A Systematic Review of the Risk of HIV Transmission with Concurrent Schistosomiasis Infection

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Abstract

Schistosomiasis and HIV are both significant causes of morbidity in low resource settings worldwide, particularly in Sub-Saharan Africa. Research has indicated that there may be a link between the two infections--specifically that schistosomiasis infection may be a risk factor for HIV transmission. After a comprehensive review was performed to understand current knowledge in the field, a systematic review with meta-analysis exploring the interaction of the two infections was conducted to analyze this relationship. An exhaustive search in PUBMED and Google Scholar of was conducted with search terms related to schistosomiasis and HIV, and studies that were published within the past 30 years in English were included. In total, eight studies with similar outcome measures were found. Odds ratios of HIV transmission in patients with schistosomiasis infection were extracted and pooled. Pooled analysis of odds ratios extracted from the studies failed to find a statistically significant correlation between schistosomiasis infection and HIV infection. The pooled OR was 1.08 with a 95% confidence interval 0.81-1.35 and a p value of 0.056. These findings may indicate that there is not a relationship between the two infections, or they may be a result of the methods chosen for the meta-analysis. Notably, both *S. mansoni* and *S. haematobium* were included in the analysis, and it is possible that only *S. haematobium* significantly impacts HIV transmission. While the study did not result in significant findings, further research is warranted because of the public health implications if schistosomiasis is in fact a risk factor for HIV. This would suggest the possibility of HIV control via community-wide schistosomiasis treatment, a much more feasible and cost-effective intervention than expensive HIV medications.

Table of Contents

Tables and Figures

Background

Schistosomiasis and HIV are both significant causes of morbidity in low resource settings worldwide, particularly in Sub-Saharan Africa. Because of the similarity of the geographic distributions of the two infections, and the large number of people affected by both, significant research has been conducted to examine their relationship. Current research indicates that it is possible that schistosomiasis infection may be a risk factor for HIV transmission.

Schistosomiasis

Schistosomiasis is a fresh water-borne parasitic disease that causes a substantial disease burden worldwide. More than 260 million worldwide are affected in endemic regions, with significant morbidity in several million people annually. The disease spans across tropical regions in Africa, South America, and Asia, but more than 90% of cases that require treatment are in Africa.[1] Infection with any of the five types of flukes that cause schistosomiasis occurs when larva penetrate the skin when in contact with infested water. Schistosomiasis is of special concern in children because of time spent swimming and playing in water and in women because domestic duties often place women in increased contact with infested water.

The lifecycle of schistosomiasis is dependent on the presence of their intermediate host, certain species of freshwater snails, and the warm fresh-water sources in which the snails are able to live. Infected humans eliminate eggs of the parasite via feces or urine. If the eggs enter an appropriate water source under optimal conditions, they hatch and infect snails. In the snails, the organisms undergo the remainder of their lifecycle and are released as cercariae, ready to infect a human. Infective cercariae live in fresh water and penetrate the skin of an exposed individual. These transform into schistosomulae, which migrate through tissues until they reach veins where they will grow into adults. The location of the adult worms varies based on species, and different locations results in different clinical disease as described below. Adult worms then reproduce and females deposit eggs into the venules where they gradually move into the lumen of either the intestine or bladder where they are expelled in the urine and feces. The eggs can be detected while in the urine and feces for diagnostic purposes[1]. Upon initial

infection, humans are generally asymptomatic but may experience some puritis. Within 1-2 months, systemic symptoms appear, including fever, chills, cough, and myalgias. This can progress to chronic infection, the symptoms of which depend on the species and site of infection.

The disease presents clinically in either an intestinal or urogenital form. In urogenital schistosomiasis, which is most often *Schistosoma haematobium* infection. The adult *S. haematobium* worm lives in the venous plexus of the urinary bladder, generally causing hematuria with frequent kidney and bladder damage. From the veins of the bladder, the worms as well as the eggs that they produce can easily travel through interconnected vessels to the genitals where they induce the formation of granulomas, particularly in the cervix where they can become trapped[4]. These granulomas and the surrounding inflammatory response result in pain, bleeding, dyspareunia, infertility, and vesicovaginal fistula[17]. Women can present with genital lesions in the vagina, cervix, and vulva. Termed female genital schistosomiasis, this form may cause increased risk of HIV infection[2]. In contrast to *S. haematobium*, *S. mansoni* resides in the gastrointestinal system, specifically the mesenteric veins draining the large intestine. Intestinal schistosomiasis can present with symptoms including abdominal pain, hematochezia, and hepatomegaly.

