Schistosomiasis and HIV-1 Infection in Rural Zimbabwe: Effect of Treatment of Schistosomiasis on CD4 Cell Count and Plasma HIV-1 RNA Load

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To determine whether treatment of schistosomiasis has an effect on the course of human immunodeficiency virus type 1 (HIV-1) infection, individuals with schistosomiasis and with or without HIV-1 infection were randomized to receive praziquantel treatment at inclusion or after a delay of 3 months; 287 participants were included in the study, and 227 (79%) were followed up. Among the 130 participants who were infected, those who received early treatment (n = 64) had a significantly lower increase in plasma HIV-1 RNA load than did those who received delayed treatment (n = 66) (P < .05); this difference was associated with no change in plasma HIV-1 RNA load in the early intervention group (P = .99) and an increase in plasma HIV-1 RNA load in the delayed intervention group (P < .01). Among the 227 participants who were followed up, those who received early treatment (n = 105) had an increase in CD4 cell count, whereas those who received delayed treatment (n = 122) did not (P < .05); this effect did not differ between participants when stratified by HIV-1 infection status (P = .17). The present study suggests that treatment of schistosomiasis can reduce the rate of viral replication and increase CD4 cell count in the coinfected host.

Immune activation caused by a higher prevalence of concurrent infections has been hypothesized to be a driving factor for increased HIV-1 replication and cytokine dysregulation in African patients with HIV-1 infection [1, 2], and increased HIV-1 replication has been described during coincident infections for malaria [3], visceral leishmaniasis [4], tuberculosis [5], and intestinal worms [6]. However, others have described similar rates of disease progression in African patients with HIV-1 infection [7, 8], and the role played by concurrent tropical infections as a general accelerating factor for HIV-1 infection in Africa is still undetermined.

Schistosomiasis remains highly prevalent in sub-Saharan Africa. This region is simultaneously hardest hit by the HIV/AIDS pandemic. Schistosomiasis, in addition to its direct morbidity, may affect HIV-1 infection by causing general immune activation and by changing the pattern of cytokine secretion. Despite the large potential for dual occurrence of HIV-1 infection and schistosomiasis, only a few studies have described how these may interact [9–13]. These studies have suggested that an impaired schistosome egg excretion [9, 10], a dysregulated immune response against schistosome infection [11], and even an increase in HIV-1 RNA load after praziquantel treatment [12, 13] occur in individuals coinfected with HIV-1 and schistosomes. However, none of these studies used a randomized design.

Participants, materials, and methods. Details on the Mufure Schistosomiasis and HIV Cohort—including screening procedures, the setting, the study population, and its creation—have been described elsewhere [14]. On inclusion, all participants infected with schistosomes within each HIV-1 group were openly randomized into 2 equally sized groups: the early intervention group (EIG) and the delayed intervention group (DIG). The participants in the EIG received treatment for schistosomiasis as a single oral dose of praziquantel (40 mg/kg) at inclusion, whereas the participants in the DIG received similar treatment after a delay of 3 months. On the basis of this randomization and the HIV-1 infection status of the participants, 4 groups were created: group A, consisting of HIV-1–positive participants with schistosomiasis who received early treatment; group B, consisting of HIV-1–positive participants with schistosomiasis who received delayed treatment; group C, consisting of HIV-1–negative participants with schistosomiasis who re-
received early treatment; and group D, consisting of HIV-1–negative participants with schistosomiasis who received delayed treatment.

All participants were followed up with scheduled clinical examinations and blood samplings 3 months after inclusion, at which time the participants in the DIG were also treated for schistosomiasis. There was no public scheme for antiretroviral therapy (ART) in Zimbabwe at the time of the study, and it can be assumed that all participants were ART naive.

The Medical Research Council of Zimbabwe (MRCZ/A/918) and the Central Medical Scientific Ethics Committee of Denmark (624-01-0031) approved the study, and informed consent was obtained from all participants. In addition, permission was given by the provincial medical director of Mashonaland Central Province, by the district medical office of Shamva District, by the village headmen, and at village meetings.

