Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Cecile Dinh Date

THE ASSOCIATIONS BETWEEN SCHISTOSOMIASIS INFECTION, PRESENCE OF GENITAL ABNORMALITIES, AND HIV PREVALENCE, TRANSMISSION, AND ACQUISITION IN LUSAKA, ZAMBIA

By

Cecile Dinh

Master of Public Health

Global Epidemiology

_____

Dr. Susan Allen, MD, MPH

Faculty Thesis Advisor

_____

Amanda Tichacek, MPH

Field Advisor

THE ASSOCIATIONS BETWEEN SCHISTOSOMIASIS INFECTION, PRESENCE OF GENITAL ABNORMALITIES, AND HIV PREVALENCE, TRANSMISSION, AND ACQUISITION IN LUSAKA, ZAMBIA

By

Cecile Dinh

Bachelor of Science, Bachelor of Arts

University of Arizona

2009

Faculty Thesis Advisor: Susan Allen, MD, MPH

Field Advisor: Amanda Tichacek, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2011

Abstract

THE ASSOCIATIONS BETWEEN SCHISTOSOMIASIS INFECTION, PRESENCE OF GENITAL ABNORMALITIES, AND HIV PREVALENCE, TRANSMISSION, AND ACQUISITION IN LUSAKA, ZAMBIA

By Cecile Dinh

Background: A reported 33.3 million people living in Sub-Saharan Africa are infected with HIV. In Zambia, the estimated HIV prevalence ranges from 13.5% - 17%. An estimated 20.7% of children in Zambia are infected with schistosomiasis, a parasitic infection second only to malaria in prevalence, morbidity and mortality in Africa. Individuals who are infected with schistosomiasis can develop symptoms that last a lifetime. Symptoms of schistosomiasis include genital abnormalities, such as ulcers or "sandy patches" that could increase the susceptibility or transmission of HIV.

Objective: This study examines the statistical associations between antibody to schistosomiasis and HIV prevalence, acquisition and transmission, and the presence of genital abnormalities.

Methods: 2168 individuals who were followed in the Zambia-Emory HIV Research Project heterosexual cohort for at least three months were included in this study. Using banked plasma and serum samples, enzyme-linked immunosorbent assays (ELISA) were completed to detect schistosomiasis antibody titers. Clinical health data were obtained from medical history and physical exams completed at ZEHRP enrollment visits. Univariate logistic regressions were conducted to analyze the associations between antibody titer to schistosomiasis; HIV prevalence, acquisition and transmission; and genital abnormalities.

Results: Antibodies to schistosomiasis, overall, were not significantly associated with being HIV-positive at baseline or transmitting HIV. Schistosomiasis infection was significantly associated with the presence of some genital abnormalities, including inguinal adenopathy, inflammation of the cervix in women, and gonorrhea.

Discussion: This study provides a snapshot of the possible complications that can arise from being previously infected with schistosomiasis, in the context of the HIV epidemic. Interestingly, it does not seem as if serologic evidence of past or present schistosomiasis infection is a significant risk factor for transmission of HIV. Future directions could take into account the timeline of events and whether an individual acquires or transmits HIV due to the presence of genital abnormalities caused by schistosomiasis, or if HIV exacerbates the effects of schistosomiasis. Furthermore, ELISA results should be followed up with Western immunoblots to identify *Schistosoma mansoni* versus *S. haematobium* infection, and to confirm previous schistosomiasis infection, particularly in individuals with intermediate titers.

THE ASSOCIATIONS BETWEEN SCHISTOSOMIASIS INFECTION, PRESENCE OF GENITAL ABNORMALITIES, AND HIV PREVALENCE, TRANSMISSION, AND ACQUISITION IN LUSAKA, ZAMBIA

By

Cecile Dinh

Bachelor of Science, Bachelor of Arts

University of Arizona

2009

Faculty Thesis Advisor: Dr. Susan Allen, MD, MPH

Field Advisor: Amanda Tichacek, MPH

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2011

ACKNOWLEDGEMENTS

Dr. Susan Allen, I am sincerely grateful for your support and guidance on this project.

Amanda Tichacek, thank you for your understanding and assistance.

Dr. Evan Secor and Molly Hyde, your expertise and time spent testing the samples are extremely valued.

Dr. Debi Boeras and the Hunter Lab staff and students, thank you for including me as a "labbie" and for braving the cold to obtain the samples I needed.

Htee Khu, your patience with me in dealing with the datasets is much appreciated.

Thank you to my family - Mom, Dad, and Chi Hai - for your unending encouragement in my educational goals, whatever they may be.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

INTRODUCTION AND BACKGROUND

Infectious diseases are found all over the world, from tuberculosis to influenza to malaria. An infectious disease that has captivated the world audience for the past three decades due to its quick and widespread transmission has been the Human Immunodeficiency Virus (HIV) (1). On the other hand, a parasitic disease that is second in prevalence only to malaria is schistosomiasis (2). It is hypothesized that if an individual has been previously infected with schistosomiasis, the chronic signs and symptoms that can arise may increase susceptibility or transmission of HIV.

HIV Prevalence

The worldwide HIV/AIDS epidemic was first realized in the 1980s (1). Since then, major efforts have been put forth to halt transmission of the disease, but as of December 2009, approximately 33.3 million people are infected with HIV (3). Two-thirds of those people live in Sub-Saharan Africa, which by far, exceeds any other area of the world (4). Although the incidence rate has slowly declined over the years, the prevalence of HIV remains an issue. Zambia, in particular, has an estimated HIV prevalence range of 13.5% to 17% as of 2009 (4-6).

Data has shown that 12% of cohabitating couples are HIV-discordant (one partner positive, the other partner negative) (7). Rates of man-to-woman and woman-to-man transmission of HIV are fairly equal (8). Couples voluntary counseling and testing (CVCT) has played an important role in decreasing the seroincidence of HIV in married or cohabitating couples. Seroconversion rates amongst HIV-discordant couples who have undergone CVCT have been reported to be between 3% and 8% annually (9). On the other hand, HIV transmission has been observed in an estimated 20-25% of serodiscordant couples who have not received CVCT services (10).

Schistosomiasis Prevalence

The species of *Schistosoma* most often found in Sub-Saharan Africa are *S. haematobium* and *S. mansoni*, which causes urinary schistosomiasis and intestinal schistosomiasis, respectively (2). Schistosome eggs are deposited in freshwater bodies through urine and feces where they hatch and snails become infected. The snails then release *cercariae* which burrow into the skin of unsuspecting humans who come in contact with the bodies of water. Past research has shown that in Lusaka, Zambia, 20.7% of children ages 5-17 were infected with schistosomiasis (11). In a study completed on women in Zimbabwe, it was found that *S. haematobium* infection was highest in women under 20 years of age at 60% (12). Praziquantel is currently the drug of choice for treatment of both types of schistosomiasis. It is a single oral dose that is considered inexpensive, effective, and safe, even for pregnant women (13). However, while praqizuantel is effective in killing adult *Schistosoma* worms, it is ineffective at getting rid of schistosomules, which are the developing parts of the parasite (14).

In general, individuals living in rural areas are more likely to become infected than those living in urban areas. Additionally, men are more likely than women to be infected, because of their knowledge of freshwater sources in their area as compared to women. Furthermore, the age of schistosomiasis infection appears to peak around 11-13 years of age (15), and rates of infection appears to decline for those 14 years of age and above as direct contact with freshwater sources decrease.

