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Jamie Humphrey Date

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Master of Public Health
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2020

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An abstract of
A thesis submitted to the Faculty of the
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**Abstract**

No association between increasing anti-schistosome specific antibody titers and increased HIV risk among a cohort of Zambian women

By Jamie Humphrey

**Introduction.** Female genital schistosomiasis (FGS) has been suggested to be a risk factor for human immunodeficiency virus (HIV) among women. Women who are coinfected with FGS and HIV may also experience a faster progression of their HIV disease, leading to an earlier onset of acquired immunodeficiency syndrome (AIDS), AIDS related illnesses, and death. Since schistosomiasis infection and FGS are common and associated with HIV, it is critical to understand the relationship between anti-schistosome specific antibody levels and HIV risk.

**Methods.** Data and samples were collected from a longitudinal cohort study that followed heterosexual couples with discordant HIV status between 1994 and 2009 in Lusaka, Zambia. Descriptive statistics and baseline characteristics are presented and stratified by HIV status and schistosomiasis ELISA antibody status. Differences between groups were evaluated using Chi-square and t-tests. Cox survival models were used to calculate associations between anti-schistosome specific antibody levels and HIV transmission and acquisition by women. Baseline characteristics were considered as potential confounders.

**Results.** Among HIV+ women, the hazard of HIV transmission among high-anti-schistosome specific antibody positive women was 1.67 times that of those who were anti-schistosome specific antibody negative at baseline, and the hazard of HIV transmission among low-anti-schistosome specific antibody positive women was 1.75 times that of those who were anti-schistosome specific antibody negative at baseline after adjusting for covariates. No statistically significant associations were found between anti-schistosome specific antibody status and HIV acquisition among HIV- women.

**Discussion.** Our results reveal a high prevalence of schistosomiasis haematobium infection in the population under investigation. Although our findings suggest that the presence of anti-schistosome specific antibodies increases the hazard of HIV transmission by women, these findings do not support a dose response relationship between anti-schistosome specific antibody status of women and HIV transmission to male partners. Those who test positive for schistosome-specific antibodies and their partners should be a targeted population to screen for HIV, however, a higher level of schistosome specific antibodies should not be used as an indicator for a higher risk of acquisition or transmission of HIV.

# No association between increasing anti-schistosome specific antibody titers and increased HIV risk among a cohort of Zambian women

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# Contents

# Introduction

Schistosomiasis is an infectious disease that can present both acutely and chronically. Transmission occurs when an individual comes into contact with water that is contaminated with the disease carrying parasite whose intermediate is a freshwater snail host. The larvae of these parasites develop into adults while in the body, and eggs later are released from the body through feces or urine to continue the parasite's lifestyle. Schistosomiasis is especially prevalent in poorer communities throughout tropical and subtropical areas.[1]

The lesions caused by urogenital schistosomiasis can lead to female genital schistosomiasis (FGS) which is thought to be a risk factor for human immunodeficiency virus (HIV) among women.[1] There are multiple proposed mechanisms through which lesions caused by urogenital schistosomiasis can increase susceptibility to HIV acquisition. For example, similarly to sexually transmitted infections (STIs), these lesions of FGS cause a breach in the cervicovaginal mucosal barrier that may serve as an entry point for HIV infection.[2] Additionally, S. haematobium infection, which may lead to FGS, has been associated with altered levels of vaginal cytokines[3], which are in turn known to be a risk factor for HIV acquisition[4]. Furthermore, women who are coinfected with FGS and HIV can experience a faster progression of their HIV disease, leading to an earlier onset of AIDS, AIDS related illnesses, and death.[5-7]

Previous studies have shown that higher levels of anti-schistosome specific antibody levels may be associated with increased HIV risk.[8] However, there is a gap in knowledge regarding the relationship between anti-schistosome specific antibody levels and the likelihood of HIV transmission and acquisition by women.[9] Investigating the relationship between anti-schistosome specific antibody status, which indicates past or current infection with schistosomiasis, and HIV coinfection is important to better understand the impact of co-infection on women's health, and to develop effective strategies for prevention, diagnosis, and treatment of both conditions. If this hypothesis is borne out, it may be important to target HIV prevention and FGS treatment activities to women with higher titers.

