MAJOR ARTICLE

Schistosomiasis and HIV-1 Infection in Rural Zimbabwe: Implications of Coinfection for Excretion of Eggs

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Background. Stunted development and reduced fecundity of *Schistosoma* parasites in immunodeficient mice and the impaired ability of human immunodeficiency virus 1 (HIV-1)–infected humans to excrete schistosome eggs have been described. This study explores the effect that HIV-1–associated immunodeficiency has on the excretion of schistosome eggs in a large cohort of coinfected individuals.

Methods. In a cross-sectional survey, urine and stool samples were obtained from and HIV-1 status was determined for 1545 individuals. More extensive data, including quantitative measures of intensity of infection in schistosomiasis and immunodeficiency, were collected in the Mupfure schistosomiasis and HIV longitudinal cohort, composed of 379 participants of whom 154 were coinfected with HIV-1 and *Schistosoma* parasites.

Results. In the cross-sectional survey, the overall prevalence of schistosomiasis was 43.4%, and 26.3% of the participants were infected with HIV-1. Schistosome infections were due to *Schistosoma haematobium* in 63.6% of cases, *S. mansoni* in 18.1% of cases, and dual infections in 18.4% of cases. Intensities of *Schistosoma* infections, measured by the number of eggs excreted and by the level of circulating anodic antigens, did not differ between HIV-1–negative and HIV-1–positive participants coinfected with *S. haematobium*, *S. mansoni*, or both. CD4 cell counts were significantly lower in HIV-1–positive participants and in *S. mansoni*–infected HIV-1–negative participants than in other participants.

Conclusion. The present study suggests that adult HIV-1–related immunodeficiency does not impair the ability to excrete eggs in low-intensity infection with *S. haematobium*, *S. mansoni*, or both and that infection with HIV-1 may not have major implications for diagnosis and surveillance of schistosomiasis.

If an interaction of importance exists between schistosomiasis and HIV-1 infection, 2 distinctly different diseases, this knowledge would be of most benefit to those living in the sub-Saharan region of Africa. Apart from hosting 85% of the world's estimated 200 million people who have schistosomiasis [1, 2], this region also has the world's highest prevalence as well as the highest total number of HIV-1–infected individuals [3]. Although antiretroviral therapy for HIV-1 infection is currently not widely available in this region, the proper diagnosis, treatment, and prevention of schistosomiasis are feasible [4–6], and such interventions could possibly moderate the HIV-1 epidemic.

Despite separate research efforts into the pathogenesis of these diseases, few studies have explored possible interactions between them. It has been proposed that immune activation mediated through a shift in cytokine balance toward a Th2-type immune response caused

Received 13 June 2004; accepted 12 November 2004; electronically published 9 March 2005.

Presented in part: 14th International AIDS Conference, Barcelona, Spain, 7–12 July 2002 (abstract WeOrC1376); Fifth Federation of African Immunological Societies Conference, Victoria Falls, Zimbabwe, 28 April–1 May 2003.

Financial support: Danish AIDS Foundation (grants F01-18 and F01-19); Essential National Health Research Fund of the Ministry of Health and Child Welfare of Zimbabwe (grant P355); Danish Embassy in Zimbabwe; Danish International Development Agency Health Program in Zimbabwe; US Centers for Disease Control and Prevention Program in Zimbabwe; Faculty of Health Sciences of the University of Copenhagen, Denmark (grant to P.K.).

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The Journal of Infectious Diseases 2005;191:1311–20

0022-1899/2005/19108-0016$15.00

by chronic infections constitutes a major factor in the pathogenesis of HIV-1 infection and AIDS in Africa [7–9]. Although such a connection has been demonstrated and accepted regarding the detrimental interactions between HIV-1 and leishmaniasis [10] and has been suggested for a range of soil-transmitted helminths [11], so far there are only indirect hints that schistosomiasis and HIV-1 infection may negatively affect one another [12].

Experimental murine models have shown that *Schistosoma mansoni* parasites are dependent on CD4 cell–mediated host immunocompetence for maturation and excretion of eggs [13–15]. Consequently, it has been hypothesized that *Schistosoma* parasites could fail to develop and be fruitful in humans who have impaired CD4 cell immunity because of concurrent infection with HIV-1.

In a study of 16 HIV-1–positive and 37 HIV-1–negative participants infected with *S. mansoni* in Kenya, Karanja et al. found that the HIV-1–positive participants had significantly lower egg counts than did the HIV-1–negative participants, despite their having similar levels of intensity in their infections as measured by levels of circulating cathodic antigen (CCA) [16]. Karanja et al. concurrently demonstrated a positive relationship between egg counts and CD4 cell counts in HIV-1–positive participants. Another study of individuals coinfected with HIV-1 and *S. mansoni* also demonstrated a significantly lower egg count in coinfected participants [17]. Again, however, sample size limits the interpretation, because in that study of sugar-estate residents in Ethiopia, only 10 coinfected participants were compared with 348 HIV-1–negative participants infected with *S. mansoni*. In a prospective cohort study conducted in Zambia of 507 *S. haematobium*–infected participants of whom 73 were HIV-1 coinfected, Mwanakasale et al. found significantly lower egg counts in the coinfected participants, but unfortunately they were unable to quantify either the intensity of the *S. haematobium* infection or the level of immunodeficiency by other measures [18].