Treatment of Schistosomiasis is fairly straightforward with a short course of praziquantel, however prevention may be an even more important strategy in managing schistosomiasis infections across an entire population. Prevention techniques include large-scale population-based prophylactic treatment with praziquantel, community education on the dangers of spending time in infected water sources, and snail control in those water sources.[1] These preventative measures would be most effective in areas with high prevalence of the disease, which unfortunately have limited access to treatment at this time. A study in 2014 indicated that only 20.7% of people requiring praziquantel treatment and prophylaxis received it, mostly because of shortages of the medication.[1]

HIV

While there have been significant advances in treatment and management during the past decade, HIV/AIDS continues to be a major global public health issue, causing the death of 1.5 million people in 2013 alone. Sub-Saharan Africa bears most of the burden of the disease with approximately 70% of both existing and new cases occurring in the region.[3] There continues to be no cure for HIV and treatment is costly, making prevention the key area in which to intervene.

Interaction between schistosomiasis and HIV

Many of the same regions with the greatest burden of Schistosomiasis also have high prevalence of HIV infections. A number of studies have examined the association between the two infections, suggesting schistosomiasis increases susceptibility for HIV infection. Although there have not been any randomized control trials because of ethical issues in study design, a number of observational studies suggest that rates of HIV are increased with concurrent schistosomiasis infection. A study in Tanzania that looked for coinfection with *S. haematobium* and HIV, Downs 2011, by testing for ova in urine samples, cervical smears, and cervical biopsies and by testing for HIV via rapid antibody tests. The results of this study supported the hypothesis that schistosomiasis increases transmission of HIV, showing that there was a greatly increased rate of HIV in women with urogenital schistosomiasis infection.[9] A similar study, Kjetland 2006, compared rates HIV infection, again as measured with antibody tests, in those with and without schistosomiasis infection measured both by ova in urine/genital samples. HIV testing was positive in 41% of the women with laboratory positive tests for schistosomiasis compared 26% of the women with negative tests for schistosomiasis.[10]

There are several potential explanations for this increased rate of transmission including the increase in physical points of entry created by genital schistosomiasis, the increased presence of HIV susceptible cells, and the change in immunologic response created by an schistosomal infection.

Physical openings in the mucosa

S. haematobium infection can cause genital lesions in women. Meanwhile, 90% of HIV infections occur via viral entry through the mucosal route. Therefore, any disruption of the mucosa, including a urogenital schistosomal infection, should increase the likelihood of viral entry.[17] These areas of mucosal lesions contain breaches in the epithelium through which the virus may gain access, particularly in the cervix where HIV acquisition is most common.[4] These lesions may also be sites of increased viral shedding that put the infected person's sexual partners at increased risk.[4]

Immunologic changes

There may also be an increased risk of transmission because infection by schistosomal ova in the genital tract results in activation of the immune response, both locally and systemically. A sequela of genital schistosomiasis infection is increased vascularity and recruitment of a number of CD4+ T cells in the genital mucosa of the vagina and cervix. These changes persist, although they are decreased, even when the granuloma surrounding the schistosomal eggs has calcified. The CD4+ T cells are the cells that HIV infects, and increased density of these CD4+ cells at the site of entry of the virus could result in increased transmission.[5] There may also be a systemic immunologic mechanism by which chronic schistosomiasis infection increases HIV susceptibility. As a parasite, *S. haematobium* triggers a Th2 immune response in the host, which largely fights allergens and parasites. This increased Th2 response downregulates the Th1 response that is used to combat infection with bacteria and viruses. Since Th1 cytotoxic T-cells are required to control initial infection with HIV, this reduction in numbers could lead to a spread of the virus.[6]

Infection with other schistosomal species

Current research presents a mixed picture of the association between schistosomiasis and HIV for other species of schistosomes. A study examining the relationship between *S. mansoni* and HIV infection, Mazingo 2014, indicated that there is no increased risk of HIV when infected with the parasite.[13] Inhabitants of a rural fishing village in Tanzania were tested for infection, and individuals who were seropositive for HIV did not have higher prevalence of *S. mansoni* infection as measured by ova in stool samples. These results, while relevant enough to be included in a systematic review, do not negate the hypothesis that genital schistosomiasis increases risk of HIV transmission by the mechanisms outlined above because *S. mansoni* causes the intestinal form of schistosomiasis rather than the urogenital form. In fact, these studies could suggest that it is the genital lesions caused by *S. haematobium* that is responsible for increased HIV transmission.

Rationale for Systematic Review

Reviews of the current research in the field existed, but prior to this systematic review no recent reviews used an unbiased statistical analysis to examine the interplay between schistosomiasis and HIV. The most recent systematic review of the subject was published in 2011, and the numerous articles published since then suggest the need for a more updated review.

