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# Prevalence and intensity of *Schistosoma mansoni* infection in pediatric populations on antiretroviral therapy in north-western Tanzania: a cross-sectional study

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## ABSTRACT

**Background** In areas where HIV and intestinal schistosomiasis are highly endemic, co-infections of the two diseases in a single human host are frequent. Evidence in adult populations indicates that HIV and intestinal schistosomiasis are associated with negative health impacts. However, the topic of HIV and schistosomiasis in paediatric populations has received little attention. The present study determined the prevalence and intensity of *Schistosoma mansoni* infection in a paediatric population on antiretroviral therapy (ART) in north-western Tanzania.

**Design, settings and participants** A cross-sectional study was conducted among HIV-infected children aged 1–16 years on ART attending a Care and Treatment Clinic at Ukerewe Designated District Hospital, north-western Tanzania.

**Main outcome measures** Single stool and urine samples were collected and screened for *S. mansoni* eggs and circulating cathodic antigen (CCA), using the Kato-Katz (KK) technique and point-of-care CCA (POC-CCA) rapid urine test, respectively.

**Results** A total of 134 children with a median age of 10 years (IQR 7–12 years) participated in the study. Of these, 44.8% (60/134) and 55.2% (74/134) were female and male, respectively. The overall prevalence of *S. mansoni* based on the KK technique and POC-CCA rapid test were 10.7% (95% CI 5.9% to 18.4%) and 33.8% (95% CI 26.2% to 42.4%), respectively. The overall geometrical mean eggs per gram of faeces was 293.9 GM-epg (95% CI 123.3 to 700.9). A small proportion of the children had moderate (4.9%, 5/103) and heavy (3.8%, 4/103) intensity of infection.

**Conclusion** Paediatric populations on ART are co-infected with *S. mansoni* infection. Screening and treatment of intestinal schistosomiasis at initiation of ART is recommended to reduce the risk of developing hepatosplenic disease, schistosomiasis-related immune reconstitution inflammatory syndrome and the possible adverse effect of schistosomiasis on outcome of ART.

## BACKGROUND

Schistosomiasis, caused either by *Schistosoma mansoni* or *Schistosoma haematobium,* is

### Strength and limitations of the study

► The study provides for the first time data on *Schistosoma mansoni* infection in HIV-infected children on antiretroviral treatment and forms a base for further studies.
► Purposive sampling and cross-sectional methods were used and the results thus limit the generalisability of the findings to other children on ART.
► Some of the collected data for this study are subject to recall bias and the study was unable to collect clinical data of the study participants which would allow assessment of the factors associated with *S. mansoni* infection in the study group.

among the most widespread infections in sub-Saharan Africa.[1 2] An estimated 93% of the approximately 290 million individuals infected with schistosomes lives in sub-Saharan Africa.[3 4] Approximately 20% of the infected population is preschool children.[5] Contrary to HIV infection, congenital transmission of schistosomiasis does not occur, however, in high transmission areas, passive and active transmission of the disease occurs even during infancy.[6 7] Unfortunately, infants and preschool children (1–5 years) have poor access to deworming and are not part of the annual mass drug administration programme, which only targets school children aged between 6 years and 17 years[5 6]. Because of this, by the time they start their primary school education, infants may have already developed schistosomiasis-related morbidities.[6] Available evidence indicates that preschool and school children carry the largest burden of the disease.[5–7]

The HIV and AIDS report of 2018 indicates that globally 36.9 million (range 31.1–43.9 million) people were living with HIV in 2017[8] and 1.8 million (range 1.4–2.4 million)

became newly infected with HIV in the same period.[8] Nearly 1000 new cases of paediatric HIV infection are recorded everyday[8] and 1.8 million (range 1.3–2.4 million) children aged <15 years have HIV/AIDS.[8] Mainly individual behaviours, including commercial sex work, concurrent or multiple partners, number of lifetime sexual partners, history of active or passive sexually transmitted diseases, and lack of male circumcision are risk factors for HIV transmission.[9] It is worthwhile to note that HIV infection in infants and young children is mainly transmitted vertically.[10] The current recommended intervention against HIV-related diseases focuses on the use of antiretroviral therapy (ART) offered in Care and Treatment Clinics (CTCs).[10]

