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

Colombe, S.

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CHAPTER 4: IMPACT OF *SCHISTOSOMA* INFECTION ON HIV TRANSMISSION TO SEXUAL PARTNERS

Soledad Colombe[1], James Beard[2], Baltazar Mtenga[3], Peter Lutonja[3], Julius Mngara[3], Claudia J. de Dood[4], Govert J. van Dam[5], Paul L.A.M. Corstjens[4], Samuel Kalluvya[6], Mark Urassa[3], Jim Todd[2,3], Jennifer A. Downs[1,6]

1. Weill Cornell Medicine, USA
2. Department of Population Health, London School of Hygiene and Tropical Medicine, UK
3. National Institute for Medical Research, Mwanza Research Centre, Tanzania
4. Department of Cell and Chemical Biology, Leiden University Medical Center, Netherlands
5. Department of Parasitology, Leiden University Medical Center, Netherlands
6. Department of Medicine, Bugando Medical Centre, Tanzania

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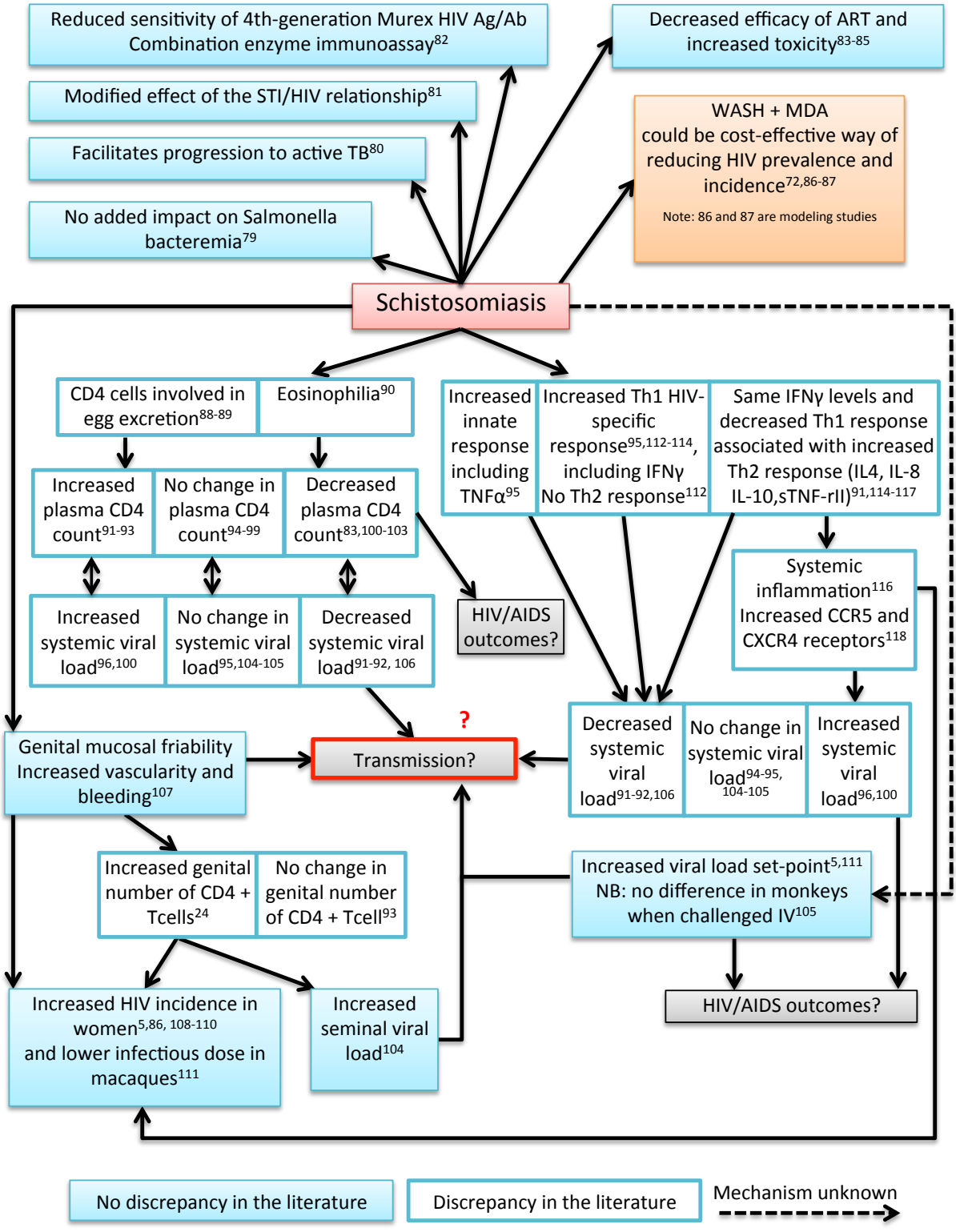
WHERE DOES THIS CHAPTER FIT?