# Methods

## *Study Participants*

Participants came from a longitudinal cohort study that followed heterosexual couples with discordant HIV status between 1994 and 2009 in Lusaka, Zambia. Follow-up visits were conducted every three months. Throughout the study, all enrolled couples participated in voluntary HIV risk reduction

counseling, including group educational sessions and joint post-test couples' counselling, and testing, including rapid HIV antibody testing at the research site. Additionally, eligible couples were provided free care that included family planning, regular STI testing, and STI treatment. Couples were censored from the study upon initiated receival of antiretroviral treatment by HIV+ partner, death of either of the partners, or dissolution of the partnership. Informed consent was obtained for all enrolled participants following study approval by Emory University and University of Zambia's Institutional Review Boards.

## *Measures and Procedures*

Demographic data were collected and stratified by the ELISA results of women at baseline. A variety of demographic information was collected including age, years cohabiting, and monthly household income. Clinical characteristics collected at baseline include pregnancy status, HIV stage of the HIV positive partner, viral load of the HIV positive partner, past year history of any STI, presence of STI- and non-STI genital inflammation, presence of a genital ulcer, and anti-schistosome specific antibody status of the male partner. STI genital inflammation of women included clinical or laboratory diagnosis or treatment of gonorrhea or chlamydia (including presumptive treatment given detection of endocervical discharge) or trichomonas. Non-STI genital of women includes reported discharge, dyspareunia, observed discharge or inflammation of external or internal genitalia, and/or laboratory diagnosis of candida or bacterial vaginosis (with no indication of an inflammatory STI). Genital ulcer of women includes observed or reported ulcers.

## *Schistosomiasis Antibodies*

Serum and blood samples were collected at study enrollment for all participants. These samples were stored in a repository at Emory University. Retrospective ELISA testing of plasma samples for antibodies of schistosome soluble worm antigen preparation (SWAP) was conducted. A nested case-control design was used and included all participants who seroconverted as cases and those who did not seroconvert as controls. Assay control included a 1:3 serial dilution on each plate and a 4-parameter curve fitting model was used to assign values to each sample based on the standard curve. 25 units was chosen as the serum low-positive cutoff as that is three standard deviations above average anti-SWAP IgG in serum from egg negative controls in the US and Europe. 50 units was chosen as the serum high-positive cutoff. A positive schistosomiasis result is defined as having a positive SWAP antibody response

with levels between 25 and 50 units. A high-positive schistosomiasis result is defined as having a positive SWAP antibody response with levels greater than 50 units. To secure free PZQ treatment for those who retrospectively tested positive, a list of positive anti-schistosome specific antibody was sent to the Director of the Lusaka research site.

### *HIV transmission*

Transmission by women of HIV to the partner was established as the occurrence of HIV among baseline sero-discordant couples where the female partner is HIV positive, and the male partner is HIV negative.

### *HIV acquisition*

Acquisition of HIV by women was established as the diagnosis of HIV among baseline sero-discordant couples where the male partner is HIV positive, and the female partner is HIV negative.

## Statistical analysis

Descriptive statistics of demographic data and baseline clinical characteristics are presented in Table 1 and stratified by HIV status and schistosomiasis ELISA antibody status at baseline. Counts and percentages are presented for categorical data whereas means and standard deviations are presented for continuous data, and differences between groups were evaluated using Chi-square and t-tests, respectively. Cox survival models were used to calculate unadjusted and adjusted associations between anti-schistosome specific antibody levels and HIV transmission and acquisition by women. Other fixed baseline characteristics were considered as potential confounders including pregnancy status, HIV stage of the HIV positive partner, viral load of HIV the positive partner, past year history of any STI, STI- and Non-STI genital inflammation, presence of a genital ulcer, and anti-schistosome specific antibody status of male partner. Of these variables, those with statistically significant associations with anti-schistosome specific antibody levels were included in final models. Variables that were included in the model were first tested for collinearity. The results from these analyses include crude (cHRs) and adjusted (aHR) hazard ratios, 95% confidence intervals (CIs), and two-tailed p-values. All analyses were performed with SAS v9.4.

