



HHS Public Access

Author manuscript

Int J Infect Dis. Author manuscript; available in PMC 2022 February 28.

Published in final edited form as:

Int J Infect Dis. 2021 January ; 102: 544–553. doi:10.1016/j.ijid.2020.10.088.

Association of schistosomiasis and HIV infections: A systematic review and meta-analysis

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Abstract

Background: Female genital schistosomiasis (FGS) affects up to 56 million women in sub-Saharan Africa and may increase risk of HIV infection.

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Author contributions

PP and WES directed the project. PP and CER designed the study. PP and EFK reviewed the literature. CER conducted the data analysis. PP, EFK, JAD, and PSM wrote the paper. All authors reviewed and commented on the manuscript.

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Ethical approval

All procedures that are required by the US government have been taken to ensure no human subject violations occurred with this data analysis. As this is a systematic review, no human subjects were involved in the development of this manuscript.

Conflicts of interest

None.

Methods: To assess the association of schistosomiasis with HIV infection, peer-reviewed literature published until 31 December 2018 was examined and a pooled estimate for the odds ratio was generated using Bayesian random effects models.

Results: Of the 364 abstracts that were identified, 26 were included in the summary. Eight reported odds ratios of the association between schistosomiasis and HIV; one reported a transmission hazard ratio of 1.8 (95% CI, 1.2–2.6) among women and 1.4 (95% CI, 1.0–1.9) among men; 11 described the prevalence of schistosomiasis among HIV-positive people (range, 1.5–36.6%); and six reported the prevalence of HIV among people with schistosomiasis (range, 5.8–57.3%). Six studies were selected for quantitative analysis. The pooled estimate for the odds ratio of HIV among people with schistosomiasis was 2.3 (95% CI, 1.2–4.3).

Conclusions: A significant association of schistosomiasis with HIV was found. However, a specific summary estimate for FGS could not be generated. A research agenda was provided to determine the effect of FGS on HIV infection. The WHO’s policy on mass drug administration for schistosomiasis may prevent HIV.

Keywords

HIV; Schistosomiasis; Association; Sub-Saharan Africa

Evidence before this study

There have been limited reports of an increased risk of human immunodeficiency virus (HIV) acquisition among people with schistosomiasis. However, randomised clinical trials to investigate this issue have not been conducted. To inform global HIV epidemic control it is imperative to understand the association between schistosomiasis and HIV acquisition.

This review of the literature was performed to identify published peer-reviewed articles about schistosomiasis among HIV-positive people in low-income and middle-income countries, specifically sub-Saharan Africa. OVID/Medline, Embase and Global Health databases were searched to identify human studies published between 01 January 1973 and 31 December 2018. Search terms were “HIV infections and schistosomiasis” to ensure that all relevant citations were found but limited to the English language. Twenty-six studies that reported data on both HIV and schistosome infections in various populations were included. The studies were categorised based on the outcome of interest because some studies provided estimates of prevalence, while others examined the association between HIV and schistosomiasis. Eleven studies reported the prevalence of schistosomiasis among HIV-positive people. Data from seven studies were combined to generate a pooled estimate of prevalence of schistosomiasis by *Schistosoma haematobium* (*S. haematobium*) or *Schistosoma mansoni* (*S. mansoni*) among HIV-positive people (6.86%; 95% CI, 1.4–21.2). Data from four studies were combined to generate a pooled estimate of prevalence of schistosomiasis by any species among HIV-positive people (20.7%; 95% CI, 2.8–49.5). Six studies reported the prevalence of HIV among people with diagnosed schistosomiasis. These studies were conducted in Africa, and estimates varied widely (range, 5.8–57.3%). One ecological analysis of 43 countries in sub-Saharan Africa established a 2.9% relative increase in HIV prevalence for each 100 individuals infected with *S. haematobium*.

Mathematical modelling demonstrated that mass drug administration to treat schistosomiasis targeting school-age children may decrease HIV incidence by 9–22% and overall HIV prevalence by 6–20%. Eight studies reported odds ratios (OR) of HIV infection in people who have schistosomiasis. Data from six studies reporting ORs on associations between schistosomiasis and HIV among women with *S. haematobium* or *S. mansoni* were combined to generate a pooled OR estimate of 2.3 (95% CI, 1.2–4.3) for having HIV among those with schistosome infections. One study reported hazard ratios (HR) of schistosomiasis on onward HIV transmission in discordant couples when women (HR = 1.8; 95% CI, 1.2–2.6) or men (HR = 1.4; 95% CI, 1.0–1.9) were the initial partner with HIV.