ABSTRACT

Heterosexual transmission is the main driver of the HIV epidemic in Tanzania. Only one estimate of the incidence rate of intra-marital HIV seroconversion in Tanzania has been reported and was derived from data collected between 1991 and 1995. Moreover, little is known about the specific risk factors for intra-marital seroconversion in Tanzania, including infection with *Schistosoma* spp. Improved evidence around factors that increase the risk of HIV transmission to a serodiscordant spouse is needed to develop and improve evidence-based interventions. We sought to investigate the rate of intra-marital HIV seroconversion among HIV sero-discordant couples in Tanzania as well as its associated risk factors, including infection with *Schistosoma* spp.. We identified all HIV positive individuals in the TAZAMA HIV-serosurvey cohort and followed up their serodiscordant spouse from 2006 to 2016. The rate of seroconversion was analyzed by survival analysis using non-parametric regressions with exponential distribution. We found 105 serodiscordant couples, 14 of which had seroconverting spouse. The overall HIV-1 incidence rate among spouses of people with HIV-1 infection was 38.0 per 1000 person/years [22.5-64.1]. Notably, the HIV-1 incidence rate among HIV-1 seronegative male spouse was 6.7[0.9-47.5] per 1000 person/years, compared to 59.3 [34.4-102.1] per 1000 person/years among female spouse. After adjusting the model for schistosome status of the baseline HIV positive individual and sex of the serodiscordant spouse, female spouses had a rate of seroconversion 8.06[1.04-62.60] times higher than male spouses (p=0.046), while schistosome status of the baseline individual was not significant (adjusted hazard ratio=1.17[0.37-3.69], p=0.789). Our study suggests that schistosome infection in HIV-1 infected individuals only slightly affects HIV-1 transmission to that person's spouse. More studies are needed to look at the link between schistosome/HIV-1 co-infection in individuals and HIV-1 transmission to sexual partners, particularly in women.

Keywords: HIV, serodiscordant, intra-marriage transmission, Tanzania, schistosomiasis

INTRODUCTION

Schistosoma sp. and HIV are co-endemic globally and an estimated 6 million individuals are co-infected worldwide[1]. *Schistosoma* sp. infection has been shown to interact with HIV-1 by modifying susceptibility to the virus and impacting AIDS outcome.

Women have both increased odds and increased incidence of HIV-1 infection when *Schistosoma* co-infected[2–7]. Schistosome eggs in the mucosal tissue of the vagina and cervix trigger local physical and immunological changes that have been hypothesized to increase susceptibility to the virus during sexual HIV-1 exposure[8–11]. In addition, schistosome infection may facilitate transmission of HIV-1 to sexual partners. This could occur through exposure to blood or through higher genital tract HIV-1 RNA viral loads in the setting of genital inflammation. Schistosome eggs have been associated with genital mucosal friability and post-coital bleeding in women [12] and a recent small study of men who were co-infected with *S. haematobium* and HIV-1 documented that treatment for *S. haematobium* decreased the HIV-1 RNA viral load in semen[13].

Schistosoma sp. modifies HIV-1 RNA viral load as well. In both men and women, co-infection with *Schistosoma* sp. leads to higher plasma viral load[14–16]. Some studies have also demonstrated that treatment of *Schistosoma mansoni* is associated with a decrease in HIV-1 viral load in individuals with HIV-1-*S. mansoni* co-infection[17,18]. The increase in HIV-1 viral load in individuals co-infected with *Schistosoma* sp. could reflect the ability of schistosome infection to increase HIV-1 transmission to sexual partners[19,20].

