

Interactions between Schistosomiasis and Human Immunodeficiency Virus in Western Kenya

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For the past ten years, we have been exploring the relationship between schistosomiasis and human immunodeficiency virus (HIV-1) and how coinfection with both agents may affect the pathology and progression of each infection. To date, given the systems we have examined, the effects of HIV-1 on schistosomiasis have been more profound than the effects of schistosomiasis on HIV-1 progression. Additional key questions with important public health implications remain unanswered, but hopefully not unanswerable.

Key words: schistosomiasis - human immunodeficiency virus - Kenya

Most research on human immunologic and pathologic responses to tropical diseases occurs in locations endemic for more than one parasitic infection. Because of the complexity inherent in effectively studying even one infection on the background of variations in patient genetic backgrounds, infection timing and infectious dose, typically only the effects of a single parasite under study are considered. However, the interaction of some co-infections is too great to ignore, presenting increased challenges for data interpretation but also providing opportunities to learn more about each infectious agent.

A prime example of such a situation is our study of schistosomiasis in car washers working along the shores of Lake Victoria. This population provides a unique study opportunity because the basis for their pay is the number of cars washed, providing an excellent proxy measure of individual water contact. As a result, it has been possible for us to evaluate resistance and susceptibility in a large number of individuals and make predictions about the factors involved in developing resistance to reinfection (Karanja et al. 2002). However, approximately one third of the car washers are also positive for human immunodeficiency virus (HIV-1). Thus, any accurate assessment of patient responses that are likely to depend on CD4⁺ T cells, such as resistance to reinfection or development of pathology, must also take into account HIV-1 infection status and CD4⁺ T cell level. At the same time, it is possible that ongoing infections with *Schistosoma mansoni* may also have effects on a patient's HIV-1 infection.

EFFECTS OF HIV-1 ON SCHISTOSOMIASIS

Our initial studies focused on straightforward investigations of if and how HIV-1 co-infection alters parasitology of *S. mansoni* infections in humans and treatment of

these infections. Consistent with studies in T cell deficient mice (Doenhoff et al. 1986), we found that schistosomiasis patients with HIV-1 infections and reduced CD4⁺ T cell levels excreted fewer eggs than HIV-1 negative persons despite having comparable circulating antigen levels (an indication of having similar numbers of adult worms, Karanja et al. 1997). Furthermore, the efficiency of egg excretion had a significant and positive correlation with CD4⁺ T cell levels in the HIV-1 positive patients. These findings support the theory that efficient egg excretion is dependent on the host's immunologic response (Damian 1987).

We next investigated whether treatment of human schistosomiasis was affected by HIV-1 coinfection. As with granuloma formation and egg excretion, mice with severe T cell immunodeficiencies do not clear their schistosome infections when treated with praziquantel (Sabah et al. 1985). In contrast to the experimental studies, praziquantel was just as effective a treatment for schistosomiasis patients with HIV-1, even those with decreased CD4⁺ T cell counts, as it was for HIV-1 negative schistosomiasis patients (Karanja et al. 1998). Part of this may be due to the likelihood that infection with schistosomes preceded infection with HIV-1, based on the age prevalence curve for both pathogens. As a result, the anti-schistosome antibody responses critical for praziquantel efficacy (Brindley & Sher 1987) may have developed prior to depletion of CD4⁺ T cell help that may be necessary for antibody production. Sera from both HIV-1 positive and negative schistosomiasis patients contained antibody reactivities to antigens that have been proposed as important targets for praziquantel efficacy (Brindley et al. 1989).

The differences between schistosomiasis and HIV-1 age-prevalence curves may also play a role in the absence of any effect of HIV-1 on schistosomiasis-associated liver and spleen pathology. We had hypothesized that the depletion of CD4⁺ T cells by HIV-1, coupled with the importance of CD4⁺ T cells in granuloma formation and subsequent fibrosis development in some individuals, may result in a decreased prevalence of ultrasound-detectable fibrosis in coinfecting patients. In addition, as in T cell

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deficient animal models (Buchanan et al. 1973, Lucas et al. 1980), we thought that coinfecting persons might demonstrate increase levels of serum liver enzymes indicative of parenchymal damage. However, neither measure was significantly different between HIV-1 positive and negative schistosomiasis patients (Mwinzi et al., in press). We did observe that hepatic fibrosis, even in the absence of severe hepatosplenomegaly, was associated with a significant decrease in CD4⁺ T cells in HIV-1 negative individuals. Thus, because schistosomiasis patients likely to develop the hepatosplenic form of disease may be well on their way to severe pathology before they ever get exposed to HIV-1, HIV-1 coinfection may not alter schistosomiasis pathology. However, the reverse situation, in which fibrogenesis in schistosomiasis leads to reduced CD4⁺ T cells, may further exacerbate HIV-1 progression and susceptibility to opportunistic infections (Mwinzi et al., in press).

When assessing susceptibility to reinfection in the car washers, we observed that persons with HIV-1 infection and reduced CD4⁺ T cell counts were more susceptible to reinfection than were persons not coinfecting with HIV-1, suggesting that host resistance to parasite reinfection may be dependent on CD4⁺ T cell help (Karanja et al. 2002). In addition, we have demonstrated that peripheral blood mononuclear cells (PBMCs) from schistosomiasis patients with HIV-1 coinfection produce decreased levels of interleukin (IL-4) and IL-10 compared to persons with schistosomiasis alone and that the magnitude of this effect correlates with the decrease in CD4⁺ T cells (Mwinzi et al. 2001). These findings are consistent with observations that HIV-1 infects and replicates more readily in Th2 cell clones than in Th1 cells (Maggi et al. 1994) and the hypothesis that persons infected with schistosomes or other helminths may be more susceptible to HIV-1 infection and progression than nonparasitized individuals (Bentwich et al. 1995).