## Results

We analyzed data from 1,099 women who were a mean age of 28.52 years. Among HIV+ women at baseline, 19% (n=111) had SWAP ELISA results above 50 units (high-positive), 33% (n=361) had SWAP ELISA results greater than 25 and less than or equal to 50 units (low-positive), and 48% (n=528) had SWAP ELISA results less than or equal to 25 units (negative). Among HIV- women at baseline, 20% (n=99) had SWAP ELISA results above 50 units (high-positive), 35% (n=176) had SWAP ELISA results greater than 25 and less than or equal to 50 units (low-positive), and 45% (n=228) had SWAP ELISA results less than or equal to 25 units (negative).

There were no significant differences in mean age, years cohabiting with partner, monthly household income, and the ability to read Nyanja between women who tested high-positive for anti-schistosome specific (SS) antibodies, women who tested low-positive for anti-SS antibodies, and those who tested negative for anti-SS antibodies when stratified by HIV status at baseline. Partners of anti-SS high-positive women were more like to be anti-SS high-positive themselves, and partners of anti-SS negative women were more likely to be anti-SS negative themselves. High positive SWAP ELISA results are associated with lower instances of baseline pregnancy in HIV+ women ($p < 0.05$).

Among HIV+ women, baseline data indicated significant associations between SWAP ELISA results and the clinical characteristics of pregnancy status, HIV stage of the woman, past year history of an STI, non-STI inflammation, STI-inflammation, the presence of an active genital ulcer, and baseline anti-SS antibody status of the male partner at an alpha level of 0.05. Baseline SWAP ELISA results, pregnancy status, HIV stage of the woman, past year history of an STI, the presence of an active genital ulcer, and baseline anti-SS antibody status of the male partner were tested for collinearity. No collinearity was found, and these covariates were included in a cox proportional hazards model to assess the relationship between SWAP ELISA results and HIV transmission by HIV+ women.

Among HIV- women, baseline data indicated significant associations between SWAP ELISA results and baseline anti-SS antibody status of the male partner at an alpha level of 0.05. SWAP ELISA results and baseline anti-SS antibody status of the male partner were tested for collinearity. No collinearity was found, and these covariates were included in a Cox proportional hazards model to assess the relationship between SWAP ELISA results and HIV acquisition by HIV- women.

Among HIV+ women, the hazard of HIV transmission among high-positive women was 1.67 times that of those who were negative at baseline after adjusting for pregnancy status, HIV stage of the woman, past

year history of an STI, the presence of an active genital ulcer, and baseline anti-SS antibody status of the male partner. Additionally, the hazard of HIV transmission among low-positive women was 1.75 times that of those who were negative at baseline after adjusting for pregnancy status, HIV stage of the woman, past year history of an STI, the presence of an active genital ulcer, and baseline anti-SS antibody status of the male partner. Although these findings suggest that the presence of a positive SWAP ELISA results (>25 units) increases the hazard of HIV transmission by women, these findings do not support a dose response relationship between anti-SS antibody status of women and HIV transmission to male partners.

Among HIV negative women, there were no meaningful or statistically significant associations between baseline schistosome infection and HIV acquisition.

## Discussion

FGS has been suggested to be a risk factor for HIV among women.[1] Women who are coinfected with FGS and HIV may also experience a faster progression of their HIV disease, leading to an earlier onset of AIDS, AIDS related illnesses, and death.[5-7] Since schistosomiasis infection and FGS are common and associated with HIV, it remains critical to identify ways to target HIV services to those at highest risk. Understanding dose response could be important to know in a clinical setting as a tool to target HIV prevention and treatment services to higher-risk schistosomiasis infected women. In this longitudinal study, we did not find that higher schistosome antibody titers in women were associated with increased HIV risk.

