

Treatment of Intestinal Worms Is Associated With Decreased HIV Plasma Viral Load

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Background: We have previously suggested that helminthic infections make the host more susceptible to HIV infection and enhance its progression due to the chronic immune activation they cause.

Objective: To study the effect of antihelminthic treatment on HIV plasma viral load (VL) in HIV- and helminth-infected individuals living in Ethiopia.

Methods: Fifty-six clinically asymptomatic HIV-1-infected individuals, 31 (55%) of whom were also infected with helminths, were studied. All participants received antihelminthic treatment at baseline and at 3 and 6 months. Worm egg excretion, HIV plasma VL, and T-cell subsets were determined at baseline and 6 months after treatment.

Results: The mean age, number of CD4 T cells, and gender distribution were similar in the helminth-infected and -noninfected groups. At baseline, HIV plasma VL was strongly correlated to the number of eggs excreted ($p < .001$) and was higher in individuals infected with more than one helminth (5.28 ± 0.35 versus $4.30 \pm 1.13 \log_{10}$ RNA copies/mL, respectively; $p = .16$). After treatment of helminths, the 6-month change in HIV plasma VL was significantly different between the successfully treated group and the persistently helminth-positive group ($p = .04$).

Conclusions: Helminth “load” is correlated to HIV plasma VL, and successful deworming is associated with a significant decrease in HIV plasma VL. The results of the current study, if confirmed in a larger study, may have important implications for slowing disease progression and reducing risks of transmission.

Key Words: HIV—Immune activation—HIV plasma viral load—Helminthic infection—Deworming.

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We have previously put forward the hypothesis that chronic immune activation caused by endemic infections, particularly helminthic infections, is a major factor in the pathogenesis of AIDS in Africa (1). Helminthic infections are almost universal in most African populations (2,3), and the chronic immune activation they cause may make the host more susceptible to the infection with HIV and less able to cope with it once infected (1). Thus,

helminthic infections may account for the higher HIV plasma viral load (VL) reported in sub-Saharan Africa (4–6) and also for the more rapid spread and progression of AIDS in Africa and developing countries (7–11). The recent immigration of Ethiopian Jews to Israel, some of who were infected with HIV-1, provided us with a unique opportunity to test and support our hypothesis by means of the following findings:

1. The vast majority of the Ethiopian immigrants were infected with helminths and had immune dysregulation with a dominant T helper 2 (Th2) type of immune profile that returned to normal with treatment of the helminth infection (12–14).
2. Peripheral blood mononuclear cells obtained from Ethiopian immigrants were highly susceptible to infection by HIV (15).
3. This susceptibility was associated with marked immune activation as well as with increased expression of HIV coreceptors and decreased secretion *in vitro* of β -chemokines (16,17).
4. The rate of progression of HIV infection, the HIV plasma VL, the immune activation profile, and the response to highly active antiretroviral treatment in the Ethiopian immigrants were similar to those of non-Ethiopian Israelis once the helminth infections were treated and these persons were living in Israel (18–20).

The next logical step was to investigate whether treatment of the helminthic infections would affect HIV disease progression. The purpose of the current study was to assess the role of helminthic infection in affecting HIV plasma VL. The study was carried out in Ethiopia, where antiretroviral treatment of HIV infection is not available and helminthic infections are common (21,22).

MATERIALS AND METHODS

The study was conducted at the Black Lion Teaching Hospital, Addis Ababa, Ethiopia. Fifty-six consecutive ambulatory asymptomatic HIV-1-infected subjects were enrolled in the study with the help of a local nongovernment organization (NGO) for people with HIV. Patients were enrolled only if they were clinically asymptomatic and had no previous AIDS-defining conditions. At entry, a detailed clinical history and complete physical examination were performed using a standard questionnaire, including a systematic review for any clinical condition included in the revised WHO clinical staging of HIV infection (23). Written informed consent was obtained from all study participants, and the study was approved by the Institutional and National Ethics Committees. No participants received any antiretroviral treatment before or during the study. Blood was obtained for a complete blood cell count and T-cell subset characterization. Plasma samples for VL determinations were collected and stored at -70°C within 4 hours of blood drawing. Stool specimens were obtained fresh for analysis of intestinal

