

Review Article

HIV and helminth co-infection: is deworming necessary?

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SUMMARY

We have previously suggested that helminth infections play a major role in the pathogenesis of HIV-1 infection in Africa and other developing areas, due to their profound effects on the host immune system, which make those infected more susceptible to HIV-1 infection and less able to cope with it. Chronic immune activation with a dominant Th2 profile, and anergy, are the hallmarks of chronic helminth infection, and may therefore account for most of these effects. In the present review, we summarize the studies that have addressed these issues and argue that despite some conflicting results, the cumulative immunological and epidemiological evidence is in favour of deworming as a preventive and possible therapeutic measure vis-à-vis HIV-1 infection. We suggest that it should be at least tested on a wider and larger scale than has been done until now, because of its immense potential impact on the still raging AIDS epidemic in developing countries.

Keywords deworming; helminths; HIV-1; vaccination

INTRODUCTION

About 10 years ago we published our hypothesis on the possible role of helminthic infections in the pathogenesis of AIDS in Africa (1). This was mostly based on our primary observations on Ethiopian immigrants (ETH) who came to Israel in the early 90s, and showed profound immunological derangements upon arrival in the country (2,3). It soon became apparent that they were heavily infected with one or more helminthic parasites, mainly with *Schistosoma mansoni*, *Necator americanus* and *Ascaris lumbricoides*, and to a lesser degree with *Trichuris trichiura*, *Taenia saginata* and *Hymenolepis nana* (3,4). A dominant Th2 immune profile with extreme elevation of eosinophils and of serum IgE accompanied by a high degree of immune activation with lowered levels of CD4 T cells, were commonly seen in these individuals and were associated with the presence of helminth infection (3,4). The decrease of these derangements in immigrants who lived in the new environment of Israel for over 5 years and in whom eradication of helminths took place (4,5), supported the notion that helminths were the cause for the immune impairments. Since helminth infections are so common in Africa, we suggested that such infections with their profound effects on the immune system of the host, may indeed be a major factor in the pathogenesis of AIDS in Africa. It was already well established that immune activation is a major enhancing factor for HIV-1 viral replication and hence plasma HIV-1 viral load (VL), and so pre-existing immune activation in the host, like that found in the helminth-infected immigrants, could possibly account for the fast spread of the epidemic in Africa, and for the differences between the epidemic in Africa and that in the developed world. We hypothesized that since people infected with helminths are immune-activated, they will be more prone to infection with HIV-1, and that once infected, they may have higher VL, and will therefore transmit the virus more easily and the infection will progress faster. Due to their dominant Th2 response, they will not develop

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Received: 19 February 2006

Accepted for publication: 22 July 2006

potent HIV-1-specific cellular immune responses, which will be detrimental for the progression of the disease and for responding to vaccination against HIV-1 (1,6–9). In the following sections we review the data on the immune changes observed in the helminth-infected host and how they impact the response to HIV-1 infection, and review the studies on HIV-1 and helminth co-infections, with emphasis on the effects of deworming. We suggest that several of these studies lend support to some of the major elements in our original hypothesis that would advocate large-scale deworming. However, since several of the issues are by no means resolved, we urge the need for much wider and larger scale studies of these issues, because of their potential impact on the AIDS epidemic.

IMMUNE ACTIVATION AND DYSREGULATION IN HELMINTH-INFECTED INDIVIDUALS

The Th1/Th2 profile

One of the hallmarks of helminth infection is the dominant Th2 immune profile they elicit (3,10–14), though the Th cytokine profile may vary during *Schistosoma* infection, or filariasis (11). Generation of a cellular immune response during helminthic infections is impaired. For example, peripheral T cells obtained from individuals chronically infected with *Onchocerca volvulus* or *Schistosoma mansoni* have decreased IL1 and IL2 secretion following *in vitro* stimulation with *Onchocerca volvulus* antigen (15), or proliferation and IL-4 and IL-5 production following *Schistosoma* adult worm antigen exposure (16), respectively. We found similar decreased proliferation and cytokine secretion to recall antigens including PPD (17) or to anti-CD3 stimulation (18) in PBMC obtained from individuals infected with one or several helminths (as specified above). Of special relevance to HIV-1 infection is the decrease in the HIV-1-specific CD8 CTL response observed in *Schistosoma mansoni*-infected animals, and the decreased cellular response in *Leishmania*–HIV co-infections (1,11,12,19–22).