Symptoms of Schistosomiasis Infection

Symptoms of schistosomiasis can be many. Acute symptoms include rash, fever, and chills (2). However, if left untreated, more adverse symptoms may occur as a result of chronic schistosomiasis. Serious signs and symptoms of *S. mansoni* may include

hepatosplenomegaly, malnutrition, and kidney failure. Those with chronic *S. haematobium* infection are at a higher risk of developing bladder cancer. More often, chronically infected individuals are known to have gastro-intestinal problems including bloody stools, abdominal cramps, hematuria, and dysuria (2, 15, 16). Many of these sequelae are due to the deposition of eggs in tissue, with resulting inflammatory responses which last for many years after the egg has died.

Female genital schistosomiasis is of great importance. Chronically infected women can be afflicted with lesions, called "sandy patches," on their genital organs, which histologically show dead eggs surrounded by granulomatous responses and do not resolve (17). Even after treatment with praziquantel has been initiated and a decrease in ova excretion has been observed, the sandy patches and contact bleeding do not appear to be reduced (18). Women who have been infected with schistosomiasis are also at greater risk for ectopic pregnancies, spontaneous abortions, and unordinary cervical and vaginal inflammation (19).

Genital Abnormalities

Although schistosomiasis infection is in the differential diagnosis of genital abnormalities, many other diseases that are prevalent in Africa may cause the same manifestations. Abnormal vaginal discharge is a symptom of sexually transmitted infections such as gonorrhea, Chlamydia, or trichomoniasis (20). Genital ulcers are commonly associated with genital herpes, syphilis, or chancroids. In fact, herpes simplex virus 2 (HSV-2), or genital herpes, is the leading cause of genital ulcer disease throughout the world (21). Erosion or friability of the cervix is often associated with cervical tumors (22).

Detection of these varied abnormalities often requires routine physical exams, a keen eye, laboratory diagnosis, and knowledge as to what diseases they could be associated with. A case was reported in Nigeria in which a woman who had an adnexal mass removed was found to have been infected with schistosomiasis, which caused the tumor, even though she did not shed any detectable schistosome ova in her urine (23). More often than not, healthcare providers attribute genital manifestations to STIs rather than urogenital schistosomiasis due to diagnostic difficulties as well as a gap in known clinical genital markers of schistosomiasis infection (24).

Rwanda-Zambia HIV Research Group

The Rwanda-Zambia HIV Research Group (RZHRG) was first created by Dr. Susan Allen in1986. Currently, RZHRG operates out of three different sites: Kigali, Rwanda, and Lusaka and Ndola, Zambia. The projects largely emphasize couples voluntary counseling and testing (CVCT) as a major cost benefit in the fight against HIV. CVCT services are offered to couples in the cities, and eligible cohabitating couples are invited to participate in a cohort of discordant, heterosexual couples in order to follow up on behavioral and clinical factors that affect HIV risk and transmission (5).

Variables that RZHRG looks at during patient study visits include social information, such as age at first sex or which language the individual speaks, and clinical markers, such as if the individual has been treated for tuberculosis in the past. As HIV transmission relies largely on sexual behavior, a good number of sexually transmitted infection (STI) related variables are also collected, such as erosion or friability of cervix or non-menstrual bleeding. These STI variables may be considered important indicators of past schistosomiasis infection and/or increased susceptibility for HIV transmission.

HIV and Schistosomiasis Co-Infection

The interaction between Human Immunodeficiency Virus and schistosomiasis is an emerging field; only a handful of studies have been published within the last decade or so. In a study completed in the Copperbelt region of Zambia between 2000 and 2001, it was found that people co-infected with HIV and schistosomiasis had lower levels of schistosome egg excretion than those who were HIV-negative (25). It is thought that this may be due to lower levels of $CD4^+$ cells, which are necessary to form granulomas around the eggs for passage through the urinary tract. Thus, it is possible that because of the depletion of T-cells in HIV-positive persons, schistosome women are unable to produce schistosome eggs, which could possibly abate usual symptoms of schistosomiasis (25). However, other research has found that although there is decreased egg excretion, hepatic morbidity can still occur in coinfected individuals, leading to increased immunocompromised conditions, as well as increased susceptibility to future schistosomiasis infection (26, 27).

A study conducted in men who were coinfected with both HIV and schistosomiasis found that the presence of urogenital schistosomiasis may increase the risk that the man will transmit HIV to his partner (28). The reasoning is hypothesized to be that schistosome egg excretion in the semen is accompanied by cell count increases, namely lymphocytes and macrophages, in the urogenital region. These particular cells are types that HIV utilizes as host cells (28). In a Tanzanian study completed recently, it was found that the prevalence of HIV was significantly associated with female urogenital schistosomiasis, although the study found no significant associations between urogenital schistosomiasis and other vaginal or sexually transmitted infections (29).

Although there has been research completed regarding the pathologies of schistosomiasis and HIV in coinfected people, there have been few studies that examine

the risk of becoming infected with or transmitting HIV when schistosomiasis infection and the resulting genital symptoms are already present. This study aims to examine the risk of HIV acquisition and transmission after an individual has been previously infected with schistosomiasis, taking into account potential clinical manifestations of schistosome infection.

METHODS

Study Design

Follow-up questionnaires were utilized to collect data from individuals in the heterosexual transmission (HT) cohort. All samples and clinical and behavioral data were obtained from the Zambia Emory HIV Research Project (ZEHRP) by the Rwanda Zambia HIV Research Group (RZHRG). Bivariate logistic regressions were conducted to analyze the relationships between schistosomiasis infection, HIV infection, and the presence of genital abnormalities. It was assumed that individuals who tested positive for schistosomiasis were infected during childhood, prior to becoming sexually active.

Study Population

All samples and data were collected from individuals who were part of the HT cohort. The study population was selected to consist of half men and half women, and half seroconverters and half nonseroconverters. Plasma and serum samples were collected between 1994 and 2009. Health variable data were collected between 1994 and 2009 as well. Only HIV-discordant couples who have been cohabitating for more than three months were eligible to participate in the study. Women were required to be between the ages of 16 and 45; men were required to be between the ages of 16 and 65.

Schistosomiasis Testing

Plasma and serum samples were obtained from the Hunter Lab Repository and sent to the Secor lab at the Centers for Disease Control and Prevention (CDC), Office of Infectious Diseases for schistosomiasis testing. Testing was completed in duplicate using Enzyme-linked immunosorbent assay (ELISA) protocols. Results were obtained on a continuous numerical scale, and the two test results for each individual were averaged to attain a single schistosomiasis result value. Values less than or equal to 25 were

considered negative for schistosomiasis; greater than 25 and less than or equal to 50 were considered low positive; and greater than 50 were considered high positive for schistosomiasis.

HIV Acquisition and Transmission

RZHRG is continuously examining seroconversion events in their heterosexual cohort. HIV DNA is extracted from samples of seroconverters taken at their first date of seroconversion and compared to HIV DNA found in the partner sample. Using phylogenetic trees, the two HIV samples can be deduced to be of the same strain, meaning that seroconversion was "linked" to the HIV-positive partner in the cohort, or the strains can be of different origins, meaning that seroconversion was acquired from an outside partner and is, therefore, "unlinked." In some cases, linkage is unknown due to the quality of the blood samples.

Seroconverters were any individuals who were HIV-negative at baseline (CJBASE) and whose serostatus (SEROSTATMAR10) equaled 1 (linked transmission), 2 (unlinked transmission), or 15 (linkage unknown or pending). Transmitters were any individuals who were HIV-positive at baseline and whose serostatus equaled 1. The coding for transmitters allows for the capture of only individuals who transmit HIV to their partners in a linked seroconversion event, and not any individual whose partner acquired HIV outside of the partnership (Appendix C).