Added value of this study

The authors are the first to provide a research agenda, including policy level needs, to address next steps in controlling the HIV/schistosomiasis syndemic in adolescent girls and young women based on meta-analysis of HIV risk due to schistosomiasis. This study also provided pooled prevalence estimates of schistosomiasis among HIV-infected people, which contributes to the understanding of the significant burden of comorbidity. This study also calculated a pooled OR to understand the association of schistosomiasis and HIV. The results are valuable because they not only provide evidence of an association between HIV and schistosomiasis among women but also provide a research agenda and suggest actionable next steps to address this problem. Controlling schistosomiasis may reduce risk of HIV among women and contribute to controlling the HIV epidemic in sub-Saharan Africa. The authors represent public health and research institutions across the globe and are members of the World Health Organization Technical Working Group on HIV and Schistosomiasis. This working group has been involved in advocacy and drawing attention to this syndemic and in offering practical actionable steps to respond with a multifactorial approach.

Implications for practice or policy and future research

The review was undertaken to inform normative guidance and policy for reducing HIV among adolescent girls and young women in sub-Saharan Africa. As the manuscript was being finalised, a related review was published that corroborated these results on the association between HIV and schistosomiasis. In addition, this study offered action steps for uptake of existing policies and service integration to address both diseases. Lastly, it developed a research agenda and work with stakeholders has been undertaken to advocate for further research as well as policy development to enact a comprehensive, multidisciplinary approach to incorporate schistosomiasis prevention into current prevention and service delivery with an aim of facilitating HIV epidemic control.

Introduction

Schistosomiasis, also known as bilharzia, is an infectious disease caused by parasitic worms. It affects more than 230 million people worldwide, 90% of whom are in Africa (WHO, 2017). In humans, infection with *Schistosoma mansoni* (*S. mansoni*), *Schistosoma haematobium* (*S. haematobium*) and *Schistosoma japonicum* (*S. japonicum*) are the

most common causes of illness and have different endemic distributions in tropical and subtropical zones (WHO, 2016). Infection occurs when the skin contacts freshwater that contains infected intermediate host snails (Anon, 2020). Schistosome cercariae are released from the snails and can infect people who are in contact with contaminated water. The parasites develop into adults within several weeks and live in the blood vessels of humans, where the female worms produce eggs (Whitty et al., 2000). Some of the eggs are found in the urine, genital specimens and stool because they travel to the bladder, genital tract or intestine, but others are retained in the body, where they cause tissue pathology associated with schistosomiasis.

Schistosome infection usually occurs in childhood, with recurrent infections possible throughout life whenever an individual encounters contaminated water. In sub-Saharan Africa, areas endemic for HIV are also burdened with schistosomiasis; communities with the highest burden of schistosomiasis often have high HIV prevalence (Kjetland et al., 2014; Brodish and Singh, 2016). Endemic schistosomiasis, specifically female genital schistosomiasis (FGS) among adolescent girls and young women (AGYW), may be associated with increased risk of HIV acquisition (Hotez et al., 2009; Chenine et al., 2008; Secor, 2012; Sturt et al., 2020). FGS, which is estimated to affect 20–56 million girls, is predominantly caused by *S. haematobium* and rarely by *S. mansoni*, when parasite eggs are deposited in the cervix and vaginal wall (Sturt et al., 2020). FGS is associated with mucosal changes in the intra-vaginal epithelium of the cervix, fornices and vagina (Figure 1) and infertility if the upper genital tract is involved (Woodall and Kramer, 2018; Miller-Fellows et al., 2017). The immunologic changes that occur during schistosomiasis may also increase HIV transmission risk (Jourdan et al., 2011; Jourdan et al., 2013; Kleppa et al., 2014).

