Treatment of *Schistosoma mansoni* Infection Increases Helminth-Specific Type 2 Cytokine Responses and HIV-1 Loads in Coinfected Ugandan Adults

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**Background.** Studies showing that helminths stimulate type 2 cytokine responses and influence responses to unrelated antigens suggest that helminths may accelerate human immunodeficiency virus type 1 (HIV-1) disease progression in coinfected individuals and that antihelminthic therapy may be beneficial. By the same logic, however, the increase in type 2 cytokines occurring immediately after antischistosomal treatment might increase viral replication and be detrimental.

**Methods.** To assess the effect of antischistosomal therapy on immune responses and HIV-1 replication, a cohort of 163 Ugandans coinfected with *Schistosoma mansoni* and HIV-1 was treated with praziquantel. CD4+ T lymphocyte counts, eosinophil counts, and plasma HIV-1 RNA concentrations were measured before treatment and 1 month and 5 months after treatment. *Schistosoma mansoni*– and *Mycobacterium tuberculosis*–specific cytokine responses and serum interleukin (IL)–10 concentrations were analyzed.

**Results.** Transient increases in viral load and sustained decreases in CD4+ T lymphocyte count were observed, especially in subjects with higher-intensity infections. Despite enhanced posttreatment *S. mansoni*–specific type 2 responses, no increase in eosinophils or in *M. tuberculosis*–specific type 2 responses nor any decline in *M. tuberculosis*–specific interferon (IFN)–γ responses were seen. A significant decline in circulating IL-10 concentrations was observed.

**Conclusion.** Although the mechanisms underlying the increase in viral load after treatment with praziquantel are unclear, these results do not support the hypothesis that treating schistosomiasis is beneficial in the management of HIV-1 disease in Africa.
S. mansoni Treatment in HIV-1 Coinfection

Figure 1. Flow diagram of the study design, for subjects infected with *Schistosoma mansoni* at enrollment. The effects specific to praziquantel treatment (PZQ) were analyzed by treating *S. mansoni*-infected subjects 1 month after empirical albendazole treatment (ABZ) had been given for intestinal nematodes. IL-10, interleukin-10.

Table 1. Number of subjects with available data for serologic, cytochemical, and virologic assays. 

<table>
<thead>
<tr>
<th>Number seen</th>
<th>CD4+ T lymphocyte count available</th>
<th>Viral load available</th>
<th>Cytokine response data available</th>
<th>Serum IL-10 data available</th>
</tr>
</thead>
<tbody>
<tr>
<td>173</td>
<td>163</td>
<td>153</td>
<td>152</td>
<td>152</td>
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<td>163</td>
<td>152</td>
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<td>138</td>
<td>119</td>
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<td>90</td>
<td>90</td>
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<tr>
<td>127</td>
<td>127</td>
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<td>127</td>
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</tbody>
</table>

AIDS Support Organisation clinic or the Uganda Virus Research Institute clinic in Entebbe, were members of the Entebbe Cohort (EC). This prospective cohort of HIV-1–infected adults was established by the UK Medical Research Council in 1995 [15], and recruitment into the cohort continues. Informed consent was obtained from all patients; ethical approval for the study was sought from and provided by the Uganda National Council for Science and Technology, the ethics committee for the Uganda Virus Research Institute, and the ethics committee of the London School of Hygiene and Tropical Medicine. Details of ethical approval and recruitment into the study of helminth–HIV-1 interactions have been described elsewhere [6]. Briefly, as illustrated in figure 1, enrollment into this study took place during participants’ routine (every 6 months) cohort visits, when a questionnaire was completed, stool and blood samples were collected, and presumptive treatment with 400 mg of albendazole was provided. Subjects identified on the basis of their enrollment specimens as having *S. mansoni* infection returned after 1 month, when repeat stool and blood samples were taken; subjects were treated with 40 mg/kg praziquantel and returned after 1 month, when blood was collected again. All participants with *S. mansoni* were treated, because it was not considered ethical to leave these infections untreated. Subjects were seen at their subsequent routine EC appointment—that is, 5 months after praziquantel treatment—when blood samples were collected. Subjects who did not attend appointments were traced at their homes by fieldworkers and were encouraged to attend