Genital Abnormality Variables

Clinical health data, specifically variables regarding genital abnormalities, were obtained from baseline past medical history and physical exam forms completed by ZERHP clinic staff during participant study visits. Data from all forms were obtained

during the enrollment visit (month = 0). Appendix A gives an overview of the list of health variables used from each form and which partner it pertains to.

Two new dichotomous variables were created: any inflammation (ANYINF) and any ulcer (ANYULC). These variables are composites of the various genital abnormality variables found on the forms given at the enrollment visit. Appendix B lists which genital variables were categorized into the two new composite variables. If any of the genital abnormality variables were recorded as 'yes,' then the corresponding composite variable was also coded as 'yes.' If all of the genital abnormality variables within that composite variable were recorded as 'no,' then that composite variable was coded as 'no.' Otherwise, if there was a missing record, then that composite variable was coded as missing to account for the possibility that the individual may have had that symptom.

Data Cleaning and Coding

RZHRG's medical forms and questions for study visits have changed slightly throughout the years. Physical Exam datasets were obtained from 1994-2001, 2002-2006, and post-2007 time periods, and similar variables were merged together. Certain variables that were found in one dataset, but not the other two, were kept as is. Datasets for Past Medical History forms were compiled similarly.

A new variable for any previous genital ulcer (ULCESCORE) was created to combine three different variables. 1994-2001 past medical history forms consisted of a variable for previous genital ulcer (H49ULCER). Post-2002, the forms contained variables for acute genital ulcer (HACGEUL) and chronic genital ulcer (HCHGEUL). Thus, in order to avoid a mass of missing data when conducting regression analyses, previous genital ulcer, acute genital ulcer, and chronic genital ulcer were all combined to create a composite ulcer variable (ULCESCORE). If any of the variables for previous,

acute, or chronic genital ulcer were recorded as 'yes,' then the composite ulcer variable was also recorded as 'yes.' If previous genital ulcer, or acute genital ulcer and chronic genital ulcer, were recorded as 'no,' then the composite ulcer variable was recorded as 'no.'

For Physical Exam and Past Medical History forms from 1994-2001, variable responses were coded dichotomously (1 – Yes, 0 – No). For Physical Exam forms completed starting in January 2002, variable responses were coded dichotomously as well, but as 1 – Yes and 2 – No. For Past Medical History forms completed after January 2002, variable responses were coded as 1 – Yes, 2 – No, or 3 – Don't know. For the gonorrhea (HGONO) and chronic genital ulcer (HCHGEUL) variables in post-2002 Past Medical History forms, only two individuals (0.28%) answered 'Don't know,' which would not have a big effect on analysis, so they were recoded as 'No.' All variables in both forms were recoded dichotomously to reflect 1 – Yes, 0 – No.

Logistic Regression Models

Three different bivariate logistic regression models were utilized to assess the relationships between schistosomiasis, HIV, and genital abnormalities:

1) Schistosomiasis infection as a predictor of baseline HIV status, and HIV seroconversion and transmission during follow-up
2) Schistosomiasis infection as a predictor of genital abnormalities
3) Genital abnormalities as predictors of baseline HIV status, and HIV seroconversion and transmission during follow-up

All three models were stratified by sex in order to obtain a more in-depth look at any possible differences between gender.

Odds ratios along with 95% confidence intervals were obtained to determine significance of association. Models in which a frequency cell equaled zero were analyzed using 0.5 as a placeholder.

IRB Approval

The Emory University Institutional Review Board and the Zambian Ethics Committee approved this study, which is covered under pre-existing RZHRG research protocols. Informed consent was obtained by RZHRG at the time of enrollment at ZEHRP.

RESULTS

The analysis of this study consisted of a total of 2,168 individuals who were previously enrolled in the RZHRG heterosexual cohort. Basic descriptive statistics of this study population are included in Table 1. 1,054 (49%) were men and 1,114 (51%) were women. The mean age of men was 34 and the mean age of women was 28. At baseline, there were 1,119 (52%) individuals who were one-half of a HIV-discordant couple in which the man was positive and the woman was negative. Conversely, there were 1,049 (48%) individuals who were part of a HIV-discordant couple in which the man was negative and woman was positive. Of the study population, 426 individuals seroconverted (46% were men, 54% were women) and 315 individuals transmitted HIV (57% were men, 43% were women). ELISA testing resulted in a 34% prevalence of high titer schistosomiasis, 25% with low titer schistosomiasis, and 41% of individuals were negative for schistosomiasis.

It was found that there is no significant difference between being HIV-positive or HIV-negative at baseline in those with high-positive schistosomiasis titers (OR: 0.86; 95% CI: 0.71-1.05). Amongst individuals who are considered low-positives for schistosomiasis infection, 22% are less likely to be HIV-positive than HIV-negative at baseline, however (95% CI: 0.63-0.97). When stratified by sex, it was found that both high-positive and low-positive schistosomiasis infected individuals were, on average, 20% less likely to be infected with HIV than not at baseline, although those odds ratios were not significant (Table 3).

There was no significant association between schistosomiasis infection and individuals who transmitted HIV. However, when looking at schistosomiasis infection and HIV seroconversion, overall, HIV seroconverters were significantly less likely to have high-positive or low-positive antibodies to schistosomiasis than non-seroconverters

(respectively, OR: 0.59; 95% CI: 0.43-0.79; OR: 0.65; 95% CI: 0.47-0.89). When stratified by sex, the results were similar (Table 3).

When assessing schistosomiasis infection as a predictor of genital abnormalities, there was significance in several, but not all, variables (Table 4). Significant associations were found in those who were found to have inguinal adenopathy > 1cm unilateral (OR: 1.48; 95% CI: 1.10-2.00); inguinal adenopathy > 1cm bilateral (OR: 1.42; 95% CI: 1.13-1.78); inflammation (OR: 2.22; 95%CI: 1.02-4.83); cervicitis (OR: 2.28; 95% CI: 1.14-4.56); circumcision in men (OR: 2.28; 95% CI: 1.33-3.91); gonorrhea (OR: 1.91; 95% CI: 1.31-2.79); syphilis (OR: 0.75; 95% CI: 0.57-0.99); lower abdominal pain (OR: 1.73; 95% CI: 1.20-2.50); and any previous ulcer (OR: 0.69; 95% CI: 0.51-0.94); as compared to those who did not present with those symptoms. Furthermore, when comparing low-positive schistosomiasis infection against no schistosomiasis infection, the odds that an individual had cystitis/dysuria was also significant (OR: 1.47; 95% CI: 1.09-1.98). In looking at the composite variables, being high-positive or low-positive for schistosomiasis infection were both significantly associated with having any inflammatory symptom (respectively, OR: 1.41, 95% CI: 1.15-1.72; OR: 1.25, 95% CI: 1.00-1.56). Only having high-positive schistosomiasis titers was a significant indicator of having any ulcerative symptom; the odds of being high-positive for schistosomiasis and having an ulcer was 0.74 the odds of being high-positive of schistosomiasis and not having any ulcer (95% CI: 0.60-0.92).

Several genital abnormality variables contributed to significant associations with HIV status at baseline (Table 5). The majority of these significant associations had odds ratios above 1.0, with the exception of male circumcision. Men who were circumsized were 0.63 times as likely to be HIV-positive at baseline as men HIV-negative (95% CI: 0.41-0.95). When composite variables were examined, HIV-positive men and women

were significantly more likely to have any infection (ANYINF) and any ulceration (ANYULC) than their HIV-negative counterparts (respectively, OR: 2.14, 95%CI: 1.79-2.55; OR: 2.28, 95% CI: 1.87-2.78), even when stratified by sex.