parasites. For ethical reasons as well as for overcoming the possibility of false-negative stool examination results, antihelminthic treatment was given to all patients on entry and at 3 months and 6 months of follow-up (200 mg of albendazole daily for 3 consecutive days for all patients and 40 mg/kg of praziquantel for those found to have schistosomiasis). Treatment was given at these same time points and after the stool samples for determination of helminth infections were taken.

Stool Examinations

Two consecutive stool samples taken 4 hours apart were collected from every patient at each time point. All samples were examined blind for helminth eggs and larvae by the Kato-Katz method and by formalin-ether concentration (24). Six smears were prepared from a single stool specimen, and mean egg counts per gram of stool were calculated. All egg counts were transformed to \log_{10} for normalizing dispersed results. Intensity of infection was assigned into one of the three categories (lowest 33%, middle 33%, and upper 33%).

Flow Cytometry

Phenotypic analysis was determined by FACScan (Becton Dickinson, U.S.A.) after lymphocyte surface staining with fluorescein isothiocyanate (FITC)-labeled anti-CD4, phycoerythrin (PE)-labeled anti-CD8, and FITC-labeled anti-human leukocyte antigen-D-related (HLA-DR) monoclonal antibodies (mAbs). Isotype mAbs (IgG₁-FITC and IgG_{2a}-PE) were used as controls. All mAbs were obtained from Becton Dickinson. In each case, at least 20,000 events were acquired, and analysis was carried out by using LYSIS II software (Becton Dickinson).

HIV Plasma Viral Load Determination

HIV-1 plasma VL in all samples was determined blind in Alan Landay's laboratory (Chicago, IL, U.S.A.) by the reverse transcriptase-polymerase chain reaction (RT-PCR) method and according to the manufacturer's instructions. Results were converted as \log_{10} RNA copies/mL of plasma. The lower detection limit (LDL) of the assay was 2.3 \log_{10} RNA copies/mL, and samples with HIV RNA concentrations below the detection limit were considered as having 2.3 \log_{10} RNA copies/mL of plasma.

Statistical Analysis

The primary outcome was HIV plasma VL with T-cell subset counts and immune activation markers taken as secondary outcomes. The effect of deworming by specific antihelminthic chemotherapy was evaluated by the change in plasma VL (\log_{10} scale) between baseline and the 6-month follow-up. At baseline, groups with and without helminthic infections were compared, whereas the analysis of follow-up data focused on comparing the group successfully treated for helminth infection with the persistently negative and persistently positive groups. Comparisons between patient groups of baseline characteristics and changes in \log_{10} HIV plasma VL values were performed using *t* tests for continuous outcomes and the χ^2 test or Fischer exact test for discrete outcomes, with .05 as the level of statistical significance. The statistical analyses were performed using the SPSS (SPSS, Chicago, IL, U.S.A.) and STATA (Intercooled Stata 6.0; Stata Corp., College Station, TX, U.S.A.) statistical packages.

