.

A. <u>*Schistosoma* spp. infection at time of HIV infection slows down AIDS progression</u>

We found a highly significant protective effect of *Schistosoma* spp. infection against HIV outcomes (**Chapter 3**). This finding is unexpected if compared to studies showing increased HIV RNA viral loads during co-infection or shortly after HIV acquisition[19, 23-25]. However it is in line with our study results described in **Chapter 5**. **Chapter 5** indeed showed that *Schistosoma*-infected individuals have lower HIV RNA viral loads for a given duration of HIV infection as compared to HIV-infected individuals without *Schistosoma* infections, while lower viral loads are usually synonym of better HIV/AIDS outcomes[30]. It also coheres with the findings of multiple other studies that have reported increased CD4 counts and decreased HIV RNA viral loads in those with *Schistosoma* spp. infection, as compared to those without[31-35]. Therefore, we posit that host immune responses to *Schistosoma* spp. could be protective against HIV/AIDS progression, particularly after a longer duration of HIV infection, and that this can affect the host's clinical outcome.

One possible mechanism of this protective effect could be via induction of Th1 HIV-specific immunity in *Schistosoma* spp. co-infected individuals[36-39]. In addition, *Schistosoma* spp. infection leads to increases in Th17 and regulatory T (Treg) cells, which plays a critical role in determining the speed of HIV/AIDS progression[40, 41]. Lower Th17/Treg ratios have been associated with more advanced HIV infection[42], while absolute increases in Treg numbers have been associated with decreased markers of immune activation[42, 43], potentially leading to better HIV outcomes. In contrast, higher absolute numbers of Th17 cells could prevent microbial translocation and thereby decrease immune hyperactivation, which has been associated with poorer HIV outcomes[41, 42]. This, in combination with the previous immunological findings, suggests that there is not one way in which *Schistosoma* spp. infection influences HIV pathogenesis (and vice versa), but rather multiple pathways, that are

all balanced, and it is the ratios and balances and imbalances that will lead to an effect of one disease on the other[44-47]. The immunological pathways also likely change over time, making it essential to consider the length of infection with each disease and the duration of co-infection itself when trying to understand HIV and *Schistosoma* spp. co-infections.

B. *Schistosoma* spp. co-infection increases HIV transmission

While several studies have shown an increased risk of HIV acquisition of nearly 3 fold in women infected with *S. haematobium* or *S. mansoni*[19, 20], the risk of HIV transmission from men and women infected with *Schistosoma spp.* to healthy non-infected individuals is not as clear in our studies (**Chapter 4**). In our study population, *Schistosoma* spp. co-infection increased HIV transmission, although it was not statistically significant. The lack of significance was likely due to an overwhelming effect of the sex of the receiving partner on HIV transmission[48]. Women are indeed more susceptible to HIV infection than males[48-49]. To remove this effect of sex of the receiving partner, further studies should investigate the effect of *Schistosoma* spp. in HIV positive male individuals and the associated risk for transmission to female sero-discordant partners. In addition, it is possible that the effect was small in our study population because most people were infected with *S. mansoni*[13, 17, 18], thus having lower prevalence of genital schistosomiasis and/or a lower density of egg-induced local changes that may facilitate HIV transmission, compared to infection with *S. haematobium*. The fact that *Schistosoma* spp. seems to be associated with higher risk of HIV acquisition and transmission (**Chapter 4**), but associated with better HIV/AIDS outcomes and lower HIV RNA viral loads (**Chapter 3 & 5**), suggests a dual (and likely opposite) effect of *Schistosoma* spp.: a local effect, associated with genital schistosomiasis, and systemic immunological changes. We found that *S. mansoni* infection leads to increased HIV transmission but only with a small effect (**Chapter 4**). We believe that the effect of *S. haematobium* on HIV transmission would have been larger, due to higher frequency and severity of urogenital schistosomiasis, and reinforces the idea that the effect of *Schistosoma* spp. co-infection on HIV transmission could be due to local genital inflammation rather than systemic immunological changes[50-53].

