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The effects of schistosomiasis on HIV/AIDS infection, progression and transmission

W. Evan Secor

Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

Purpose of review—The recent findings pertaining to the public health impact of schistosomiasis on the epidemiology of HIV/AIDS are summarized.

Recent findings—Both empiric data and mathematical models support the hypothesis that schistosome infections lead to increased susceptibility to infection with HIV-1, a more rapid progression to disease through more vigorous viral replication and immunosuppression, and a higher likelihood of transmitting the infection to others through both vertical and horizontal routes. Different species of schistosome infection vary in the magnitude of their effects on these mechanisms with *Schistosoma haematobium* playing a greater role for increased susceptibility and transmission because of its association with urogenital disease.

Summary—Schistosomiasis appears to be a cofactor in the spread and progression of HIV/AIDS in areas wherein both diseases are endemic; increased emphasis on treatment of schistosome infections in persons at risk of HIV/AIDS should be pursued.

Keywords

coinfection; female urogenital schistosomiasis; HIV-1; schistosomiasis

INTRODUCTION

The effect of schistosome infection on HIV/AIDS has provided one of the most compelling topics for investigation into the mechanisms and sequelae of coinfections. If schistosomiasis exacerbates transmission and progression of HIV-1, low-cost treatment for the parasitic infection could also impart a public health benefit by reducing viral infections in areas wherein both pathogens are endemic [1■]. The challenge of ethical protocol design and the expense of randomized intervention trials have precluded the performance of definitive studies to directly address this question but recent investigations have begun to move beyond hypotheses and associations to reveal potential mechanisms of interactions. In addition, interest by the WHO and funding by the Bill and Melinda Gates Foundation have helped

Correspondence to William E. Secor, PhD, Division of Parasitic Diseases and Malaria, Center for Global Health, Centers for Disease Control and Prevention, 1600 Clifton Road N.E. MS-D65, Atlanta, GA 30329-4018, USA. fax: +1 404 718 4193; was4@cdc.gov.

Conflicts of interest

There are no conflicts of interest.

to increase the number of researchers pursuing studies of schistosome/HIV coinfections [2■■], which in turn has led to new ideas as well as important confirmatory work. For example, Downs *et al*. [3■] recently observed that Tanzanian women with female urogenital schistosomiasis (FUS) caused by *Schistosoma haematobium* infections are four-fold more likely to be HIV-1 seropositive than women who do not have FUS. These findings are consistent with the observations of Kjetland *et al*. [4] that showed a three-fold increase in HIV-1 seropositivity among women with demonstrated *S. haematobium* eggs in their genital tissue. Similarly, in an area of Uganda endemic for *Schistosoma mansoni*, individuals who had antibodies to schistosome antigens were significantly more likely to be HIV-1 seropositive than were persons with no evidence of schistosome infection [5■].

There are three phases of HIV infection that schistosomiasis may affect: first, susceptibility to infection, second, progression to disease, and third, transmission to others. Further, the species of schistosome makes a difference; *S. haematobium* infections appear to have a bigger effect on the susceptibility and transmission phases than do *S. mansoni* infections. This review will present recent findings pertinent to the role schistosome infection may play in promotion of viral infection and progression as well as propose future investigations to determine the magnitude of the influence of schistosomiasis on the epidemiology of HIV/AIDS.

EFFECT OF SCHISTOSOMIASIS ON SUSCEPTIBILITY TO INFECTION WITH HIV

Some of the most persuasive rationale for controlling schistosomiasis as a strategy to reduce HIV comes from evidence that infections with schistosomes, especially with *S. haematobium*, enhance susceptibility to viral entry. Approximately, 90% of all HIV-1 infections occur via the mucosal route [6]. Thus, any condition that disrupts the integrity of a mucosal barrier or recruits greater numbers of HIV-1-susceptible cells to a site of virus exposure will increase host susceptibility to infection. In women with *S. haematobium* infections, both mucosal disruption and cellular recruitment occur.

Adult *S. haematobium* worms typically reside in the veins of the urinary bladder plexus, but the interconnected vascular network in the pelvic region allows for easy migration of worms and eggs to any genital organ [7]. Granulomas can form at any location wherein eggs have been deposited, causing a number of genital disorders associated with FUS such as pain, vesicovaginal fistula, spontaneous or contact bleeding, dyspareunia, infertility, and sterility [2■■,8,9]. In cross-sectional studies, genital disorder is present in 33–75% of women who have *S. haematobium* infections, which is impetus enough to address FUS. However, the three-fold to four-fold increased risk of HIV-1 infection in women with FUS further strengthens the argument for preventive interventions [3■,4].