Plasma HIV-1 RNA loads and circulating anodic antigen (CAA) levels were \( \log_{10} \) transformed, to approximate a normal distribution. Data were analyzed in accordance with the intention-to-treat principle: participants in the EIG who failed to clear their schistosome infections were not excluded from the analysis. \( \Delta \) values for plasma HIV-1 RNA load were compared between participants who received early treatment and those who received delayed treatment by the unpaired Student’s \( t \) test. Changes within groups were quantified by the paired Student’s \( t \) test. Analyses of covariance (ANCOVA) were performed to verify the results of the \( t \) tests. A 2-way analysis of variance (ANOVA), with HIV-1 infection and treatment status as classifying variables, was used to identify effects on CD4 cell count. To evaluate whether treatment randomization influenced the probability of follow-up, a logistic regression model was used. Because the main comparisons were made using only patients who were followed up, a test was also performed in which missing participants were coded as having experienced failure and added to the groups, which then had increased plasma HIV-1 RNA loads and decreased CD4 cell counts. This dichotomized plasma HIV-1 RNA and CD4 cell count response was then compared between the early and delayed treatment arms within each HIV-1 infection status stratum.

**Results.** The established cohort consisted of a total of 287 participants, who were included on the basis of their schistosomiasis and HIV-1 infection status. Three months later, 227 (79%) of them were followed up. Of the 60 participants lost to follow-up, information on the reason for dropping out was available for 50, and the distribution of both the number of participants lost to follow-up and their reasons for dropping out—such as migration, lack of transport, and not feeling well—were evenly distributed among the 4 groups, with the exception of group C, which had a higher number of losses to follow-up due to migration.

Selected baseline demographic, clinical, and laboratory characteristics of the 227 participants in the various study groups are presented in table 1. There was a difference in sex distribution between the 2 coinfected groups (A and B; \( P = .01 \)) (possible influence on results was adjusted statistically by an ANCOVA; see below). The HIV-1–positive participants had significantly lower body mass indices than did the HIV-1–negative participants (mean difference [HIV-1 negative – HIV-1 positive], 1.5 kg/m\(^2\) [95% confidence interval [CI], 0.6 to 2.5 kg/m\(^2\)]; \( P < .01 \)), as well as significantly lower hemoglobin levels (mean difference, [HIV-1 negative – HIV-1 positive], 1.5 g/dL [95% CI, 1.0 to 2.0 g/dL]; \( P < .0001 \)).

Figure 1 displays \( \Delta \) values for plasma HIV-1 RNA load between baseline and the 3-month follow-up time point in the 2 coinfected groups (A and B). The \( t \) test revealed a significant difference between the groups (mean difference [A – B], –0.21 \( \log_{10} \) copies/mL [95% CI, –0.39 to –0.02 copies/mL]; \( P = .03 \)). Changes within groups were quantified by a paired \( t \) test; the EIG showed no difference in plasma HIV-1 RNA load between the 2 time points (mean difference [follow-up – baseline], 0.001 \( \log_{10} \) copies/mL [95% CI, –0.14 to 0.14 \( \log_{10} \) copies/mL]; \( P = .99 \)), whereas plasma HIV-1 RNA load increased significantly in the DIG over the 3 months (mean difference [follow-up – baseline], 0.21 \( \log_{10} \) copies/mL [95% CI, 0.08 to 0.34 \( \log_{10} \) copies/mL]; \( P < .01 \)).

There was a tendency for groups A and B to differ at baseline with respect to plasma HIV-1 RNA load and CD4 cell count after exclusion of those who were lost to follow-up (see the analysis of losses to follow-up below). We attempted to control for these differences by constructing an ANCOVA model. Multiple regressions with plasma HIV-1 RNA load at follow-up as the dependent parameter and baseline plasma HIV-1 RNA load, CD4 cell count, age, sex, CAA level, hemoglobin level, and white blood cell count as covariates showed effects only for plasma HIV-1 RNA load and CD4 cell count. The ANCOVA was adjusted accordingly for baseline plasma HIV-1 RNA load and CD4 cell count and revealed a difference between the 2 groups similar to that revealed by the \( t \) test (mean difference [A – B], –0.21 copies/mL [95% CI, –0.40 to –0.03 copies/mL]; \( P = .02 \)).

A strict intention-to-treat analysis was performed by a sign test, for which a loss to follow-up was coded as an increase in plasma HIV-1 RNA load. This test showed that, after 3 months, 18 of 78 patients in the DIG had a decrease in plasma HIV-1 RNA load, and 27 of 76 patients in the EIG had a decrease in plasma HIV-1 RNA load (\( P = .09 \)).