RESULTS

Helminthic Infections, Immune Activation, and HIV Plasma Viral Load at Baseline

Of the 56 patients enrolled, 26 were male and 30 were female; the age range was 19 to 53 years (median = 30 years). Using the WHO staging system of HIV infection (25), 39 (68.4%), 13 (22.8%), and 4 (7.0%) of the patients were categorized to stages I, II, and III, respectively. At baseline, 31 (55%) had helminthic infection of one or more species in their stools, with the most frequently detected helminths being *Trichuris trichiura* ($n = 14$) and *Ascaris lumbricoides* ($n = 13$) and only few patients having *Schistosoma mansoni* ($n = 4$) or *Strongyloides* ($n = 2$). These results are in agreement with an earlier report from Ethiopia on the prevalence of nematodes in Addis Ababa (22). The two groups, with or without helminths, had similar age and sex distributions and did not differ in CD4 T-cell counts at baseline (mean \pm SD CD4 T-cell count: 245 ± 228 versus 290 ± 187 cells/mL, respectively). The rather low levels of CD4+ T-cell counts in the current study concur with those reported previously by us and others, showing that CD4 counts in Ethiopians are remarkably low (14,25–27). The level of activated (HLA-DR⁺) lymphocytes was increased in patients with helminths compared with those without helminths (mean \pm SD: 24.4 ± 19.1 versus 15.6 ± 16.0 , respectively), but the difference was not statistically significant. Mean baseline log₁₀ HIV plasma VL was similar in the helminth-infected group in comparison to the noninfected group (mean \pm SD: 4.56 ± 1.13 versus 4.49 ± 1.06 , respectively). Among those infected with helminths, however, a strong statistically significant ($p < .001$) association was found between the amount of eggs excreted in stools (representing helminth “load”) and HIV plasma VL at baseline (Fig. 1). Also, individuals infected with multiple helminth species ($n = 6$) had greater egg excretion in the stools and a higher mean HIV plasma VL than those infected with a single helminth species ($n = 25$) (5.28 ± 0.35 versus 4.30 ± 1.13 log₁₀ RNA copies/mL, respectively; $p = .16$). No correlation was found between egg excretion and either WHO staging or CD4 counts.

Effect of Treatment of Helminthic Infections

HIV-1 plasma VL data were available both at baseline and 6 months after treatment, with antihelminths in only 28 participants. Of the 56 individuals enrolled at baseline, 4 died (2 with helminths and 2 without helminths) and 2 were lost to follow-up. The group with follow-up

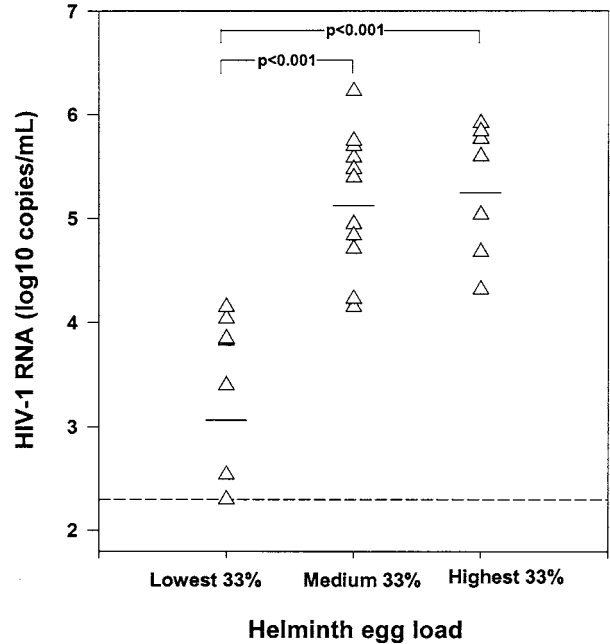


FIG. 1. Correlation between helminthic load and HIV plasma viral load in helminth- and HIV-1-infected patients. *Horizontal dashed line* represents the lower detection limit of the HIV-1 RNA assay.

did not differ from the whole group at baseline in age and sex distribution, clinical staging, or baseline immunologic and virologic parameters. Furthermore, the anti-worm treatment was successful by 6 months of follow-up to a similar extent. There was a clear reduction in the proportion of helminth-infected patients and in individuals' egg loads in the whole group similar to that seen in the 28 patients for whom we had had VL data at 6 months. Thus, of 31 patients with helminths at baseline, 22 (70%) became helminth-negative compared with 13 of 19 (68%) who became helminth-negative of the total of 28 patients available for the final analysis. Using the WHO staging system, similar changes in clinical stage were found at 6 months in the analyzed group (28) as well as in the whole group. Only 1 patient from each of the three groups depicted in Table 1 progressed from stage I to II, and 1 additional patient from the persistently helminth-infected group progressed from stage II to III.