HIV-1 RNA viral load set-points have also been found to be higher in both men and women who were infected with schistosomiasis at time of HIV-1 seroconversion[4]. HIV-1 RNA viral load set-points are highly predictive of transmission to sexual partners[21–23]. Finally, infection with *Schistosoma* sp. at time of HIV-1 seroconversion affects HIV-1 survival, with longer survival time and fewer symptoms, likely affecting sexual behavior and thus HIV-1 transmission[24].

We had a unique opportunity to investigate the impact of schistosome-HIV-1 co-infection on the rate of HIV-1 seroconversion within married couples in an ongoing HIV-seroincidence study of 30,000 people in northwest Tanzania. Our goal was to identify all HIV-seroconverters within this cohort within a 10-year time-period and to determine whether there appeared to be an increased rate of HIV transmission or acquisition among those with schistosome infection. We hypothesized that people co-infected by *Schistosoma* sp. and HIV-1 would be twice as likely to transmit HIV-1 to their sexual partners as people infected with HIV-1 alone, even after controlling for sex and sexual behavior.

METHODS

Identification of HIV-1 infected individuals

Our study was conducted within the ongoing TAZAMA project, a community-based longitudinal open HIV-testing cohort in Kisesa, northwest Tanzania, which documents detailed demographic, sexual, and behavioral data and collects dried blood spots (DBS) approximately every three years from a population of ~30,000 individuals. Those wishing to know their HIV status may undergo voluntary HIV testing and counseling on the same day as collection of the DBS. The HIV testing (sero-survey) is nested within a Demographic Surveillance System (DSS) which visits every household in the catchment area approximately every nine months to document household members and relationships. Additional details have been previously described[25]. Details collected from both the DSS and sero-surveys included the start and end dates of sexual relationships with both the spouse with whom they lived and with external sexual partners and the frequency of sexual intercourse.

For this project, we identified all individuals whose DBS tested positive for HIV-1 or who were found to be HIV-1 positive at an HIV testing clinic within the TAZAMA cohort between 2006 and 2013. Throughout the rest of the methods we will refer to these individuals as "baseline individuals" for clarity and brevity.

Identification of serodiscordant spouse and relationship time period

Through the DSS we identified all spouses of baseline individuals and obtained their HIV-1 test results from both the sero-surveys and from HIV tests at other clinics. We excluded couples that were never serodiscordant from the analysis, and couples for which the spouse had HIV-1 seroconverted more than 6 months after either partner reported the end of the relationship. For each couple, we determined the at-risk dates for HIV-1 seroconversion during which they reported being in a sexual relationship with a partner who was HIV-1 positive. We collected demographic and sexual behavior data from the first DSS or sero-survey following the start of the serodiscordant relationship. Sexual behavior data included the number of extra-marital partners, having sex with sex workers, and traveling men. Condoms are rarely used within the context of marriage in Tanzania[26, 27].
We used data from all sero-surveys until the last sero-survey with questions pertaining to the relationship time period. Seroconverters were defined as individuals who had been HIV-1 seronegative in one sero-survey and who were found to be HIV-1 seropositive in a subsequent sero-survey. All DBS available until the date of the spouse potential seroconversion were tested for Schistosoma circulating anodic antigen for both the baseline individual and his or her spouse.

Follow-up

The follow-up period started either from the start of the relationship or from the first positive HIV result for the baseline individual. The follow-up period ended either at the spouse's seroconversion date, or at the end of the relationship, or at the last sero-survey for which a spouse had an available HIV-1 test result and remained HIV-seronegative. The seroconversion date was approximated as the mid-point between the last negative DBS and the first positive test, either at a sero-survey or at another clinic.

Schistosome infection status

We measured schistosome Circulating Anodic Antigen (CAA) in banked DBS to determine schistosome infection status. The CAA test is a genus-specific assay that detects a gut-associated antigen secreted into the host bloodstream by adult schistosome worms. The test does not differentiate between the Schistosoma mansoni and haematobium species present in the Kisesa area of Tanzania. We defined schistosome positivity during the relationship as having at least one positive test for schistosome infection in all DBS available during the follow-up period. Both schistosome positivity as a binary variable and worm load defined as the natural logarithm of CAA were used in the analysis.