C. *Schistosoma* spp. co-infection decreases HIV RNA viral load

Chapter 5 highlighted the need to account for the duration of HIV infection, through an approach taking into account CD4 counts at enrollment[54]. This is a straightforward calculation, requiring minimal data, to account for duration of HIV infection that we would suggest to include in future study on HIV and *Schistosoma* spp. co-infection. The technique behind this method has been used in multiple studies and is drawing from several data sources[54-59]. Time infected with HIV is defined as the sum of the time between HIV acquisition and enrollment at a clinic and the time between enrollment at a clinic and enrollment in the study. The time infected with HIV before enrolling in a clinic is defined using the first CD4 counts reported at the clinic, which is used to approximate the time delay between HIV infection and enrollment as a function of normal CD4 decay per calendar year

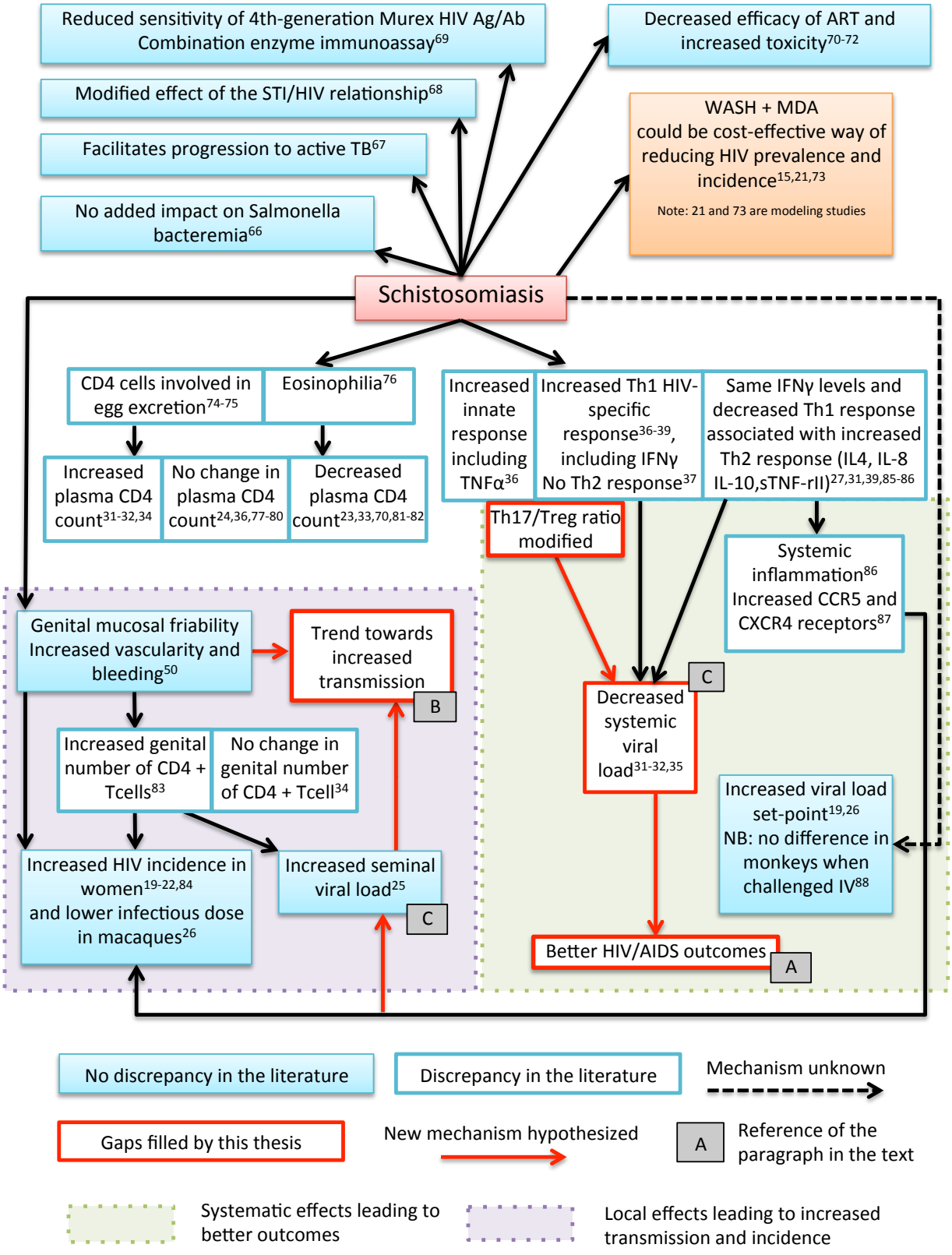
in drug naïve individuals. The time between the first CD4 count reported at the clinic and the date of study testing is then added to this variable to obtain the duration of HIV infection.