Immune activation and dysregulation

Imbalance in peripheral lymphocyte populations is observed in association with helminthic infections. These changes were observed in studies in which several helminthic infections were grouped together (3,4,23–25) or in studies where a single helminth species was studied (e.g. *Trichuris muris* (26), *Loa loa* (27,28) and *Schistosoma mansoni* (29)) and include: (a) decrease in CD4+ (4,26,30) and increase in CD8+ T lymphocytes (4,30); (b) marked increase in the proportion of activated (HLA-DR+) CD4+ (4,23,24,27,29) and CD8+ T cells (4,24, 25, 29); (c) significant increase in memory

(CD45RO+) CD4+ and CD8+ T cells (4,23,24,25) with concomitant significant decrease in the proportion of naive (CD45RA+) CD4+ cells (4,23,24); (d) major decrease in CD8+CD28+ T cells (4,24,29–31); and (e) increase in proportion of apoptotic lymphocytes (4). Though similar findings have been found by different investigators in different settings (2,4) it is quite clear that in different geographical regions and maybe different helminth species, different degrees of such immune dysregulation can be found. Of interest, individuals constantly exposed to filarial infections have greater expression of CD28 in both CD4+ and CD8+ T cell subsets (32), suggesting possible compensatory mechanisms in some situations of chronic exposure to parasitic antigens (4,24). Furthermore, expatriates from regions endemic to filarial infections, who do not harbour the parasite any more, do have lower CD8+CD28+ in comparison to normal individuals (32). Interestingly, we also found increased CCR5 and CXCR4 expression on CD4(+) cells with decreased beta chemokine secretion in HIV-1 seronegative ETH compared with non-Ethiopian Israeli individuals (23,33). This may also account for the increased susceptibility of cells obtained from such individuals to infection with HIV-1 (34).

Hyporesponsiveness and anergy

TGF-β and IL-10

Several studies support the notion that IL-10 and TGF-β mediate the antigen-specific hyporesponsiveness characteristic of chronic human or primate helminth infections (21,28,35–39). TGF-β plays an essential role in T cell regulation, including its anti-proliferative effects on T cells and acquisition of effector functions by naïve T cells (40). Production of TGF-β is at least partially responsible for the failure to elicit protective immunity against *Schistosoma mansoni* by certain vaccination protocols (41). We have found that helminth-infected individuals had 2–3 times higher plasma TGF-β than helminth-uninfected subjects, and that the TGF-β levels were correlated with HLA-DR expression on peripheral T cells (18), indicating that immune activation results in increased levels of down-regulatory cytokines such as TGF-β, which we have also found to up-regulate Cbl-b, an upstream intracellular negative regulator of T cell activation (42–44).

CTLA-4 up-regulation

We found increased CTLA-4 expression in CD4+ T cells obtained from HIV-1 seronegative helminth-infected individuals (5,17). The increased CTLA-4 expression was correlated to immune activation as determined by the levels of HLA-DR+CD3+ and CD8+CD38+ cells. Blocking of CTLA-4 enhanced the proliferative responses of PBMC to

tuberculosis (TB) and HIV-1 antigens in non-responsive PBMC obtained from highly immune-activated individuals (5,17). Similar results were found in individuals with long-standing filarial infections (32). These infected individuals had significantly higher percentages of CD4+CTLA-4+ and CD8+CTLA-4+ cells than did uninfected individuals. *In vitro* blocking of CTLA-4 expression in PBMC from filaria-infected individuals induced a mean increase of 44% in IL-5 production to microfilarial antigen, whereas there was a concurrent mean decrease of 42% in IFN γ production, suggesting that CTLA-4 may alter the Th1/Th2 balance in filaria-infected individuals. These data indicate that CTLA-4 has a significant role in regulating the host response to helminths by contributing to the anergy observed in these individuals.

