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Schistosoma mansoni and HIV acquisition in fishing communities of Lake Victoria, Uganda: a nested case–control study

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Abstract

OBJECTIVE It has been suggested that Schistosoma mansoni, which is endemic in African fishing communities, might increase susceptibility to human immunodeficiency virus (HIV) acquisition. If confirmed, this would be of great public health importance in these high HIV-risk communities. This study was undertaken to determine whether S. mansoni infection is a risk factor for HIV infection among the fishing communities of Lake Victoria, Uganda. We conducted a matched case–control study, nested within a prospective HIV incidence cohort, including 50 HIV seroconverters (cases) and 150 controls during 2009-2011.

METHODS S. mansoni infection prior to HIV seroconversion was determined by measuring serum circulating anodic antigen (CAA) in stored serum. HIV testing was carried out using the Determine rapid test and infection confirmed by enzyme-linked immunosorbent assays.

RESULTS About 49% of cases and 52% of controls had S. mansoni infection prior to HIV seroconversion (or at the time of a similar study visit, for controls): odds ratio, adjusting for ethnicity, religion, marital status, education, occupation, frequency of alcohol consumption in previous 3 months, number of sexual partners while drunk, duration of stay in the community, and history of schistosomiasis treatment in the past 2 years was 1.23 (95% CI 0.3–5.7) P = 0.79. S. mansoni infections were chronic (with little change in status between enrolment and HIV seroconversion), and there was no difference in median CAA concentration between cases and controls.

CONCLUSIONS These results do not support the hypothesis that S. mansoni infection promotes HIV acquisition.

keywords Schistosoma mansoni, circulating anodic antigen, HIV, susceptibility, fishing communities, Uganda

Introduction

Fishing communities in Uganda are disproportionately affected by HIV infection with incidence and prevalence four times the national average, or more [1, 2]. These figures are attributed to high-risk sexual behaviour and limited access to health services [1, 2]. Schistosoma mansoni, a chronic, immunomodulating helminth infection, highly prevalent in fishing communities, may be an additional risk factor in these communities [3]. It is estimated that over 16 million Ugandans are at risk of schistosomiasis and more than 4 million infected [4]. S. haematobium is a potential risk factor for HIV acquisition, because it directly affects the genital mucosa [5]. S. mansoni infection has also been linked to increased risk of acquiring simian–human immunodeficiency virus (SHIV) and HIV in primate and human studies, respectively [3, 6, 7]. Proposed systemic
immunological mechanisms for this include up-regulation of HIV co-receptors and of Th2 T cells in which HIV may replicate more efficiently [3, 8]. If confirmed, this would imply that control of S. mansoni, as well as of S. haematobium, could contribute to reducing the HIV reservoir among fishing communities and hence spread to the general population.

We conducted a matched case–control study, nested within a prospective HIV incidence study, to determine whether S. mansoni infection promotes HIV acquisition in Ugandan fishing communities.

**Methods**

The study was conducted among five fishing communities on Lake Victoria, Uganda. This was a matched case–control study nested within a prospective HIV incidence cohort of 1000 individuals (males and females, aged 13–49 years) recruited in 2009, and followed for 18 months [2].

Within the prospective cohort, data on risk factors for HIV acquisition, and serum samples for HIV testing and storage, were obtained at enrolment and at six-monthly follow-up intervals. HIV testing was carried out using Determine rapid tests (Abbott Laboratories, Chicago, IL, USA), confirmed by enzyme-linked immunosorbent assays (ELISA; Vironostika HIV Uni-Form II plus 0 microelisa system, Biomerieux, Boxtel, Netherlands and Murex HIV-1.2.0, Murex, Biotech Limited, Dartford, UK), with Western blot (Calypte Biomedical Corporation, Rockville, Maryland, USA) if ELISA results were indeterminate. During follow-up, 59 individuals became HIV-1 positive [2].

All cases available and willing to participate were selected. Fifty HIV seroconverters were included as cases, with 150 controls selected from those who remained HIV negative. For every case, three controls matched on age, sex and community of residence were randomly selected using log likelihood ratio test. If the effect measure changed by 10% or more, the covariate was assessed for confounding by adding them individually to the multivariable model and tested for goodness of fit using log likelihood ratio test. If the S. mansoni–HIV effect measure changed by 10% or more, the covariate was retained in the final model.

Baseline age, sex and community of residence were matching factors. Matched conditional logistic regression was used to investigate univariable associations between HIV seroconversion and other demographic factors (marital status, education status, occupation, religion and behavioural risk factors; being away from home for at least two nights in the previous month; frequency of alcohol use; and number of sexual partners while under the influence of alcohol or drugs during the previous 3 months) and to investigate risk factors for S. mansoni infection (duration of stay in fishing community and history of treatment for schistosomiasis in the preceding 2 years). Covariates considered a priori to be potential confounders (marital status, religion and ethnicity) and those associated with S. mansoni at $P \leq 0.1$ were assessed for confounding by adding them individually to the multivariable model and tested for goodness of fit using log likelihood ratio test. The S. mansoni–HIV effect measure changed by 10% or more, the covariate was retained in the final model.

The study was approved by Uganda Virus Research Institute Science and Ethics Committee (FWA number...
Results

Socio-demographic characteristics

Characteristics of the cohort have been described [2]. Among the 200 participants enrolled into this nested study, median age was 25 years (IQR 22–30 years). The highest proportion was males (56%), Roman Catholics (41%), married (63%), with incomplete primary-level education (41%) and worked in fishing-related jobs (66%).