Because of the co-distribution of HIV and intestinal schistosomiasis in sub-Saharan Africa, co-infection in a single human host does occur.[11–13] The paediatric population is not an exception; depending on the geographical location, it remains at high risk of being co-infected with HIV and *S. mansoni* from the early years of life.[14] For example, children living in fishing communities in East Africa, where HIV and *S. mansoni* are highly endemic, remain at high risk of being co-infected.[11] The immunological interactions between HIV and *S. mansoni* and their synergistic effects in exacerbating the infection caused by each other within a single human host or animal model have been reviewed elsewhere.[15] However, the health effects of HIV and *S. mansoni* in paediatric populations have received little attention. Perhaps, a potential detrimental synergy of co-infection of HIV and *S. mansoni* in this age group could be severe hepatosplenic disease, a disorder that was thought for many years to occur mainly in adult individuals.[16] Furthermore, in paediatric populations starting or on ART, HIV and *S. mansoni*, co-infection could be associated with poor ART outcomes as measured in terms of viral load suppression and CD4$^+$ increase.[12]

The WHO promotes multidisease approaches for research and operational control, however, to date a platform for control of HIV and schistosomiasis does not exist.[17] This could partly explain the paucity of information on HIV and schistosomiasis in paediatric populations.[14] In addition, there are multiple ethical challenges to including screening of HIV infection in school-based schistosomiasis surveys. Understanding the paucity of data on HIV and *S. mansoni* co-infection in paediatric populations and taking one step forward on this topic, we conducted a cross-sectional survey among a paediatric population on ART attending a single CTC in an intestinal schistosomiasis-endemic area of north-western Tanzania. The primary objective was to understand the prevalence and intensity of *S. mansoni* in this group.

## METHODOLOGY
### Study area
The study was conducted at Ukerewe district, which is an island on Lake Victoria, in north-western Tanzania. Specifically, the study was conducted at a CTC of the Ukerewe Designated District Hospital. The CTC is responsible for diagnosis of HIV and initiation of ART for children and adults. The clinic runs specific days for paediatric populations, with Saturdays reserved for paediatric populations to allow children who are attending school on week days to access treatment and undergo clinical assessment. Children visit the CTC together with their parents or guardians.

Ukerewe district is located in an *S. mansoni*-endemic region and previous studies have reported a high prevalence of the infection and its associated morbidities both in children and adults.[7 18] Kardorff *et al* recorded a prevalence 86.3% of *S. mansoni* among children and adults in four villages of Ukerewe district.[19] Our recent study has noted a high prevalence (80%) and intensity of *S. mansoni* infection among preschool-aged children (1–5 years).[7] The main approach for control of intestinal schistosomiasis in this district is through mass drug administration campaigns which only target school children.[2] The overall prevalence of HIV infection in the district is 3.5%.[20]

### Study design, study population, sample size and sampling procedures
A descriptive cross-sectional study was conducted between July and August 2017 among children aged 1–16 years attending the CTC at Ukerewe Designated District Hospital, in north-western Tanzania. By the time this study was conducted, the CTC had registered 150 children and the study aimed to include all the registered children. Children were recruited serially for six consecutive Saturdays and a total of 134 children participated in the study.

## DATA COLLECTION
### Questionnaire
A questionnaire was used to collect demographic information (age, sex) and clinical data on CD4$^+$ counts while booking at the CTC the first time. The questionnaire also collected information on water contact behaviours of the children and their deworming history.

### Parasitological screening for *S. mansoni* infection
A single stool sample was collected from each participating child using a labelled stool container and four Kato-Katz (KK) slides were prepared from each collected stool sample using a template of 41.7 mg (Vestergaard Frandsen, Lausanne, Switzerland).[21] All prepared slides were examined after 24 hours for presence of *S. mansoni* eggs by two independent laboratory technicians experienced in the KK technique. For quality control, 10% of the negative and positive slides were re-examined by a reference laboratory technician.

### Screening for circulating cathodic antigen using the circulating cathodic antigen test
A single urine sample was collected in a labelled container from each participant and tested for the presence of circulating cathodic antigen (CCA) using point-of-care (POC)-CCA tests following the manufacturer's

instructions (batch number 33800).[22] All trace results were considered positive. All laboratory technicians involved in CCA testing were blinded to the KK parasitological and HIV-1 results of the study participants.