In our study, the results derived from this method concorded with results issued from surveillance data alone and approximation of the start of HIV infection by the middle date between two discordant DBS (**Chapter 2**). Several studies on HIV alone suggest that the relationship between immunological responses and HIV RNA viral load or CD4 count does not remain constant throughout the entire course of HIV infection, which further complicates the understanding of the immunological interactions between HIV infection and *Schistosoma* spp. infection[9-11, 60].

Duration of *Schistosoma* spp. infection is more difficult to measure than for HIV, as natural clearance and reinfection happen regularly in the adult population[61]. Even when people report having recently taken praziquantel (PZQ), yet test positive for *Schistosoma* spp., one cannot always distinguish between reinfection, decreased responsiveness to PZQ, and poor adherence[62-64]. As PZQ is made more widely available to populations in need, its administration and impact must be evaluated but the lack of gold standard diagnosis test for *Schistosoma* spp. further complicates analyses[65]. It can render studies that used microscopy and detected the presence of eggs in urine or stool difficult to compare to studies using, CAA or CCA and detecting worm derived antigens in blood or urine. Results are then also difficult to interpret. For example, how can a researcher measure the impact of HIV status on PZQ efficacy if he or she relies on microscopy since HIV status potentially impacts egg excretion?

The results from this thesis thus suggest two pathways through which *Schistosoma* spp. co-infections impact HIV epidemiology. The first pathway is a local one: genital mucosal friability and increased vascularity and bleeding, as well as increased seminal viral load lead to both increased transmission of HIV from an HIV/Schistosome co-infected individual to an HIV serodiscordant partner, and increased incidence of HIV in Schistosome infected women. The second pathway is a systemic one: Schistosomiasis leads to a modification in the Th17/Treg ratio, which in turn leads to decreased systemic viral load and better HIV/AIDS outcomes. We updated our conceptual framework of the mechanisms of the impact of *Schistosoma* spp. co-infections on HIV in **Figure 3.** The added mechanisms are shown in red.

Figure 1 - Updated conceptual framework of the epidemiology of HIV-Schistosome co-infections - Effect of Schistosoma spp. on HIV susceptibility and disease.