Results showed that not many baseline genital abnormality variables were significant predictors of HIV seroconversion or transmission during follow-up amongst both men and women (Table 6). Men were more likely to have seroconverted than not if they had syphilis (OR: 2.08; 95% CI: 1.12-3.85) or previous ulcers (OR: 2.75; 95% CI: 1.40-5.41). Men were also 64% less likely to have seroconverted if they were circumsized (95% CI: 0.18-0.71). Women were more likely to have seroconverted than not if they had vaginal discharge (OR: 3.38; 95% CI: 1.86-6.13). Out of the composite variables, only the any ulceration composite for men was considered to be a significant predictor of HIV seroconversion; the odds of men who had any ulcer and acquired HIV over time were about two times the odds of men who had any ulcer and did not seroconvert (95% CI: 1.26-3.33).

In looking at HIV transmitters, having gonorrhea was a significant predictor of transmitting HIV; the odds of those who had gonorrhea and transmitted HIV to their partner was 1.62 times the odds of men who had gonorrhea and did not transmit HIV to their partner (95% CI: 1.05-2.50). No other genital abnormality variables, nor composite variables, were significant predictors of HIV transmission, even when stratified by sex (Table 7).

DISCUSSION

In general, the results of the study did not confirm the original hypothesis that serologic evidence of past or current schistosomiasis infection is a risk factor for HIV. Schistosomiasis, while not a sexually transmitted infection, does appear to cause several inflammatory genital abnormalities, such as inguinal adenopathy or inflammation of the cervix. However, in contrast to previous studies, serologic evidence of schistosomiasis was not a significant predictor of HIV prevalence in this Zambian study population. Furthermore, the results showed a protective effect between schistosomiasis infection and HIV seroconversion. This etiology warrants further investigation. Nonetheless, a few hypotheses can be formulated to give an explanation.

The ELISA procedure utilized to test plasma and serum samples for schistosomiasis measured titers of schistosome antibodies. These values cannot distinguish if an individual is currently infected with schistosomiasis, nor can the titers give an accurate indication of how severe the infection was. Because schistosomiasis can be cured and infection can be resolved, and in some cases resolves on its own when the adult worm dies, being previously infected is not necessarily the best gauge of whether or not one is at a higher risk for HIV acquisition. Thus, while ELISA was useful in determining if an individual still possesses antibodies to schistosomiasis, it is really the lingering and chronic symptoms that may arise from schistosomiasis that should be taken into consideration when assessing the association with HIV.

In this study, schistosomiasis was associated with several genital abnormalities that, in turn, were significantly associated with HIV prevalence. For example, inguinal adenopathy greater than one centimeter unilateral (PAINAD) and external genitalia inflammation (PINFGE) were both statistically associated with schistosomiasis; past schistosomiasis infection was a significant predictor of the manifestation of these clinical

variables. Consequently, these two variables were then also significant predictors of being HIV-positive at baseline. When looking at HIV acquisition and transmission however, there was no significant difference between those who did and did not acquire HIV, nor was there a significant difference between those who transmitted HIV and those who did not. Therefore, it is quite possible that the true association between schistosomiasis infection and HIV acquisition is inconclusive.

One other explanation for the observed results is the use of the intermediate category for ELISA results. This grouping arose due to the fact that in testing some samples using the assay, the detection of antibodies could not clearly distinguish whether or not the individual was previously infected with schistosomiasis. There are a total of 533 individuals who fall into this category; some may well have had previous or current schistosomiasis infection, while for others the antibody titer is a false positive result. Unfortunately, this cannot be resolved without further testing. Thus, a good majority of the individuals in the study, along with the clinical health data collected on them, are possibly affecting the results of the analysis, due to the uncertainty of their previous schistosomiasis infection status.

STRENGTHS AND WEAKNESSES

Strengths of this study include the size of the study population and the variety of genital abnormality variables that were collected. With over two thousand individuals, this allowed for greater precision when analyzing overall HIV prevalence. Moreover, the sample size made available a sort of "snapshot" for what is found in the heterosexual cohort. Additionally, the number of variables that are related to genitals collected by ZEHRP allows for a broader picture of exactly which signs and symptoms may be related to schistosomiasis, and how those symptoms in turn, may be associated with HIV prevalence, acquisition, and transmission. This assortment of clinical manifestations provides insight into which signs and symptoms should be examined further.

There are a few weaknesses to this study that led to the observed results. First, in looking at the third model which utilized genital abnormalities as a predictor of HIV status, individuals were separated into seroconversion and transmission groups, and stratified further by gender. This decreased greatly the frequencies of individuals who were divided into each cell. Thus, as the prevalence of certain abnormalities were already low, some of the analyses may have been distorted by small numbers.

Secondly, the testing procedure for schistosomiasis used in this study, ELISA, detects only antibodies to schistosomiasis, which is a fairly good indicator of previous schistosomiasis infection. However, these titers are not able to fully inform on the severity of infection, or if the individual was treated with praziquantel before genital abnormalities, if present, appeared. Unfortunately, as this study does include adult couples whose data are analyzed retrospectively, it is difficult to assess current infection, especially because schistosomiasis is oftentimes a childhood illness.

Furthermore, ELISA can provide questionable results. As mentioned previously, each sample was tested in duplicate, with the average value indicating the result category

that the individual fell into. In some cases, for a single individual, one value would be considered “high-positive” while the second value would be considered negative, and the average between the two raw numbers fell into the intermediate category. This intermediate group was designated as “low-positive.” However, the samples of these individuals should be further assessed to conclusively distinguish whether they are positive or negative for schistosomiasis antibodies. As nearly a quarter of the study population were in this “low-positive” category, statistical values of the analyses could change greatly if the schistosomiasis exposure variable was dichotomous rather than ordinal.

FUTURE DIRECTIONS

Several steps can be taken to further examine the associations between schistosomiasis; genital abnormalities; and HIV prevalence, acquisition, and transmission. First and foremost, the Zambia-Emory HIV Research Project's heterosexual cohort consists of more than 5000 individuals over the past seventeen years. For this study, a little more than two thousand samples were examined. It would be beneficial to test the remaining individuals' banked plasma and serum samples for schistosomiasis antibodies as well to examine if the statistical associations between schistosomiasis and HIV prevalence, with genital abnormalities as intermediate variables, may change. Although a snapshot of the cohort is helpful, the sheer amount of banked plasma and serum samples that RZHRG has available makes a full description of the study participants fairly accessible.

In order to confirm whether an individual was infected with schistosomiasis or not, other methods of testing can be used including the Kato-Katz technique or Western immunoblots. Western blots would also be able to distinguish between *Schistosoma haematobium* and *S. mansoni* as well, which could add a regional aspect of infection into the analysis. These secondary tests would serve as a confirmation for the ELISA tests; like ELISAs, Western blots detect antibodies, whereas the Kato-Katz procedure searches for parasite ova, which could be useful in determining current cases of schistosomiasis infection.

Another possible avenue to consider is the association between schistosomiasis and other sexually transmitted infections. As much research has concluded that sexually transmitted infections are significant factors in the acquisition and transmission of HIV, adding in a schistosomiasis component could broaden the scope of the interactions between sexually transmitted infections and parasitic diseases.

It may be worth looking into conducting a prospective longitudinal study to consider the time component of HIV infection and the appearance of genital abnormalities, given that schistosomiasis-positive individuals were infected during childhood before becoming sexually active. This, however, may take many long years and much funding to be carried out successfully.

It is crucial to further investigate the etiology of the association between schistosomiasis and HIV, as well as any genital abnormalities that stem from one and could induce the other. Thus far, results are inconclusive; however, with the high prevalence of HIV in the world, it may be important to realize whether or not a neglected tropical disease further exacerbates the pandemic.