Because quantitation of eggs is the classic and simplest way to approximate the intensity of schistosomiasis [19], the hypothesis that HIV-1–coinfected individuals have defective excretion of schistosome eggs deserves to be assessed in a large study that includes complementary measures of schistosomiasis intensity and HIV-1–induced immunodeficiency. In the present study, we present the prevalence and intensity of active schistosomiasis, as determined by egg count and detection of schistosome circulating anodic antigen (CAA) in an HIV-1–infected population and describe the effect that HIV-1–associated immunodeficiency has on the excretion of schistosome eggs.

PARTICIPANTS, MATERIALS, AND METHODS

Setting and study population. The study was conducted from October 2001 to June 2003 in Mupfure and adjacent areas in Shamva District, Mashonaland Central Province, Zimbabwe. This rural area is characterized by subsistence farming, and the main source of water for irrigation, bathing, and washing is the Mupfure River, which is infested mainly by *Bulinus* species snails but also by *Biomphalaria* species snails [20]. No schistosomiasis control program has previously targeted the adult population here.

The study population was composed of adults (≥18 years old) residing in the area who were willing to submit urine, stool, and blood samples and to be tested for HIV-1. Recruitment of participants was achieved through community meetings and was facilitated by local village health workers.

The Medical Research Council of Zimbabwe and the Central Medical Scientific Ethics Committee of Denmark approved the present study, and informed consent was obtained from all participants. In addition, permission was given by the provincial medical director of Mashonaland Central Province, the district medical officer of Shamva District, and the village leaders.

Screening procedure for HIV-1 serological and parasitological testing. Screening procedures were performed on 2281 participants. HIV-1 testing was performed confidentially, and pretest and posttest counseling was provided in the participants' native language (Shona) by qualified personnel. In the field, a rapid HIV-1/2 test kit was used on a dry blood spot (Determine; Abbott Laboratories). All individuals who were initially found to be HIV-1 positive were retrospectively retested using a different rapid test kit (Oraquick by Orasure Technologies, Serodia by Fujirebio, or Capillus by Trinity Biotech). For participants subsequently included in the cohort, 2 ELISAs were performed on serum samples; 1 test was performed in Harare (Recombigen; Cambridge Biotech), and the other was performed in Copenhagen (Ortho). No discrepancies were found between the results of the initial rapid HIV-1/2 test and those of the 2 subsequent ELISAs.

Microscopic examination of fixed-volume urine samples filtered on Nytrel filters (VesterGaard Frandsen) was used to identify and quantitate eggs of *S. haematobium* by the syringe urine filtration technique [21]. Because of the diurnal and day-to-day variation in egg output, the urine samples were collected on 3 consecutive days [22, 23]. The modified formol-ether concentration technique was used on 1 stool sample from each participant to detect eggs of *S. mansoni* and other helminth eggs or parasites [24]. The use of exactly 1 g of stool for the procedure rendered this technique appropriate for quantitative diagnosis of *S. mansoni* infection and was particularly useful in individuals with low-intensity infections [25]. At all stages, when performing parasitological examinations, the technician was blinded to clinical and serological information.

Establishment of cohort. After the screening procedure, HIV-1–infected individuals who were coinfected with *Schistosoma* parasites were included in a prospective cohort. Simultaneously,

Table 1. Sex and age distribution and prevalence of schistosome and HIV-1 infections in the cross-sectional survey.

Cross-sectional survey (n = 1545)	HIV-1 negative (n = 1138)	HIV-1 positive (n = 407)
Female sex[a]	851 (74.8)	311 (76.4)
Age, years[b]	37 (25/48)	34 (28/42)
No schistosomiasis[a]	653 (57.4)	222 (54.5)
Infected with *Schistosoma haematobium*[a]	316 (27.8)	110 (27.0)
Urine egg count, eggs/10 mL of urine[b]	3.8 (1.0/13.9)	3.5 (1.0/12.6)
Infected with *S. mansoni*[a]	81 (7.1)	40 (9.8)
Fecal egg count, eggs/g of feces[b]	3.0 (1.0/6.0)	2.0 (1.0/5.0)
Infected with *S. haematobium* and *S. mansoni*[a]	88 (7.7)	35 (8.6)
Urine egg count, eggs/10 mL of urine[b]	8.0 (2.1/26.3)	5.7 (1.3/16.0)
Fecal egg count, eggs/g of feces[b]	3.0 (2.0/7.0)	4.0 (1.0/13.0)

[a] Data are no. (%).
[b] Data are median (25th/75th percentiles).

a number of HIV-1–negative but schistosomiasis-positive individuals were included as controls, as were individuals infected only with HIV-1 and individuals with neither infection. Allocation of participants to these 3 control groups was done randomly: 1 participant with schistosomiasis was selected for every 2 coinfected participants, and 1 HIV-1–positive participant or 1 healthy participant was selected for every 4 coinfected participants. The 379 participants included in the cohort were interviewed to obtain sociodemographic data and medical history, and a clinical examination was performed.

Exclusion criteria were applied to participants presenting with clinical signs/symptoms of tuberculosis, terminal stages of schistosomiasis, or severe anemia, but no participants were excluded for these reasons. Pregnant women were excluded from the study but were diagnosed and were offered praziquantel as treatment for schistosomiasis after delivery and termination of breast-feeding.

Forty milliliters of blood was drawn from each participant. CD4 cell counts were measured by flow cytometry (FacsCalibur; Becton Dickinson) at the Department of Hematology, Parirenyatwa Hospital, Harare, where full blood counts were also performed (Hematology Analyzer SF 3000; Sysmex) within 36 h of collection of the samples. Levels of CAA, which originates from the parasite gut and is a unique marker of an active schistosome infection, were measured in serum samples by an ELISA performed at the Department of Parasitology in Leiden [26–28].