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

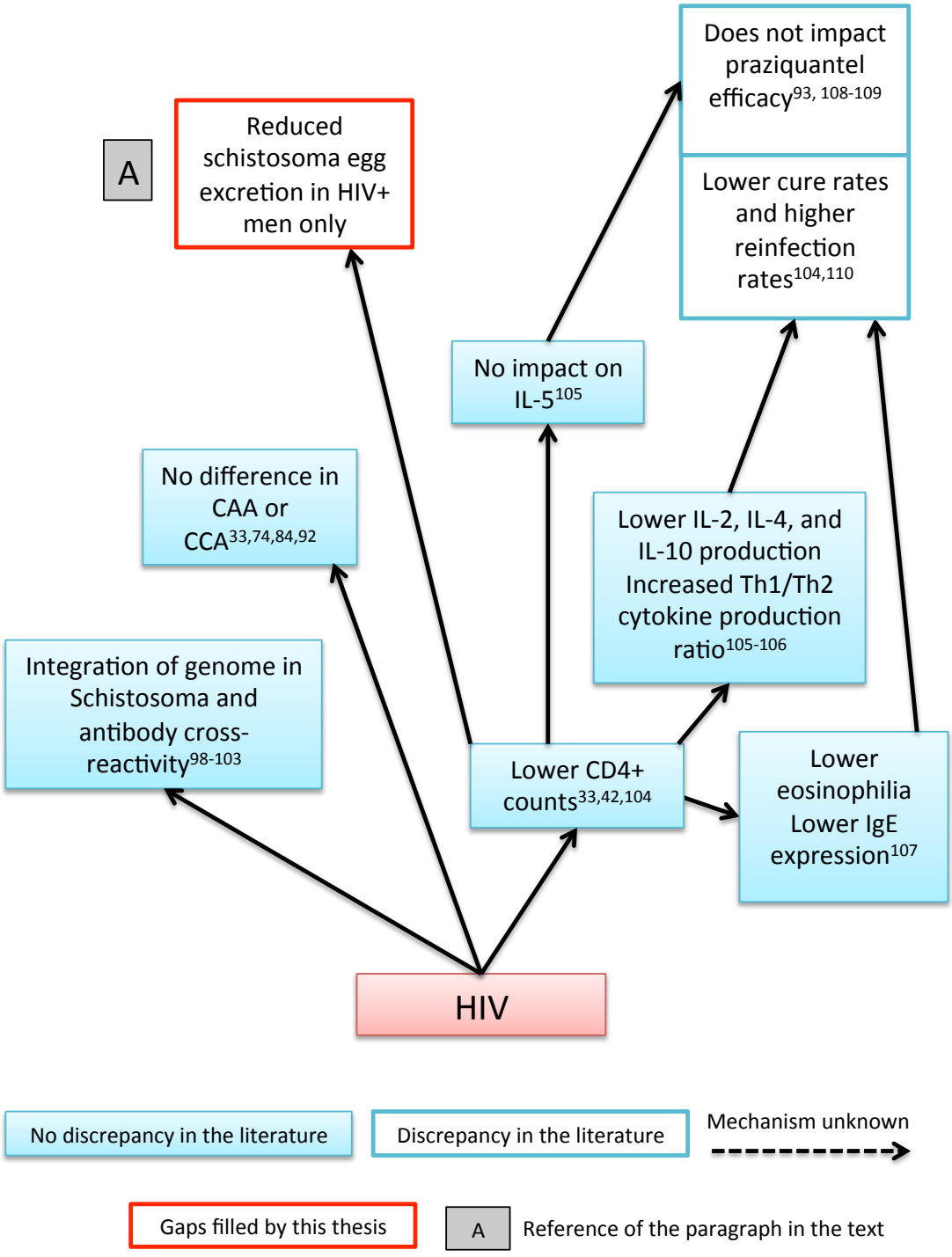
A. HIV co-infection reduces *Schistosoma* spp. egg excretion in men

Chapter 6 is the first large study to show an impact of HIV positivity on egg excretion. It demonstrates that the female to male ratio of the population studied was likely the main reason for conflicting results among previous studies[33, 74, 77, 89-93]. HIV infection status does not significantly affect *Schistosoma* spp. egg excretion in women, with the sensitivity of microscopy in both HIV-infected people and women only approximating 40%. Because most of the previous large studies done on this subject included mostly or entirely women, a difference in egg excretion based on HIV status was not detected[33, 77]. In contrast, the studies that included men, such as the Kenyan carwasher cohort, did report a difference in egg excretion[74]. The impact of sex on *Schistosoma* spp. infections is intriguging, with differential effects in women and men also demonstrated in epidemiologic studies of HIV acquisition[16, 17, 19, 94] and systemic immune responses to schistosome infection (Dupnik K, manuscript under review). Since the ratios of egg excretion to worm burden were lower in women infected with *S. mansoni*, the sex difference cannot be attributed to worm burden alone for this species. It is possible that CD4 counts could have been lower in men[95, 96] and that this could have impacted egg excretion via an effect on T cells[74, 75]. It is also possible that anatomical pelvic differences between men and women could lead to higher numbers of migrating parasite eggs trapped in female pelvic tissues than in males, or that worm fecundity could be affected by disparate immunological responses to *Schistosoma mansoni* worms in men versus women[53, 97].

The results of this thesis allowed us to explain part of the discrepancy in the results regarding the impact of HIV infection on *Schistosoma* pathophysiology: HIV infection leads to lower systemic CD4 counts, which in turn reduced *Schistosoma* spp. egg excretion in men but not in women. We updated our conceptual framework of the mechanisms of the impact of HIV co-infections on *Schistosoma spp.* in **Figure 4**. The added results are show in red.

Given the multiple studies indicating that host sex is a main distorting factor in the interaction between HIV and *Schistosoma* infections, sex should be taken into account and stratified for in any future study.

Figure 2 - Updated conceptual framework of the epidemiology of HIV-Schistosome co-infections - Effect of HIV on Schistosoma spp. infection.