REFERENCES

1. CDC. HIV/AIDS Basics. In. Atlanta; 2006.

2. CDC. Parasites - Schistosomiasis. In. Atlanta; 2010.

3. WHO. Global summary of the AIDS epidemic. In: WHO, UNAIDS; 2009.

4. UNAIDS. UNAIDS Report on the Global AIDS Epidemic: UNAIDS; 2010.

5. Allen S, Karita E, Chomba E, Roth DL, Telfair J, Zulu I, et al. Promotion of couples' voluntary counselling and testing for HIV through influential networks in two African capital cities. Bmc Public Health 2007;7.

6. Stephenson R, Barker J, Cramer R, Hall MA, Karita E, Chomba E, et al. The demographic profile of sero-discordant couples enrolled in clinical research in Rwanda and Zambia. Aids Care-Psychological and Socio-Medical Aspects of Aids/Hiv 2008;20(3):395-405.

7. DHS. HIV/AIDS Data from the 2007 Zambia Demographic and Health Survey; 2007.

8. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infectious Diseases 2009;9(2):118-129.

9. Allen S, Meinzen-Derr L, Kautzman M, Zulu I, Trask S, Fideli U, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. Aids 2003;17(5):733-740.

10. Dunkle KL, Stephenson R, Karita E, Chomba E, Kayitenkore K, Vwalika C, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. Lancet 2008;371(9631):2183-2191.

11. Agnew-Blais J, Carnevale J, Gropper A, Shilika E, Bail R, Ngoma M. Schistosomiasis Haematobium Prevalence and Risk Factors in a School-age Population of Peri-urban Lusaka, Zambia. Journal of Tropical Pediatrics 2010;56(4):247-253.

12. Ndhlovu P, Mduluza T, Kjetland EF, Midzi N, Nyanga L, Gundersen SG, et al. Prevalence of urinary schistosomiasis and HIV in females living in a rural community of Zimbabwe: does age. matter? Transactions of the Royal Society of Tropical Medicine and Hygiene 2007;101(5):433-438.

13. Southgate VR, Rollinson D, Tchuente LAT, Hagan P. Towards control of schistosomiasis in sub-Saharan Africa. Journal of Helminthology 2005;79(3):181-185.

14. Obonyo CO, Muok EMO, Mwinzi PNM. Efficacy of artesunate with sulfalene plus pyrimethamine versus praziquantel for treatment of Schistosoma mansoni in Kenyan children: an open-label randomised controlled trial. Lancet Infectious Diseases 2010;10(9):603-611.

15. Kapito-Tembo AP, Mwapasa V, Meshnick SR, Samanyika Y, Banda D, Bowie C, et al. Prevalence Distribution and Risk Factors for Schistosoma hematobium Infection among School Children in Blantyre, Malawi. Plos Neglected Tropical Diseases 2009;3(1).

16. Berhe N, Myrvang B, Gundersen SG. Gastro-intestinal symptoms associated with intense Schistosoma mansoni infection affect class-attentiveness of schoolchildren in Ethiopia. Acta Tropica 2009;110(1):52-56.

17. Kjetland EF, Ndhlovu P, Gomo E, Mduluza T, Midzi N, Gwanzura L, et al. Treatment of schistosomiasis as intervention against HIV transmission in Africa. In; 2010; Copenhagen, Denmark; 2010.

18. Kjetland EF, Mduluza T, Ndhlovu PD, Gomo E, Gwanzura L, Midzi N, et al. Genital schistosomiasis in women: a clinical 12-month in vivo study following treatment with praziquantel. Transactions of the Royal Society of Tropical Medicine and Hygiene 2006;100(8):740-752.

19. Poggensee G, Feldmeier H. Female genital schistosomiasis: facts and hypotheses. Acta Tropica 2001;79(3):193-210.

20. Ward E, Spruyt A, Fox L, Johnson L, Wong E, Behets F, et al. Strategies for detection of sexually transmitted infection among family planning clients in Jamaica. International Family Planning Perspectives 2001;27(4):201-207.

21. Abu-Raddad LJ, Magaret AS, Celum C, Wald A, Longini IM, Self SG, et al. Genital Herpes Has Played a More Important Role than Any Other Sexually Transmitted Infection in Driving HIV Prevalence in Africa. Plos One 2008;3(5).

22. Lallas TA, Mehaffey PC, Lager DJ, Van Voorhis BJ, Sorosky JI. Malignant cervical schwannoma: An unusual pelvic tumor. Gynecologic Oncology 1999;72(2):238-242.

23. Schanz A, Richter J, Beyer I, Baldus SE, Hess AP, Kruessel JS. Genital schistosomiasis as a cause of female sterility and acute abdomen. Fertility and Sterility 2010;93(6).

24. Leutscher PDC, Ramarokoto CE, Hoffmann S, Jensen JS, Ramaniraka V, Randrianasolo B, et al. Coexistence of urogenital schistosomiasis and sexually transmitted infection in women and men living in an area where Schistosoma haematobium is endemic. Clinical Infectious Diseases 2008;47(6):775-782.

25. Mwanakasale V, Vounatsou P, Sukwa TY, Ziba M, Ernest A, Tanner M. Interactions between Schistosoma haematobium and human immunodeficiency virus type 1: The effects of coinfection on treatment outcomes in rural Zambia. American Journal of Tropical Medicine and Hygiene 2003;69(4):420-428.

26. Secor WE. Interactions between schistosomiasis and infection with HIV-1. Parasite Immunology 2006;28(11):597-603.

27. Lloyd-Smith JO, Poss M, Grenfell BT. HIV-1/parasite co-infection and the emergence of new parasite strains. Parasitology 2008;135(7):795-806.

28. Leutscher PDC, Pedersen M, Raharisolo C, Jensen JS, Hoffmann S, Lisse I, et al. Increased prevalence of leukocytes and elevated cytokine levels in semen from Schistosoma haematobium-infected individuals. Journal of Infectious Diseases 2005;191(10):1639-1647.

29. Downs JA, Mguta C, Kaatano GM, Mitchell KB, Bang H, Simplice H, et al. Urogenital Schistosomiasis in Women of Reproductive Age in Tanzania's Lake Victoria Region. American Journal of Tropical Medicine and Hygiene 2011;84(3):364-369.

Table 1. Demographic, and HIV and Schistosomiasis Statuses of Individuals in Study (n = 2168), Lusaka, Zambia 1994-2010

Characteristic	***Total*,n (%)**
Sex	
Men	1054 (49)
Women	1114 (51)
Mean Age (SD)	
Men	34 (8.23)
Women	28 (6.84)
HIV Status at Baseline **MF**	
+-	*1119 (52)*
Men	605 (54)
Women	514 (46)
-+	*1049 (48)*
Men	449 (43)
Women	600 (57)
HIV Status in Followup	
Seroconverters	*426 (20)*
Men	195 (46)
Women	231 (54)
Non-Seroconverters	*537 (25)*
Men	254 (47)
Women	283 (53)
Transmitters	*315 (15)*
Men	179 (57)
Women	136 (43)
Non-Transmitters	*785 (36)*
Men	376 (48)
Women	409 (52)
ELISA Result Code	
1 - High Positive	*728 (34)*
Men	423 (58)
Women	305 (42)
2 - Low Positive	*533 (25)*
Men	270 (51)
Women	263 (49)
3 - Negative	*892 (41)*
Men	358 (40)
Women	534 (60)
Missing	*15 (1)*