Laboratory testing

Dried blood spots - DBS were collected by finger prick onto a Whatman Protein Saver 903 card (GE Healthcare Bio-Sciences, Pittsburgh, PA). DBS cards were dried out of direct sunlight and sealed in a gas-impermeable zip bag with desiccant and humidity indicator. Cards were stored at the National Institute for Medical Research (NIMR) laboratory in Mwanza at -20°C.

HIV-1 testing - Diagnosis of HIV-1 infection was confirmed using a screening and subsequent confirmatory test, as recommended by national HIV guidelines, at each time point. These were: Uniform II Category III Ab test followed by Enzygnost test (sero-surveys 5 and 6), Uniform II Category IV Ab+Ag test followed by Enzygnost test (sero-survey 7), and Determine test followed by Unigold test (sero-survey 8). Samples that were negative at the screening test were reported as negative. Samples that were positive at the screening test were tested with the confirmatory test. If the confirmatory test was negative, the final result was reported as negative. If the confirmatory test was positive, the final result was reported as positive.

Schistosoma *sp. testing* - DBS were tested for schistosome by CAA at Leiden University Medical Center by eluting whole blood from DBS and then concentrating the sample as previously described[28]. A lower limit threshold of 2 pg CAA per mL of eluted blood was used for the assay. 35 individuals had stored serum samples but no DBS samples available for testing and underwent serum CAA testing at NIMR with a lower limit threshold of 30 pg CAA per mL[29]. Samples scoring values above the threshold were designated positive for *Schistosoma* infection.

Statistical analysis

Analysis included all couples as described above. Binary variables were described as proportions and continuous variables were described using median and interquartile range. We assessed differences in baseline characteristics using Chi-square or Fisher's exact test for proportions and the nonparametric equality test for medians.

A survival analysis was conducted to investigate the difference in HIV-1 seroconversion rates between spouse of a baseline individual co-infected versus not co-infected with Schistosoma. The event of interest was defined as HIV-1 seroconversion. Data was censored at the end of the relationship or for loss to follow-up, defined as the last negative sero-survey at which the spouse provided a DBS. The Kaplan-Meyer method was used to compare time to seroconversion between the HIV-serodiscordant spouses of baseline individuals who did and did not have schistosome infection. A non-parametric regression with exponential distribution, adjusted for all significantly different baseline factors as well as biologically sound variables, was used to assess endpoint incidence difference by schistosome infection status. Time-dependent variables characterized at each sero-survey (such as number of extra-marital sex partners, frequency of sex, etc) were defined as representative of the time period following the sero-survey and are called "survey-dependent variables" for the rest of the manuscript.

Variables that were associated with failure at 10% significance were individually included into the model and model goodness-of-fit assessed through step-wise analysis. Based on the results of the analysis, a second analysis was performed after stratifying by sex of the serodiscordant spouse. All analyses were performed in STATA 14.1 (College Station, TX, USA). All results were expressed with 95% confidence intervals (CIs) and statistical significance was set at $P < 0.05$ (two-tailed).

A sensitivity analysis was conducted where schistosome infection was considered a survey-dependent variable. We conducted a second sensitivity analysis in which survey-dependent variables were defined as representative of the time period preceding the sero-survey results. Finally we conducted a third sensitivity analysis in which we excluded all couples for which the baseline individual was on ART.

Ethical considerations

Ethical approval for retrospective and prospective analysis of these data was obtained from Bugando Medical Centre in Mwanza (BREC/001/04/2011), the National Institute for Medical Research in Dar es Salaam (NIMR/HQ/R.8a/Vol.IX/2446), and Weill Cornell Medicine in New York (1108011883). Study participants provided consent during enrollment into the cohort study as per the approved procedures of the TAZAMA project, which included consent for future testing of DBS samples[25].

