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EDITORIAL COMMENT

The helminth HIV connection: time to act

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In 1995, we hypothesized that helminthic infections have a major impact on the pathogenesis of AIDS in Africa by increasing the susceptibility to HIV and undermining the host capacity to generate a potent immune response against the viral infection [1]. These ideas were driven by the profound immunological changes we found in the Ethiopian immigrants (ETH) to Israel [2,3]. ETH were seemingly healthy, only 1–2% of them were infected with HIV or tuberculosis, but they were heavily infected with helminthic parasites, mainly *Ascaris lumbricoides*, *Schistosoma mansoni*, and *Necator americanus* [3,4]. They had a dominant TH2 immune profile with extreme elevation of eosinophils and serum IgE, elevated secretion of IL-4, IL-5, and IL-10, decreased secretion of IL-2 and IFN-γ, and marked degree of immune activation, manifested by elevated levels of immune activated CD4(+) and CD8(+) cells, with spontaneous apoptosis and lowered levels of CD4(+) cells [2,3]. These impressive immunological impairments were normalized in ETH living in Israel for over 5 years and in whom the helminthes were eradicated [3,5,6], supporting our notion that the helminths caused the immune impairments. Being an immunologist, I thought that the profound TH2 dominance and the chronic immune activation had to have an impact on the pathogenesis of HIV infection. We hypothesized that because people infected with helminths are immune activated, they will be more prone to HIV infection, have enhanced HIV-1 replication (and thus higher viral load), transmit the virus more easily and the infection will progress faster. Due to their dominant TH2 response, they will not be able to develop potent HIV-1-specific cellular immune responses, being detrimental to the disease progression and for responding to vaccination against HIV-1 [1,7–10]. The preexisting immune activation of the host, like that found in the helminth-infected immigrants, could possibly reflect the situation common to almost a quarter of the world's population infected with helminths [11], accounting for the fast spread of the epidemic in developing countries and mostly in Africa, and for the differences between the epidemic in Africa and that in the developed world.

In the following years, we and others have explored the immune changes accompanying helminthic co-infection on HIV. These studies have been inconclusive and even controversial. Several studies lent further support to our hypothesis [6,12–25], whereas others did not [26–30]. It became clear that large scale, well controlled and well designed human studies are needed [31–33]. On this background, it is important to mention the recent and only primate studies addressing these issues [34,35]. The conditions of such experiments are carefully controlled, the studied population is homogenous, and less confounding factors bias the studies. A significant effect of helminth infection (*Schistosoma mansoni*) on Simian human immunodeficiency virus (SHIV) viral load was clearly demonstrated: acute infection with SHIV resulted in higher plasma viral load of SHIV in those animals infected with *S. mansoni* [35]; re-exposure to *Schistosoma* of monkeys previously infected with both *Schistosoma* and SHIV resulted in additional significant increase of the SHIV viral load; and infection of SHIV-infected animals with *Schistosoma* resulted in significant increase of SHIV plasma viral load together with a decrease in the percentage of their CD4(+) cells [34]. Additionally, the effect of helminth infection on susceptibility to infection with SHIV was also clearly demonstrated, with even more dramatic potential implications [36]. The 50% animal infectious SHIV-C dose was 17-fold lower in parasitized animals compared to that in nonparasitized

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animals ($P < 0.001$), and co-infected animals had significantly higher peak viral load as well as increased viral replication in CD4(+) cells.

Another major development in the field of HIV pathogenesis has been the hypothesis and studies on the role played by intestinal lymphoid organs and mucosa in the primary infection with SIV and HIV, and in its progression [37,38]. A key element in this concept is the contribution of the impaired intestinal mucosa to the immune activation caused by bacterial translocations and thereby to HIV acute infection susceptibility and progression. The possible connection between these ideas and helminth infections, which infect intestinal tissues, is very clear.

The report by Walson *et al*. [39] in this issue of the Journal has studied the effect of worm eradication on plasma HIV viral load and CD4 blood levels in patients co-infected with HIV-1 and helminths. The strength of this study is in its being the first randomized double-blind placebo-controlled study addressing this question and demonstrating that eradication of *A. lumbricoides* resulted in a significant elevation of CD4 cell counts and in a trend for HIV-1 plasma viral load decrease of 0.54 logs after 12 weeks of follow-up. These benefits were seen despite the overall light intensities of the helminth infection and some degree of persistence and or reinfection with the helminths. Together with the other most recent studies of this issue, this study clearly lends strong support to the notion that helminth co-infection has a significant effect on CD4 cell levels and HIV viral load [33]. We have previously reported on a decrease of a mean of 0.34 logs in HIV-1 viral load following deworming, in mostly Ascaris-infected individuals [25]. However, other studies have found no effect [30] or even an increase in HIV-1 viral load and decrease of CD4(+) cells following helminth eradication in co-infected individuals [18,40].

Interestingly, in the study by Walson *et al*., the positive effects of deworming were only seen in individuals co-infected with *A. lumbricoides* and not with other helminths. Walson *et al*. argue that the stronger TH2 skewing effect of Ascaris infection may account for this remarkable effect. Although consistent with previous reports [26], there are reports including the primate studies mentioned above [2–4,34–36] that have demonstrated significant outcomes with *Schistosoma* infections alone or with mixed infections, and thus this issue has to be further validated.

The report by Walson *et al*. highlights the potential wide public health implication of deworming in the context of the HIV epidemic. Prior to the era of antiretroviral therapy (ART), considerable attention was given to HIV co-infections and their impact on host immune responses [41]. It was reasoned that down-modulation of non-specific immune response that some chronic infections elicit might be exploited for HIV-related therapeutic benefits [42–44]. This literature has marshaled scant attention in the face of highly active antiretroviral therapy (HAART) that drops HIV RNA copy levels by 2–5 logs. But a large proportion of the world's HIV-infected population are not treated [45]. Small reductions in HIV RNA – on a logarithmic order of 0.3–0.5 – resulting from relatively simple interventions, such as clearing co-infections, may translate into large benefits in survival and transmission [46–48]. Moreover, the significant elevation of CD4(+) levels, observed after deworming in our own studies and in the study by Walson *et al*., has other immediate implications to ART. Because most HIV-1-positive patients are not eligible for ART before their CD4(+) levels reach 200–300 cells/μm, delaying such decrease by deworming is relatively cheap and easily achieved. Additionally, there is a clear correlation between plasma viral load and HIV-1 transmission through breastfeeding [49]. Breastfeeding was estimated to have contributed 33–50% of mother-to-child transmission (MTCT) cases worldwide [50]. In many helminth endemic areas, over 50% of adults living with HIV/AIDS are women of childbearing age [51]. However, breastfeeding remains the recommendation of the WHO, UNICEF, and CDC in developing countries. Although ART of HIV-1-infected woman is problematic and may lead to development of resistant virus, reducing the viral load through deworming is relatively straightforward and may impact HIV-1 MTCT.

Taken together, the report by Walson *et al*. highlights the importance and wide potential implications of helminth–HIV co-infection. It underscores the urgent need for wider well controlled human clinical trials to address the impact of helminths on susceptibility, transmission and progression of HIV; the potential effect of deworming on CD4(+) levels with delaying ART and improving outcomes in HIV-infected people; and the effects of deworming on the immune response to vaccines in general and to HIV vaccines in particular.

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