Table 2. Prevalences of Genital Abnormality Variables

	Men (n = 1054)	Women (n = 1114)
Genital Abnormality	**n (%)**	**n (%)**
Inguinal adenopathy > 1cm unilateral (PAINAD)[a]	193 (18.3)	63 (5.7)
Inguinal adenopathy > 1cm bilateral (PBINAD)[a]	377 (35.8)	142 (12.8)
External Genitalia Inflammation (PINFGE)[a]	24 (2.3)	15 (1.4)
External Genitalia Ulceration (PEXGUL)[a]	60 (5.7)	36 (3.2)
Inflammation cervix/cervicitis (PAINGI)[a]	-[c]	45 (4.0)
Inflammation vagina (PBINGI)[a]	-[c]	11 (1.0)
Ulcer cervix (PAULCE)[a]	-[c]	11 (1.0)
Ulcer vagina (PBULCE)[a]	-[c]	6 (0.5)
Discharge/pus cervix (PADISC)[a]	-[c]	26 (2.3)
Discharge vagina (PBDISC)[a]	-[c]	133 (11.9)
Erosion or friability cervix (PAEROS)[a]	-[c]	55 (4.9)
Erosion or friability vagina (PBEROS)[a]	-[c]	2 (0.2)
Non-menstrual bleeding cervix (PABLEE)[a]	-[c]	26 (2.3)
Non-menstrual bleeding vagina (PBBLEE)[a]	-[c]	7 (0.6)
Adnexal tenderness (PANNEX)[a]	-[c]	20 (1.8)
Adnexal mass (PMASSE)[a]	-[c]	5 (0.5)
Urethral Discharge (PDISCH)[a]	33 (3.1)	-[c]
Deposit/Poor Hygiene (PHYGIE)[a]	134 (12.7)	-[c]
Circumsized (PCIRC)[a]	96 (9.1)	-[c]
Cystitis/dysuria (HCYSD)[b]	190 (18.0)	119 (10.7)
Lower abdominal pain (HAPAIN)[b]	178 (16.9)	183 (16.4)
Gonorrhea (HGONO)[b]	147 (14.0)	19 (1.7)
Syphilis (HSYPH)[b]	141 (13.4)	196 (17.6)
Ulcer (H49ULCER)[b,d]	76 (7.2)	46 (4.1)
Acute genital ulcer (HACGEUL)[b,e]	71 (6.7)	25 (2.2)
Chronic/Recurrent genital ulcer (HCHGEUL)[b,e]	41 (3.9)	27 (2.4)
Inguinal Adenopathy (H16ADENO)[b,d]	98 (9.3)	42 (3.8)
Dyspareunia (HDYSPAR)[b,e]	-[c]	21 (1.9)
Vaginal discharge (HVAGIN)[b]	-[c]	154 (13.8)
Urethral discharge (HURETH)[b]	114 (10.8)	-[c]
Previous ulcer (ULCESCORE)[f]	173 (16.4)	95 (8.5)
Any Inflammation (ANYINF)[g]	716 (67.9)	536 (48.1)
Any Ulcer (ANYULC)[h]	299 (28.4)	335 (30.1)

[a]Variable from Physical Exam Forms

[b]Variable from Past Medical History Forms

[c]Variable not collected for this gender

[d]Variable only in 1994-2002 forms

[e]Variable only in post 2002 forms

[f]Variable created to combine H49ULCER, HACGEUL, HCHGEUL

[g]Composite variable for any inflammatory abnormality

[h]Composite variable for any ulcerative abnormality

Table 3. Bivariate Odds Ratios of Schistosomiasis Infection as a Predictor of HIV Status[a]

	High Positive[b] (n = 728)	**Low Positive[b] (n = 533)**
HIV status	**cOR (95% CI)**	**cOR (95% CI)**
HIV-positive at baseline	0.86 (0.71, 1.05)	**0.78 (0.63, 0.97)**
Men	0.78 (0.58, 1.03)	0.75 (0.55, 1.04)
Women	0.91 (0.68, 1.20)	0.78 (0.58, 1.04)
HIV Seroconverters	**0.59 (0.43, 0.79)**	**0.65 (0.47, 0.89)**
Men	**0.59 (0.38, 0.92)**	0.67 (0.41, 1.09)
Women	**0.58 (0.38, 0.89)**	**0.63 (0.41, 0.97)**
HIV Transmitters	0.87 (0.64, 1.17)	0.83 (0.59, 1.17)
Men	0.74 (0.49, 1.11)	0.66 (0.41, 1.06)
Women	0.89 (0.56, 1.43)	0.98 (0.60, 1.62)

[a]Bolded OR indicates significant association
[b]Negative schistosomiasis titers are the referent group.

Table 4. Bivariate Odds Ratios of Schistosomiasis Infection as a Predictor of Genital Abnormalities[a]

	High Positive[e] (n = 728)	**Low Positive[e] (n = 533)**
Genital Abnormality	**cOR (95% CI)**	**cOR (95% CI)**
Inguinal adenopathy > 1cm unilateral	**1.48 (1.10, 2.00)**	1.16 (0.82, 1.63)
Inguinal adenopathy > 1cm bilateral	**1.42 (1.13, 1.78)**	1.28 (0.99, 1.65)
External Genitalia Inflammation	**2.22 (1.02, 4.83)**	1.87 (0.79, 4.43)
External Genitalia Ulceration	1.19 (0.72, 1.95)	1.57 (0.95, 2.61)
Inflammation cervix/cervicitis[b]	**2.28 (1.14, 4.56)**	1.55 (0.70, 3.43)
Inflammation vagina[b]	1.74 (0.43, 7.03)	1.57 (0.35, 7.06)
Ulcer cervix[b]	3.08 (0.90, 10.63)	0.52 (0.06, 4.68)
Ulcer vagina[b]	-[d]	-[d]
Discharge/pus cervix[b]	1.58 (0.63, 3.93)	1.48 (0.56, 3.93)
Discharge vagina[b]	0.65 (0.41, 1.03)	0.93 (0.60, 1.46)
Erosion or friability[b]	1.56 (0.85, 2.85)	0.96 (0.46, 1.99)
Erosion or friability vagina[b]	-[d]	-[d]
Non-menstrual bleeding cervix[b]	1.49 (0.66, 3.36)	0.32 (0.07, 1.42)
Non-menstrual bleeding vagina[b]	0.35 (0.04, 2.96)	0.42 (0.05, 3.59)
Adnexal tenderness[b]	2.55 (0.96, 6.79)	0.90 (0.23, 3.51)
Adnexal mass[b]	3.54 (0.32, 39.16)	4.24 (0.38, 46.95)
Urethral Discharge[c]	0.93 (0.39, 2.23)	1.48 (0.62, 3.54)
Deposit/Poor Hygiene[c]	0.96 (0.63, 1.47)	1.01 (0.63, 1.62)
Circumsized[c]	**2.28 (1.33, 3.91)**	1.80 (0.98, 3.30)
Cystitis/dysuria	1.18 (0.89, 1.58)	**1.47 (1.09, 1.98)**
Lower abdominal pain	**1.73 (1.20, 2.50)**	1.30 (0.87, 1.95)
Gonorrhea	**1.91 (1.31, 2.79)**	**1.69 (1.12, 2.57)**
Syphilis	**0.75 (0.57, 0.99)**	0.81 (0.60, 1.08)
Inguinal Adenopathy	1.02 (0.69, 1.51)	0.70 (0.43, 1.12)
Dyspareunia[b]	1.17 (0.37, 3.71)	0.77 (0.21, 2.76)
Vaginal discharge[b]	0.85 (0.57, 1.28)	0.76 (0.49, 1.18)
Urethral discharge[c]	1.25 (0.79, 1.99)	1.24 (0.74, 2.07)
Previous ulcer	**0.69 (0.51, 0.94)**	0.84 (0.61, 1.16)
Any Inflammation	**1.43 (1.17, 1.75)**	1.24 (0.99, 1.55)
Any Ulcer	**0.74 (0.60, 0.92)**	0.84 (0.66, 1.07)