RESULTS

We identified 1439 baseline individuals who were found to be HIV-1 seropositive at a sero-survey between 2006 and 2012. Of these 554 had at least one spouse registered in the DSS after the time of the baseline individual's first positive test. Among the 554, 289 had at least one spouse who had HIV-1 test results and 105/289 were serodiscordant couples between 2006 and 2015 who met criteria for inclusion in this analysis. From these serodiscordant couples, this yielded 368.8 years of total analysis time at risk and under observation.

63.8% (67/105) of couples had a male baseline individual and a female serodiscordant spouse. An overwhelming proportion of baseline individuals and spouses were of Sukuma ethnicity (97.1% (102/105) and 92.4% (97/105), respectively), Christian (83.8% (88/105) and 92.4% (87/105), respectively), and reported having only one spouse (87.6% (92/105) and 90.5% (95/105), respectively). 52.2% (48/92) of the baseline individuals were schistosome positive. 54.5% (55/101) of the serodiscordant spouses were schistosome positive. All couples were heterosexual. The demographics of the population are presented in **Table 1** as a comparison between the 14 people who HIV-seroconverted during follow-up and the 91 people who did not. Serosurvey-dependent variables are presented in **Table 2**.

Table 1 - Characteristics of the spouse, baseline individual and couple by spouse seroconversion status.

Variable	Non-seroconverters N=91	Seroconverters N=14	p-value
Variables concerning the baseline individual			
Schistosome CAA positivity	51.3% (41/80)	58.3% (7/12)	0.647
Sex (Female)	40.7% (37/91)	7.1% (1/14)	0.016
Education (Received at least one year of formal schooling)	24.4% (22/90)	0.0% (0/14)	0.037
ART intake	12.1% (11/91)	0% (0/14)	0.353
Marital status (Polygamy)	13.2% (12/91)	7.1% (1/14)	1
Age in years at the start of the time period of interest	39[33-45]	44[37-53]	0.125
Variables concerning the serodiscordant spouse			
Schistosome CAA positivity	54.0% (47/87)	57.1% (8/14)	0.828
Sex (Female)	59.3% (54/91)	92.9% (13/14)	0.016
Education (Received at least one year of formal schooling)	42.9% (39/91)	21.4% (3/14)	0.037
Marital status (Polygamy)	12.1% (11/91)	0% (0/14)	0.353
Age in years at the start of the time period of interest	37[31-46]	35.5[32-46]	0.828
Male and circumcised	46.4% (13/28)	--	--
Variables concerning the couple			
Age difference between the baseline individual and his/her spouse	-3[-9;4]	-5[-8;-4]	0.246
Length of the time period of interest (in days)	1029 [691-1882]	1093.5[571-1150.5]	0.228

Table 2 - Results of the univariable analysis for factors associated with HIV-1 seroconversion.

Variable		Person-time (in years)	Number of events	HR [95%CI]	p-value
Variables concerning the baseline individual					
Schistosome CAA positivity	Negative	167.80	5		
	Positive	172.27	7	1.35[0.43-4.24]	0.611
Sex	Male	221.50	13		
	Female	149.43	1	0.11 [0.015-0.87]	0.036
Education	Never attended school	294.91	14		
	Ever attended school	71.01	0	0[0]*	0.992
ART intake	No	318.72	14		
	Yes	50.06	0	0[0]*	0.992
Ln(CAA)#	---	-----	---------	1.18 [0.93-1.49]	0.177
STI symptoms	No	291.31	11		
	Yes	77.46	3	1.03[0.29-3.68]	0.969
Variables concerning the serodiscordant spouse					
Schistosome CAA positivity	Negative	152.33	6		
	Positive	196.75	8	1.03[0.36-2.98]	0.953
Sex	Male	149.43	1		
	Female	221.50	13	8.77[1.15-67.04]	0.036
Education	Never attended school	234.99	11		
	Ever attended school	135.94	3	0.48[0.13-1.72]	0.258
Other risks for HIV#**	No	297.77	14		
	Yes	71.00	0	0[0]*	0.994
Risky sex behavior^#	No	66.43	4		
	Yes	19.15	0	0[0]*	0.994