FGS increases susceptibility to HIV infection through disruption of the vaginal and cervical epithelium caused by erosion or inflammation. As demonstrated with trauma or ulcerative sexually transmitted diseases, neovascularisation and disruptions in the integrity of the epithelial barrier are associated with an increased risk for HIV infection (Sturt et al., 2020; Sheffield et al., 2007; Masese et al., 2015; Powers et al., 2008). The friable epithelium and bleeding during coitus in women with FGS facilitates access to deeper genital cell layers by HIV in semen (Jourdan et al., 2011; Powers et al., 2008; Helling-Giese et al., 1996). In a schistosomiasis endemic area, the risk of transmission of HIV from HIV-positive men to HIV-negative women could be mitigated by praziquantel treatment among men, as it has been shown to reduce HIV viral load in semen (Stecher et al., 2015; Midzi et al., 2017; Downs et al., 2017a). In addition, the pathological alterations caused by FGS may increase HIV shedding and promote transmission of HIV from HIV-positive women to HIV-negative men (Downs et al., 2017). Therefore, as in men, praziquantel treatment may be beneficial to prevent HIV transmission from women who are also co-infected.

Schistosomiasis also can alter the immune responses to HIV. The immunoregulatory responses associated with helminth infection downregulate the T-helper-1-type immune response associated with control of viral infections. HIV replicates more readily in the T-helper-2-type cells associated with helminth infections (Fairfax et al., 2012; Turner et al., 2011). Similarly, activated immune cells, such as those present around schistosome eggs in the genital lesion or in adjacent areas, are more susceptible to HIV infection (Jourdan

et al., 2011; Kleppa et al., 2014). Schistosome eggs elicit a complex cellular and humoral immune response, which includes upregulation of the cellular CD4 receptors and chemokine co-receptors that are used by HIV-1 to enter host cells. Cells with higher levels of these receptors are more susceptible to HIV invasion, further increasing the risk of women with FGS for HIV acquisition and viral propagation.

Although the association between schistosomiasis, specifically FGS, with HIV infection is biologically plausible, it has not been definitively established by previous studies. Although the treatment for schistosomiasis is readily available and deemed beneficial, a randomised controlled trial (RCT, the gold-standard for proving causality) to evaluate the effect of schistosomiasis on HIV acquisition has not been pursued (Kjetland et al., 2012; Walson and John-Stewart, 2008). Most studies are observational studies. Therefore, the literature was examined for studies on the association of HIV and schistosomiasis, and this meta-analysis was conducted to generate a summary estimate.

Methods

Literature search and review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to guide this systematic review (Liberati et al., 2009). A review of the literature was conducted to identify published peer-reviewed articles about schistosomiasis among HIV-positive people in low-income and middle-income countries, specifically sub-Saharan Africa. The OVID/Medline, Embase and Global Health databases were searched to identify human studies published between 01 January 1973 and 31 December 2018. To ensure that all relevant citations were found but limited to the English language the search terms were “HIV infections and schistosomiasis”. EndNote X8 (Clarivate Analytics, London, UK) was used to compile, clean, categorise, and assess citations.

Study selection

The titles and abstracts of the identified articles were screened for reference to HIV and schistosomiasis. Next, two authors (PP and EFK) reviewed selected articles' titles and abstracts to identify those reporting prevalence of HIV among people with schistosomiasis, prevalence of schistosomiasis among people with HIV, and the association of HIV with schistosomiasis. The full texts of those articles reporting relevant data were reviewed. To ensure reproducibility and precision, studies with statistically robust methods were included, such as standardised and unbiased data collection with adequate sample size. Figure 2 details the study selection procedure. Of the 364 abstracts identified (Figure 2), 29 focused on HIV and *S. haematobium* and/or *S. mansoni*, and 26 were included in the summary (Brodish and Singh, 2016; Downs et al., 2017b; Colombe et al., 2018; Noormahomed et al., 2014; Stete et al., 2018; Sanyaolu et al., 2016; Costiniuk et al., 2012; Sadlier et al., 2013; Efraim et al., 2013; Lar et al., 2016; Tegegne et al., 2017; Marti et al., 2017; Olusegun et al., 2011; Kallestrup et al., 2005; Mazigo et al., 2014; Kleppa et al., 2015; Mwanakasale et al., 2003; Ndhlovu et al., 2007; Kjetland et al., 2006; Downs et al., 2012; Woodburn et al., 2009; Sanya et al., 2015; Ssetaala et al., 2015; Downs et al., 2011; Wall et al., 2018) (Table 1): nine reported the association of HIV and schistosomiasis; 11

reported the prevalence of schistosomiasis among people with HIV; and six reported the prevalence of HIV among people with schistosomiasis (one of these papers also reported an odds ratio for the association between schistosomiasis and HIV). One ecological analysis, one mathematical modelling paper and one summary of HIV and schistosomiasis among children were also evaluated.

