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SCHISTOSOMIASIS AND IMPAIRED RESPONSE TO ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED PATIENTS IN TANZANIA

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Schistosomiasis affects over 230 million people worldwide, 90% of whom live in sub-Saharan Africa(1). Data suggests helminthic infections like schistosomiasis may hasten HIV progression in co-infected patients(2,3). Helminths induce chronic immune activation, shifting from a T-helper cell type 1 (Th1) to type 2 (Th2) immune response. Th2-lymphocytes down-regulate cytotoxic effects of $CD8^+$ T-lymphocytes, leading to an altered cytokine profile with increased viral replication(4–7). Studies have shown that treating ascariasis or filariasis improves $CD4^+$ T-cell counts (CD4 counts) and viral loads in HIV-infected patients(8, 9).

Little research has explored the specific interaction between schistosomiasis and HIV, but one study yielded concerning results. Antiretroviral therapy (ART)-naïve HIV-infected patients with schistosome co-infection who were randomized to delayed anti-schistosome treatment with praziquantel after three months had larger increases in HIV RNA levels and greater declines in CD4 counts than patients treated immediately(10). Despite this possible interaction, schistosomiasis screening is not currently recommended for HIV-infected patients in many endemic countries, including Tanzania. Also, no study has yet assessed impact of schistosomiasis on ART response.

We hypothesized that schistosome infection may adversely affect HIV-infected patients' responses to ART. We conducted a retrospective cohort study to explore this issue at

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Bugando Medical Centre (BMC) near Lake Victoria in Tanzania, where schistosomiasis is hyper-endemic.

Methods

Study participants

This study was conducted from August-December 2011 at BMC's HIV clinic. HIV-infected adults who had taken ART for 6–15 months were enrolled serially. Patients who had received praziquantel since beginning ART, or who were currently receiving anti-tuberculous therapy and therefore had another concomitant infection that could cause CD4 decrease(11), were excluded.

Data collection

Demographic information was collected by structured questionnaire. Baseline data (at ART initiation) was obtained from the patient database, including CD4 count, weight, and height. At the time of enrollment and sample collection, we measured CD4 count by FACSCount system (BD Biosciences, San Jose, CA), height, and weight. We used the World Health Organization (WHO) definition of immunological failure as either CD4 count falling below baseline or CD4 count persistently <100 cells/mm^3(11).

Patients provided single mid-day stool and urine samples. Kato-Katz stool smears were prepared using 41.7mg templates (Vestergaard Frandsen, Switzerland). Five slides were prepared from different sites of each stool sample, which has a reported sensitivity comparable to examination of specimens from different days(12). A trained parasitologist quantified *S. mansoni* eggs/gram.

Urine was examined microscopically and tested for circulating cathodic antigen (CCA) (Rapid Medical Diagnostics, South Africa). CCA, an antigen secreted into the bloodstream by adult schistosomes during active infection, is detectable in urine by rapid reagent test strip(13,14). Schistosome infection was defined as ova in stool or urine and/or a positive CCA test, a strategy shown to increase diagnostic sensitivity without compromising specificity for low-intensity *S. mansoni* infections typical of adult populations(15).

Data analysis

Logistic regression models (adjusting baseline CD4 count, which we call 'bivariate analysis,' and multivariate analysis adjusting for additional factors) were used to examine factors associated with immunological failure. In all models, we adjusted baseline CD4 count for more valid analyses, noting that the outcome, immunological failure, is defined as a function of baseline CD4 count. We used backward elimination, deleting variables with the largest p-value one by one, to reach a final parsimonious model including all factors with $p<0.05$.

We used analysis of covariance (ANCOVA) to compare CD4 count increases between groups with and without schistosomiasis while adjusting for baseline CD4 count(16). Two-sided 95% confidence intervals and p-values were used throughout. Data were analyzed using STATA IC/10.1 (College Station, Texas).

Ethics

Ethical approval was obtained from BMC and Weill Cornell. Patients diagnosed with schistosomiasis immediately received praziquantel (40mg/kg).