T-cell signal transduction impairments

We found generally defective or no early transmembrane signalling (phosphorylation and/or dephosphorylation of tyrosine kinases), deficient degradation of phosphorylated I κ B α , and attenuated phosphorylation of MAPK kinases, such as ERK1/2 and p38, in chronically immune-activated helminth-infected individuals (17). These signal transduction impairments were correlated with the immune activation state of the cells as determined by HLA-DR, CTLA-4 (17) and Cbl-b expression (45).

T regulatory cells

As summarized above, we observed increased secretion and levels of immunosuppressive cytokines IL-10 and TGF- β , increased proportions of CTLA-4 and of CD25+ positive CD4 cells, and elevation in the levels of Cbl-b expression, in chronic helminth carriers (reviewed also in Ref (45)). Further support for the role Treg cells play in suppressing Th1 responses in helminthic infections was reported by McKee and Pearce (46), who found in mice infected with *Schistosoma mansoni* that CD4+CD25+ cells produced IL-10 and suppressed proliferation of CD4+ T-cells following worm egg antigen stimulation. Furthermore, by conducting adoptive transfer experiments, they demonstrated that CD4+CD25+ cells from naive mice could inhibit the development of Th1 responses in egg-immunized IL-10(-/-) mice. All these features characterize Treg cells/T suppressor cells, which we think are increased in number in response to the chronic immune-activation of the helminth infection and account for the anergy that is associated with such infection. The generation of Treg cells under these circumstances allows the host to attenuate the 'dangerous' outcomes of the immune response to the host itself, yet at the same time may jeopardize the host's ability to contain the infection and more importantly to cope with some other types of infections such as HIV and tuberculosis.

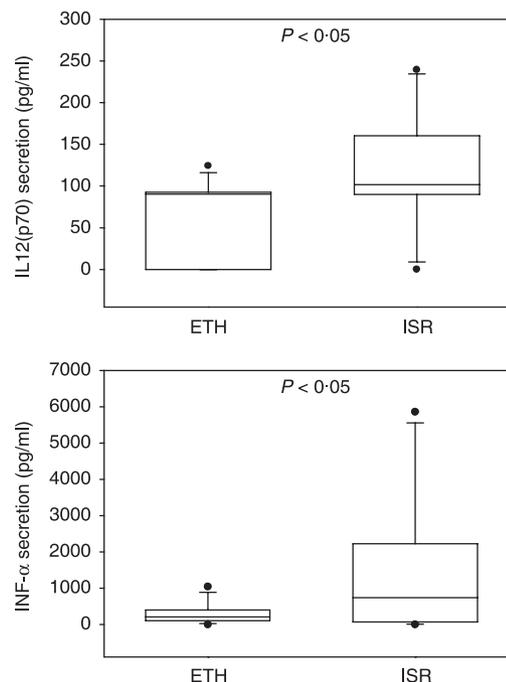


Figure 1 Diminished responsiveness to CpG-DNA stimulation of PBMC obtained from helminth-infected individuals (ETH) compared to PBMC obtained from non-immune-activated individuals (ISR). PBMC were obtained from the blood of 12 ETH and 13 ISR by centrifugation over Ficoll®. PBMC (10^5 cells/100 μ L) were cultured in the presence 6 μ g/mL CpG ODN 2216 (class A; for INF- α determination) or 2006 (class B; for IL12 determination) and 50 μ g/mL CD40L for 48 h. IFN- α and IL-12 (p70) levels were determined in the supernatants by ELISA.

Impaired TLR-9 expression

We found a distinctive Toll-like receptor 9 (TLR9) expression pattern in PBMC of chronically immune-activated individuals due to helminthic infections (47). PBMC from these individuals had a different overall pattern of TLR9 expression, including reduced up-regulation of this receptor following *in vitro* stimulation, and diminished responsiveness to CpG-DNA stimulation (47) (Fig. 1). The impaired TLR-9 expression in several immune cell subsets of the helminth-infected individuals may influence their capacity to mount effective immune responses to pathogens as well as to vaccinations, especially with Th1-inducing adjuvants.