[a]Bolded OR indicates significant association

[b]Women only variable

[c]Men only variable

[d]Variable contained a zero in frequency cell; cOR and 95% CI not obtained

[e]Negative schistosomiasis titers are the referent group

Table 5. Bivariate Odds Ratios of Genital Abnormalities as a Predictor of Being HIV-positive at Baseline[a]

	All Subjects (n = 2168)	**Men (n = 1054)**	**Women (n = 1114)**
Genital Abnormality	**cOR (95% CI)**	**cOR (95% CI)**	**cOR (95% CI)**
Inguinal adenopathy > 1cm unilateral	**1.43 (1.09, 1.87)[b]**	1.15 (0.83, 1.58)	**2.41 (1.36, 4.26)[b]**
Inguinal adenopathy > 1cm bilateral	**3.57 (2.84, 4.48)[b]**	**3.50 (2.64, 4.62)[b]**	**4.48 (2.87, 6.99)[b]**
External Genitalia Inflammation	**2.04 (1.01, 4.13)[c]**	1.51 (0.64, 3.56)	3.44 (0.96, 12.25)
External Genitalia Ulceration	**2.61 (1.62, 4.21)[b]**	**2.84 (1.52, 5.32)[b]**	**2.26 (1.08, 4.73)[c]**
Inflammation cervix/cervicitis[d]	-	-	1.16 (0.63, 2.12)
Inflammation vagina[d]	-	-	3.83 (0.82, 17.79)
Ulcer cervix[d]	-	-	2.25 (0.59, 8.54)
Ulcer vagina[d]	-	-	1.68 (0.31, 9.22)
Discharge/pus cervix[d]	-	-	**2.86 (1.14, 7.18)[c]**
Discharge vagina[d]	-	-	1.06 (0.73, 1.53)
Erosion or friability[d]	-	-	1.27 (0.73, 2.22)
Erosion or friability vagina[d]	-	-	4.22 (0.20, 88.03)
Non-menstrual bleeding cervix[d]	-	-	1.60 (0.71, 3.63)
Non-menstrual bleeding vagina[d]	-	-	2.11 (0.76, 5.25)
Adnexal tenderness[d]	-	-	2.00 (0.76, 5.25)
Adnexal mass[d]	-	-	1.27 (0.21, 7.61)
Urethral Discharge[e]	-	0.61 (0.30, 1.22)	-
Deposit/Poor Hygiene[e]	-	1.38 (0.95, 2.01)	-
Circumsized[e]	-	**0.63 (0.41, 0.95)[c]**	-
Cystitis/dysuria	**1.44 (1.12, 1.84)[c]**	**1.38 (1.00, 1.91)[c]**	1.46 (0.99, 2.16)
Lower abdominal pain	**1.37 (1.08, 1.73)[b]**	1.30 (0.93, 1.81)	**1.43 (1.04, 1.98)[c]**
Gonorrhea	1.22 (0.88, 1.68)	1.14 (0.80, 1.63)	1.45 (0.57, 3.70)
Syphilis	**1.84 (1.44, 2.36)[b]**	**1.60 (1.10, 2.33)[c]**	**2.10 (1.51, 2.92)[b]**
Inguinal Adenopathy	**1.45 (1.02, 2.07)[c]**	1.1 (0.72, 1.69)	**2.22 (1.15, 4.29)[c]**
Dyspareunia[d]	-	-	0.73 (0.30, 1.77)
Vaginal discharge[d]	-	-	1.24 (0.88, 1.75)
Urethral discharge[e]	-	0.91 (0.61, 1.34)	-
Previous ulcer	**2.49 (1.87, 3.32)[b]**	**2.80 (1.93, 4.08)[b]**	**2.03 (1.29, 3.19)[b]**
Any Inflammation	**2.14 (1.79, 2.55)[b]**	**2.61 (2.00, 3.41)[b]**	**1.83 (1.44, 2.34)[b]**
Any Ulcer	**2.28 (1.87, 2.78)[b]**	**2.59 (1.93, 3.47)[b]**	**2.06 (1.57, 2.70)[b]**

[a]Bolded OR indicates significant association

[b]p-value < 0.01

[c]p-value < 0.05

[d]Women only variable

[e]Men only variable

Table 6. Bivariate Odds Ratios of Genital Abnormalities as a Predictor of HIV Seroconversion

	All Subjects (n = 2168)	**Men (n = 1054)**	**Women (n = 1114)**
Genital Abnormality	**cOR (95% CI)**	**cOR (95% CI)**	**cOR (95% CI)**
Inguinal adenopathy > 1cm unilateral	0.68 (0.44, 1.06)	0.80 (0.49, 1.32)	0.36 (0.12, 1.11)
Inguinal adenopathy > 1cm bilateral	0.80 (0.54, 1.19)	0.90 (0.56, 1.43)	0.62 (0.27, 1.42)
External Genitalia Inflammation	0.27 (0.06, 1.27)	0.43 (0.09, 2.14)	0.17 (0.01, 3.27)
External Genitalia Ulceration	0.79 (0.34, 1.84)	1.53 (0.51, 4.62)	0.29 (0.06, 1.38)
Inflammation cervix/cervicitis[d]	-	-	0.54 (0.20, 1.43)
Inflammation vagina[d]	-	-	0.24 (0.01, 4.93)
Ulcer cervix[d]	-	-	0.59 (0.05, 6.54)
Ulcer vagina[d]	-	-	1.18 (0.07, 19.03)
Discharge/pus cervix[d]	-	-	1.19 (0.24, 5.93)
Discharge vagina[d]	-	-	**3.38 (1.86, 6.13)[b]**
Erosion or friability cervix[d]	-	-	0.66 (0.27, 1.61)
Erosion or friability vagina[d]	-	-	-[f]
Non-menstrual bleeding cervix[d]	-	-	1.49 (0.40, 5.62)
Non-menstrual bleeding vagina[d]	-	-	5.97 (0.28, 124.92)
Adnexal tenderness[d]	-	-	0.59 (0.11, 3.23)
Adnexal mass[d]	-	-	0.23 (0.01, 4.88)
Urethral Discharge[e]	-	0.82 (0.31, 2.14)	-
Deposit/Poor Hygiene[e]	-	0.68 (0.37, 1.27)	-
Circumsized[e]	-	**0.36 (0.18, 0.71)[b]**	-
Cystitis/dysuria	1.25 (0.85, 1.85)	1.42 (0.85, 2.37)	1.08 (0.59, 1.99)
Lower abdominal pain	1.07 (0.74, 1.54)	1.25 (0.74, 2.12)	0.94 (0.57, 1.56)
Gonorrhea	1.25 (0.76, 2.06)	1.31 (0.76, 2.27)	1.57 (0.35, 7.09)
Syphilis	**1.50 (1.00, 2.24)[c]**	**2.08 (1.12, 3.85)[c]**	1.16 (0.68, 1.98)
Inguinal Adenopathy	1.64 (0.94, 2.88)	1.73 (0.87, 3.41)	2.03 (0.69, 5.90)
Dyspareunia[d]	-	-	2.53 (0.30, 21.03)
Vaginal discharge[d]	-	-	0.82 (0.48, 1.39)
Urethral discharge[e]	-	1.41 (0.79, 2.53)	-
Previous ulcer	**1.81 (1.11, 2.97)[c]**	**2.75 (1.40, 5.41)[b]**	1.09 (0.52, 2.32)
Any Inflammation	0.97 (0.75, 1.26)	0.91 (0.62, 1.32)	1.08 (0.75, 1.55)
Any Ulcer	1.30 (0.95, 1.79)	**2.05 (1.26, 3.33)[b]**	0.90 (0.59, 1.38)