Methods

Searches were conducted within PUBMED and Google Scholar to obtain an exhaustive collection of articles. A search term from each of the categories below was used in every search. Within PUBMED, searches were conducted both with and without MESH terms in order to avoid excluding any potentially useful studies.

The search results were refined by language then primary research articles within the past 30 years will be selected. Of these, case studies and studies that only examine one of the diseases or the other were eliminated. Only primary research articles in English that were published within the last 30 years and which directly analyze schistosomiasis and HIV were included. The primary research articles were assessed for strength based on study design and number of participants. Articles were chosen that included odds ratios or data from which odds ratios could be calculated. Odds ratios for transmission of HIV in those with Schistosomiasis were extracted. A pooled analysis of the odd ratios was conducted with the assistance of the UA College of Medicine Statistics Department.

Table 1: Search terms

“schistosomiasis”	“HIV”
“schistosoma haematobium”	“human immunodeficiency virus”
“genital schistosomiasis”	“HIV/AIDS”
“schistosoma”	“AIDS”
“bilharzia”	

Results

The comprehensive literature search resulted in eight studies that matched the criteria above. The articles chosen were all case-control studies examining large populations in Sub-Saharan Africa. All studies took place in either the areas surrounding Lake Victoria and in Zimbabwe. The studies are further described below.

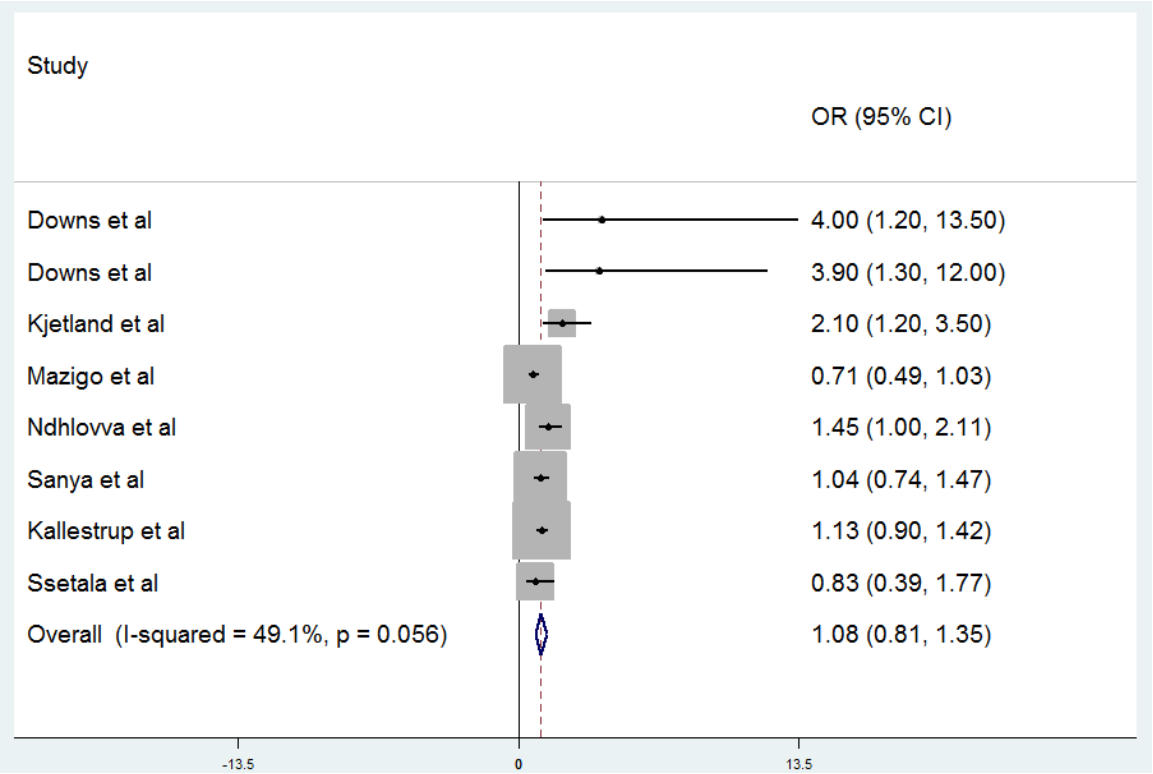
Pooled analysis of odds ratios extracted from the studies failed to find a statistically significant correlation between schistosomiasis infection and HIV infection. The pooled OR was 1.08 with a 95% confidence interval 0.81-1.35 and a p value of 0.056.