Is deworming an effective measure to correct the immune impairment of the helminth-infected population?

We have tried to look at the effect of deworming on the immune system in a number of ways. First, we showed that most of the immune system changes that were present in new ETH upon arrival to Israel (described extensively

Table 1 Normalization of various immune parameters following eradication of helminthic infections

Immune parameter	Group A			Group B		
	0 ^a	6–12 ^b	<i>P</i> ^c	0 ^a	6–12 ^b	<i>P</i> ^c
Eosinophils (cells/μL)	809 ± 558	484 ± 420	0.002	905 ± 617	1149 ± 732	0.006
IgE (IU/mL)	1687 ± 1374	1494 ± 1427	0.03	2226 ± 1456	2597 ± 1293	ns ^d
CD4+ (%)	37.5 ± 7.36	40.3 ± 6.8	0.025	36.7 ± 6.7	36.3 ± 5.8	ns
CD4 (cells/μL)	690 ± 193	754 ± 350	ns	650 ± 222	697 ± 283	ns
CD8+ (%)	36.1 ± 7.2	30.9 ± 4.2	0.001	36.7 ± 8.4	34.3 ± 8.1	ns
CD8 (cells/μL)	702 ± 324	567 ± 188	0.017	670 ± 287	661 ± 288	ns
CD4/CD8 (ratio)	1.07 ± 0.4	1.32 ± 0.33	0.002	1.06 ± 0.36	1.13 ± 0.43	ns
HLA-DR+CD3+ (%)	9.3 ± 7	5.2 ± 3.8	0.001	11.6 ± 9.7	10.26 ± 6.6	ns
CD4+ CD45RA+ (%)	25.8 ± 10.4	23.8 ± 7.2	ns	21.6 ± 10.9	24.6 ± 9.3	ns
CD28+ CD8+ (%)	42.7 ± 14.6	43.6 ± 12.3	ns	40.2 ± 12.1	44 ± 15	ns

Immune parameters (mean ± SD) in Group A (in which helminths were eradicated) and Group B (in which helminths were not eradicated) at time 0 and 6–12 months later. ^aBlood samples were taken 1–3 months after arrival of new Ethiopian immigrant to Israel. ^bBlood samples were taken 6–12 months after the first blood sample was taken. ^cThe statistical difference between each parameter at time 0 and time 6–12 was examined by using a paired *t*-test. ^dThe differences were not statistically significant.

above) reverted completely or almost completely to our local Israeli normal levels, in ETH living in Israel for several years and after eradication of the helminths (2–4). Second, in order to determine if indeed all the immune changes were the result of the helminthic infections and not due to other factors, such as nutrition, hygiene, etc., we carried out a prospective study of ETH to Israel, and compared the immune profile of two groups – one that underwent deworming successfully shortly after arriving in Israel, and the other group, that did not receive such treatment (by chance and not preplanned). Both groups lived in the same geographical locations and in a similar environment, and were studied a short time after arriving and a year later. The results of this study, not yet published, depicted in Table 1, clearly demonstrate that 6–12 months after deworming a significant decrease in eosinophilia, blood IgE, and immune-activation (HLA-DR on CD3+ cells), as well as a clear trend for normalization of blood T-cell subsets, is present. This clearly suggests that indeed the helminths themselves are responsible for the immune changes that were found in new ETH. The deworming itself brought a normalization of the immune profile that was not found in the immigrants who continued to harbour the helminths. Similar significant decline in activated cells and a significant increase in resting CD8+ T cells was reported in 64 subjects (41 HIV seronegative and 23 HIV seropositive) living in Ethiopia following antihelminthic treatment (25). Regarding the skin reactivity and lymphoproliferative response to PPD that were both significantly diminished in the ETH with helminths, eradication of the worms brought a significant reversion to positive proliferative response, while not affecting significantly the skin test responses (45).