III. IMPLICATIONS FOR DIAGNOSIS AND PREVENTION

1) Diagnosis of **Schistosoma** *spp.: microscopy testing is not recommended for women and HIV-infected individuals*

Chapter 6 highlighted the need for new WHO recommendations regarding the use of microscopy for detection of *Schistosoma* spp., especially in women and HIV-infected individuals. This is particularly important in the context of large reductions in the burden of schistosomiasis through mass drug administration[64]. As the prevalence of *Schistosoma* spp. infections decreases, the sensitivity of microscopy decreases too. One of the 2015-2030 United Nations Sustainable Development Goals is to eliminate schistosomiasis and other neglected tropical diseases altogether[111]. Given the ability of the diagnostic tool detecting the worm derived CAA that can now detect as little as one worm pair, and the CAA half-life of two days after successful killing of the worm[12, 112, 113], this test is extremely well-suited to quantify cure rates and to estimate the impact of HIV on response to PZQ treatment or reinfection.

CAA testing also has the advantage of reflecting the worm burden better than microscopy[12]. This allows detection of highly infected individuals, who might have differing immunity to *Schistosoma* compared to the rest of the population[114]. This in return allows for individual targeted treatment, and being able to detect highly infected individuals with unique immune responses might help better understand the immunological mechanisms at stake in *Schistosoma* spp. infections and co-infections.

In addition, Downs et al. came up with a proof-of-concept showing that DBS can be reliably used to quantify CAA: infection status can be determined even in DBS that had been stored for up to 8 years[13]. This opened new possibilities for other research studies on interactions between HIV and *Schistosoma* spp.. Of note, CAA testing is genus specific and additional testing is needed to indicate intestinal or urogenital infection[65, **Chapter 4**].

2) HIV prevention: targeting individuals present in **Schistosoma** *spp.-endemic areas to contain the HIV epidemic*

Our study results may add and improve current guidelines for HIV prevention. If *Schistosoma* spp. has a protective effect against poor HIV/AIDS outcome (**Chapter 3**), it does not mean that we should be stopping efforts to fight co-infections. Both diseases separately trigger millions of deaths and disabilities every year[1], and *Schistosoma* spp. infection is still a risk factor for HIV acquisition[19, 20], which is a main target of most HIV programs. Additional studies to determine whether PZQ treatment can prevent HIV acquisition should be prioritized, as PZQ treatment could be a safe, low-cost, acceptable way to prevent ongoing incident HIV infections in endemic regions. Current HIV/AIDS programs are aiming at improving care and ART availability for those who do get infected or were already infected in order to ultimately reduce the incidence of HIV[115]. **Chapter 2** shows that linkage to care is still poor in Tanzania and highlights the need for better integration from testing to enrollment into care. This chapter also calls for other ways to reduce the number of

people infected with HIV. Targeting individuals present in *Schistosoma* spp.-endemic areas, or those with known *Schistosoma* spp. infection, might help to curb the HIV epidemic. Both treating these individuals with PZQ and recommending more frequent HIV testing could lead to decreased seroconversion rates and better linkage to care. **Chapter 4** also suggests that future HIV/AIDS programs should focus their efforts on sero-discordant spouses.

Awareness regarding the relationship between HIV and *Schistosoma* spp. needs to be raised, not only among HIV/AIDS as well as *Schistosoma* spp. infection advocates, but clearly also among the general public. This could lead to an increase in the likelihood of HIV testing in populations exposed to both diseases such as fishermen, farmers, and those of lower socioeconomic status who do not have easy access to uncontaminated water sources. However, like with any disease campaign, public perceptions need to be managed appropriately and it will be essential to ensure that individuals with schistosomiasis do not become stigmatized[116], to keep high uptake of routine anti-schistosome treatment and HIV testing.