Statistical analyses. All statistical analyses were performed using SAS software (version 8.2; SAS Institute). Egg counts and CAA levels were log-transformed to approximate normal distribution. Because detection of CAA does not allow for species to be distinguished, results from egg counts were used to stratify the schistosomiasis status of the participants into 4 subgroups (no schistosomiasis, infection with *S. haematobium* only, infection with *S. mansoni* only, and infection with both species). A 2-way analysis of variance (ANOVA), with HIV-1 status and schistosomiasis status as classifying variables, was used to identify differences between groups with respect to egg counts, age, CD4 cell counts, and blood subsets. When this test revealed an interaction, a subsequent 2-way ANOVA, with the 2 schistosome species as classifying variables, was applied within each HIV-1 stratum to explore the magnitude of this effect. If there was no interaction, the ANOVA was performed on the combined HIV-1 strata. A t test was performed to evaluate differences in egg counts between HIV-1 groups and was complemented with an analysis of covariance (ANCOVA) to allow for adjustments according to age, sex, CAA levels, and schistosome species. The magnitude of effects was evaluated by back transformation of the log-transformed difference in means and 95% confidence intervals (CIs) between groups. Hence, the difference is presented as a ratio of means and 95% CIs. Multiple regression models of egg counts with the covariates CD4 cell counts, CAA levels, age, sex, schistosomiasis status, and HIV-1 status were performed, and results are presented as regression coefficients (RCs) and 95% CIs. Normality and independence of residuals were checked graphically. Regarding the ANCOVA, slopes did not differ. $P < .05$ was considered to be significant.

RESULTS

Cross-sectional survey. From the initially screened 2281 individuals, we obtained 3 consecutive urine samples, 1 stool sample, and information on HIV-1 status from 1545 individuals. Overall, 26.3% were HIV-1 positive, 43.4% had schistosomiasis, and there were no differences in distribution of schistosome infections according to HIV-1 status (table 1).

The prevalence of other helminth infections was negligible: very few individuals were diagnosed with *Taenia saginata* (n = 2), *Strongyloides stercoralis* (n = 2), or *Trichuris trichiura* (n = 1). Other identified intestinal parasites were the protozoans *Entamoeba histolytica* (n = 54; 47 [4.7%] were HIV-1–negative par-

ticipants and 7 [1.7%] were HIV-1–positive participants; $P < .05$) and *Giardia lamblia* ($n = 9$; 8 were HIV-1–negative participants and 1 was an HIV-1–positive participant). Table 1 also presents the sex and age distribution of the screened population. Predominantly women participated in the present study (75%), and there were no differences in sex distribution across the subgroups according to HIV-1 status or schistosomiasis status.

In a 2-way ANOVA of age by HIV-1 status and schistosomiasis status, there was no effect attributable to the interaction ($P = .17$), and there was no effect attributable to HIV-1 status ($P = .30$; mean difference in uninfected vs. infected participants, 1.0 years; 95% CI, −0.9 to 2.8 years), but a significant difference was attributable to the effect of schistosomiasis ($P < .001$). A subsequent 2-way ANOVA of *S. haematobium* infection and *S. mansoni* infection on the combined HIV-1 strata revealed no interaction ($P = .22$), a weak tendency toward lower age in *S. mansoni*–infected participants ($P = .13$; mean difference in uninfected vs. infected participants, 1.3 years; 95% CI, −0.4 to 3.0 years), and a significantly lower age in *S. haematobium*–infected participants ($P < .0001$; mean difference in uninfected vs. infected participants, 4.8 years; 95% CI, 3.1–6.5 years).

Egg counts are shown in figure 1*A* and 1*B*. In a 2-way ANOVA of egg counts in urine and stool by HIV-1 status and schistosomiasis status, there was no interaction (urine egg counts, $P = .45$; fecal egg counts, $P = .22$), and no difference was attributable to HIV-1 status (urine egg counts: $P = .30$; mean HIV-1–positive participants:HIV-1–negative participants, 0.83; 95% CI, 0.59–1.18; fecal egg counts: $P = .65$; mean HIV-1–positive participants:HIV-1–negative participants, 0.93; 95% CI, 0.68–1.27). There was, however, an effect of schistosomiasis status (urine egg counts: $P < .01$; mean *S. mansoni*–positive participants:*S. mansoni*–negative participants, 1.64; 95% CI, 1.16–2.33; fecal egg counts: $P = .01$; mean *S. haematobium*–positive participants:*S. haematobium*–negative participants, 1.50; 95% CI, 1.10–2.04). Both tests showed increased egg counts when coinfection was present.

Because the ANOVA revealed no significant interaction between HIV-1 status and schistosomiasis status, the direct effect of HIV-1 status was further analyzed by *t* tests and ANCOVA. The *t* test comparing urine egg counts confirmed no difference according to HIV-1 status for *S. haematobium*–infected participants ($P = .51$; mean HIV-1–positive participants:HIV-1–negative participants, 0.91; 95% CI, 0.67–1.22). An ANCOVA that tested the same relationship but was adjusted for age and sex gave similar results ($P = .68$; mean ratio, 0.94; 95% CI, 0.70–1.26), with a significant effect according to age ($P < .0001$; see regression analyses) and a tendency for men to have higher egg counts ($P = .06$; RC, 0.12 $\log_{10}$ egg count in men/$\log_{10}$ egg count in women; 95% CI, −0.005 to 0.247 $\log_{10}$ egg count in men/$\log_{10}$ egg count in women). Further adjustments for *S. mansoni* status did not alter the results. Also, application of the *t* test to fecal egg counts in *S. mansoni*–infected individuals revealed no difference according to HIV-1 status ($P = .55$; mean HIV-1–positive participants:HIV-1–negative participants, 0.91; 95% CI, 0.67–1.24), and the equivalent ANCOVA adjusted for age, sex, and *S. haematobium* infection gave similar results.