HELMINTH INFECTIONS AND HIV-1

Helminthic infections and susceptibility to HIV-1

Several studies have tried to address this issue. We and others have demonstrated that peripheral blood cells obtained from helminth-infected individuals are more susceptible to HIV-1 infection than similar cells obtained from normal donors (34,48). Moreover, we could show that such susceptibility was correlated with the state of chronic immune activation of these cells. No large-scale field studies have been carried out in human populations to determine if helminth-infected individuals are more susceptible to HIV-1 infections. This could be determined either in helminth-treated individuals in comparison with a helminth-infected population, or in prospective studies in which helminth-infected and non-infected people (including those never infected with helminths and those who have received effective treatment against helminths), are followed up for HIV-1 infection over the course of at least 3 years. Moreover, since WHO- and World Bank-sponsored large-scale deworming programmes are in place now in several developing countries (49,50), and some of these countries are in areas of high incidence and prevalence of HIV-1, prospective studies on the effects of deworming on the incidence of HIV-1 infection, could indeed be carried out.

Does co-infection with helminths affect ongoing HIV-1 infection?

This question has been addressed by several investigators and the results of their studies have not been the same. In a

study carried out in Ethiopia, we observed a highly significant correlation between helminth load (amount of eggs excreted in the stools) and HIV-1 plasma VL, in Ethiopians co-infected with helminths and HIV-1 (51). In a more recent study in Kenya (52), mother-to-child transmission of HIV-1 was found to be significantly associated with the presence of helminth infection in the mother and with immune reactivity of the mother's lymphocytes to the helminth infection, suggesting that indeed helminths impact on HIV-1 infection and probably on HIV-1 VL, though this was not reported in that article. However, in another study that we have carried out in Zambia (53), as well as in studies carried out in Kenya and Uganda (54,55), such associations were not observed. With regard to other co-infections, Wolday *et al.* observed increased HIV-1 VL in *Leishmania* HIV-1 co-infected individuals (51) and likewise, increased HIV-1 VL has been observed in malaria and TB dually infected patients (56–59). In a recent small but very convincing study on this issue in primates, Chenine *et al.* showed that rhesus macaques infected with *Schistosoma mansoni*, developed higher SHIV plasma levels in comparison with *Schistosoma* non-infected animals, following inoculation of the virus, and regardless of the intensity of the parasite infection (60). Furthermore, re-exposure of the SHIV-infected animals to *Schistosoma*, resulted in significant increase of SHIV viral load. Thus, this study demonstrated for the first time that primates co-infected with schistosomes, showed increased replication of immunodeficiency viruses, both in the acute and the chronic phases of the parasite infection, and that this was accompanied by a Th2 shift of the immune profile. With regard to the natural course of the HIV-1 infection, we suggested at the time, that helminth co-infection may contribute to an increase in HIV-1 VL in dually infected populations, and that therefore this could account for the faster progression of HIV-1 infection presumed to be present in Africa. By now, however, it is quite clear that the natural course of HIV-1 infection in Africa may be quite similar to that observed in the developed world, though poor medical, nutritional and other environmental factors may still be dominant in the outcome and contribute to increased mortality and morbidity in the HIV-1-infected population in Africa (61). Moreover, in studies carried by us on HIV(+) ETH in Israel, we have not seen any differences in the rate of progression between the ETH and the non-Ethiopian HIV(+) people living in Israel (24), though this study was carried out after eradication of worms in the Ethiopian immigrants.

What is the effect of deworming on HIV-1 plasma VL in HIV-1 helminth co-infection?

This issue has also been addressed by a number of investigators, and the results are also not uniform. In the study