## Patient and public involvement

Patients/participants did not participate in the design and conception of the proposed study. In addition, none of the patients/participants were asked to advise on the interpretation or writing of any section of this work. The result of the diagnostic test was immediately made available to the participants after diagnosis.

## Data analysis

Data analysis was performed using Stata V.15 (Stata Statistical Software, StataCorp, College Station, Texas, USA). Numbers and percentages were used to describe categorical variables. Comparison of either proportions or categorical variables was done using $\chi^2$ or Fisher's exact test, where appropriate. For continuous variables descriptive statistics were reported as means with SD for normally distributed variables and medians with IQRs for variables that were not normally distributed. The arithmetic mean of *S. mansoni* egg counts for each participant was calculated from the counts of four KK thick smears and multiplied by 24 to obtain individual eggs per gram of faeces (epg). Geometrical mean (GM)-epg was calculated as the antilog of the mean of the transformed eggs counts. Intensity of infection was categorised according to WHO criteria as: 1–99 epg, 100–399 epg, ≥400 epg defined as low, moderate and heavy intensities of infection, respectively.

## Ethical considerations

The study received further permission from the district administrative and medical departments. Kiswahili-translated informed consent forms were used to obtain parents'/guardians' consent for all participating children before recruitment. Informed assent forms were prepared for children aged 8–16 years, and a social scientist was responsible for informing children about the study objectives and why they were requested to participate. All the sections of the assent form were read and explained to the children individually. Confidentiality of the information collected was maintained throughout the study. All study participants infected with *S. mansoni* were treated with praziquantel (40 mg/kg) according to WHO guidelines.

## RESULTS

A total of 134 children aged 1–16 years, 44.8% (60/134) female and 55.2% (74/134) male, participated in this study (table 1). The median age of the study participants was 10 years (IQR 7–12 years). Of these children, 61.2% (82/134) reported having received deworming (against schistosomiasis) at least once and 38.8% (52/134) had no deworming history. Almost, 50% of the children reported having a history of water contact, the main reason for which was swimming in Lake Victoria.

**Table 1** Age and sex distributions of children on antiretroviral therapy

| Sex | Age groups (in years) | | |
| --- | --- | --- | --- |
| | 1–5 | 6–10 | 11–16 |
| Female | 13 (65%) | 29 (54.7%) | 32 (52.5%) |
| Male | 7 (35%) | 24 (45.3%) | 29 (47.5%) |
| Total | 20 | 53 | 61 |

## Historical CD4$^+$ cell counts

Historical CD4$^+$ cell counts were collected from study participants' medical files at the health facility. Of the children recruited in the study, at first booking at the CTC, 105 children had their CD4$^+$ cell counts checked before initiation of ART and the mean CD4$^+$ cell count was 806.50±469.75 cells/µL. At 6 months, only 69 children were checked for their CD4$^+$ cell count level and the mean CD4$^+$ cell count was 788.01±462.52 cells/µL. At 12 months, CD4$^+$ cell count records were available only for 30 children and the mean CD4$^+$ cell count was 833.13±333.01 cells/µL. For ART, the majority of the children were on a combination of Zidovudine (AZT) + Lamivudine (3TC) + Nevirapine (91/134, 67.9%), and 15.7% (21/134) were on a combination of AZT +3TC+Lopinavir. The remaining were using another drug combination.

## Prevalence and intensity of *S. mansoni* infection
### Based on the POC-CCA test

Based on the POC-CCA test, the overall prevalence of *S. mansoni* was 33.8% (95% CI 26.2% to 42.4%). In relation to sex, 42.2% (19/45) of girls and 57.8% (26/45) of boys had *S. mansoni* infection ($\chi^2$=0.2295, p=0.63). In relation to age, though the age groups 6–10 years (39.6%) and 11–16 years (31.7%) had higher prevalence, the difference was not statistically significant ($\chi^2$=1.6164, p=0.45) (table 2).