**SUBJECTS, MATERIALS, AND METHODS**

**Study population.** Study subjects, who attend either the AIDS Support Organisation clinic or the Uganda Virus Research Institute clinic in Entebbe, were members of the Entebbe Cohort (EC). This prospective cohort of HIV-1–infected adults was established by the UK Medical Research Council in 1995 [15], and recruitment into the cohort continues. Informed consent was obtained from all patients; ethical approval for the study was sought from and provided by the Uganda National Council for Science and Technology, the ethics committee for the Uganda Virus Research Institute, and the ethics committee of the London School of Hygiene and Tropical Medicine. Details of ethical approval and recruitment into the study of helminth–HIV-1 interactions have been described elsewhere [6]. Briefly, as illustrated in figure 1, enrollment into this study took place during participants’ routine (every 6 months) cohort visits, when a questionnaire was completed, stool and blood samples were collected, and presumptive treatment with 400 mg of albendazole was provided. Subjects identified on the basis of their enrollment specimens as having *S. mansoni* infection returned after 1 month, when repeat stool and blood samples were taken; subjects were treated with 40 mg/kg praziquantel and returned after 1 month, when blood was collected again. All participants with *S. mansoni* were treated, because it was not considered ethical to leave these infections untreated. Subjects were seen at their subsequent routine EC appointment—that is, 5 months after praziquantel treatment—when blood samples were collected. Subjects who did not attend appointments were traced at their homes by fieldworkers and were encouraged to attend

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The dilution, were classified as 2,000,000 copies/mL (6.3 log 10) because there was an insufficient amount of specimen for further examination. Samples from 5 subjects were above the detectable range and, therefore, were left unstimulated. Cultures were harvested on day 1 for IL-4, on day 4 for IL-13, and on day 6 for interferon-γ (IFN-γ) and IL-5. Viral inactivation of supernatants with 0.03% tributyl phosphate (Sigma T4908) and 1% Tween 80 (Sigma P1754) was performed before freezing at −80°C. Crude culture filtrate proteins (CFPs) of *M. tuberculosis* H37Rv were provided by J. T. Belisle (Colorado State University, Fort Collins), courtesy of the National Institutes of Health (National Institute of Allergy and Infectious Diseases grant NO1 AI 75320). This antigen is composed primarily of antigen 85, a secreted protein complex that is involved in the synthesis of the cell wall and is immunogenic in humans [20–23]. *S. mansoni* adult worm antigen (SWA) and *S. mansoni* egg antigen (SEA) were prepared as described elsewhere [24].

Supernatants from all time points were analyzed on the same ELISA plate, to minimize the effects of interplate variability on the comparison of results between time points. Plates were deemed unacceptable and the ELISA was repeated if positive control results were >2 SDs from the mean control result, if the correlation coefficient for the standard curve was <0.96, or if the lowest detectable standard was >22.2 pg/mL. Cytokine responses were defined as positive for any result >7 pg/mL (the lowest point on the standard curve in the majority of assays). Low-level production of cytokines in unstimulated wells was subtracted from the concentration produced in response to stimulation.

**Serum IL-10 ELISA method.** ELISAs for IL-10 were performed on sera (separated and stored at or below −20°C within 24 h of sample collection) from all subjects at all time points. ELISAs were performed using an OPTEIA kit (Becton Dickinson) in accordance with the manufacturer’s protocol. Standard series of dilutions of recombinant IL-10 (1800 to 2.4 pg/mL) were used. The lowest standard (2.4 pg/mL) was defined as the cutoff and was subtracted from all values to give the response above the limit of detection.

**Statistical analysis.** Study data were entered into Foxpro for Windows (version 2.6; Microsoft) and analyzed with STATA (version 7.0; STATA Corporation). Comparisons of median CD4+ T lymphocyte counts and median absolute eosinophil counts were performed by Wilcoxon signed rank tests, and comparisons of mean log_{10} viral load were performed by Student’s paired *t* test, where appropriate. Analyses of association were performed using standard 2 × 2 tables.

The observed distribution of serum IL-10 responses was skewed, requiring log_{10} transformation or nonparametric statistical techniques; for most whole-blood assay cytokine responses, <50% of subjects displayed concentrations above background values, so most analyses compared proportions of subjects with detectable cytokine responses; median values were used only after restricting analyses to subjects with a detectable response. McNemar’s *χ²* test was used for paired longitudinal analyses.
RESULTS

Baseline characteristics. Of 663 subjects enrolled in the study, 116 were excluded because of incomplete parasitological data or other reasons, as discussed elsewhere [6]. Of the remaining 547 subjects, 173 were infected with S. mansoni. Of these, 9 failed to attend follow-up visits for praziquantel treatment. CD4+ T lymphocyte count was unavailable for 1 subject at this visit. The remaining 163 S. mansoni–infected subjects were included in subsequent analyses. Baseline characteristics of these subjects are displayed in table 1.