The successful treatment of helminthic infection (group B) was accompanied by a mean decrease in HIV plasma log₁₀ VL of $-0.36 (\pm 0.83)$ (see Table 1; Fig. 2) that was not correlated to CD4 levels. In contrast, there was a mean increase in HIV plasma log₁₀ VL₁₀ in both the persistently helminth-negative (group A: $+0.14, \pm 0.24$) and helminth-positive (group C: $+0.69, \pm 0.27$) groups; the rate of change was significantly different between group B and group C ($p = .04$). There were,

TABLE 1. HIV viral load after deworming

	Patient no.	Sex	Age (years)	Baseline			6 months follow-up		
				Helminth	Egg count ^a	HIV load ^b	Helminth	Egg count	HIV load
Group A	1	M	40	Negative	—	4.99	Negative	—	5.26
	2	F	37	Negative	—	5.60	Negative	—	5.62
	3	F	28	Negative	—	5.11	Negative	—	4.95
	4	M	30	Negative	—	4.41	Negative	—	4.54
	5	F	45	Negative	—	2.30	Negative	—	2.30
	6	M	39	Negative	—	4.89	Negative	—	5.23
	7	F	31	Negative	—	5.91	Negative	—	6.52
	8	F	23	Negative	—	5.49	Negative	—	5.40
	9	M	33	Negative	—	4.23	Negative	—	4.40
Δ Mean (±SD) HIV-1 RNA load +0.14 (±0.24)									
Group B	10	F	37	<i>A. lumbricoides</i>	3.82	4.68	Negative	—	4.53
	11	M	29	<i>A. lumbricoides</i>	2.60	5.48	Negative	—	5.15
	12	F	25	<i>A. lumbricoides</i>	1.70	4.23	Negative	—	5.36
	13	F	19	<i>A. lumbricoides</i>	1.70	4.04	Negative	—	3.20
	14	M	40	<i>T. trichiura</i>	2.48	5.59	Negative	—	5.67
	15	M	27	<i>T. trichiura</i>	2.10	4.71	Negative	—	4.43
	16	M	23	<i>T. trichiura</i>	2.00	4.15	Negative	—	3.36
	17	M	41	<i>S. stercoralis</i>	1.70	2.54	Negative	—	2.30
	18	M	26	<i>S. stercoralis</i>	1.70	3.83	Negative	—	4.08
	19	M	33	<i>S. mansoni</i>	1.70	2.30	Negative	—	2.30
	20	M	37	<i>T. saginata</i>	—	2.30	Negative	—	2.30
	21	M	38	<i>T. saginata</i>	—	5.70	Negative	—	4.68
	22	F	24	<i>A. lumbricoides</i> + <i>T. trichiura</i>	4.74 2.40	5.60	Negative	—	3.15
	Δ Mean (±SD) HIV-1 RNA load -0.36 (±83)								
Group C	23	F	43	<i>A. lumbricoides</i>	2.63	5.52	<i>A. lumbricoides</i>	3.32	5.77
	24	F	32	<i>A. lumbricoides</i>	1.70	3.40	<i>A. lumbricoides</i>	1.70	4.23
	25	M	29	<i>T. trichiura</i>	1.70	4.15	<i>A. lumbricoides</i>	3.57	5.04
	26	F	30	<i>T. trichiura</i>	2.18	4.95	<i>T. trichiura</i>	3.65	5.84
	27	F	40	<i>T. trichiura</i>	1.70	3.85	<i>A. lumbricoides</i>	3.41	4.32
	28	M	31	<i>T. trichiura</i> + <i>T. saginata</i>	2.40 —	5.40 —	<i>T. trichiura</i>	3.10	6.23
Δ Mean (±SD) HIV-1 RNA load + 0.69 (±27)									

^a Eggs log₁₀ per gram of stool. ^b HIV-1 log₁₀ RNA copies per milliliter of plasma.