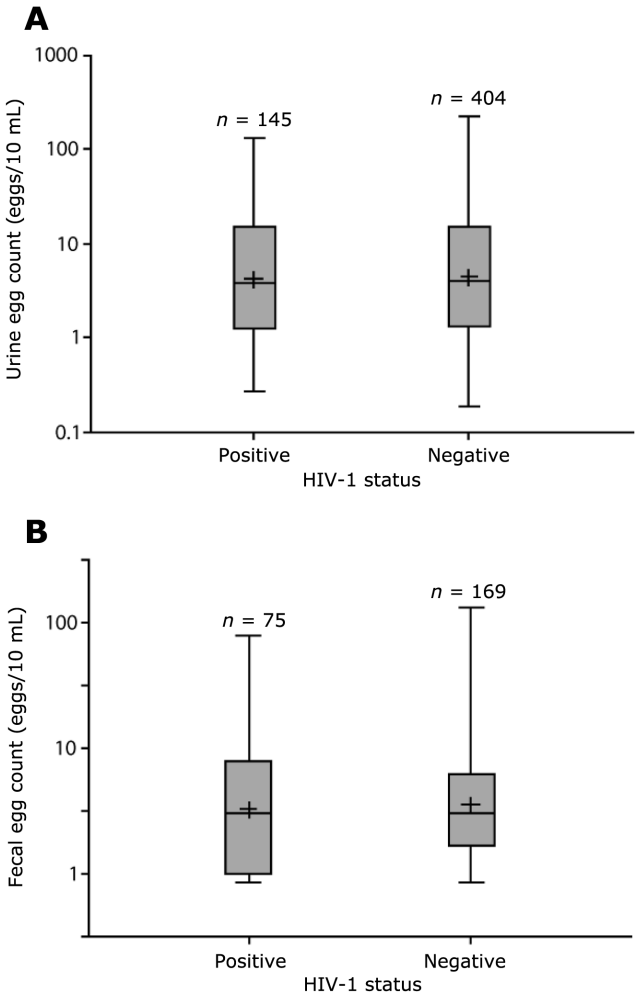

Figure 1. *A,* Mean urine egg count by HIV-1 status. No difference was found between the HIV-1 groups. Data are presented as group means (+), medians *(center lines),* 25th–75th percentiles *(boxes),* and extremes *(whiskers).* Egg counts have been adjusted to median age and female sex. *B,* Mean fecal egg count by HIV-1 status. No difference was found between HIV-1 groups. Data are presented as group means (+), medians *(center lines),* 25th–75th percentiles *(boxes),* and extremes *(whiskers).* Egg counts have been adjusted to median age and female sex.

Cohort study. Of the 379 participants included in the prospective cohort, complete baseline information was available on 356 participants. The characteristics of the cohort population and the distribution of the schistosome and HIV-1 infections are presented in table 2. Mean body mass index (BMI) of the HIV-1–positive participants was lower than that of the HIV-1–negative participants ($P < .001$), but there were no differences in BMI between the schistosomiasis subgroups within the HIV-1 strata.

Table 2. Sex, age, body mass index (BMI), and distribution of schistosome and HIV-1 infections and circulating anodic antigen (CAA) levels in the cohort study.

Cohort study (n = 356)	HIV-1 negative (n = 171)	HIV-1 positive (n = 185)
Sex, males/females (females)[a]	41/130 (76.0)	31/154 (83.2)
Age, years[b]	29 (21/45)	31 (26/39)
BMI[b]	21.5 (19.7/23.5)	20.8 (19.2/22.4)
No schistosomiasis[a]	47 (27.5)	42 (22.7)
CAA, ng/mL[b]	0.1 (0.0/0.7)	0.1 (0.0/0.6)
Infected with *Schistosoma haematobium*[a]	104 (60.8)	102 (55.1)
CAA, ng/mL[b]	2.3 (0.4/7.4)	3.3 (0.7/8.9)
Infected with *S. mansoni*[a]	9 (5.3)	15 (8.1)
CAA, ng/mL[b]	4.9 (1.5/6.4)	5.9 (1.9/14.0)
Infected with *S. haematobium* and *S. mansoni*[a]	11 (6.4)	26 (14.1)
CAA, ng/mL[b]	4.8 (2.7/24.4)	19.0 (5.1/35.5)

[a] Data are no. (%).
[b] Data are median (25th/75th percentiles).

There were no differences in egg counts attributable to either the interaction between HIV-1 and schistosomiasis or to HIV-1 status or schistosomiasis status separately. Performance of the ANCOVA on urine egg count as in the cross-sectional survey and adjustment by CAA level, age, sex, and *S. mansoni* infection still did not reveal an effect attributable to HIV-1 status ($P = .28$; mean HIV-1–positive participants:HIV-1–negative participants, 0.87; 95% CI, 0.61–1.24), nor did the equivalent ANCOVA performed on fecal egg count change conclusions from those found in the cross-sectional survey when adjustments were made for CAA level, age, sex, and *S. haematobium* infection ($P = .98$; mean HIV-1–positive participants:HIV-1–negative participants, 0.99; 95% CI, 0.49–2.27).