S. mansoni infection was diagnosed by Kato-Katz smear in 91 subjects and was diagnosed by CAA ELISA in an additional 72 subjects. Estimates of infection intensity in subjects with positive Kato-Katz smears correlated well with CAA concentrations (Spearman rank correlation coefficient $r = 0.63; P < .0001$). There was no association between infection intensity and CD4+ T lymphocyte count (CAA concentration vs. baseline CD4+ T lymphocyte count, $r = 0.01; P = .86$) or viral load (CAA concentration vs. baseline viral load, $r = 0.04; P = .62$).

CD4+ T lymphocyte count and viral load after treatment with praziquantel. During the follow-up period, 3 subjects defaulted, 3 subjects were too sick to attend follow-up visits, and 4 subjects died. Measurement of CD4+ T lymphocyte count failed for 1 subject at the 5 month follow-up, leaving 152 subjects with follow-up data. Because of insufficient plasma sample volumes, viral load data were not available at all time points for 33 subjects. There were no differences in CD4+ T lymphocyte count or S. mansoni infection intensity between subjects with and subjects without complete viral load data (data not shown).

Figure 2A and 2B shows mean log_{10} viral load and median CD4+ T lymphocyte count before and after praziquantel treatment for 119 subjects with complete CD4+ T lymphocyte count and viral load data. A statistically significant increase in viral load 1 month after treatment, from 4.76 to 4.89 log_{10} copies/mL ($P = .001$, paired t test), was not sustained at 5 months after treatment. There was a concomitant but not statistically significant decline in CD4+ T lymphocyte count 1 month after praziquantel treatment in these subjects (as displayed in figure 2B, median CD4+ T lymphocyte count did not fall, but rank values declined; $P = .10$, Wilcoxon signed rank test); however, a significant decline in median CD4+ T lymphocyte count after praziquantel treatment (from 306 to 261 cells/μL at 1 month; $P = .03$, Wilcoxon signed rank test) was observed when all 152 subjects with CD4+ T lymphocyte count data at all time points were analyzed.

The increase in viral load seen after praziquantel treatment was greater in subjects with higher S. mansoni infection intensities (figure 2C and 2D). A weak correlation between initial CAA concentration and viral load increase was observed ($\rho = 0.21, P = .02$). CD4+ T lymphocyte decline was 22 cells/μL in subjects with >100 S. mansoni eggs/g and 17 cells/μL in subjects with <100 eggs/g ($P = .84$).

No statistically significant changes in viral load ($P = .28$, paired t test) or CD4+ T lymphocyte count ($P = .09$, Wilcoxon signed rank test) occurred in the month before praziquantel treatment (figure 2). When the analysis was restricted to subjects free of other helminths, mean viral load was 4.84 log_{10} copies/mL at enrollment and 4.83 log_{10} copies/mL at the pre–praziquantel treatment visit ($n = 63; P = .91$, paired t test); for the same subjects, the median CD4+ T lymphocyte count was 263 cells/μL at enrollment and 286 cells/μL at the pre–praziquantel treatment visit ($P = .24$, Wilcoxon signed rank test).

Antigen-specific cytokine responses. Complete data on antigen-specific and mitogen-induced cytokine responses were unavailable for 62 subjects, because of plate contamination, insufficient sample, or ELISAs that failed despite the repeated assay of initially unacceptable plates. There were no significant differences in CD4+ T lymphocyte count, log_{10} viral load, or S. mansoni infection intensity between subjects with and subjects without complete cytokine data (data not shown). Complete cytokine data were available at all time points in 90 subjects (with the exception of data on SEA-specific responses, which