This analysis was conducted to investigate the presence of a dose response relationship between anti-schistosome-specific antibody levels and the rate of HIV transmission and acquisition among a cohort of women from Lusaka, Zambia. Our results indicated that 52% of baseline HIV+ women and 55% of baseline HIV- women had SWAP ELISA results greater than 25 units. These findings reveal a high prevalence of current and past schistosomiasis haematobium infection in the population under investigation, which aligns with previous findings that schistosomiasis haematobium and FGS are widespread and common health concerns. [10]

Additionally, partners of anti-SS high-positive women were more like to be anti-SS high-positive themselves, and partners of anti-SS negative women were more likely to be anti-SS negative themselves. This finding aligns with the expectations for this disease since schistosomiasis infection occurs upon contact with contaminated water, and water sources may be shared by partners. Improved focus on

treating individuals, education on how to prevent the spread of disease, and further research on the mechanism of transmission and effective methods for transmission prevention are needed.

Among HIV+ women, the hazard of HIV transmission among anti-SS high-positive women was 1.67 times that of those who were negative at baseline and the hazard of HIV transmission among anti-SS low-positive women was 1.75 times that of those who were negative at baseline after adjusting for covariates. Although these findings suggest that the presence of a positive SWAP ELISA results (>25 units) increases the hazard of HIV transmission by women, these findings do not support a dose response relationship between anti-schistosome specific antibody status of women and HIV transmission to male partners. Consequentially, those who test positive for anti-schistosome specific antibodies, and their partners, should be a targeted population to screen for HIV, however, a higher level of anti-schistosome specific antibodies should not be used as an indicator for a higher risk of acquisition or transmission of HIV by women and therefore not be prioritized above others with lower levels of anti-schistosome specific antibodies.

Although there were no meaningful or statistically significant associations between baseline schistosome infection and HIV acquisition among baseline HIV- women, it would be beneficial to repeat this study or conduct a similar to one to update prevalence estimates, improve our understanding of risk factors for FGS and HIV, expand the geographic scope of this research, and generate new research questions that will lead to a more wholistic understanding of the epidemiology of these diseases.

In this study, high positive SWAP ELISA results were found to be associated with lower instances of baseline pregnancy in HIV+ women ($p < 0.05$). This finding suggests a need for more research to further explore the relationship between FGS and HIV among pregnant women. Specifically, it would be beneficial to investigate whether the presence of pregnancy hormones offer a protective effect or if pregnant women are less likely to test positive for FGS for other reasons. Furthermore, literature suggests access and delays to maternity care among women in Zambia may be influenced by their interpersonal relationships during pregnancy.[11] In fact, previous studies have found that men in Zambia have the primary decision-making power in a relationship. [12-15] Understanding health challenges that may arise for pregnant women living in Zambia, such as autonomy over their access to care, could help to inform the allocation of resources to research and treatment programs that target pregnant women and address gender inequality.

There were limitations to this study. ELISA testing of participant samples was done retrospectively for a subset of the total cohort the gold standard tests for detecting active infection was not used.[16] Instead, antibody testing was used to identify individuals with infection. Additionally, the relationship between schistosome-specific antibody status and HIV may have been by confounded by factors that were not measured in the study or not considered in this analysis (such as access to healthcare, which could be hard to measure and control for in a longitudinal study). Furthermore, there is limited generalizability beyond the specific population of interest. In conclusion, this study is subject to limitations that should be considered when interpreting the results and designing future studies.