As expected, there were significantly lower CD4 cell counts in the HIV-1–positive participants than in the HIV-1–negative participants ($P < .0001$; mean difference, 552 cells/μL; 95% CI, 482–622 cells/μL) (figure 2). The 2-way ANOVA showed an effect of the interaction between HIV-1 status and schistosomiasis status ($P = .02$). The subsequent 2-way ANOVA of *S. haematobium* and *S. mansoni* in HIV-1–negative participants revealed no interaction ($P = .20$) and no effect of *S. haematobium* infection ($P = .89$; mean difference in uninfected vs. infected participants, 13 cells/μL; 95% CI, −176 to 202 cells/μL) but a significant effect of *S. mansoni* infection ($P = .01$; mean difference in uninfected vs. infected participants, 239 cells/μL; 95% CI, 52–428 cells/μL). In the HIV-1–positive participants, no effects attributable to schistosome species were found (figure 2).

REGRESSION ANALYSES

Cross-sectional survey. In a multiple linear regression performed on urine egg count in *S. haematobium*–infected participants with the covariates age and HIV-1 status, there was a tendency toward the interaction of HIV-1 status and age ($P = .07$; RC, 0.12 $\log_{10}$ egg count/1 unit increase in HIV-1 status × 10 years; 95% CI, −0.01 to 0.25 $\log_{10}$ egg count/1 unit increase in HIV-1 status × 10 years). When HIV-1 strata were combined, lower egg count was associated with higher age ($P < .001$; RC, −0.13 $\log_{10}$ egg count/10 years; 95% CI, −0.18 to −0.08 $\log_{10}$ egg count/10 years; $R^2 = 0.05$). However, because of the tendency toward interaction, separate regressions were performed on each HIV-1 stratum. In HIV-1–positive participants, age had no evident effect ($P = .68$; RC, −0.03 $\log_{10}$ egg count/10 years; 95% CI, −0.15 to 0.10 $\log_{10}$ egg count/10 years; $R^2 < 0.01$), whereas in HIV-1–negative participants, higher age was associated with lower egg count ($P < .0001$; RC, −0.15 $\log_{10}$ egg count/10 years; 95% CI, −0.20 to −0.10 $\log_{10}$ egg count/10 years; $R^2 = 0.08$). Regressions were performed on both HIV-1 strata, with adjustments for sex, and both had similar results (data not shown). We cannot conclude that there is a difference between the HIV-1 strata in these correlations, because the 95% CIs of slopes just meet, but we note that the negative correlation between age and urine egg count is found only in HIV-1–negative participants.

In a multiple linear regression performed on fecal egg count in *S. mansoni*–infected participants, no interaction between age and HIV-1 status was found ($P = .70$; RC, −0.03 $\log_{10}$ egg count/10 years; 95% CI, −0.17 to 0.11 $\log_{10}$ egg count/10 years; $R^2 < 0.01$). When HIV-1 strata were combined, age had no effect ($P = .87$; RC, −0.005 $\log_{10}$ egg count/10 years; 95% CI, −0.061 to 0.051 $\log_{10}$ egg count/10 years).

Cohort. In a multiple linear regression performed on urine egg count, there was no interaction between CAA level and HIV-1 status ($P = .48$; RC, −0.031 $\log_{10}$ egg count/1 unit increase in HIV-1 status × 10-fold increase in CAA level; 95% CI, −0.118 to 0.056 $\log_{10}$ egg count/1 unit increase in HIV-1 status × 10-fold increase in CAA level). When HIV-1 strata were combined, we found the expected effect of CAA level ($P < .0001$; RC, 0.114 $\log_{10}$ egg count/10-fold increase in CAA

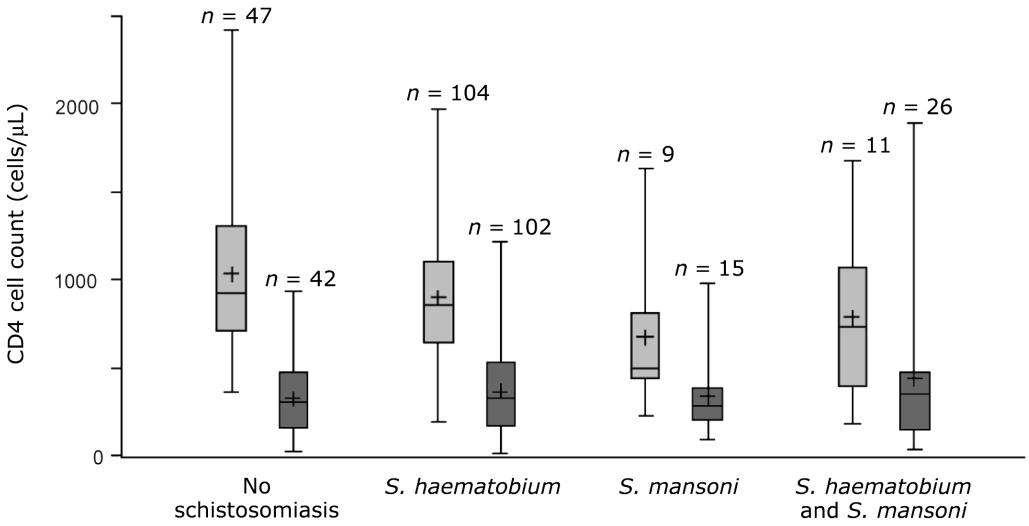

Figure 2. CD4 cell count by *Schistosoma* infection and HIV-1 status. The marked difference in CD4 cell count is attributable to HIV-1 status ($P < .0001$). Data are presented as group means (+), medians *(center lines),* 25th–75th percentiles *(boxes),* and extremes *(whiskers).* HIV-1–positive participants are indicated by dark box plots.