[a]Bolded OR indicates significant association

[b]p-value < 0.01

[c]p-value < 0.05

[d]Women only variable

[e]Men only variable

[f]No '+-' women recorded 'yes' for abnormality; OR and 95% CI not obtained

Table 7. Bivariate Odds Ratios of Genital Abnormalities as a Predictor of HIV Transmission[a]

	All Subjects (n = 2168)	**Men (n = 1054)**	**Women (n = 1114)**
Genital Abnormality	**cOR (95% CI)**	**cOR (95% CI)**	**cOR (95% CI)**
Inguinal adenopathy > 1cm unilateral	0.92 (0.63, 1.36)	0.79 (0.50, 1.27)	1.01 (0.49, 2.07)
Inguinal adenopathy > 1cm bilateral	0.90 (0.68, 1.18)	0.86 (0.60, 1.23)	0.67 (0.40, 1.13)
External Genitalia Inflammation	0.73 (0.29, 1.84)	0.83 (0.26, 2.70)	0.58 (0.13, 2.69)
External Genitalia Ulceration	1.02 (0.60, 1.75)	1.01 (0.52, 1.97)	0.92 (0.36, 2.36)
Inflammation cervix/cervicitis[c]	-	-	0.97 (0.38, 2.50)
Inflammation vagina[c]	-	-	0.41 (0.05, 3.38)
Ulcer cervix[c]	-	-	0.41 (0.05, 3.38)
Ulcer vagina[c]	-	-	0.97 (0.10, 9.43)
Discharge/pus cervix[c]	-	-	1.04 (0.37, 2.95)
Discharge vagina[c]	-	-	1.13 (0.64, 1.99)
Erosion or friability[c]	-	-	0.81 (0.34, 1.91)
Erosion or friability vagina[c]	-	-	0.58 (0.03, 12.10)
Non-menstrual bleeding cervix[c]	-	-	0.44 (0.10, 1.97)
Non-menstrual bleeding vagina[c]	-	-	2.94 (0.41, 21.07)
Adnexal tenderness[c]	-	-	0.47 (0.10, 2.15)
Adnexal mass[c]	-	-	0.41 (0.02, 7.95)
Urethral Discharge[d]	-	1.17 (0.39, 3.54)	-
Deposit/Poor Hygiene[d]	-	1.11 (0.67, 1.85)	-
Circumsized[d]	-	0.90 (0.46, 1.77)	-
Cystitis/dysuria	0.93 (0.65, 1.32)	0.81 (0.51, 1.27)	1.02 (0.58, 1.82)
Lower abdominal pain	0.89 (0.64, 1.25)	0.76 (0.47, 1.21)	1.07 (0.66, 1.73)
Gonorrhea	**1.62 (1.05, 2.50)[b]**	1.34 (0.83, 2.17)	2.17 (0.68, 6.95)
Syphilis	1.15 (0.83, 1.59)	1.09 (0.67, 1.77)	1.29 (0.82, 2.03)
Inguinal Adenopathy	1.63 (0.99, 2.65)	1.33 (0.73, 2.43)	2.09 (0.90, 4.89)
Dyspareunia[c]	-	-	0.80 (0.20, 3.10)
Vaginal discharge[c]	-	-	1.02 (0.60, 1.75)
Urethral discharge[d]	-	1.02 (0.57, 1.83)	-
Previous ulcer	1.08 (0.77, 1.53)	1.37 (0.90, 2.09)	0.51 (0.25, 1.04)
Any Inflammation	0.77 (0.58, 1.02)	0.65 (0.43, 1.02)	0.75 (0.50, 1.10)
Any Ulcer	1.06 (0.81, 1.38)	1.31 (0.91, 1.89)	0.84 (0.56, 1.26)

[a]Bolded OR indicates significant association

[b]p-value < 0.05

[c]Women only variable
[d]Men only variable

Appendix A. Genital abnormality variables

	Description	Variable	Men	Women
Physical Exam Form	Inguinal adenopathy > 1cm unilateral	P21AINAD, PAINAD	X	X
	Inguinal adenopathy > 1cm bilateral	P21BINAD, PBINAD	X	X
	Inflammation	P22INFGE, PINFGE	X	X
	Ulceration	P23EXGUL, PEXGUL	X	X
	Inflammation cervix/cervicitis	P24AINGI, PAINGI		X
	Inflammation vagina	P24BINGI, PBINGI		X
	Ulcer cervix	P25AULCE, PAULCE		X
	Ulcer vagina	P25BULCE, PBULCE		X
	Discharge/pus cervix	P26ADISC, PADISC		X
	Discharge vagina	P26BDISC, PBDISC		X
	Erosion or friability cervix	P27AEROS, PAEROS		X
	Erosion or friability vagina	P27BEROS, PBEROS		X
	Non-menstrual bleeding cervix	P28ABLEE, PABLEE		X
	Non-menstrual bleeding vagina	P28ABLEE, PBBLEE		X
	Adnexal tenderness	P29ANNEX, PANNEX		X
	Adnexal mass	P30MASSE, PMASSE		X
	Urethral Discharge	P24DISCH, PDISCH	X	
	Deposit/Poor Hygiene	P25HYGIE, PHYGIE	X	
	Circumsized	P26CIRC, PCIRC	X	

Past Medical History Form	Vaginal discharge	H33VAGIN, HVAGIN		X
	Cystitis/dysuria	H34CYSD, HCYSD	X	X
	Lower abdominal pain	H35APAIN, HAPAIN		X
	Dyspareunia	HDYSPAR		X
	Inguinal Adenopathy	H16ADENO	X	X
	Gonorrhea	H47GONO, HGONO	X	X
	Syphilis	H48SYPH, HSYPH	X	X
	Acute genital ulcer	HACGEUL	X	X
	Chronic/Recurrent genital ulcer	HCHGEUL	X	X
	Ulcer	H49ULCER	X	X
	Urethral discharge	H33URETH, HURETH	X	
Created Variables	Combination of HACGEUL, HCHGEUL, and H49ULCER	ULCESCORE	X	X
	Any Inflammation	ANYINF	X	X
	Any Ulcer	ANYULC	X	X

Appendix B. Composite variables

ANYINF	**ANYULC**
P21AINAD, PAINAD	P23EXGUL, PEXGUL
P21BINAD, PBINAD	P25AULCE, PAULCE
P22INFGE, PINFGE	P25BULCE, PBULCE
P24AINGI, PAINGI	P27AEROS, PAEROS
P24BINGI, PBINGI	P27BEROS, PBEROS
P26ADISC, PADISC	P28ABLEE, PABLEE
P26BDISC, PBDISC	P28BBLEE, PBBLEE
P29ANNEX, PANNEX	H48SYPH, HSYPH
P30MASSE, PMASSE	ULCESCORE
P24DISCH, PDISCH	
H33VAGIN, HVAGIN	
H33URETH, HURETH	
H34CYSD, HCYSD	
H35APAIN, HAPAIN	
H16ADENO	
H47GONO, HGONO	

Appendix C. Key of Variable Coding

Variable	Description	Coding
SEX	Male	M
	Female	F
CJBASE	At month = 0, man HIV-positive, woman HIV-negative	+-
	At month = 0, man HIV-negative, woman HIV-positive	-+
ELISA_RESULT	Raw data from ELISA test for Schistosomiasis	Continuous numeric
RESULTCODE	High positive	1
	Low positive	2
	Negative	3
SEROSTATMAR10	No seroconversion	0
	Linked seroconversion	1
	Unlinked seroconversion	2
	Unknown seroconversion	15