Group A, persistently helminth-negative; Group B, successful treatment of helminths; Group C, persistently helminth-positive.

however, no significant changes in CD4 T-lymphocyte counts between baseline and the 6-month visit for all groups.

DISCUSSION

The main results of the current study are that helminth load in HIV-infected individuals is strongly correlated with HIV plasma VL and that eradication of helminthic infections significantly decreases HIV plasma VL in dually infected individuals. Considering the small size of the study population and the short duration of the study, the significance of these findings is notable.

The highly significant correlation between helminth load (e.g., the number of eggs excreted) and HIV plasma VL may at least partially explain the increased mean HIV plasma VL observed in sub-Saharan regions (4–6),

where helminthic infections are widespread and heavy (2,3). The notion that HIV infection spreads and progresses faster in developing countries is still controversial, mainly due to the paucity of well-controlled longitudinal studies (7–11,28). Nevertheless, there is compelling evidence that high HIV plasma VLs are associated with increased HIV transmission and faster progression (29,30). Although there may be other potential factors that could contribute to the increase in HIV plasma VL, it may well be that helminth infections in themselves, mainly through the immune activation that they cause, are sufficient to be a major factor for the observed HIV plasma VL increase. This proposition is supported by our previous studies among HIV-negative and HIV-positive Ethiopian immigrants to Israel, where we found that helminthic infections were associated with chronic immune activation that decreased after treatment

Relative Changes in Log₁₀ HIV RNA Copies

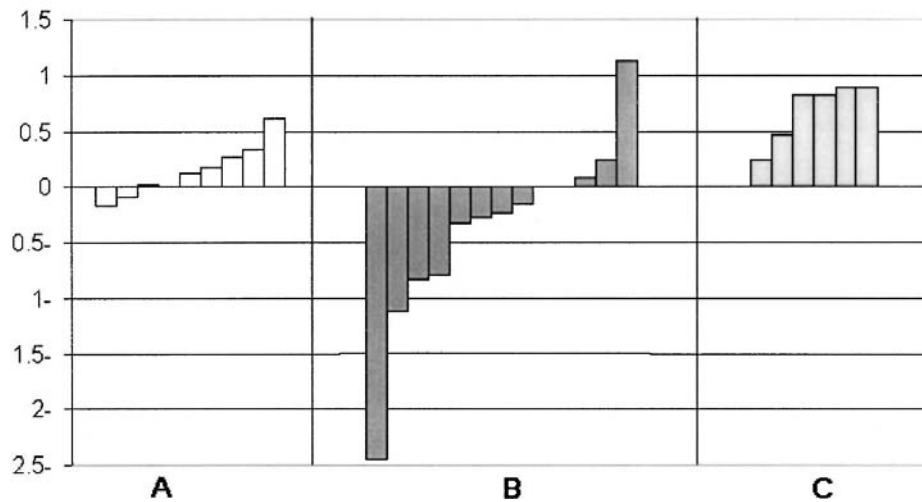


FIG. 2. Changes in HIV plasma viral load after treatment of helminths. Group A: persistently helminth-negative. Group B: successful treatment of helminths. Group C: persistently helminth-positive.

of the helminths (12–14) and that this decrease was indeed the result of helminthic infection alone and not the result of other environmental factors such as nutrition and hygiene associated with the immigration to Israel (20). Our observation that the progression rate of HIV infection among Ethiopian immigrants (once they were living in Israel and after eradication of helminths) was similar to that found in non-Ethiopians living in Israel also lends support to this notion (18,19).