Results

Patient characteristics

Of 364 eligible HIV-infected outpatients coming to clinic during the study period, one had received praziquantel and 10 were being treated for tuberculosis. Of the remaining 353 patients, 351 provided written informed consent, urine, and stool and were enrolled. Of these, 248 (71%) were females. The median age was 36 (interquartile range 31–43) years. Over 90% had primary school education or less, and >80% were unemployed or petty traders. Baseline CD4 count at ART initiation was 173 (76–249) cells/μL and baseline body mass index (BMI) was 21.6 (19.7–23.9) kg/m^2. Baseline WHO clinical stages were: Stage 1--54 patients (15%), Stage 2—130 (37%), Stage 3—127 (36%), Stage 4—40 (11%). Patients had taken ART for a median of 338 (265–376) days.

Prevalence of schistosomiasis

Schistosomiasis was diagnosed in 97 patients (27.6%). All 97 were CCA-positive, and 46/97 had ova in urine or stool. All 46 of these had *Schistosoma mansoni*, and one had concurrent *S. haematobium*. All 46 patients with schistosome ova were CCA-positive, and 41/46 had low-intensity infections of <100 eggs/gram of stool.

Outcomes after ART

The median CD4 count change was +190 (104–303) cells/μL. Median BMI increase was +1.4 kg/m^2. Twenty-five patients (7%) met ≥1 WHO criterion for immunological failure: 22 had CD4 counts below baseline and 7 had CD4 counts persistently <100 cells/μL.

Factors Associated with Immunological Failure

Table 1 shows univariate and multivariate analyses. In the multivariate model, education and baseline BMI were moderately associated with immunological failure (p=0.04), while schistosome infection was strongly associated (Odds ratio 4.6 [95% confidence interval: 1.9–11.2], p=0.0009).

Secondary analysis by ANCOVA, with change in CD4 count as a continuous outcome, showed that CD4 count increase on ART was significantly associated with schistosome infection, baseline CD4 count, and age in the multivariate, parsimonious model. These effects were most strongly driven by schistosome infection status, with an estimated difference of 65.5 cells/μL in CD4 count change between those with and without schistosomiasis (p=0.0004). Unadjusted and adjusted mean CD4 count changes were +163 versus +226 cells/μL and +161 versus +227 cells/μL, respectively.

Discussion

Among these adult HIV-infected outpatients living in a schistosome-endemic area, nearly one-third had active schistosome infection. Odds of developing immunological failure were four times greater in patients with schistosome co-infection. To our knowledge this is the first study assessing the association between schistosomiasis and ART treatment failure. Our findings have major implications for ART management in millions of HIV-infected outpatients living in schistosome-endemic areas who are managed based on immunological and clinical criteria because viral load measurements are not routinely available.

Schistosome-infected patients also had significantly lower CD4 count increases on ART than schistosome-uninfected patients. More frequent immunological failure and smaller CD4 count gains in schistosome-infected patients could both be explained by chronic helminth-induced Th2-type immune activation, which may permit increased viral

replication(4). Our work extends findings of a study in which Zimbabwean HIV- and schistosome-co-infected patients randomized to delayed praziquantel had larger HIV RNA increases and CD4 count declines than patients treated immediately(10). Other studies have suggested similar effects from other helminth infections, but not unanimously(8,9,17). Notably, other studies have not explored helminth infections' effects on patients receiving ART.

Our finding that schistosomiasis is both common and associated with immunological failure supports implementation of schistosomiasis screening at ART initiation. Unfortunately, stool and urine testing alone, particularly when done as the thin preparation of stool and unfiltered urine typical of many African clinical laboratories, has low sensitivity for detecting schistosome ova. Antigen tests including urine CCA used in this study may provide rapid, more sensitive screening for schistosomiasis, particularly since HIV-infected individuals may excrete fewer eggs(18,19). Further operational research is needed to determine costs, benefits, and optimal screening strategies.