Table 1. Baseline characteristics of 163 Schistosoma mansoni–infected HIV-1–positive adults in Uganda.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value at baseline</th>
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<tbody>
<tr>
<td>Age, median (range), years</td>
<td>32 (19–51)</td>
</tr>
<tr>
<td>Male sex</td>
<td>67 (41.1)</td>
</tr>
<tr>
<td>World Health Organization clinical stage 3 or 4</td>
<td>61 (38)</td>
</tr>
<tr>
<td>CD4+ T lymphocyte count, median (interquartile range), cells/μm²</td>
<td>298 (151–477)</td>
</tr>
<tr>
<td>log_{10} viral load, mean (SD), log_{10} copies/mL ($n = 138$)</td>
<td>4.80 (0.82)</td>
</tr>
<tr>
<td>S. mansoni infection intensity &gt;100 eggs/g</td>
<td>26 (16.0)</td>
</tr>
<tr>
<td>Detectable mitogen-induced interferon-γ response ($n = 90$)</td>
<td>67 (74.4)</td>
</tr>
<tr>
<td>Infected with other helminths</td>
<td>71 (43.6)</td>
</tr>
<tr>
<td>Eosinophil count, median (interquartile range), cells×10^3/L ($n = 139$)</td>
<td>0.29 (0.13–0.52)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of subjects, unless otherwise indicated.
Figure 2. Change in mean log_{10} viral load (log_{10} copies/mL) (A) and median CD4^{+} T lymphocyte count (cells/μL) (B) before and after praziquantel treatment in 119 HIV-1–positive subjects with Schistosoma mansoni infection and complete CD4^{+} T lymphocyte count and viral load data at all time points. C and D, Changes in viral load when S. mansoni infection intensity is <100 eggs/g (n = 99) (C) and >100 eggs/g (n = 20) (D). Asterisks indicate P values for comparison between pre-praziquantel treatment values (month 0) and values at visits 1 month before (A and B), 1 month after, and 5 months after praziquantel treatment: ** P < .01. Paired t tests were used for the analysis of viral load, and Wilcoxon signed rank tests were used for the analysis of CD4^{+} T lymphocyte count.

were available in only 67 subjects because of limited supplies of antigen).

Figure 3 displays the prevalences of detectable cytokine responses to SEA, SWA, and CFP, before and after praziquantel treatment. Statistically significant increases in the proportion of subjects with detectable IL-4, IL-5, IL-13 and, to a lesser extent, IFN-γ responses to S. mansoni antigens were seen. These were not sustained at 5 months after treatment.

Significant increases in median S. mansoni–specific IL-5 and IL-13 concentrations were seen after praziquantel treatment in subjects in whom these responses were detectable before treatment (table 2). The number of IFN-γ and IL-4 responders was too low (<15 subjects) for measurement of median antigen-specific concentrations. Similar increases in S. mansoni–specific IL-5 and IL-13 concentrations were seen at high and low S. mansoni infection intensities (data not shown); the numbers of responders for other cytokines were too small to allow analysis of the effect of infection intensity on posttreatment changes in response.

No significant changes in the prevalence of cytokine responses to mycobacterial antigen or in median CFP-specific cytokine concentrations (data not shown) were seen, either before or after praziquantel treatment. Positive responses to PHA were observed before praziquantel treatment in 74% of subjects for IFN-γ, 60% of subjects for IL-4, 66% of subjects for IL-5, and 88% of subjects for IL-13. There were no statistically significant changes 1 month after praziquantel treatment, in the proportion of subjects with positive responses or in the median cytokine concentration (table 2), for any cytokine (data for IFN-γ and IL-4 not shown).

Eosinophil counts after praziquantel treatment. The increase in S. mansoni–specific type 2 cytokine responses after praziquantel treatment was not reflected in increases in eosinophil count. The median eosinophil count was $0.29 \times 10^9$ cells/
Figure 3. Schistosoma mansoni– and Mycobacterium tuberculosis–specific cytokine responses before (pre-PZQ) and 1 month and 5 months after praziquantel treatment, as measured in a whole-blood assay, in 90 S. mansoni–infected HIV-1–positive adults with data at all time points. CFP, culture filtrate protein of M. tuberculosis; IFN, interferon; IL, interleukin; SEA, S. mansoni egg antigen; SWA, S. mansoni adult worm antigen. SEA was unavailable for 23 consecutive subjects; therefore, for SEA responses, McNemar’s $\chi^2$ values comparing responses with the pre-PZQ response are shown above each bar.

Serum IL-10 concentrations after praziquantel treatment.
Data on serum IL-10 concentrations were missing at some time points for 25 subjects, as a result of insufficient amounts of serum. Among the remaining 127 subjects, higher S. mansoni infection intensities were associated with a higher median IL-10 concentration (22.6 pg/mL if infection intensity was $>100$ eggs/g vs. 11.7 pg/mL if infection intensity was $<100$ eggs/g; $P = .01$, Wilcoxon rank sum test).