Ln(CAA) [#]	--	---	---	1.11[0.85-1.44]	0.453
Number of extramarital partners[#]	None	303.95	14		
	One or more	66.97	0	0[0]*	0.994
STI Symptoms[#]	No	285.8	12		
	Yes	82.94	2	0.57[0.13-2.57]	0.468
	Variables concerning the couple				
Age difference between the baseline individual and his/her spouse in years	---	---	---	1.00[0.9991-1.001]	0.734
Sex frequency[#]	Less than once a month	37.22	1		
	Between once a month and once a week	134.64	6	1.66[0.20-13.78]	0.639
	More than once a week	166.50	5	1.12[0.13-9.57]	0.919

**No convergence of the model due to presence of zeros. No conclusion on the association between the variable and seroconversion can be made due to short person-time available. ART was still included in the final model stepwise analysis.*

***Other risks for HIV include incisions and transfusions*

^Risky sex behaviors include having sex with women at bars or with traveling men.

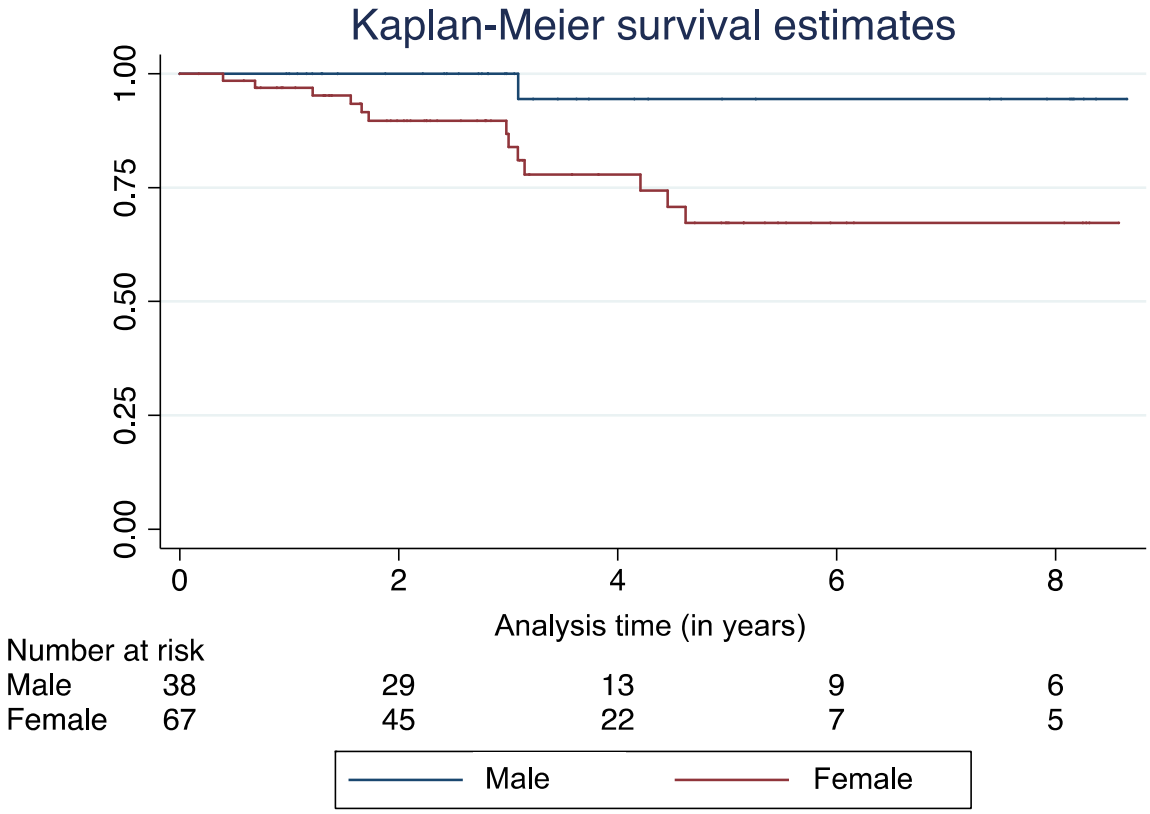
#Survey-dependent variables

14/105 (13.3%) partners HIV-1 seroconverted, and 13 of these were women. The overall HIV-1 incidence rate among spouses of people with HIV-1 infection was 38.0 per 1000 person/years [22.5-64.1]. Notably, the HIV-1 incidence rate among HIV-1 seronegative male spouse was 6.7[0.9-47.5] per 1000 person/years, compared to 59.3 [34.4-102.1] per 1000 person/years among female spouse.