EFFECTS OF SCHISTOSOMIASIS ON HIV-1

Although almost a decade has passed since promulgation of the hypothesis that helminth infections exacerbate HIV-1 progression in humans, definitive proof or refutation of an effect of schistosomiasis or other helminths on the course of HIV-1 infection and disease in humans has been difficult to obtain. This is in part due to necessary ethical considerations that require indirect study designs. For example, two groups of HIV-1 patients, one with and one without helminth infection, cannot be compared longitudinally because patients diagnosed with a helminth infection must be treated for their parasites, not simply followed to compare their HIV-1 disease progression. Nevertheless, there are some data from human studies that support the hypothesis that people with helminth infections are more susceptible to HIV-1 infection and/or experience increased viral replication. Cells from persons with schistosomiasis, intestinal helminths, or filariasis are more susceptible to HIV-1 infection *in vitro* than are cells from persons without helminth infection (Shapira-Nahor et al. 1998, Gopinath et al. 2000, Mwinzi et al., unpublished observations). Levels of the chemokine receptors that also serve as HIV-1 coreceptors may provide a mechanis-

tic explanation for these observations. We have recently observed that CD4⁺ T cells and monocytes from schistosomiasis patients express higher levels of CXCR4 and CCR5 than do cells from patients who have previously had schistosomiasis but have been treated (Secor et al. 2003). Together with the data suggesting that Th2 cells are more readily eliminated *in vivo* in co-infected individuals (Mwinzi et al. 2001), these *in vitro* data support the hypothesis that cells from helminth-infected persons are more susceptible to infection with HIV-1. However, a more important public health question is whether a similar effect occurs *in vivo*.

Because it is not ethical to follow helminth infected individuals for HIV-1 progression without treatment, we addressed this question by measuring viral loads of HIV-1-positive schistosomiasis patients at single time points before and after treatment of the patients' schistosomiasis with praziquantel (Lawn et al. 2000). While both fecal egg and circulating antigen levels were reduced by praziquantel treatment, we did not observe a drop in viral load following successful treatment. Given the constraints associated with this study (e.g., follow-up ranging between 1 and 15 months, no knowledge of initial date of HIV-1 infection, and confounding reinfections), we are not convinced that the failure to observe a significant drop in viral load eliminates the possibility that helminth infections do not promote HIV-1 replication. However, we are confident from our results that treatment of a person's schistosome infection was not detrimental to an individual's well being through release of a presumably immunostimulatory bolus of parasite antigens. This is important information at a time when World Health Assembly Resolution 54.19 urges repeated annual or bi-annual treatment for those with schistosomiasis.

To better address the effects of schistosomiasis on host susceptibility and viral replication, we have initiated non-human primate studies using a simian immunodeficiency virus constructed with HIV-1 coat proteins. Preliminary results suggest that schistosome infected animals develop a prominent Th2 response and are more easily infected and/or demonstrate a higher rate of viral replication than do control animals (Chenine et al., manuscript in preparation). If helminth infections promote increased plasma viral loads, this could in turn result in greater shedding of infectious virus into mucosal secretions, thus increasing the transmissibility of HIV-1. Indeed, persons with increased viral loads are more likely to transmit virus to their sexual partners (Quinn et al. 2000). Consequently, chronic helminth infections in sub-Saharan Africa may not only accelerate HIV-1 disease progression in coinfecting individuals themselves, but may also significantly contribute to the rapid spread of the HIV-1 epidemic in this part of the world by rendering coinfecting individuals more infectious to their sexual partners.

Another aspect worthy of consideration is what effect schistosomiasis may have on HIV-1 vaccine efficacy if and when a vaccine is developed. Presumably, effective vaccines against HIV-1 will stimulate a CTL response with the help of Th1-type cells. However, the induction of a Th2 cytokine profile by schistosome eggs is so dominant that responses to other, unrelated antigens or infec-

tions can be altered in the presence of this parasite. For example, immunization of mice with sperm whale myoglobin normally generates a Th1-type CD4⁺ T-cell response; however, if the mice are chronically infected with *S. mansoni* at the time of immunization, the Th1 response is downregulated and replaced by a more Th2-like response to the immunogen (Kullberg et al. 1992). Similarly, human PBMCs collected following tetanus toxoid immunization of individuals who had schistosomiasis at the time of immunization produced less interferon- γ (IFN- γ) and more IL-4 when restimulated in vitro with tetanus toxoid than PBMC collected from non-infected control vaccine recipients, suggesting that the immune response in the *S. mansoni*-infected vaccinees was skewed towards a Th2-like response to the "bystander" tetanus toxoid antigen (Sabin et al. 1996). Thus, persons with schistosomiasis or other Th2-inducing helminth infections may have impaired Th1 and CTL responses to HIV-1 vaccines, making these immunizations less effective in areas endemic for helminths. Indeed, similar effects could be possible for any vaccine dependent on inducing a Th1 response for efficacy that is delivered in countries endemic for parasitic helminths. We are also pursuing these questions using non-human primate infection models.

Clearly, additional questions remain with respect to schistosome and HIV-1 coinfections; principally whether in vitro and animal model observations translate into exacerbating effects on HIV-1 transmission and progression in human populations. Fortunately, should schistosomiasis prove to be detrimental in terms of HIV-1 pathogenesis or prevention of HIV-1 infection by vaccination, praziquantel provides a safe, affordable and efficacious public health intervention to remedy the situation.

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