The effect of treatment on CD4 cell count was studied in a 2-way ANOVA between treatment and HIV-1 infection status in groups A–D. There was no interaction (\( P = .17 \)), indicating that there was no difference in effect between the HIV-1–positive participants and the HIV-1–negative participants. A main effect of HIV-1 infection was found, as expected (mean dif-
Table 1. Baseline characteristics of the 227 participants who were followed up 3 months after study inclusion.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-1 positive with schistosomiasis</th>
<th>HIV-1 negative with schistosomiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A (n = 64)</td>
<td>Group B (n = 66)</td>
</tr>
<tr>
<td>Sex distribution, F:M</td>
<td>48:16</td>
<td>61:5</td>
</tr>
<tr>
<td>Age, median (IQR), years</td>
<td>32 (28–39)</td>
<td>30 (26–37)</td>
</tr>
<tr>
<td>Body mass index, mean (95% CI), kg/m²</td>
<td>21.1 (20.4–21.8)</td>
<td>20.6 (19.7–21.5)</td>
</tr>
<tr>
<td>Urine egg count, a mean (95% CI), eggs/10 mL of urine</td>
<td>13 (9–18) [n = 58]</td>
<td>10 (6–14) [n = 57]</td>
</tr>
<tr>
<td>Fecal egg count, b mean (95% CI), eggs/g of feces</td>
<td>3 (2–5) [n = 15]</td>
<td>4 (2–5) [n = 20]</td>
</tr>
<tr>
<td>CAA level, median (IQR), ng/mL</td>
<td>3.6 (0.9–12.5)</td>
<td>5.4 (1.2–15.1)</td>
</tr>
<tr>
<td>Hemoglobin level, mean (95% CI), g/dL</td>
<td>11.5 (11.1–12.0)</td>
<td>11.4 (11.0–11.9)</td>
</tr>
<tr>
<td>CD4 cell count, mean (95% CI), cells/µL</td>
<td>350 (296–403)</td>
<td>421 (362–491)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA load, mean (95% CI), log₁₀ copies/mL</td>
<td>4.7 (4.5–4.9)</td>
<td>4.5 (4.3–4.7)</td>
</tr>
<tr>
<td>CDC clinical stage distribution, A:B:C</td>
<td>43:20:1</td>
<td>44:20:2</td>
</tr>
</tbody>
</table>

**NOTE.** The participants in groups A and C received early treatment with praziquantel, and the participants in groups B and D received delayed treatment. CAA, circulating anodic antigen; CDC, Centers for Disease Control and Prevention; CI, confidence interval; IQR, interquartile range.

*a* Schistosoma haematobium and *S. haematobium* plus *S. mansoni* infected.

*b* *S. mansoni* and *S. mansoni* plus *S. haematobium* infected.
Figure 1. Differences between 3-month follow-up and baseline values for plasma HIV-1 RNA load (light gray bars) and CD4 cell count (dark gray bars). Changes in plasma HIV-1 RNA load between the HIV-1–positive participants with schistosomiasis who received early treatment with praziquantel (group A) and the HIV-1–positive participants who received delayed treatment (group B) were compared by the unpaired \( t \) test \((P = .03)\). Changes in CD4 cell count between all participants who received early treatment (group A plus group C [HIV-1–negative participants]) and all participants who received delayed treatment (group B plus group D [HIV-1–negative participants]) were compared by a 2-way analysis of variance \((P = .01)\). Bars represent mean differences in \( \log_{10} \) HIV-1 RNA loads or CD4 cell counts, and error bars represent 95% confidence intervals.

Discussion. Our initial hypothesis was that, if the immunological effects of schistosome coinfection favors HIV-1 replication, then treatment of chronic schistosomiasis might lead to a decrease in plasma HIV-1 RNA load and improved prognosis. However, our main finding was that, although the plasma HIV-1 RNA loads of the participants with HIV-1 and schistosome coinfection continued to increase, treatment of schistosomiasis in the coinfected host arrested this increase. Plasma HIV-1 RNA load is a strong predictor of HIV-1 disease progression to AIDS and subsequent death, especially early during infection. As estimated by Cox analysis of data from Danish patients with HIV-1 infection before the advent of highly active
ART, a praziquantel-induced decrease in plasma HIV-1 RNA load of 0.21 log₁₀ copies/mL would be associated with a decrease in mortality between 1.9- and 7-fold [15]. However, because the CI for the effect of praziquantel treatment includes a value as low as 0.02 log₁₀ copies/mL, the true beneficia effect of praziquantel treatment could be much smaller.