After praziquantel treatment, a significant decline in median IL-10 concentration (from 13.5 to 11.3 pg/mL; $P = .04$, Wilcoxon signed rank test) was seen, which was not sustained at 5 months after treatment. There was no significant decline in serum IL-10 concentration during the month before praziquantel treatment. The decline in IL-10 concentration at 1 month after treatment was more marked in subjects with higher-intensity infections (from 23 to 18 pg/mL; $P = .06$) than in subjects with lower-intensity infections (from 12 to 11 pg/mL; $P = .17$). There was no correlation between decline in IL-10 concentration and decline in CD4$^+$ T lymphocyte count ($P = .02$) or viral load decline ($P = .61$).

DISCUSSION
This study demonstrates that treatment of S. mansoni infection in adults coinfected with HIV-1 in Uganda results in a transient increase in viral replication. This increase was temporally associated with an increase in S. mansoni–specific type 2 cytokine responses; however, no overall bias toward a type 2 cytokine milieu was seen: eosinophil counts did not increase, and cytokine responses to M. tuberculosis antigen and PHA were not affected. There was, however, an associated decline in serum IL-10 concentrations. The changes after praziquantel treatment contrast with the stable viral loads and IL-10 concentrations.
Table 2. Median *Schistosoma mansoni*-specific interleukin (IL)-5 and IL-13 concentrations before and 1 month and 5 months after praziquantel (PZQ) treatment of *S. mansoni*-infected HIV-1–positive adults with detectable baseline *S. mansoni*-specific responses.

<table>
<thead>
<tr>
<th>Cytokine, measurement</th>
<th>SWA-specific response(^a)</th>
<th>SEA-specific response(^b)</th>
<th>PHA-induced response(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-PZQ</td>
<td>1 month</td>
<td>5 months</td>
</tr>
<tr>
<td>IL-5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration, median (interquartile range), pg/mL</td>
<td>131 (56–458)</td>
<td>615 (222–1534)</td>
<td>289 (8–1223)</td>
</tr>
<tr>
<td>Wilcoxon signed rank (P) value(^d)</td>
<td>.0001</td>
<td>.005</td>
<td>.01</td>
</tr>
<tr>
<td>IL-13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration, median (interquartile range), pg/mL</td>
<td>26 (5–159)</td>
<td>138 (12–513)</td>
<td>79 (0–481)</td>
</tr>
<tr>
<td>Wilcoxon signed rank (P) value(^d)</td>
<td>.001</td>
<td>.02</td>
<td>.07</td>
</tr>
</tbody>
</table>

**NOTE.** PHA, phytohemagglutinin; SEA, *S. mansoni* egg antigen; SWA, *S. mansoni* adult worm antigen.

\(^{a}\) Sample sizes: IL-5, \(n = 32\); IL-13, \(n = 38\).

\(^{b}\) Sample sizes: IL-5, \(n = 20\); IL-13, \(n = 24\).

\(^{c}\) Sample includes all 90 subjects with complete cytokine data at all time points.

\(^{d}\) \(P\) values compare follow-up concentrations with pre–PZQ treatment concentrations.
observed during the preceding month. These results do not support the hypothesis that treatment of *S. mansoni* infection has a beneficial effect on HIV-1 disease progression in people coinfected with HIV-1.

There is evidence that HIV-1 infection may suppress fecal egg excretion and result in unreliable egg counts [17]; however, we were unable to replicate this finding in the present study. We found good correlations between CAA concentrations and egg counts and found no association between infection intensity and CD4+ T lymphocyte count.

A preliminary study of this cohort demonstrated a similar increase in viral load 1 month after antihelminthic therapy in 39 helminth-infected subjects, 28 of whom were infected with *S. mansoni* and received praziquantel [21]. In the present study, an increase in viral load was seen only after praziquantel treatment and not after albendazole treatment; a slight decline in viral load in the month before praziquantel treatment was seen in the subjects coinfected with other helminths. Furthermore, greater increases in viral load were seen in subjects with higher-intensity *S. mansoni* infections. Similarly, greater declines in CD4+ T lymphocyte count were seen after praziquantel treatment than after albendazole treatment, and slightly greater declines were seen in subjects with higher-intensity *S. mansoni* infections. The transient nature of the increase in viral load and the absence of an increase during the preceding month suggest an effect of praziquantel rather than merely the natural progression of HIV-1 disease. CD4+ T lymphocyte counts declined at 5 months after treatment, as expected with HIV-1 progression and as seen among helminth-free subjects (from 265 to 244 cells/μL; \( P < .0001 \)), but the rate of decline appeared to be greater during the first month after treatment; furthermore, we have already reported greater declines in CD4+ T lymphocyte count in those whose *S. mansoni* infections had cleared at follow-up than in those with persistent infection [6]. Reinfection with *S. mansoni* or other helminths during the follow-up period, the high level of comorbidity in subjects with advanced immunosuppression, or other factors may have overwhelmed the praziquantel treatment–induced effects and, thus, may explain the transient nature of the changes we observed.