# Tables and Figures

**Table 1.** Characteristics of the study population at baseline stratified by women's baseline ELISA results (to represent distribution in source population)

| | Woman HIV+ (N = 596) | | | | | | | Woman HIV- (N = 503) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | High Positive (N=111) | | Low Positive (N=185) | | Negative (N=300) | | p-value | High Positive (N=99) | | Low Positive (N=176) | | Negative (N=228) | | p-value |
| **Baseline Characteristic[1]** | **N** | **%** | **N** | **%** | **N** | **%** | | **N** | **%** | **N** | **%** | **N** | **%** | |
| **Demographics** | | | | | | | | | | | | | | |
| **Age (mean, SD)** | 28.2 | 7.1 | 28.2 | 7.4 | 28.3 | 6.9 | 0.817 | 27.7 | 7.3 | 27.5 | 6.9 | 26.6 | 6.9 | 0.100 |
| **Years cohabiting (mean, SD)** | 6.4 | 7.6 | 6.1 | 6.9 | 5.7 | 5.8 | 0.198 | 8.2 | 6.8 | 7.3 | 6.2 | 7.4 | 6.7 | 0.488 |
| **Monthly household income (mean, SD) (USD)** | 54.0 | 57.2 | 63.9 | 85.9 | 71.3 | 107.1 | 0.116 | 64.6 | 103.0 | 57.1 | 60.5 | 67.1 | 70.3 | 0.412 |
| **Reads Nyanja** | | | | | | | 0.798 | | | | | | | 0.798 |
| Yes, easily | 16 | 16% | 34 | 20% | 40 | 18% | | 16 | 16% | 34 | 20% | 40 | 18% | |
| With difficulty/not at all | 81 | 84% | 139 | 80% | 184 | 82% | | 81 | 84% | 139 | 80% | 184 | 82% | |
| **Clinical characteristics** | | | | | | | | | | | | | | |
| **Pregnant at baseline** | | | | | | | 0.0002 | | | | | | | 0.082 |
| Yes | 8 | 7% | 20 | 11% | 64 | 21% | | 10 | 10% | 23 | 13% | 43 | 19% | |
| No | 103 | 93% | 165 | 89% | 236 | 79% | | 89 | 90% | 153 | 87% | 185 | 81% | |
| **HIV stage (of positive partner)** | | | | | | | 0.001 | | | | | | | 0.2067 |
| Stage I | 24 | 22% | 60 | 32% | 120 | 40% | | 27 | 27% | 31 | 18% | 54 | 24% | |
| Stage II | 32 | 29% | 52 | 28% | 93 | 31% | | 36 | 36% | 71 | 40% | 73 | 32% | |
| Stage III-IV | 55 | 50% | 73 | 39% | 87 | 29% | | 36 | 36% | 74 | 42% | 101 | 44% | |
| **Viral load (log10 copies/ml)**** | 4.5 | 1.0 | 4.6 | 0.8 | 4.4 | 0.9 | 0.129 | 5.0 | 5.3 | 4.9 | 0.8 | 4.9 | 0.8 | 0.708 |
| **Past year history of any STI** | | | | | | | 0.081 | | | | | | | 0.649 |
| Yes | 60 | 54% | 76 | 41% | 145 | 48% | | 38 | 38% | 58 | 33% | 77 | 34% | |
| No | 51 | 46% | 109 | 59% | 155 | 52% | | 61 | 62% | 118 | 67% | 149 | 66% | |
| **Non-STI inflammation** | | | | | | | 0.040 | | | | | | | 0.786 |
| Yes | 31 | 28% | 42 | 23% | 51 | 17% | | 25 | 25% | 38 | 22% | 52 | 23% | |
| No | 80 | 72% | 143 | 77% | 249 | 83% | | 74 | 75% | 138 | 78% | 176 | 77% | |
| **STI gen inflammation** | | | | | | | 0.024 | | | | | | | 0.822 |
| Yes | 20 | 18% | 36 | 19% | 33 | 11% | | 13 | 13% | 22 | 12% | 25 | 11% | |
| No | 91 | 82% | 149 | 81% | 267 | 89% | | 86 | 87% | 154 | 88% | 203 | 89% | |
| **Genital ulcer** | | | | | | | 0.022 | | | | | | | 0.564 |
| Yes | 25 | 23% | 37 | 20% | 38 | 13% | | 13 | 13% | 19 | 11% | 21 | 9% | |
| No | 86 | 77% | 148 | 80% | 262 | 87% | | 86 | 87% | 157 | 89% | 207 | 91% | |
| **Baseline anti-schistosome specific antibody status of male partner** | | | | | | | 0.001 | | | | | | | 0.0001 |
| High Positive | 43 | 45% | 44 | 29% | 49 | 31% | | 49 | 52% | 55 | 33% | 52 | 25% | |
| Low Positive | 31 | 33% | 70 | 46% | 48 | 30% | | 26 | 27% | 67 | 41% | 80 | 38% | |
| Negative | 21 | 22% | 39 | 25% | 62 | 39% | | 20 | 21% | 43 | 26% | 76 | 37% | |

[1]Reported as n (%) unless otherwise specified.