Meta-analyses

Of the 26 papers included in the summary, nine were reviewed and six were selected for quantitative analysis, given the heterogeneity of studies. A random-effects logistic regression model was used to estimate pooled odds and prevalence of HIV among people with schistosomiasis. For available studies, each outcome was treated as the random effect. Data stratified by sex were combined to generate an overall estimated adjusted odds ratio (OR). In addition, the pooled prevalence of schistosomiasis caused by *S. haematobium* or *S. mansoni* among HIV-positive people was calculated. A pooled estimate for the prevalence of HIV among people with schistosomiasis was unable to be calculated due to the heterogeneity of study design and methods; specifically, the population studied and schistosome species detected varied between studies. All statistical analyses were conducted using PROC NL MIXED in SAS 9.4 (Cary, NC).

Geographic mapping

UNAIDS estimated HIV incidence among young women in 21 countries at the end of 2019. Using ARCGIS, the HIV district estimates were overlaid with data from WHO-supported school-based schistosomiasis prevalence surveys (Bowie et al., 2004; Knowles et al., 2017). The analysis showed the two sets of prevalence estimates in terciles, displaying where prevalence for both infections were relatively high.

Results

Included studies

This review included 26 studies (Brodish and Singh, 2016; Downs et al., 2017b; Colombe et al., 2018; Noormahomed et al., 2014; Stete et al., 2018; Sanyaolu et al., 2016; Costiniuk et al., 2012; Sadlier et al., 2013; Efraim et al., 2013; Lar et al., 2016; Tegegne et al., 2017; Marti et al., 2017; Olusegun et al., 2011; Kallestrup et al., 2005; Mazigo et al., 2014; Kleppa et al., 2015; Mwanakasale et al., 2003; Ndhlovu et al., 2007; Kjetland et al., 2006; Downs et al., 2012; Woodburn et al., 2009; Sanya et al., 2015; Ssetaala et al., 2015; Downs et al., 2011; Wall et al., 2018) that reported data on both HIV and schistosome infections in various populations (Table 1). The studies were categorised based on the outcome of interest because some studies provided estimates of prevalence, while others examined the association between HIV and schistosomiasis.

Studies of prevalence of schistosomiasis among people living with HIV

Eleven studies reported the prevalence of schistosomiasis among HIV-positive people. All but two studies were performed in Africa. The remaining two (Costiniuk et al., 2012; Sadlier et al., 2013) were performed in clinics in Western countries that cared for patients who originated from endemic areas, predominantly in Eastern and Southern Africa and South

America (Table 1). The studies varied widely in the prevalence of schistosome infections, ranging from 0.3% among HIV-positive adults in urban Nigeria who were screened for *S. haematobium* using urine microscopy to 36.6% among a community-based sample of HIV-positive people living in an endemic region of Tanzania who were screened using the more sensitive serum schistosome circulating anodic antigen test. Data from seven studies (Costiniuk et al., 2012; Sadlier et al., 2013; Efraim et al., 2013; Lar et al., 2016; Tegegne et al., 2017; Marti et al., 2017; Olusegun et al., 2011) were combined to generate a pooled estimate of prevalence of schistosomiasis by *S. haematobium* or *S. mansoni* among HIV-positive people (6.86%; 95% CI, 1.4–21.2). Data from four studies (Colombe et al., 2018; Noormahomed et al., 2014; Stete et al., 2018; Sanyaolu et al., 2016) were combined to generate a pooled estimate of prevalence of schistosomiasis by any species among HIV-positive people (20.7%; 95% CI, 2.8–49.5).