Table 2: *Studies selected for analysis*

Author and Title	Year	Summary of Study
Downs, et al. Urogenital Schistosomiasis in Women of Reproductive Age in Tanzania's Lake Victoria Region	2011	457 women ages 18-50 from rural Tanzania were tested for schistosomal infection by urine and genital ova. There was a significantly higher rate of HIV in women with schistosomiasis.
Downs, et al. Association of Schistosomiasis and HIV Infection in Tanzania	2012	345 women ages 15-50 from fishing villages in Tanzania where *S. mansoni* is common were tested for schistosomal infection by serum antigens. Schistosomiasis significantly predicted HIV infection.
Kjetland, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women	2006	527 sexually active, nonpregnant women ages 20-49 from rural Zimbabwe were tested for schistosomal infection by urine or genital ova. Women with schistosomiasis were determined to have higher risk of being infected with HIV.
Mazingo, et al. Co-infection with Schistosoma mansoni and Human Immunodeficiency Virus-1 (HIV-1) among residents of fishing villages of north-western Tanzania	2014	1,785 adults aged 21-55 in fishing villages in Tanzania were tested for schistosomal infection by stool ova. There was no association between schistosomal and HIV infections, including when stratified by intensity of infection.
Ndhlovu, et al. Prevalence of urinary schistosomiasis and HIV in females living in a rural community of Zimbabwe: does age matter?	2007	544 women aged 15-49 from rural Zimbabwe were tested for schistosomal infection by urine ova. No significant association was shown between the infections in total but there was a significantly higher rate of HIV in women with schistosomiasis over age 35.
Sanya, et al. Schistosoma mansoni and HIV infection in a Ugandan population with high HIV and helminth prevalence	2015	1,412 adults over the age of 13 in a fishing village in Uganda were tested for schistosomal infection by stool ova. Schistosomiasis was not found to be associated with HIV infection.
Kallestrup, et al. Schistosomiasis and HIV-1 Infection in Rural Zimbabwe: Implications of Coinfection for Excretion of Eggs	2005	1,545 adults over the age of 18 from rural Zimbabwe were tested for schistosomal infection by urine and stool ova. There was no significant association found between the two infections.

Ssetala, et al. Schistosoma mansoni and HIV acquisition in fishing communities of Lake Victoria, Uganda: a nested case control study	2015	200 adults from a fishing village in Uganda where *S. mansoni* infection is common were tested for schistosomal infections by serum antigens. No significant infection was found between schistosomal and HIV infections.

Figure 1: Pooled odds ratios of HIV infection in patients with schistosomiasis infection from the relevant studies.



Discussion

The meta-analysis of existing literature about HIV and schistosomiasis did not find a statistically significant increased risk of HIV infection in those with schistosomiasis infection. It is possible that this indicates that there is no relationship between the two infections, but it may also be because of the methods used in this study. This systematic review included studies with both *S. haematobium* and *S. mansoni*, and it may be that only *S. haematobium* is associated with increased risk of HIV infection. This would be consistent with the proposed pathophysiology discussed prior, as it is primarily *S. haematobium* infections that cause mucosal damage that could be an entry point for HIV infection. It was not possible in this study to limit the analysis to only one of the infection types because several of the studies did not specifically measure or report the species involved. However, this is a possible area of additional research in the future. An additional factor that may have contributed to the lack of significant findings include that some studies specifically studied women while others examined both genders. It is feasible that an increased risk of HIV transmission caused by schistosomiasis would be gender dependent, especially if that increased risk is related to mucosal lesions.

Future Direction and Conclusions

While the systematic review with meta-analysis did not result in a statically significant association between schistosomiasis and HIV, there are individual studies with significant results to suggest that there may be a connection between the two infections. Additional research is needed to clarify this connection and the direction of causality. While it would be of scientific interest if existing HIV infections predisposed patients to schistosomal infections, the public health implication is much more significant if the reverse is true. If schistosomal infections cause increased risk of HIV transmission, it is possible that schistosomiasis treatment with antiparasitics would decrease HIV transmission. If campaigns to treat schistosomiasis, which have been shown to be feasible on a large scale, did decrease HIV transmission, the high cost in both lives and dollars of HIV infections could be prevented with a relatively cheap and simple intervention. The potential benefits of such an intervention warrant continued research into the relationship between these two infectious diseases despite the findings of this meta-analysis.