Schistosomiasis

The majority of participants (76%) had not received *S. mansoni* (praziquantel) treatment in the previous 2 years. Determination of *S. mansoni* infection status was based on serum CAA.

Half (51%) had *S. mansoni* infection at cohort enrolment, 48%, 52% and 52% at 6, 12 and 18 months, respectively. There was 96% agreement between the CAA status at enrolment and CAA status at the pre-seroconversion (or equivalent control) time point \( (k=0.91, P < 0.001) \). Compared to the stool results, serum CAA had a sensitivity of 84%, specificity 92% and a positive predictive value of 94%. Intensity of *S. mansoni* infection was assessed in 79 samples examined by the Kato–Katz method. Of those infected, 61% had light, 29% moderate and 10% heavy infections.

*S. mansoni* prevalence was highest in the 25–29 years age group, [66%, \( P < 0.001 \)], higher among males than females [75% vs. 21%, \( P < 0.001 \)] and increased with declining education level \( (P = 0.035) \). Almost all participants who were engaged in fishing had *S. mansoni* infection [54/58, 93%; \( P < 0.001 \) compared to other occupational groups]. Being away from home frequently \( (P = 0.009) \) and long-term residence in the fishing community \( (P = 0.012) \) were associated with *S. mansoni* infection.

Association between *S. mansoni* infection and HIV acquisition

There was no difference between cases who acquired HIV infection, and controls who had not, in *S. mansoni* infection status based on CAA results at the preceding visit: 49% of cases and 52% of controls had *S. mansoni* infection [OR 0.83 (95% CI 0.39–1.77) \( P = 0.63 \)]. The result was similar after adjusting for ethnicity, religion, marital status, education, occupation, frequency of alcohol consumption in previous 3 months, number of sexual partners while drunk, duration of stay in the community and history of schistosomiasis treatment (praziquantel) in the past 2 years \( [\text{aOR} 1.23 (95\% \text{ CI} 0.3–5.7) P = 0.79] \).

There was also no difference in median CAA concentration between cases and controls: 2906 and 6530 pg/ml, respectively \( (P = 0.16) \).

Factors associated with HIV acquisition in the case–control study were similar to those previously reported for the whole cohort: occupation, religion, frequency of alcohol consumption [2]; Table 1. In addition, not having taken praziquantel treatment for *Schistosomiasis* in the last 2 years was associated with HIV acquisition \( [\text{OR} 8.25 (95\% \text{ CI} 1.3–51.1) P = 0.03] \).

Discussion and conclusion

We found that *S. mansoni* infection was not associated with HIV acquisition among adults in Lake Victoria fishing villages. As opposed to *S. haematobium*, *S. mansoni* is unlikely to cause genital lesions. This result therefore suggests that systemic immune modulation by *S. mansoni* does not significantly increase susceptibility to HIV acquisition.

By contrast, an experiment in macaques showed increased susceptibility to a simian–human immunodeficiency virus (SHIV) infection in *S. mansoni*-infected animals [6]. However, the macaque schistosome infections were recent at the time of SHIV exposure (7 weeks), egg counts were equivalent to moderate to heavy human infections, and the virus was administered rectally, encountering tissues directly affected by *S. mansoni* egg-induced lesions. By contrast, our human participants had chronic *S. mansoni* infections (few had recently been treated, and status had not changed between enrolment and the pre-seroconversion visit), many had light infections, and HIV infection would usually have occurred via the genital mucosa. Indeed, in a second macaque study, *S. mansoni* infection did not increase susceptibility when SHIV was administered intravenously, implying that route of infection was critical [7].

Cross-sectional studies have provided conflicting evidence regarding HIV–*S. mansoni* associations. A survey focussing on women on the Tanzanian shores of Lake Victoria using serum CAA to determine *Schistosoma* infection found a positive association with HIV infection,
and higher CAA levels among HIV-positive women [12].
However, the number of HIV-infected women was small (21 of 345) so confidence intervals were wide, the prevalence of HIV infection was approximately 4.5 times lower than in the Ugandan fishing villages, and the catchment area extended to 25 km from the lake, so that a wide array of potential confounding factors in terms of environment and lifestyle may have come into play. A low prevalence of S. haematobium (3%) might also have contributed.

The cross-sectional design of the Tanzanian study means that the sequence in which the infections occurred is unknown. An earlier study showed no positive association between S. mansoni and HIV infection and highlighted differences in occupation and origin of members of the population affected by the two infections [13].
Given the lack of association we observed between *S. mansoni* infection and HIV acquisition, we were surprised to observe a strong association between HIV infection and lack of praziquantel treatment in the last 2 years. It is difficult to draw robust conclusions from self-reported behaviour. We presume this may be a marker for poor health-seeking behaviour, rather than for a biological process. Participants were not examined or treated for *S. mansoni* by the research team during the cohort study.

Strengths of our study were prospective sample collection, recruitment restricted to a relatively uniform (fishing village) community, and matching and adjustment for potential confounders. The CAA assay allowed assessment of *S. mansoni* infection status at enrolment and immediately prior to HIV seroconversion, demonstrating chronicity of infection, and avoided potential concerns about differential egg excretion among HIV-positive and HIV-negative people [14]. Although it can be difficult to assess causality in case–control studies, the prospective design of our cohort did allow us to assess *Schistosomiasis* status prior to HIV acquisition – an important improvement over studies with a cross-sectional design.

While there are many potential benefits of *S. mansoni* control in heavily infected communities, our results suggest that an impact on HIV transmission is not one of them.

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