IV. REMAINING QUESTIONS AND METHOLOGY IMPROVEMENTS

1) More longitudinal studies are needed

At the epidemiological level, more longitudinal studies are needed to further clarify the impact of *Schistosoma* spp. infection on HIV RNA viral load set point, incidence, outcomes, and transmission. Longitudinal studies are often expensive, time-consuming, and ethically challenging[117]. A number of studies have used PZQ treatment to conclude on an effect of *Schistosoma* spp. infection on HIV pathogenesis[23, 25, 31, 35, 79, 86, 105]. Yet one cannot take the effect of PZQ treatment as a proxy for being *Schistosoma* spp.-free. In itself, PZQ treatment highly modifies the immune system response by killing the worms and thus activates a Th2 immune response[31]. The impact of PZQ treatment in co-infected individuals should be a whole research question(s) in itself, as should be the impact of ART treatment in co-infected individuals. It is challenging to compare a population of ART naïve HIV positive individuals in regards to HIV RNA viral load to a population not entirely ART naïve or on ART[118]. With the increasing use of DBS in HIV care for HIV RNA viral load testing[119], even in children, and the growing number of large sero-survey cohorts[120], CAA testing on DBS offers a cost-effective and convenient alternative to obtain human prospective data on the relationships between HIV and *Schistosoma* spp., with the potential to impact health policy and HIV prevention strategies throughout sub-Saharan Africa.

2) The immunological processes at stake are still not fully understood

At the immunological level, the impact of *Schistosoma* spp. infection on Th1 and Th2 immunity is still unclear in the context of HIV co-infections[27, 31, 36-39, 85, 86]. As mentioned earlier, the discrepancies are likely coming from an interpretation based on absolute immunological responses rather than ratios and imbalances, as well as the lack of a time variable in most immunological studies done until now.

In addition, the differences in the human immune response to *S. haematobium* and *S. mansoni* are still poorly understood[121]. While the local differences in the genital tract have been well studied[51-53], it is still unknown whether there are some systemic differences in the pathogenesis of the interaction between HIV and *S. haematobium* or HIV and *S. mansoni*. As the majority of our study population was infected with *S. mansoni* it is possible that we would have seen different effects, especially regarding transmission, in an *S. haematobium* infected population.

3) Children are missing from the picture

Finally, despite Bustinduy et al. raising the attention on the lack of studies on HIV/*Schistosoma* spp. co-infections in children in 2014[122], the literature on co-infections in children, or the impact of *Schistosoma* spp. infection during childhood on HIV infection as an adult, still only gathers one research study[123] and one literature review[122]. Given that the human immune response to schistosome infection changes with age and exposure, insight on co-infections in children will further add understanding to this complex issue[44].

V CONCLUDING REMARKS

The studies presented in this thesis have yielded further insight into the complex relationship between HIV and *Schistosoma* infection. They suggest a local interaction with urogenital schistosomiasis leading to increased incidence and transmission of HIV. They suggest as well a systemic interaction with *Schistosoma* spp. infection. The latter modifies immune responses to HIV, protecting against poor HIV outcomes. And HIV infection decreases CD4 counts, leading to decreased *Schistosoma* egg excretion.

The use of stored DBS from an HIV serosurvey cohort to test for *Schistosoma* spp. offered a unique opportunity to investigate the questions of outcomes and transmission in the context of HIV/*Schistosoma* spp. co-infections, by overcoming logistical and ethical difficulties associated with prospective cohort studies. Our work also highlighted the added benefit of using CAA as a diagnostic test for *Schistosoma* spp. Finally it offered new ways to include duration of HIV infection using CD4 counts in future research and suggested that *Schistosoma* spp. infection lowers HIV RNA viral load in ART naïve individuals.

Future research should focus on longitudinal studies and immunological studies, taking into account duration of infection, sex of the host, and infecting species of *Schistosoma*.

KEY FINDINGS

- People with *Schistosoma* spp. infection at the time of HIV-seroconversion develop adverse HIV outcomes more slowly than those without.
- Current infection with *Schistosoma* spp. is associated with significantly lower HIV viral loads after adjusting for time infected with HIV in ART naïve populations.
- Both women and HIV-infected individuals are significantly less likely to excrete *Schistosoma* spp. eggs when infected, even after controlling for a given worm antigen level.
- *Schistosoma* spp. infection in the transmitting partner has only a small effect on transmission of HIV due to the major effect of the sex of the receiving partner in HIV transmission
- Host sex and duration of HIV infection are likely main confounders, leading to the discrepancy in results in previous studies.
- More longitudinal studies are needed to further clarify the impact of *Schistosoma* spp. infection on HIV RNA viral load set point, incidence, outcomes, and transmission.
- Our Tanzanian study population demonstrates some moderate successes in linkage to care, with 80% of HIV-infected people knowing their HIV status and 62% of these being on ART.

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