Pathologic manifestations in Malawian women with *S. haematobium* infections and egg deposition in genital tissue include increased vascularity of the cervix and vagina compared with nonendemic controls and increased numbers of $CD4^+$ T cells in the genital mucosa that are targets for viral infection [10■■,11]. Interestingly, even eggs that had become calcified, indicating that they had been in the tissue for an extended time, were associated

with increased vascularization and $CD4^+$ T cells, albeit less than that of recently deposited living eggs. These data suggest that egg deposition can have a very long-lasting effect on increased susceptibility to HIV-1 and are consistent with the observation that genital disorder following treatment of *S. haematobium* infection is still evident 12 months after cure [12]. Furthermore, reversal of disorder only occurs in younger women; women older than 20 years were less likely to resolve genital lesions associated with FUS following treatment [13]. These studies further highlight the importance of control programs focused on treatment of schistosomiasis in children [14■■].

Demonstration that the effect of schistosomiasis on increased host susceptibility to viral infection occurs primarily at mucosal sites comes from studies of *S. mansoni*-infected rhesus macaques exposed to simian–human immunodeficiency virus (SHIV). In *S. mansoni* infections, eggs pass through the intestinal mucosa and granulomatous inflammation is present in rectal tissues. Thus, because of the similarities in local tissue injury, intrarectal exposure of these animals to SHIV is analogous to *S. haematobium*-infected women exposed to HIV-1 through vaginal intercourse. Viral titration studies to determine the animal infectious dose necessary to infect 50% of the macaques (AID_{50}) indicated that 17-fold less virus ($P < 0.0001$) was needed to infect animals with acute *S. mansoni* infection than controls [15]. In contrast, when the experiment was repeated using the same viral stock and the same iterative determination of AID_{50} in schistosome infected and control animals using intravenous SHIV exposure, there was only a 3.3-fold, nonstatistically significant difference between the groups [16■]. Comparison of the two routes of viral infection suggests that the predominant influence of schistosome infection on host susceptibility is a consequence of inflamed mucosae that permit establishment of infection at lower concentrations of virus. Early treatment of schistosome infections to reduce genital inflammation could therefore be an important intervention to reduce risk of HIV-1 infection in *S. haematobium*-endemic areas and should be investigated. Though less common, there are studies of female genital manifestations resulting from *S. mansoni* [17,18]. Studies to evaluate both hypotheses are needed.

EFFECT OF SCHISTOSOMIASIS ON HIV VIRAL LOAD AND PROGRESSION TO DISEASE

Along with increasing host susceptibility to HIV infection, infection with schistosomes may promote progression to disease, primarily by increasing viral load. The most direct demonstration of this in humans came from an intent-to-treat study in an area endemic for both *S. mansoni* and *S. haematobium*. Individuals coinfected with schistosomes and HIV that received early treatment had a significantly slower rate of viral load increase than those whose treatment was delayed for 3 months [19]. The early treatment group also had an increase in $CD4^+$ cell count that was missing in the delayed treatment controls. In the rhesus macaque studies, animals with schistosome infection demonstrated higher peak viral loads despite being exposed to lower concentrations of virus than the control group [15] and animals with chronic SHIV infections and undetectable viral set points had a reactivation of viral replication following infection with *S. mansoni* [20]. In contrast, several studies comparing viral loads during active schistosome infection with viral loads following

treatment did not detect a drop in HIV-1 RNA levels [21,22]. Together, these data suggest that presence of schistosome infection drives viral replication to a higher set point that is not necessarily reversed upon cure; suggesting the need to treat coinfected individuals for their schistosome infection as soon as possible.

Higher viral loads in schistosome-infected hosts have been associated with increased viral replication within cells [15] as well as increased infection and depletion of cells associated with the immune response to schistosome infection [23,24]. Increased HIV-1 infection and depletion is also observed in cells involved in the immune response to some nonhelminth pathogens such as *Mycobacterium tuberculosis* [25■■], consistent with the concept that pathogens inducing Th2-type immune profiles are not the only infectious agents that can exacerbate HIV-1 progression. However, not all antigen-specific CD4 cells are more susceptible to HIV-1 infection, indicating that more than generalized inflammation is needed to increase the spread of virus within a host [25■■]. Even different worm infections can affect HIV-1 coinfection in distinct ways, such that generalizing all helminth/HIV-1 coinfections as one phenotype is inaccurate [26■,27■]. Nevertheless, treatment of most pathogens during HIV-1 coinfection is advisable as even small reductions in viral load may have long-term benefits to delay a person's need to begin antiretroviral therapy or postpone their susceptibility to opportunistic infections [27■,28■].

In addition to increasing viral replication, whether directly within antigen-specific cells [15,23] or indirectly through activating other mechanisms associated with greater viral replication [24,29,30■], schistosome infections may contribute to HIV-1 progression through reducing the ability of the host immune response to control virus. Ugandans coinfected with *S. mansoni* and HIV-1 demonstrated decreased $CD8^+$ T-cell cytolytic activity to viral antigens compared with individuals infected with HIV-1 alone [31]. In animal models of HIV-1 infection, T regulatory cells (Treg), which are elevated in both *S. mansoni* and *S. haematobium* infections [32,33], inhibit the ability of $CD8^+$ cells to control viral replication [34■■]. The effect schistosome-induced Treg activity on anti-HIV-1 immune responses and viral replication in coinfected individuals still needs investigation.

