ADDENDUM:

ENGLISH SUMMARY
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## English Summary

HIV infections have claimed more than 39 million lives since the HIV epidemic began more than 35 years ago. The HIV epidemic began in sub-Saharan Africa and continues disproportionately to affect this region. Though sub-Saharan Africa accounts for only ~12% of the world's population, it is home to over two-thirds of global HIV infections, incident new infections, and 2/3 of HIV-attributable deaths.

It is well-known that individuals with infections such as gonorrhea, syphilis, and herpes simplex virus have a higher risk of becoming HIV-infected than individuals without these infections. In addition, people with HIV who have concurrent infections—including the sexually-transmitted infections mentioned above and tuberculosis—have higher concentrations of HIV-1 RNA in their blood. This increased HIV viral load causes these individuals with co-infections to transmit HIV more readily to their sexual partners, and also it speeds their progression from HIV to symptomatic AIDS and death in the absence of treatment. In addition, a growing body of evidence suggests that some tropical parasitic infections may also have these effects on HIV viral load and on an individual's susceptibility to HIV. Thus it is plausible that co-infections such as these may have played a major role in the spread of the HIV epidemic in sub-Saharan Africa.

Schistosomiasis is a helminthic worm infection that affects 260 million people worldwide, 90% of whom live in sub-Saharan Africa. In Tanzania, where the research in this thesis was conducted, two species of schistosomes are highly endemic (*Schistosoma haematobium* and *S. mansoni),* with more than 50% of adults infected with one or both schistosome species in many regions. In and of itself, schistosomiasis causes significant morbidity and mortality, with an estimated 200,000 deaths annually and 3.31 million disability-adjusted life-years. The possibility that it additionally impacts HIV transmission and disease progression render treatment and control of this neglected tropical disease even more urgent.

This thesis focuses on HIV prevention and disease management in sub-Saharan Africa. It will first describe population-based epidemiological work in Tanzania associating HIV with *S. haematobium* and with *S. mansoni.* Subsequent chapters focus on treatment of *S. haematobium* infection in women, where it causes genital tract disease, and on the effects of schistosome infection on immunological response to treatment in people living with HIV infection. The final chapters focus on implementation science work with high potential to improve HIV prevention and early diagnosis in Tanzania.

In **Chapter 1**, the background and context of the work presented in this thesis is presented. The literature to date is reviewed, and objectives of the thesis are outlined.

In **Chapter 2**, we conducted a community-based study of 457 women from 8 different villages in northwest Tanzania. Women were screened for *S. haematobium* and *S. mansoni* as well as for trichomoniasis, syphilis, and HIV infection. We observed a significant association between HIV and *S. haematobium* infection, with women with *S. haematobium* having a four-fold greater odds of being HIV-infected than women without *S. haematobium*. This finding independently confirmed results from a single other study done in Zimbabwe, which reported a similar odds ratio for HIV infection among women with *S. haematobium*. Taken together, these two studies argue strongly for the urgency of additional work to determine prospectively whether *S. haematobium* is a risk factor for HIV acquisition, as well as whether efforts to control *S. haematobium* infection will decrease the incidence of HIV in endemic communities.

**Chapter 3** describes a similar community-based study of 345 women living in communities in which *S. mansoni* is endemic. Women received HIV voluntary counseling and testing and had schistosome Circulating Anodic Antigen (CAA) quantitated in their serum. We found that over 50% of women had schistosome infections. In this population, the odds of HIV infection among those with *S. mansoni* infection was 3.9. Moreover, the prevalence of HIV was highest (12.5%) among women with the highest quantities of CAA in serum, as compared to the HIV prevalence in women with light to moderate schistosome infection (8.3%) or the HIV prevalence among those with no detectable schistosome antigen (2.5%). These findings were novel, as previous studies had focused on women with *S. haematobium*, and led us to generate new hypotheses about the mechanisms of HIV susceptibility in women with schistosomiasis.

In **Chapter 4**, we explored the problem that women with urogenital schistosomiasis, caused by *S. haematobium*, had been reported to have persistent clinical disease even after treatment with the anti-schistosome medication praziquantel. We treated women with praziquantel and performed periodic follow-ups over the subsequent 6 months. This work expanded on prior studies by using polymerase-chain reaction (PCR) and serum schistosome antigen measurements to quantify schistosome infections with increased sensitivity. We documented that, even six months after praziquantel treatment, women with urogenital schistosomiasis had persistent gynecologic abnormalities and detectable schistosome DNA in urine and genital specimens. This highlights the urgency of preventing gynecologic damage and controlling schistosomiasis early, since its effects may not be entirely reversible.

**Chapter 5** represents the laying of important groundwork that will facilitate new studies of schistosomiasis. We demonstrated that schistosome CAA can be eluted from, and quantitated in, dried blood spots, which are used widely in resource-poor settings for both research and clinical care. CAA values obtained from the dried blood spots were strongly correlated with serum CAA levels, and the correlations remained strong even among dried blood spots that had been stored for 8 years. We used the Whatman ProteinSaver 903 cards for this work, which are the most widely-used dried blood spot collection cards worldwide.

We then turned to interactions between HIV and schistosomiasis in **Chapter 6**. We enrolled 351 HIV-infected outpatients who had been taking antiretroviral therapy for at least six months. We documented that the ~30% of HIV-infected individuals with schistosome co-infection had a four-fold greater odds of immunological treatment failure than did HIV-infected individuals without schistosomiasis. Because many HIV-infected patients in sub-Saharan African are switched from first- to second-line antiretroviral treatment if they develop immunological failure, these findings are clinically relevant and highlight the critical need for additional studies in this area.

The final chapter of this thesis maintains the focus on improving HIV management in Tanzania, albeit via different research techniques. In **Chapter 7**, we present an implementation science study conducted to optimize the efficiency of dried blood spot testing for early infant diagnosis of HIV in a rural clinic in Tanzania. Using a series of low-cost, locally-driven interventions implemented sequentially, we were able to decrease the turn-around time between collection of the dried blood spot from the infant and the provision of the HIV test result to the patient's caretaker from 55 to 38 days, and to ensure that over 90% of infants' caretakers received results. This project is not only locally valuable, but is also more broadly applicable because it serves as a model for implementation of inexpensive, innovative interventions led by local healthcare staff.

The work presented in this thesis was conducted by a physician-scientist who both provides patient care and conducts research in Mwanza, Tanzania. Many of the findings have direct clinical implications for patient management and HIV prevention, as well as sparking essential follow-up studies to further improve health in Tanzania and beyond.