After univariable analysis, schistosome status of the baseline individual was associated with an increase in rate of spouse seroconversion, although not significant (Hazard Ratio (HR)= 1.35[0.43-4.24], p=0.611 for the variable "schistosome positivity", and HR=1.18[0.93-1.49], p=0.177 for the variable ln(CAA+1), as a continuous, survey-dependent, variable). Sex of the serodiscordant partner was the only variable that was significantly associated with HIV-1 seroconversion. Specifically, HIV-1 uninfected female spouses of HIV-1 infected male baseline individuals were found to have higher incidence rates of seroconversion than HIV-1 uninfected male spouses of HIV-1 infected female baseline individuals (HR=8.77, p=0.036). Results of the univariable analyses are presented in **Table 2**.

After stepwise multivariable analysis, sex of the serodiscordant partner was the only variable that yielded a best of fit model, even when forcing the variable "schistosome status of the baseline individual" into the model. After adjusting the model for schistosome status of the baseline individual and sex of the serodiscordant spouse, female spouses had a rate of seroconversion 8.06[1.04-62.60] times higher than male spouses (p=0.046), while schistosome status of the baseline individual was not significant (adjHR=1.17[0.37-3.69], p=0.789). After stratification by sex, schistosome status of the baseline individual was still not significant for female spouses (HR=1.41[0.41-4.83], p=0.582). The Kaplan-Meyer survival curves by spouse sex are presented in **Figure 1**.

Figure 1 - Kaplan-Meier survival estimates for seroconversion by sex of the spouse.
The curve represents the risk of seroconverting over time by sex of the serodiscordant spouse.



All sensitivity analyses led to similar results and are presented in **Table 3**.

Table 3 - Results of the sensitivity analyses.

Sensitivity analysis	Variable	adjHR[95%CI]	p-value
Schistosomiasis as a survey-dependent variable	Schistosome CAA positivity in the baseline individual	2.08[0.61-7.12]	0.24
	Sex of the serodiscordant spouse	7.65[0.98-59.76]	0.052
Excluding ART from the analysis	Schistosome CAA positivity in the baseline individual	1.22[0.39-3.84]	0.74
	Sex of the serodiscordant spouse	8.32[1.07-64.43]	0.043
Survey dependent variables representative of the time period preceding the survey results	Schistosome CAA positivity in the baseline individual	1.96[0.33-11.75]	0.46
	Sex of the serodiscordant spouse	0[0]	0.99

DISCUSSION

In this in-depth study of a community of approximately 30,000 individuals, the intra-marriage HIV-incidence in our study population was overall 19 times the general national HIV-incidence[30]. This effect was largely due to women being highly susceptible to incident HIV infection, yielding an incidence of 60 seroconversions per 1000 person-years in women and only 7 per 1000 person-years in men. This is a greater than eight-fold increase in HIV acquisition in women as compared to men, and far higher than observed elsewhere in Africa. Our results suggest that intra-marriage seroconversion in serodiscordant couples deserves more attention in Tanzania, and that disproportionate transmission from men to women, particularly in the absence of female-controlled HIV-prevention measures, may continue to push the HIV epidemic towards female predominance.

To our knowledge, our study is the first to look at the role of schistosome infection in the transmitting partner on HIV-1 incidence and to give an estimate of the hazard ratio of HIV-transmission from schistosome co-infected transmitting partners compared to non-co-infected transmitting partners. It shows a directional trend towards an increased transmission of HIV-1 from baseline individuals infected with *Schistosom*a spp. . This could be due to genital schistosomiasis caused by both *S. haematobium* and *S. mansoni* in men and women[8, 31]. The local physical damage done to the mucosal barrier might make *Schistosoma*-infected individuals more prone to transmitting HIV during intercourse[12, 32, 33]. In addition, genital schistosomiasis triggers inflammation and increased genital vascularity, which in turn leads to the accumulation of CD4 cells, higher local shedding and facilitated transmission of HIV virions[11, 15, 34, 35].