In a previous study that compared baseline characteristics of schistosome-infected and uninfected HIV-positive patients, schistosome-infected patients had higher baseline CD4 counts and CD4:CD8 ratios but comparable viral loads(6). Patients in that study were ART-naive, as were ours during baseline investigations. Neither study observed other baseline differences between patients with and without schistosomiasis that might explain the higher CD4 counts. Schistosomiasis may cause distinct immunological alterations in peripheral blood $CD4^+$ T-lymphocyte subsets, and these alterations may impair patients' responses to ART. Additional studies are needed to better-characterize peripheral blood $CD4^+$ T-lymphocyte subsets in HIV and schistosomiasis co-infection.

The retrospective nature of our study is an ethically-necessary limitation since our hypothesis could not be studied prospectively. Based on the Zimbabwean study showing worse virological and immunological outcomes in HIV-infected patients with untreated schistosomiasis, it would not have been ethical to leave schistosomiasis untreated in patients initiating ART. Another limitation was our inability to test viral loads. Without virological data, we cannot determine whether schistosomiasis was associated with immunological failure alone or with concomitant virological failure. We plan further studies using viral load testing to explore this question.

In conclusion, nearly one-third of our Tanzanian HIV-infected outpatients had schistosome infection. Schistosome infection was significantly associated with immunological failure and poorer CD4 count gain following ART use. Untreated schistosomiasis may be a major cause of immunological failure among HIV-infected patients in schistosome-endemic areas. Further studies are needed to investigate whether this represents an immunological phenomenon or true virological failure, and whether screening and treatment for schistosomiasis among HIV-infected patients will improve response to ART. This is an urgent finding with major implications for ART management in resource-limited settings, where choices of antiretroviral medications are limited and success of patients on first-line ART must be maximized.

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Table 1

Baseline Factors Associated with Immunological Failure in HIV-infected Adults after at least Six Months of Antiretroviral Therapy.

Factors	Immunological failure (n=25)	No Immunological failure (n=326)	Bivariate Analysis Odds ratio	p-value	Multivariate Analysis Odds ratio	p-value
Male gender	7 (28%)	96 (29%)	1.1 [0.4–2.7]	0.91		
Age in years	36 (32–49)	36 (31–43)	1.03 [0.99–1.08]	0.14		
Level of Education *			0.4 [0.2–1.05]	0.062	0.3 [0.1–0.9]	0.036
No formal education	7 (28%)	24 (7%)				
Primary education	17 (68%)	270 (83%)				
Secondary education	0 (0%)	18 (6%)				
College/higher education	1 (4%)	14 (4%)				
Occupation						
Business/Professional	3 (12%)	34 (10%)	---	---		
Petty trading	13 (52%)	202 (62%)	0.7 [0.2–2.8]	0.52		
Unemployed	7 (28%)	68 (21%)	1.0 [0.2–4.2]	0.97		
Farming	1 (4%)	18 (5%)	0.5 [0.05–5.3]	0.45		
Fishing	1 (4%)	4 (1%)	2.3 [0.2–28.7]	0.36		
CD4 count (cells/(μL) at time of ART initiation **	258 (189–298)	168 (73–239)	1.006 to 1.007	0.002 to 0.004	1.005 [1.001–1.009]	0.010
BMI (kg/m^2) at time of ART initiation	22.6 (20.8–24.4)	21.5 (19.5–23.8)	1.1 [0.98–1.2]	0.13	1.12 [1.01–1.24]	0.035
WHO clinical stage at time of ART initiation	3 (2–3)	2 (2–3)	0.9 [0.5–1.5]	0.72		
Days since ART initiation	336 (225–380)	333 (265–373)	1.0 [0.99–1.01]	0.91		
Schistosome infection	15 (60%)	82 (25%)	3.9 [1.6–9.1]	0.002	4.6 [1.9–11.2]	0.0009

Binary variables are reported with number and percent, and continuous variables are reported with median and interquartile range. For continuous variable/factors, odds ratios correspond to that for a one unit increase in variable (e.g., age 50 to 51).

* In regression models, education was modeled as a continuous variable.

** In all regression models, baseline CD4 was always adjusted as the outcome is defined as a function of baseline CD4. Thus, in bivariate analyses, results for baseline CD4 are summarized as a range rather than a single number.