Increases in *S. mansoni*-specific type 2 cytokine responses after praziquantel treatment have been described. It is believed that such treatment-induced responses may be useful in generating protective antischistosomal immunity [9, 25]. Studies have demonstrated that HIV-1 infection suppresses posttreatment cytokine responses, which may partly explain increased reinfection rates among HIV-1–infected adults [14, 26, 27]. In this study, concentrations of SWA-specific IL-5 and IL-13 and SEA-specific IL-5 increased significantly after treatment, as did the proportion of subjects with detectable SWA-specific IL-4, IL-5, and IL-13 and SEA-specific IL-5 responses; the absence of significant increases in posttreatment SEA-specific IL-4 and IL-13 responses may partly reflect smaller numbers of subjects but does accord with findings in HIV-1–negative subjects [9]. The cohort in our study comprised subjects with varying degrees of HIV-1–induced immunosuppression, and the expected increase in posttreatment responses was observed even in subjects with lower CD4+ T lymphocyte counts (data not shown). We did not have an HIV-1–negative control group for assessment of whether posttreatment responses were suppressed by HIV-1 infection, and comparison of our study with previous studies suggests that the magnitude of the responses may be smaller in the present study. Nevertheless, these findings do demonstrate that, despite immunological impairment, there is still a type 2 cytokine increase after praziquantel treatment.

Despite the increase in type 2 cytokine responses to *S. mansoni* antigens, no concomitant increase in eosinophil counts was observed. This was despite preserved posttreatment responses of IL-5, a cytokine implicated in eosinophil production [28]. This may be a matter of timing: previous data have shown an increase in eosinophil counts at 3 weeks after treatment [11]. Alternatively, it may be a real effect of HIV-1 immunosuppression. Data showing failure to augment antibody responses in HIV-1–infected subjects suggest that some posttreatment type 2 responses are impaired [14]; presumably, mechanisms of eosinophil proliferation independent of—or requiring higher levels of—type 2 cytokines explain this impaired eosinophil production.

Some studies have demonstrated enhanced type 2 and impaired type 1 cytokine responses to unrelated antigens in helminth-infected subjects [29–31]. Assessment of the effect of helminth infection on HIV-1–specific immune responses is hampered by the low numbers of HIV-1–specific CD4+ T lymphocytes in subjects with chronic HIV-1 infection. Studies have more successfully explored the impact of helminth infection and treatment on response to mycobacterial antigens. Many have failed to demonstrate any type 2 bias in the immune response to mycobacterial antigens but have shown impaired type 1 responses to these antigens [32–36]. *M. tuberculosis*–specific responses in our study were infrequent (a response to any cytokine assessed was detectable in only 45% of subjects), which reflects the level of immunodeficiency in the cohort. No evidence of increased *M. tuberculosis*–specific type 2 cytokine or reduced IFN-γ production was seen after praziquantel treatment, despite the increase in schistosome-specific type 2 cytokine responses.

How might praziquantel treatment of HIV-1–positive people with schistosomiasis lead to an increase in viral load? The lack of evidence of suppression of responses to mycobacterial antigens suggests that suppression of beneficial, type 1 responses to HIV-1 may be an unlikely explanation. However, an increase in viral load concomitant with the increase in schistosome type 2 cytokine responses after praziquantel treatment could be due to increased HIV-1 replication in activated Th2 lymphocytes.
Alternatively, the demonstrated decline in serum IL-10 concentrations after treatment may be relevant: IL-10 is known to suppress immune activation and type 2 responses and is capable of inhibiting viral replication by binding the long terminal repeat sequence of proviral HIV-1 DNA [37–39]. The role of IL-10 in suppressing host immune responses in helminth infections is the subject of increasing interest, with the discovery of regulatory T cells expressing this cytokine [40–42]. A decline in regulatory T cell activity after antischistosomal treatment could also explain the IL-10 decline, but very little is known about the role of these cells in HIV-1 disease pathogenesis. Available evidence suggests that they suppress antiviral immune responses and, therefore, might enhance viral replication [43]. Examination of the regulatory T cell axis should be the subject of specific consideration in future studies of the impact of helminth infection on HIV-1 disease progression.

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References