Abbreviations: SD, Standard Deviation; STI sexually transmitted infection; RPR: rapid plasma reagin; ELISA: enzyme-linked immunosorbent assay; USD: United States Dollar

STI genital inflammation of women includes clinical or laboratory diagnosis or treatment of gonorrhea or chlamydia (including presumptive treatment given detection of endocervical discharge) or trichomonas.

Non-STI genital inflammation of women includes reported discharge, dysuria, dyspareunia; observed discharge or inflammation of external or internal genitalia; and/or laboratory diagnosis of candida or bacterial vaginosis (with no indication of an inflammatory STI)
Genital ulcer of women includes observed or reported ulcers.
Values may not sum to the total due to missing data.

**Table 2.** Baseline anti-schistosome specific antibody status of women stratified by HIV status.

| | All Women | | HIV+ Women | | HIV- Women | | |
|---|---|---|---|---|---|---|---|
| **ELISA units** | **N** | **col %** | **N** | **col %** | **N** | **col %** | **p-value** |
| **>50** | 210 | 19% | 111 | 19% | 99 | 20% | 0.237 |
| **25 - <50** | 361 | 33% | 185 | 31% | 176 | 35% | |
| **< 25** | 528 | 48% | 300 | 50% | 228 | 45% | |
| **Total (row%)** | 1099 | 54% | 596 | 54% | 503 | 46% | |

ELISA: enzyme-linked immunosorbent assay
p-values are two-tailed.

**Table 3.** Unadjusted and adjusted associations between women's baseline anti-schistosome specific (SS) antibody status and HIV transmission and acquisition

| **Women's baseline schistosome-specific antibody status** | **Woman HIV-** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **HIV transmissions** | | **Non-HIV transmitting** | | **cHR** | **95%CI** | | **p-value** | **aHR*** | **95%CI** | | **p-value** |
| **>50 (N intervals, %)** | 34 | 15% | 586 | 17% | 1.17 | 0.83 | 1.65 | 0.360 | 1.18 | 0.83 | 1.68 | 0.360 |
| **25 - <50 (N intervals, %)** | 75 | 33% | 1,119 | 33% | 1.11 | 0.83 | 1.48 | 0.461 | 1.10 | 0.83 | 1.47 | 0.510 |
| **< 25 (N intervals, %)** | 118 | 52% | 1,699 | 50% | ref | | | | ref | | | |
| **Women's baseline schistosome-specific antibody status** | **Woman HIV+** | | | | | | | | | | | |
| | **HIV acquisition** | | **Non-HIV acquiring** | | **cHR** | **95%CI** | | **p-value** | **aHR**** | **95%CI** | | **p-value** |
| **>50 (N intervals, %)** | 27 | 15% | 761 | 12% | 1.63 | 1.06 | 2.51 | 0.027 | 1.67 | 1.06 | 2.64 | 0.026 |
| **25 - <50 (N intervals, %)** | 60 | 32% | 1468 | 24% | 1.81 | 1.27 | 2.57 | 0.001 | 1.75 | 1.22 | 2.50 | 0.002 |
| **< 25 (N intervals, %)** | 98 | 53% | 3913 | 63% | ref | | | | ref | | | |

*Controlling for factors associated with both the exposure and outcome of interest: Genital inflammation of woman, genital ulcer of woman
**Controlling for factors associated with both the exposure and outcome of interest: Male partner's baseline anti-schistosome specific antibody status
cHR: crude hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio

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