References

1. World Health Organization (2015) Schistosomiasis. Fact Sheet No. 115, May 2015. Available at: http://www.who.int/mediacentre/factsheets/fs115/en/
2. Norseth HM, Ndhlovu PD, Kleppa E, et al. The colposcopic atlas of schistosomiasis in the lower female genital tract based on studies in malawi,zimbabwe, madagascar and south africa. PLoS Negl Trop Dis. 2014;8(11):e3229.
3. World Health Organization (2015) HIV/AIDS. Fact Sheet No. 360, November 2014. Available at: http://www.who.int/mediacentre/factsheets/fs360/en/
4. Kjetland EF, Leutscher PD, Ndhlovu PD. A review of female genital schistosomiasis. Trends Parasitol. 2012;28(2):58-65.
5. Jourdan PM, Holmen SD, Gundersen SG, Roald B, Kjetland EF. HIV target cells in schistosoma haematobium-infected female genital mucosa. Am J Trop Med Hyg. 2011;85(6):1060-1064.
6. Mbabazi PS, Andan O, Fitzgerald DW, Chitsulo L, Engels D, Downs JA. Examining the relationship between urogenital schistosomiasis and HIV infection. PLoS Negl Trop Dis. 2011;5(12):e1396.
7. Baggaley RF, Hollingsworth TD. Brief report: HIV-1 transmissions during asymptomatic infection: Exploring the impact of changes in HIV-1 viral load due to coinfections. J Acquir Immune Defic Syndr. 2015;68(5):594-598.
8. van Bogaert LJ. Biopsy-diagnosed female genital schistosomiasis in rural limpopo, south africa. Int J Gynaecol Obstet. 2011;115(1):75-76.
9. Downs JA, van Dam GJ, Changalucha JM, et al. Association of schistosomiasis and HIV infection in tanzania. Am J Trop Med Hyg. 2012;87(5):868-873.
10. Kjetland EF, Ndhlovu PD, Gomo E, et al. Association between genital schistosomiasis and HIV in rural zimbabwean women. AIDS. 2006;20(4):593-600.
11. Kleppa E, Klinge KF, Galaphaththi-Arachchige HN, et al. Schistosoma haematobium infection and CD4+ T-cell levels: A cross-sectional study of young south african women. PLoS One. 2015;10(3):e0119326.

12. Kotze SR, Zinyama-Gutsire R, Kallestrup P, et al. HIV and schistosomiasis in rural zimbabwe: The association of retinol-binding protein with disease progression, inflammation and mortality. Int J Infect Dis. 2015;33:159-164.
13. Mazigo HD, Dunne DW, Wilson S, et al. Co-infection with schistosoma mansoni and human immunodeficiency virus-1 (HIV-1) among residents of fishing villages of north-western tanzania. Parasit Vectors. 2014;7:587-014-0587-2.
14. Ndeffo Mbah ML, Poolman EM, Drain PK, Coffee MP, van der Werf MJ, Galvani AP. HIV and schistosoma haematobium prevalences correlate in sub-saharan africa. Trop Med Int Health. 2013;18(10):1174-1179.
15. Ndhlovu PD, Mduluza T, Kjetland EF, et al. Prevalence of urinary schistosomiasis and HIV in females living in a rural community of zimbabwe: Does age matter? Trans R Soc Trop Med Hyg. 2007;101(5):433-438.
16. Noormahomed EV, Nhacupe N, Mascaro-Lazcano C, et al. A cross-sectional serological study of cysticercosis, schistosomiasis, toxocariasis and echinococcosis in HIV-1 infected people in beira, mozambique. PLoS Negl Trop Dis. 2014;8(9):e3121.
17. Sanya RE, Muhangi L, Nampijja M, et al. Schistosoma mansoni and HIV infection in a ugandan population with high HIV and helminth prevalence. Trop Med Int Health. 2015.
18. Ssetaala A, Nakiyingi-Miiro J, Asiki G, et al. Schistosoma mansoni and HIV acquisition in fishing communities of lake victoria, uganda: A nested case-control study. Trop Med Int Health. 2015.
19. Zinyama-Gutsire RB, Chasela C, Madsen HO, et al. Role of mannose-binding lectin deficiency in HIV-1 and schistosoma infections in a rural adult population in zimbabwe. PLoS One. 2015;10(4):e0122659.
20. Ndeffo Mbah ML, Poolman EM, Atkins KE, et al. Potential cost-effectiveness of schistosomiasis treatment for reducing HIV transmission in africa--the case of zimbabwean women. PLoS Negl Trop Dis. 2013;7(8):e2346.
21. Downs JA, Mguta C, Kaatano GM, et al. Urogenital Schistosomiasis in Women of Reproductive Age in Tanzania's Lake Victoria Region. Am J Trop Med Hyg. 2011; 84(3):364-69.