In the current study, the observed differences in HIV plasma VL at baseline between the helminth-negative and helminth-positive groups were not statistically significant, although there was a trend for higher levels of HIV plasma VL and a larger proportion of immune-activated cells (HLA-DR⁺) in the helminth-positive group. The lack of significance could be due to the small size of the study group but could also reflect a false-negative misclassification problem whereby some individuals with a negative stool examination by standard laboratory procedures were actually infected.

The lowering of the HIV plasma VL after deworming was indeed significant when the change in VL observed in the successfully treated group (B) is compared with that in either the persistently infected group (C: $p = .04$) or the two other groups (A + C: $p = .02$). Although the mean change in VL after treatment was only -0.36 log, this was statistically significant, is outside the range of variability for the VL assay, and is most probably of biologic relevance, although this remains to be shown in larger studies. The change in HIV plasma VL cannot be ascribed to the antihelminthic treatment itself, because all the participants received such treatment during fol-

low-up visits, and this did not cause any significant decrease in HIV plasma VL in the helminth-free participants of the study. It cannot be ascribed to differences between the groups—those that cleared the helminths and those that either had persistent helminthic infections or were not infected at all—in terms of CD4 or VL levels at baseline. Decreased egg excretion has been observed to be associated with lower CD4 levels (31,32), but this is clearly not the case in our study, and no significant change in CD4 levels followed the antihelminthic treatment.

Altogether, the results of the current study support our original hypothesis on the role of helminthic infections and chronic immune activation that they cause in enhancing the progression of HIV infection (1). As is by now well established, HIV plasma VL is strongly correlated to disease progression (30); thus, factors that lead to increased levels of HIV plasma VL like the helminthic infection in the current study lead to faster progression. Our findings are also in line with previous studies showing the mutual interactions between HIV infection and other concurrent infections such as tuberculosis, leishmaniasis, and probably malaria (6,33–36). In all these situations, the concurrent infections aggravate and enhance the progression of HIV infection. In all of them, the major mechanism responsible for these effects is chronic immune activation by the coinfecting pathogens, which increases the replication of HIV and thereby increases HIV plasma VL (36). Furthermore, as may well be expected, treating each of these infections has led to a decrease in HIV plasma VL as well as to relative improvements in the clinical course of HIV infection (6,32, 37).

As may well be expected, the relation of concurrent infections to HIV is not necessarily uniform and may depend on several additional parameters. Although immune activation is probably the common denominator for such interaction, the degree and character of the immune activation caused by the concurrent infection may differ, depending on the different etiologic agents, the severity and chronicity of the infections, the type and character of the immune activation (38), and the stage of progression of HIV infection. It is thus likely that antihelminthic treatment may not be uniformly successful in lowering HIV plasma VL in all instances and circumstances. Indeed, in a recent study performed in Kenya, HIV plasma VL did not decrease significantly after treatment of schistosomiasis in people heavily and dually infected with HIV and *S. mansoni* (39). In more recent studies, we have found that the effects of *Schistosoma* infection on the immune functions may be more prolonged and slower to change after eradication in comparison with other more superficial helminthic infections such as *Ascaris* and *Trichuris* (Z. Weisman et al., unpublished observation). Because the majority of the participants in this study were infected with *Ascaris* and *Trichuris*, this may account for the stronger response to antihelminthic treatment that we observed.

Although the results of the current study are intriguing, additional larger controlled studies should be carried out on populations living in different geographic locations and infested with different helminthic infections. The effect of antihelminthic treatment on risks of HIV transmission, horizontal transmission, and mother-to-child transmission should be explored. The potential implications and importance of these findings cannot be overemphasized, particularly for developing countries. Our data suggest that routine treatment of helminthic coinfections among HIV-1-infected individuals may help to reduce the rate of progression of HIV disease. Deworming is a low-cost way of decreasing viral levels, which makes it an attractive addition to the list of therapy of coinfections associated with HIV/AIDS.

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