### Based on the KK technique

Results for the KK technique were available for 103 children who managed to submit a single stool sample on the examination day. The arithmetic mean egg count was 0.11±0.31 epg and the overall prevalence of *S. mansoni* infection was 10.7% (95% CI 5.9% to 18.4%). The prevalence of *S. mansoni* infection in relation to age groups is shown in table 2. The overall GM-epg was 293.9 GM-epg (95% CI 123.3 to 700.9). Majority of the children had low intensity of infection (91.3%, 94/103). A small proportion of the children had moderate (4.9%, 5/103) and heavy (3.8%,4/103) intensity of infection.

## DISCUSSION

In general, findings indicate that *S. mansoni* is present among children on ART in schistosomiasis-endemic areas. In the same geographical area, high prevalence of *S. mansoni* among preschool-aged[7] and school-aged children has been reported.[18] Our previous community-based

**Table 2** Prevalence of *S. mansoni* infection based on the Kato-Katz technique and point-of-care circulating cathodic antigen test categorised by age and sex

| Variables | Kato-Katz technique | | χ² or Fisher's exact test | Point-of-care circulating cathode antigen tests | | χ² or Fisher's exact test |
|---|---|---|---|---|---|---|
| | Negative n (%) | Positive n (%) | | Negative n (%) | Positive n (%) | |
| Sex | | | | | | |
| Female | 42 (93.3) | 3 (6.7) | Exact=0.34 | 41 (68.3) | 19 (31.7) | χ²=0.2295, p=0.63 |
| Male | 50 (86.2) | 8 (13.8) | | 47 (64.4) | 26 (35.6) | |
| Age groups (in years) | | | | | | |
| 1–5 | 13 (81.3) | 3 (18.7) | Exact=0.34 | 15 (75) | 5 (25) | χ²=1.6164, p=0.45 |
| 6–10 | 39 (97.5) | 1 (2.5) | | 32 (60.4) | 21 (39.6) | |
| 11–16 | 40 (85.1) | 7 (14.9) | | 41 (68.3) | 19 (31.7) | |

study in the same area among preschool-aged children recorded a prevalence of 44.4% using the KK technique and 80.1% using the POC-CCA rapid test.[7] Based on the KK technique, the overall prevalence of *S. mansoni* in school-aged children was 60.4% in Nansio island and 64.3% in Ukara island.[18 23] In relation to intensity of *S. mansoni* infection, the majority of the infected children had low intensity of infection and a proportion had moderate to heavy intensity of infection. This observation is common in schistosomiasis-endemic areas.[7 18] Of concern is heavy intensity of infection seen in the young age groups left out of antischistosomiasis treatment as per the current mass drug administration policy.[5] These children may end up developing hepatosplenic morbidities associated with *S. mansoni* infection by the time they are old enough to enter school and participate in mass administration programmes.[24] Thus, there is a need to positively respond to this unmet need if schistosomiasis elimination remains a priority agenda of the WHO. Infants and school-aged children should be included in the mass drug administration programme.[5 25]

Based on the KK technique, the prevalence of *S. mansoni* infection was very low in this age group, compared with the what has been recorded by previous studies in the same age group.[7 18] HIV infection has been known to affect excretion efficiencies of *S. mansoni* eggs in co-infected individuals.[26–28] This results in retention of *S. mansoni* eggs in the host's affected organs, especially the liver.[27 29] This potentially affects the performance of a diagnostic test which depends on detection of the parasite eggs, especially the KK technique.[30] This can partly explain the low prevalence of *S. mansoni* based on the eggs detection technique compared with the antigen-based technique in the current study population. It is worthwhile to note that the current study population was on ART, the effect of which increases CD4⁺ T lymphocyte cells. These are immune cells responsible for the efficiency of excretion of eggs in human hosts. Thus, the interpretation of low prevalence of *S. mansoni* based on detection of eggs observed in the present study population needs to be interpreted with caution.

In the same line, effectiveness and efficacy of praziquantel treatment depends on intact immune responses.[29 31] In animal models, immunodeficient mice infected with *S. mansoni* had decreased parasitological cure rates.[27 28 32] By contrast, studies in HIV-infected adult individuals have concluded that HIV immune suppression does not affect the efficacy and effectiveness of praziquantel treatment.[32 33] It is important to note that, in adult individuals, schistosomiasis precedes HIV infections and the immune suppression caused by HIV may not affect the already developed antischistosomiasis-related immunity. In children, HIV infection precedes schistosomiasis and this may present a different immunological picture which may have profound effects on the effectiveness of praziquantel treatment. More research will be needed in this topic.