level; 95% CI, 0.071–0.158 $\log_{10}$ egg count/10-fold increase in CAA level; $R^2 = 0.11$). There was an interaction between CAA level and HIV-1 status on fecal egg counts ($P < .05$; RC, 0.166 $\log_{10}$ egg count/1 unit increase in HIV-1 status × 10-fold increase in CAA level; 95% CI, 0.030–0.302 $\log_{10}$ egg count/1 unit increase in HIV-1 status × 10-fold increase in CAA level). Separate modeling of HIV-1–positive participants demonstrated an effect ($P < .01$; RC, 0.146 $\log_{10}$ egg count/10-fold increase in CAA level; 95% CI, 0.041–0.251 $\log_{10}$ egg count/10-fold increase in CAA level; $R^2 = 0.18$) not seen in HIV-1–negative participants ($P = .59$; RC, −0.020 $\log_{10}$ egg count/10-fold increase in CAA level; 95% CI, −0.099 to 0.059 $\log_{10}$ egg count/10-fold increase in CAA level; $R^2 = 0.02$). We note here that the 95% CI overlap between the HIV-1 groups and adjustments by age, sex, and *Schistosoma* species did not alter these results.

In a multiple linear regression performed on urine egg count in *S. haematobium*–infected individuals with the covariates age, sex, CD4 cell count, HIV-1 status, and the interaction of CD4 cell count and HIV-1 status, we found significance toward the interaction ($P < .01$; RC, 0.08 $\log_{10}$ egg count/1 unit increase in HIV-1 status × increase of 100 cells in CD4 cell count; 95% CI, 0.03–0.13 $\log_{10}$ egg count/1 unit increase in HIV-1 status × increase of 100 cells in CD4 cell count; $R^2 = 0.05$). A significant effect of CD4 cell count on urine egg count was found in HIV-1–positive participants ($P < .01$; RC, 0.06 $\log_{10}$ egg count/increase of 100 cells in CD4 cell count; 95% CI, 0.02–0.10 $\log_{10}$ egg count/increase of 100 cells in CD4 cell count; $R^2 = 0.07$), and a tendency toward interaction in HIV-1–negative participants was also found ($P = .08$; RC, −0.04 $\log_{10}$ egg count/increase of 100 cells in CD4 cell count; 95% CI, −0.07 to 0.002 $\log_{10}$ egg count/increase of 100 cells in CD4 cell count; $R^2 = 0.08$) in this age-adjusted and sex-adjusted model (figure 3*A*). Adjusting for CAA level and *S. mansoni* infection did not alter these results.

A similar multiple linear regression was performed on fecal egg count. No interaction between CD4 cell count and HIV-1 status was found ($P = .99$; RC, 0.000 $\log_{10}$ egg count/1 unit increase in HIV-1 status × increase of 100 cells in CD4 cell count; 95% CI, −0.059 to 0.060 $\log_{10}$ egg count/1 unit increase in HIV-1 status × increase of 100 cells in CD4 cell count; $R^2 = 0.16$), and no effect of CD4 cell count was found ($P = .20$; RC, 0.030 $\log_{10}$ egg count/increase of 100 cells in CD4 cell count; 95% CI, −0.017 to 0.077 $\log_{10}$ egg count/increase of 100 cells in CD4 cell count) (figure 3*B*).

DISCUSSION

The most important conclusion from the present study is that no differences in egg counts were found between HIV-1–positive participants and HIV-1–negative participants infected with *S. haematobium, S. mansoni,* or both. This finding was the same even after adjustments were made for differences in age, sex, and dual infection in the large survey population and in the cohort, in which further adjustment for CAA level was possible.

This conclusion is in contrast to those of previous studies by Karanja et al. [16] and Mwanakasale et al. [18], who found a significantly lower egg count in *S. mansoni*– and *S. haematobium*–infected participants, respectively, who were coinfected with HIV-1, compared with that in HIV-1–negative participants. These findings—and in particular those of Karanja et al., which are supported by the demonstration of similar levels of CCA (another schistosome gut–associated antigen) in the