Studies of prevalence of HIV among people with schistosomiasis

Six studies (Downs et al., 2017b; Mazigo et al., 2014; Kleppa et al., 2015; Mwanakasale et al., 2003; Ndhlovu et al., 2007) reported the prevalence of HIV among people with diagnosed schistosomiasis (Table 1). These studies were conducted in Africa, and estimates varied widely (range, 5.8–57.3%). Three studies of people with *S. haematobium* infections examined the prevalence of HIV, which ranged 14.4–33.3%. All studies used microscopy to detect schistosome infection but had different populations. Three studies focused on both men and women, and two focused on only women, of which one was limited to AGYW. Thus, a pooled estimate was not generated. One ecological analysis of 43 countries in sub-Saharan Africa established that each *S. haematobium* infection per 100 individuals was associated with a 2.9% relative increase in HIV prevalence (Ndeffo Mbah et al., 2013). Mathematical modelling demonstrated that mass drug administration to treat schistosomiasis targeting school-age children may decrease HIV incidence by 9–22% and overall HIV prevalence by 6–20% (Ndeffo Mbah et al., 2014).

Association of HIV and schistosomiasis

Of eight studies that reported ORs of the effect of *S. haematobium* or *S. mansoni* infection on HIV, five of six found significantly increased odds of HIV infection among women with schistosomiasis (Table 1) (Brodish and Singh, 2016; Downs et al., 2017b; Mwanakasale et al., 2003; Ndhlovu et al., 2007; Kjetland et al., 2006; Downs et al., 2012; Woodburn et al., 2009; Sanya et al., 2015; Downs et al., 2011). The other two studies did not separate data by sex (Sanya et al., 2015; Ssetaala et al., 2015). Combining the data from women generated a pooled OR estimate of 2.3 (95% CI, 1.2–4.3) for having HIV among those with schistosome infections (Figure 3). In one study that reported hazard ratios (HR), *S. haematobium*-infected men (HR, 1.4, 95% CI, 1.0–1.9; $p = 0.042$) and women (HR, 1.8, 95% CI, 1.2–2.6; $p = 0.002$) who were HIV positive transmitted virus to their HIV-negative partners in a shorter time than discordant couples where the HIV-positive partner was not infected with *S. haematobium* (Wall et al., 2018).

Geographic mapping

One article showed the substantial geographic overlap between HIV and schistosomiasis, particularly in sub-Saharan Africa (Bustinduy et al., 2014). In 2020, UNAIDS mapped

modelled district-level HIV incidence among young women (15–24 years) in 2019 and *S. haematobium* prevalence as measured in the school-aged population in Malawi in 2012 and 2013 (Figure 4). Similar maps are being prepared for other countries in the region. The maps suggest a potential ecological association between *S. haematobium* prevalence and HIV incidence among young women in districts along Lake Malawi and some southern districts around Blantyre.

Research gaps

This systematic review enabled a research agenda to be identified that would improve understanding of HIV and schistosomiasis and thus facilitate effective public health program integration to address both diseases. The gaps and opportunities related to HIV susceptibility, disease progression and transmission are summarised in Table 2. In addition, other considerations that are warranted for schistosomiasis prevention and control were identified. Focus was on research that would inform integrated public health programming to address multiple issues that young women face in sub-Saharan Africa. For example, a need for better diagnostics for FGS as well as increased healthcare worker training to detect FGS in resource-limited areas were emphasised. Future studies could focus on sexual and reproductive health throughout the lifetime of patients and ideally incorporate multifactorial issues such as exposure to schistosome-infected waters, history of praziquantel use and comorbidities. Operational research and implementation science could help to assess the association between FGS and HIV.

Discussion

In sub-Saharan Africa, AGYW are disproportionately affected by HIV due to behavioural, biological and structural factors (UNAIDS, 2020a). These structural factors are related to gender roles, societal norms and limited access to education and resources, all of which contribute to lack of autonomy for AGYW. These inequities prevent AGYW from making self-protective decisions about their health and lives, thus increasing their risk of several diseases, including HIV and FGS (UNAIDS, 2020b). The President's Emergency Plan for AIDS Relief (PEPFAR) supports comprehensive HIV prevention using a multi-sectoral approach that involves programming among individuals and communities to empower AGYW and change norms and laws to improve their access to, and use of, HIV prevention services. In addition, this multi-sectoral approach aims to identify and treat male partners living with HIV (Saul et al., 2018). This platform can be strengthened and leveraged to provide comprehensive sexual and reproductive health services to address various issues, including sexually transmitted diseases and FGS, that increase AGYW's risk of HIV infection (Engels et al., 2020).