Another intriguing connection between the immune response to schistosomes and HIV-1 progression that merits exploration is the role of arginase. During *S. mansoni* infections, the Th2 cytokines interleukin (IL) 4 and IL-13 induce arginase-1 production in alternatively activated macrophages [35■■]. It was at first thought that arginase-1 promoted chronic fibrosis, but instead, its depletion resulted in exacerbated pathology; a result that suggests that that arginase-1 in fact performs feedback regulation of granulomatous pathology [35■■]. In HIV-1 infected individuals, increased arginase activity is correlated with high viral loads, decreased T-cell counts, and reduced CD3ζ expression [36■]. When viral loads are brought down by antiretroviral therapy, CD3ζ expression is restored and low T-cell counts are no longer associated with higher arginase activity. Neutrophils are the cells implicated in the elevated arginase activity of HIV-1 patients [36■]. The authors of this study propose that the elevated cellular arginase depletes L-arginine levels, resulting in cell cycle arrest of T cells. Whether the arginase-1 in macrophages from schistosome infection combines with the arginase activity from neutrophils during HIV-1 infection to worsen immune hyporesponsiveness and susceptibility to opportunistic infections is

unknown. Possible similarity in arginase induction between the two infections is also a relevant question. Interestingly, adolescents and young adults with schistosomiasis have a high rate of false positivity in a fourth-generation HIV diagnostic assay that detects both antigen and antibody, suggesting that the two pathogens may share cross-reactive antigens [37■] but whether they share pathways of arginase induction requires further investigation.

EFFECT OF SCHISTOSOMIASIS ON TRANSMISSION OF HIV

The third major mechanism by which schistosomiasis may aggravate the spread of HIV-1 is through increased transmission of infection. This has been demonstrated for other coinfecting pathogens and could operate both vertically by increasing the probability of an HIV-infected mother transmitting viral infection to her child as well as horizontally by extending the period of elevated viral load associated with risk of HIV transmission between sexual partners [38]. Helminth infection has previously been demonstrated as a risk factor for mother to child transmission (MTCT) of HIV, although lymphatic filariasis was the predominant disease driving the effect in this study [39]. No study with a sufficient number of schistosome-infected individuals has yet been performed to address the question but should be pursued. Further, considering the genital inflammation that can occur during FUS, studies to investigate the effect of schistosome species on MTCT of HIV-1 should be performed to differentiate effects of systemic increase in viral load that may be seen with any schistosome infection from local inflammation, which would be specific for *S. haematobium* infections.

Investigations into horizontal transmission of HIV-1 in the setting of schistosome coinfection should also control for parasite species to determine the relative contribution of systemic versus local viral load in transmission and whether there is directionality in that transmission. Current evidence suggests the bias to preferential male to female transmission because levels of $CD4^+$ cells are elevated in the semen of men with *S. haematobium* infections [40]. However, women with genital tract inflammation and increased inflammatory cytokines in cervicovaginal lavage samples also demonstrate elevated shedding of HIV-1 [41]. Although this study was not performed in an area endemic for schistosomiasis, the results are suggestive that women with *S. haematobium* infections would have higher vaginal concentrations of virus and would therefore be more infectious to their male sex partners than women with no genital tract inflammation.

CONCLUSION

The hypothesis that the highly disproportionate prevalence of HIV/AIDS in sub-Saharan Africa is the result of more frequent risky sexual behavior or increased number of concurrent partners has been disproven [42■■]. Thus, new critical analyses are required to discern the drivers of HIV-1 epidemiology in this region. Although the 2003 launch of the US President's Emergency Plan for AIDS Relief and contributions from private donors have provided antiretroviral therapy for millions of Africans, millions more lack access to the drugs. Thus, additional strategies should be pursued to control the factors contributing to the rampant spread of HIV-1 infection and progression to AIDS in Africa. Likewise, these differences cannot be solely attributed to schistosomiasis; however, there

are strong biologic bases and increasing empirical data that suggest that schistosome infections increase susceptibility, elevate viral replication, exacerbate immunosuppression, and increase transmission of HIV infection. Furthermore, mathematical models of HIV/schistosomiasis coinfection suggest that treatment of schistosomiasis would not only have definitive impact on the control of HIV/AIDS but could also be one of the most successful and cost effective ways to slow its spread [43■,44■]. Schistosomiasis treatment programs are also becoming more common and over the next few years results from operational research studies will provide information on the most effective treatment approaches for different levels of prevalence. In areas of co-endemicity, HIV and schistosomiasis control programs should cooperate to provide integrated treatment and evaluation to optimize resource utilization and public health impact.

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 286).

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KEY POINTS

- There is growing evidence that schistosomiasis adversely impacts every phase of HIV/AIDS in coinfected individuals.
- Depending on the species of schistosome infection present in the host, susceptibility to infection with HIV, HIV load and disease progression, and risk of vertical and horizontal virus transmission may all increase.
- Well tolerated, low-cost treatment of schistosome infections should be pursued both for alleviating the morbidity associated with schistosomiasis as well as for its potential public health impact on HIV/AIDS.