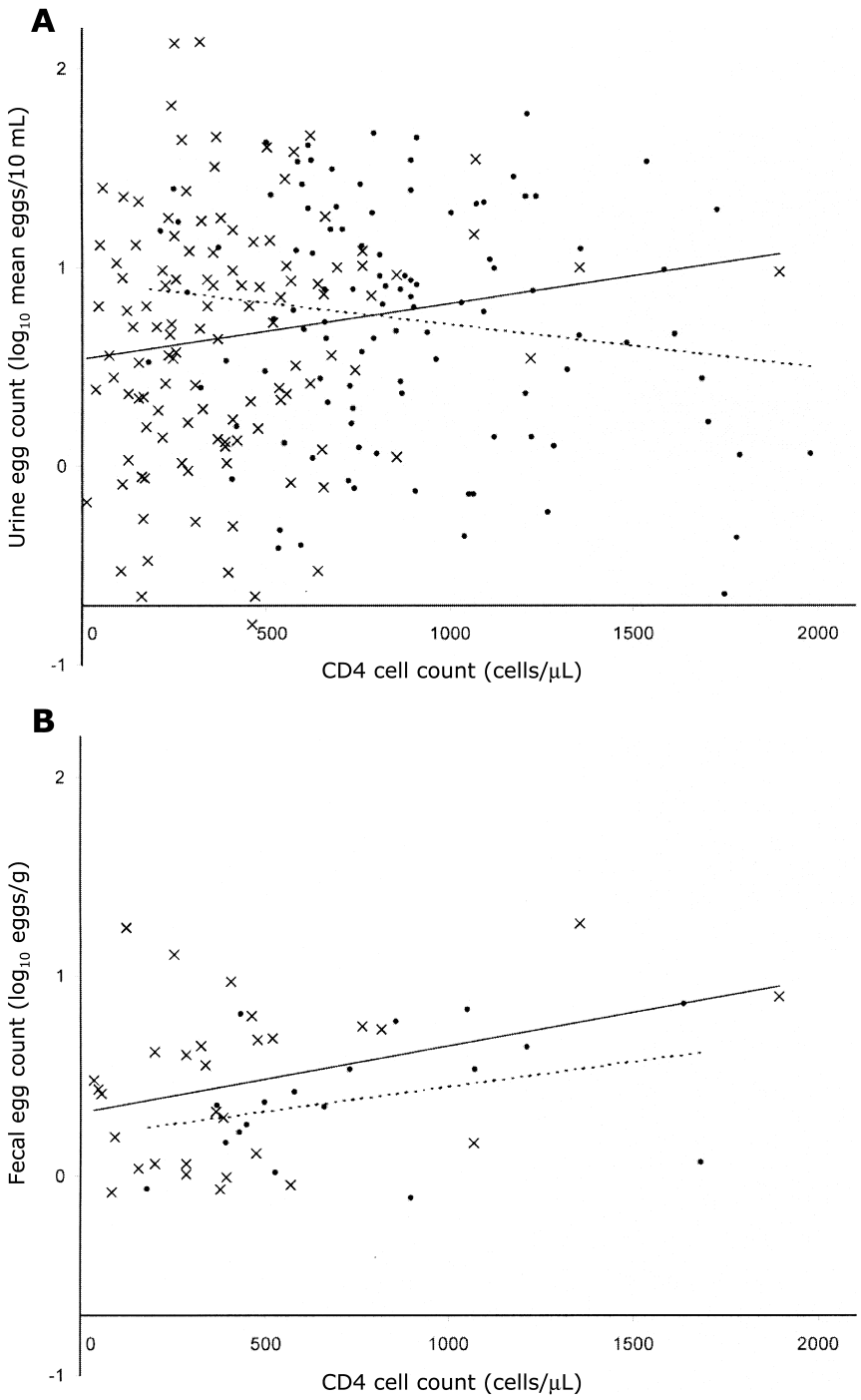

Figure 3. *A,* Scatterplot of mean urine egg counts and CD4 cell count for HIV-1–positive participants (× and *solid line*) and HIV-1–negative participants *(circles* and *dotted line).* Egg counts were adjusted for age, sex, *Schistosoma mansoni* infection, and circulating anodic antigen (CAA) level. Multiple regression, HIV-1–negative participants: $P = .08$; regression coefficient (RC), −0.029 log_{10} egg count/increase of 100 cells in CD4 cell count; 95% confidence interval (CI), −0.062 to 0.003 log_{10} egg count/increase of 100 cells in CD4 cell count; $R^2 = 0.22$; multiple regression, HIV-1–positive participants: $P < .05$; RC, 0.049 log_{10} egg count/increase of 100 cells in CD4 cell count; 95% CI, −0.007 to 0.091 log_{10} egg count/increase of 100 cells in CD4 cell count; $R^2 = 0.13$. *B,* Scatterplot of fecal egg count and CD4 cell count for HIV-1–positive participants (× and *solid line*) and HIV-1–negative participants *(circles* and *dotted line).* Egg counts were adjusted for age, sex, *S. haematobium* infection, and CAA level. Multiple regression, HIV-1–negative participants: $P = .75$; RC, 0.01 log_{10} egg count/increase of 100 cells in CD4 cell count; 95% CI, −0.04 to 0.05 log_{10} egg count/increase of 100 cells in CD4 cell count; $R^2 = 0.13$; multiple regression, HIV-1–positive participants: $P = .31$; RC, 0.02 log_{10} egg count/increase of 100 cells in CD4 cell count; 95% CI, −0.02 to 0.06 log_{10} egg count/increase of 100 cells in CD4 cell count; $R^2 = 0.26$.

2 groups and correlations between egg counts and CD4 cell counts—have led to speculation of an immunomodulatory inhibition of the human host's ability to excrete *Schistosoma* eggs when immunodeficient because of HIV-1 coinfection. Complementary to these suggestions are the findings of Doenhoff et al., Davies et al., and other researchers who demonstrated attenuated development of *S. mansoni*—characterized by overall reduction in body size, delayed development, and a reduction in fecundity—in immunocompromised mice [13–15, 29, 30]. Our data set is larger than that of both Karanja et al. and Mwanakasale et al. [16, 18], in terms of both the combined schistosomiasis subgroups and each subgroup considered separately. Using our ANCOVA models, we estimate that HIV-1–positive participants excrete 94% and 91% of the eggs in urine and feces, respectively, that their HIV-1–negative counterparts excrete. Because with lower CIs, HIV-1–positive participants excrete at least 70% and 67% of the eggs in urine and feces, respectively, that their HIV-1–negative counterparts excrete, these data argue against any clinical relevant difference between egg counts in HIV-1–positive participants and HIV-1–negative participants.