we have carried out in Ethiopia and mentioned above (51) we found a significant decrease of HIV-1 VL following eradication of worm infection in dually infected patients. Such effects on HIV-1 VL were not found in a number of other studies (55,62), including the one we performed in Zambia, and cited above (53). However, in a recently published study from Zimbabwe (63) a significant association between eradication of *Schistosoma* infection and a lower increase in HIV-1 VL in a dually infected population was found, with a significant increase in CD4 blood levels in the treated population. The reasons for the discrepancies between the different studies are not clear. In both the Zambian (53), and the Ugandan (55) studies, the intensity of the helminth infection (as measured by the egg count) was an order of magnitude lower than that in the population followed by us in Ethiopia (51). In the Ugandan study (55), another confounding element is the lack of complete response to the anti-schistosoma treatment in a third of the participants. At the time we ascribed the lack of effect of deworming in the study by Lawn *et al.* (55) to the difference between *Ascaris* and *Trichuris* infections and that of *Schistosoma*, and to the possibly more profound and long-term effects of the latter on the immune system. However, the results of the more recent studies in Kenya (51), Zimbabwe (63) and the studies in primates (60), do not support such an interpretation. Taken together, it is clear that only much larger scale and well-designed studies will be able to give a better and more balanced answer.

How do helminth infections affect immune responses to HIV-1 and vaccination?

Could the generally weaker responsiveness to all or most vaccines, such as to polio or Bacille Calmette-Guerin (BCG), in developing countries be related to pre-existent immunocompromised immunity that may be accounted for by the high prevalence of helminth infections in these areas? Several studies, including ours, have demonstrated impaired Th1 and specific CTL responses in immunized animals with a pre-existing dominant Th2 profile, as a result of schistosomal infections (19,64–67). We and others found impaired response to tuberculin purified protein derivative (PPD) in helminth-infected individuals either exposed to *Mycobacterium tuberculosis* or immunized previously with BCG, and that impaired response was significantly improved after deworming (68). A recent study of people co-infected with HIV and *Schistosoma mansoni* found that they had decreased CD8+ cytolytic HIV-1-specific T cell responses and increased IL-10 production compared to individuals infected with HIV-1 only (69), strengthening the notion that this parasitic infection damages the capacity to cope with HIV infection, and may lead to faster disease progression. As summarized in some

detail above, helminth-infected people have several impairments in their immune system, most prominently, a dominant Th2 profile, chronic immune activation, and anergy, all of which could account for the poor response to vaccination and particularly to vaccination against microorganisms dependent on a potent cellular response, such as HIV-1 and mycobacteria.

Protective HIV-1 vaccines are clearly the only realistic solution to stop the AIDS epidemic. It is well accepted by the scientific community that a protective HIV vaccine should not only generate neutralizing antibodies but also potent long-lived Th1-dependent memory CD8⁺ CTL (70). It may be that the dominant pre-existing Th2 profile may undermine the ability to generate a Th1 type of response and therefore a HIV-specific cellular immunity (71). This has been clearly shown previously in the study of the murine model of schistosomiasis, where infected animals with a pre-existent Th2 immune profile were not able to mount CTL responses against HIV envelope peptides, while the normal non-infected animals could do so (19). Thus, it may be that eradication of the helminthic infections may be a prerequisite for effective HIV-1 immunization, as we have recently suggested (8), or an HIV-1 vaccine should be designed so as to induce Th1-dependent immune responses in spite of the pre-existent Th2 immune background. Recently we demonstrated the capacity to generate specific potent Th1 immune responses, including to an HIV-1 antigen, in *Schistosoma*-infected mice with pre-existent Th2 profile, by the use of potent Th1-inducing adjuvants (64,65).

CONCLUDING REMARKS

As suggested by us previously, immune activation of the host is a critical determinant in the pathogenesis of HIV infection, and chronic immune activation of the host is a major component of helminthic infections, which are commonly found in developing countries. In this review we have summarized the data on co-infections of HIV-1 and helminths that clearly reflect the intense interaction between the two pathogens and their human host. We believe that these data support the notion that helminth infections are detrimental to our ability to cope with HIV-1, and therefore argue that deworming should be used as a measure to curb the AIDS epidemic in Africa and developing countries elsewhere. Though the evidence supporting this view is by no means conclusive, it does justify a much greater effort for larger and more definitive field studies to resolve the main issues satisfactorily. Moreover, effective vaccinations may fail in areas endemic for helminthic parasites, due to the same factors, and thus eradication of persistent parasitic infections may turn out to be a critical prerequisite for effective HIV protective vaccination in parasite-endemic areas.

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