Notably, despite a wide confidence interval, our point estimate for the increased hazard of HIV transmission is rather small. The fact that CAA also led to a hazard ratio close to 1 does suggest that schistosome positivity of the transmitting partner might play only a small role in transmission of HIV-1. Our previous study looking at the impact of schistosome infection on HIV/AIDS outcomes also showed surprising results of a protective effect of schistosome infection at time of HIV-1 seroconversion on HIV-1 disease progression[24]. Both studies align with the possibility that despite higher viral load set points in schistosome positive individuals at time of HIV-1 seroconversion[4, 15], there might be some immunological long term changes that decrease the viral load, possibly to lower values than seen in those with HIV infection alone. Several other studies support this possibility, documenting no difference in viral load among co-infected versus non- co-infected people[13, 36, 37], transitory higher viral loads after praziquantel treatment[38, 39], or lower viral loads in co-infected individuals[40].

It is also possible that the clinical effect is not as strong as expected due to the schistosome species involved. While the eggs of both *S. mansoni* and *S. haematobium* can lead to genital lesions, *S. mansoni* eggs accumulate in genital tissue at lower concentrations and therefore are less likely to create such lesions[8, 41, 42]. Our Kisesa cohort is more likely to be infected with *S. mansoni* than *S. haematobium*[2, 6, 28, 43]. It is thus possible that despite being infected with schistosomes, the baseline individuals were infected with *S. mansoni* and had low

prevalence of genital schistosomiasis and/or a lower density of egg-induced local changes that may facilitate HIV transmission.
More surprisingly, the schistosome status of the receiving partner did not appear to have a major impact on HIV-seroconversion here[2–5]. It is biologically possible that sex of the receiving partner was so strongly associated with HIV-1 seroconversion[44] that any other risk factor for transmission became relatively inconsequential. Women are indeed more at risk of HIV-1 infection than men, as widely recognized in the literature[44, 45].

The usual risk factors for HIV-1 seroconversion within marriage, such as sex frequency, count of extra-marital sex partners and age difference with the spouse, were not significant within our cohort either[45, 46]. It is possible that this was due to the higher age of our study participants than has been observed in most other serodiscordant couple studies[47]. In these older adults, traditional HIV risk factors may be less important. Our results are consistent with the well-described finding that, per sex act, women are indeed more at risk of HIV-1 infection than men,[44] likely due to a larger surface area of the vagina and the ability of the virus to pass easily through the cells of the vaginal lining. Too few partners were on ART to assess the role of ART on seroconversion in our study, although the finding that no partners of baseline individuals on ART seroconverted is consistent with other studies that showed lower incidence of HIV when HIV positive partner was on ART.

Our results are to be interpreted in light of some limitations. Our study had only enough power (80%) to detect significance for a hazard ratio of 3.7 or above. To detect significance for a hazard ratio of 1.5, we would have needed approximately 2250 person-years in each schistosome infection group, or a total of 4500 person-years, which is more than 10 times the follow-up of our study. As a result, we cannot conclude on the statistical significance of our findings regarding schistosome infection, and our confidence intervals are large. More studies with a larger number of HIV-1 serodiscordant couples are needed to obtain a better estimate of the hazard ratio of HIV-transmission from schistosome positive/HIV-1 positive individuals compared to from schistosome negative/HIV-1 positive individuals. In addition, studies conducted in regions with higher prevalence of *S. haematobium* infection may more easily detect a significant difference in hazard ratios for those with versus without infection.

We were unable to test for viral loads, or additional immunologic markers that might provide insight into the reasons for our observations, due to insufficient quantity of blood in DBS. We were also unable to perform phylogenetic analyses that would have permitted determination of whether the HIV-seroconverting partner had been infected from a partner outside of the marriage. Partners might also under or overestimate the number of extra-marital sexual partners based on their gender[48]. Despite those limitations, our finding that all sensitivity analyses gave the same results strengthens confidence in the quality and accuracy of our analysis.

In conclusion, our study suggests that schistosome infection in HIV-1 infected individuals only slightly affects HIV-1 transmission to that person's spouse. More studies are needed to look at the link between schistosome/HIV-1 co-infection in individuals and HIV-1 transmission to sexual partners, particularly in women.

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