The main concern from our findings is the high prevalence of *S. mansoni* infection among children receiving ART in a single health facility located in schistosomiasis-endemic areas. The immunological interactions of HIV and schistosomiasis co-infection in paediatric populations have received little attention.[14] The immunological interactions of HIV and intestinal schistosomiasis and its health effects in adults and animal models has been reviewed elsewhere.[15] In adult individuals, HIV infection was associated with reduced excretion of *S. mansoni*[26] and individuals co-infected with HIV and schistosomiasis had an extraenlarged left hepatic lobe,[16] indicating that HIV and *S. mansoni* co-infection could be associated with severe hepatosplenic disease.[16] There is no evidence of this observation among children; however, immune dysregulation relating to HIV infection preceding the onset of intestinal schistosomiasis-related hepatosplenic disease could result in more cellular damage of the liver.[34] To date, there is no evidence of the role of HIV infection on the efficiency of excretion of eggs in infants and preschool children. Epidemiological studies have shown that infants and preschool children excrete few eggs as compared with other age groups.[7 24] Development of immunity with increased age and exposure to *S. mansoni* infection may partly explain this observation,[35] but the

role of diseases associated with immune deficiencies such as HIV, which impairs efficient egg excretion, should be considered. This has a significant impact on the parasitological diagnosis of *S. mansoni* infection which depends on detection of excreted parasite eggs.[13]

For the current study group, another concern is the effects of *S. mansoni* on immune responses following initiation of ART. In HIV-infected adults, the odds of developing immunological failure following initiation of ART was four times greater in individuals with *S. mansoni* co-infection.[12] In addition, *S. mansoni* infected individuals had significantly lower CD4$^+$ cell counts increase on ART than *S. mansoni* uninfected individuals.[11] Partly, the immunological alterations caused by schistosomiasis in Th$_2$ CD4$^+$ lymphocyte subsets can explain the impaired response to ART. On the other hand, evidence is emerging on the association between immune reconstitution inflammatory syndrome (IRIS) and *S. mansoni* infection in adult individuals on ART.[36–39] IRIS is mainly characterised by acute inflammatory responses due to chronic infection such as intestinal schistosomiasis.[37 38] IRIS is mainly accompanied by a stage of immunosuppression, with the immune system recovering with a response to previous chronic infection which results in a heightened inflammatory response that makes the symptoms of chronic infection worse.[39 40] IRIS is thought to complicate the desired outcome of ART.[37] Although not yet studied in children, these observations may have significant implications for ART management among HIV-infected paediatric populations living in schistosomiasis-endemic areas. In clinical practice, these observations highlight the need for implementation of routine screening of schistosomiasis at ART initiation.[41] In paediatric populations, the use of antigen-based rapid tests such as the POC-CCA test is recommended because of its high sensitivity.[30] It is worth noting that more research is needed on this topic in paediatric populations.

## Limitations

This study has some limitations. The cross-sectional study design did not allow us to answer some of the questions raised in the above sections. Using this design, for the first time, we were able to describe the prevalence of *S. mansoni* infection in paediatric populations on ART in schistosomiasis-endemic areas. In addition, the use of a single health facility may limit the generalisability and external validity of our findings. Furthermore, the study collected only retrospective clinical data which were available in the patients' files and no ultrasound data were collected from the study participants. Lastly, because of the fact that this was a descriptive cross-sectional survey, no comparison group was needed.

## CONCLUSION

Our descriptive cross-sectional survey has shown that approximately a third of paediatric patients on ART who live in an *S. mansoni*-endemic area are co-infected with *S.* *mansoni.* The largest proportion of children on ART had a low intensity of infection and a small proportion had moderate to heavy intensity of infection. Screening and treatment of intestinal schistosomiasis at initiation of ART is recommended to reduce the risk of developing hepatosplenic disease and the detrimental effects of schistosomiasis on the outcome of ART.

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