Other explanations may contribute to our contrasting findings. In particular, the average intensities of both *S. haematobium* and *S. mansoni* infections in the present study groups were considerably lower than those in the groups studied by Karanja et al. and Mwanakasale et al. It is plausible that the ability to excrete eggs is more disturbed by reduced immunocompetence when the worm burden is larger. The observed differences in intensities may also be the result of differences in age between the study populations. In the study by Karanja et al., the mean ± SD age was 27.7 ± 9.6 years, whereas in the study by Mwanakasale et al., the mean ± SD age of HIV-1–positive participants was 23.0 ± 11.1 years, and the mean ± SD age of HIV-1–negative participants was 18.8 ± 9.5 years. In contrast to this, in the present study population, the mean ± SD age of HIV-1–negative participants was 37.1 ± 13.4 years, and the mean ± SD age of HIV-1–positive participants was 35.4 ± 9.7 years. Mwanakasale et al. reported that the mean age of the HIV-1–positive participants in their study was significantly higher than that of the HIV-1–negative participants. In the present study, the age did not differ significantly between groups, and the conclusions did not change when adjustments were made for age. Furthermore, our results are supported by CAA measurements indicating similar levels of intensity in active schistosome infections and allowing for CAA adjustments.

In accordance with the findings of Karanja et. al., we also found lower egg counts in both urine and feces with lower CD4 cell counts in HIV-1–positive participants. However, the association was weak and it was evident that even HIV-1–positive participants with very low CD4 cell counts could have egg counts close to those observed in HIV-1–negative participants. It is notable that the HIV-1–positive participants had very low CD4 cell counts, indicating that we primarily studied HIV-1–positive participants with advanced infections. This might restrict our conclusions to refer to only moderately to severely immunocompromised individuals.

The observation of measurable CAA levels in individuals not excreting eggs (table 2) is probably the result of false negative egg counts, because the ELISA for CAA is highly specific. It is known that the egg count can vary greatly, so that even after examination of repeated stool or urine samples, not all schistosome-positive cases will be found [31]. In the presentation of our data, however, the egg count was used as the primary diagnostic criteria for schistosomiasis, primarily because that was the only tool available in the field work of the study (this formed the basis for treatment decisions), but also because use of the CAA level would not permit a distinction between schistosome species. In the subsequent data analyses, adjustment for CAA level did not alter the conclusions.

The present results differ from the findings of the murine experimental models, because we did not find lower egg counts despite marked immunodeficiency in these participants and because the CAA levels did not suggest reduced intensities of *Schistosoma* infection because of immunodeficiency. Apart from the evident differences between an observational study with humans and an experimental animal model, another important difference may be that, in the murine model, the mice are initially immunocompromised and subsequently exposed to schistosomes. In the present study, the sequence is likely the reverse: the participants probably had been exposed to schistosomes as children, before they acquired their HIV-1–related immunodeficiency. It is possible that, under these circumstances, an adaptation of the host-parasite relationship can develop that leads to other outcomes, including perhaps both normal parasite development and excretion of eggs.

To our knowledge, this is the first report on findings of interactions between HIV-1 and concurrent infections with 2 schistosome species, and it is interesting to observe that higher egg counts are the apparent outcome of simultaneous schistosomiasis. A behavioral explanation might be that an individual dually infected with *Schistosoma* parasites has been more heavily or more frequently exposed and therefore harbors an infection of higher intensity.

Interestingly, our cohort data showed decreased CD4 cell counts in *S. mansoni*–infected HIV-1–negative participants. This finding is in agreement with other reports of an association between CD4 lymphocytopenia and helminthic and other infections [32, 33]. These differences in CD4 cell counts apparently disappear in *S. mansoni*–infected HIV-1–positive participants, indicating that any possible subtle effect of schistosomiasis on CD4 cell counts seems to be masked by the dramatic HIV-1–related decline in CD4 cell counts.

We did find that HIV-1–positive participants had a lower

BMI than did HIV-1–negative participants. However, within their respective HIV-1 groups, there were no differences in BMI between subgroups of participants with schistosomiasis. Surprisingly, even in the HIV-1–negative participants, there were no differences in BMI between the participants without schistosomiasis and the other subgroups. This similarity may reflect that the intensities of schistosomiasis in the population in the present study were moderate to low and therefore did not give rise to physiological implications that affect BMI.

In summary, despite the difference between the intensities of the *Schistosoma* infections in the population in the present study and those in other studies, it appears that HIV-1–induced immunodeficiency does not impair the ability of participants with low-intensity schistosomiasis to excrete either *S. haematobium* or *S. mansoni* eggs. Our results further question the applicability of murine studies that show a dependency of adequate CD4 cell immunity for *S. mansoni* development and fecundity to human conditions. One may assume that, in our cohort, some antischistosome immune responses were already established when HIV-1 was encountered. This may imply that the CD4 cells acquired the capacity to react with the parasite so that it could undergo a normal life cycle. However, after this process is established, a secondary CD4 cell immunodeficiency, such as the one that occurs in HIV-1–positive participants, does not appear to dramatically change the development of *S. haematobium* or *S. mansoni* or the ability of the human host to excrete their eggs.

Acknowledgments

We thank the Mupfure community and in particular the village health workers and the environmental health technician, for the willing participation and contribution to our study; Mupfure Secondary School, for accommodations; the technical team and in particular its core members—E. N. Kurewa, N. Taremeredzwa, W. Mashange, C. Mukahiwa, S. Nyandoro, W. Soko, B. Mugwagwa, and E. Mashiri—for tireless, hard work under difficult circumstances; D. Kornelis of the Department of Parasitology at the Leiden University Medical Center, the Netherlands, for diligent and accurate testing of the serum samples for circulating anodic antigen; and the Department of Hematology of Parirenyatwa Hospital, Harare, and in particular B. Mudenge, for continual laboratory support.

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