We also found that treatment of schistosomiasis signifi cantly increased CD4 cell count. This fi nding may lend support to the hypothesis that helminthic infections are a general cause of immunodeficiency in Africa.

In the present controlled, randomized—but unblinded—study, one might anticipate that follow-up would depend on receipt of treatment. Although we cannot disregard this potential selection bias and other possible biases, we tried to pursue possible refl entia trends by a thorough analysis of participants who were lost to follow-up. We found that those who were lost to follow-up had lower CD4 cell counts and a tendency toward higher plasma HIV-1 RNA loads at baseline. However, logistic regression demonstrated that follow-up was not infl uence by early versus delayed treatment. Furthermore, although the study was not powered for this kind of analysis, plasma HIV-1 RNA load was also compared between groups under strict intention-to-treat analysis, with losses to follow-up classifi ed as having experienced failure. This analysis confirmed an insignifi cant tendency of treatment to be associated with a decrease in Δ values for plasma HIV-1 RNA load. We therefore consider it to be unlikely that the observed differences between groups were caused by differences in losses to follow-up.

To preempt bias in relation to sampling, groups were compared with regard to the day of the week of inclusion, the time of year of inclusion, and the interval between inclusion and follow-up. No differences were found. Furthermore, the clinical stage, as measured by the Centers for Disease Control and Prevention classifi cation system for HIV infection, was not different at inclusion between the participants in groups A and B (table 1).

Lawn et al. studied samples from 30 coinfected individuals in Kisumu, Kenya, and found that effective treatment of schistosomiasis was associated with a mean increase in plasma HIV-1 RNA load of 0.33 log₁₀ copies/mL [12]. However, the follow-up periods of the participants varied considerably, and when the results were stratifi ed by duration of follow-up, the authors found that mean plasma HIV-1 RNA load increased by only 0.08 log₁₀ copies/mL in the 15 individuals for whom the interval between sample collection was <5 months, whereas a significantly greater mean increase of 0.56 log₁₀ copies/mL was observed in the 15 individuals for whom duration of follow-up was >6 months [12]. Recently, Brown et al. reported a transient increase in viral load 1 month after treatment of schistosomiasis in a large cohort of 163 Ugandans coinfected with Schistosoma mansoni and HIV-1 [13]. The increase was noticeably greater among the individuals with higher-intensity S. mansoni infections (>100 eggs/g), but for all the increase vanished at follow-up 5 months after treatment.

Our observation of an unchanged plasma HIV-1 RNA load 3 months after treatment could be interpreted as being in accordance with the results of Lawn et al. [12], when considering their patients with similar follow-up, whereas it could be read as being in confl ict with the results of Brown et al. [13]. Differences in time points for data collection may be an infl uence but we also found plasma HIV-1 RNA loads to be unchanged 6 weeks after treatment in the EIG (data not shown) (P = .46), which is in contrast to the fi nding of Brown et al. A higher intensity of infection, as determined by egg count, in our cohort may have contributed to this difference. However, the major difference between the results of our study and those of the previous studies is the increase in plasma HIV-1 RNA load in the DIG, which we were able to detect because of our randomized design. Our major contribution is, therefore, more related to the basic eff ect of Schistosoma infection on HIV-1 replication than to the treatment eff ect per se.

In conclusion, our results add schistosomiasis to the list of concurrent infections that may increase HIV-1 replication and suggest that schistosomiasis may cause a reduction in CD4 cell count irrespective of HIV-1 infection. However, it needs to be emphasized that the magnitude of the increase in HIV-1 replication during untreated schistosomiasis has not been estimated very precisely and that the eff ect of treatment on CD4 cell count could not be distinguished by HIV-1 infection status because of the limited power of the interaction test. Further operational research on the eff ects of schistosomiasis coinfection are strongly needed to delineate whether schistosomiasis intervention should be incorporated into the current initiatives for providing ART in areas where both HIV-1 infection and schistosomiasis are endemic.

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References