The current data suggest that girls and women with schistosomiasis may be at higher risk of HIV infection compared with those without schistosomiasis, and that this association is similar to that seen with genital ulcer disease (GUD) (Patel et al., 2014). The HIV risk for women with FGS may be even higher than suggested in previous studies because of the difficulty of diagnosing FGS and because the current analysis included women with urinary schistosomiasis who may not have had FGS. One study from Zimbabwe corroborates these

findings, showing that HIV was associated with FGS (OR 2.1, 95% CI 1.2–3.5; $p = 0.008$) (Kjetland et al., 2006). The association between FGS and HIV transmission is biologically plausible because, similar to GUD, FGS contributes to cervical mucosal friability and lesions that could increase the vulnerability of women to HIV infection (Jourdan et al., 2011; Helling-Giese et al., 1996). Similar to GUD (Sheffield et al., 2007), FGS also causes an immune reaction that upregulates the receptors that HIV uses to enter cells (Miller-Fellows et al., 2017; Jourdan et al., 2011; Jourdan et al., 2013; Kleppa et al., 2014), possibly further facilitating infection.

The current findings suggest that controlling all forms of schistosomiasis could help to control HIV. Preventing and treating schistosome infections could decrease the risk of HIV by reducing genital lesions and/or restoring mucosal or systemic antiviral immunity (Kjetland et al., 2007; Yegorov et al., 2019; Secor et al., 2003). In addition, for people co-infected with HIV, treating schistosomiasis could decrease viral load levels (Midzi et al., 2017), facilitating viral load suppression, decreasing risk of progression to AIDS and decreasing risk of HIV transmission to partners (Wall et al., 2018; Cohen et al., 2011). The overall decrease in community viral load is necessary for HIV epidemic control. Therefore, further research is needed to understand the effects of treating schistosomiasis on HIV progression and transmission in both individuals and communities in co-endemic areas.

It is believed that strengthening population-level efforts to control schistosome infection would not only reduce morbidity and mortality related to schistosomiasis but may also prevent a substantial number of new HIV infections each year (Bowie et al., 2004; Baggaley and Hollingsworth, 2015). The World Health Organization recommends that schistosomiasis treatment should be routinely provided to entire communities in endemic areas (World Health Organization, 2006; WHO, 2020a). However, many schistosomiasis control programs in Africa target schistosomiasis treatment to children aged 5–15 years, among whom the prevalence and intensity of infection is highest. Basing treatment in schools can disproportionately exclude adolescent girls, who have one of the highest global HIV incidence rates and who often attend fewer years of school than boys (UNICEF, 2020; UNAIDS, 2020c). PEPFAR's effort to keep young girls in school may improve their access to treatment for schistosomiasis (Saul et al., 2018). Furthermore, due to a global shortage of praziquantel (Anon, 2010), community treatment for schistosomiasis is limited; 16.9% of at-risk adults received treatment in 2017, which is far below the established threshold for attaining public health goals for control and elimination of schistosomiasis morbidity (WHO, 2018; Anon, 2013). As a result, AGYW may have vaginal lesions throughout their sexually active and reproductive years (Kjetland et al., 2006; Poggensee et al., 2000). Ensuring that treatment reaches more individuals would decrease the global burden of schistosomiasis and would also likely decrease associated complications in women, including subfertility (Miller-Fellows et al., 2017; Wall et al., 2018; Kjetland et al., 2010) and HIV, and could be part of an overall implementation package to improve the sexual health of women⁶⁰.

It is unclear whether urogenital schistosome infection during pregnancy can facilitate vertical transmission of HIV; however, this warrants consideration (Freer et al., 2018). Even though the World Health Organization recommends schistosomiasis treatment during

pregnancy, some country guidelines and pharmaceutical companies still restrict praziquantel for pregnant women. Given their increased risk of HIV and to prevent the development of FGS throughout their reproductive years AGYW and pregnant women could be targeted for schistosomiasis treatment in endemic areas (Hotez et al., 2020). Treatment of schistosomiasis with praziquantel could also be incorporated into routine antenatal care (Fridman et al., 2018). Pregnant women can be assured that praziquantel will not harm the foetus, and pharmaceutical companies should consider updating praziquantel tablet package warnings (Poggensee et al., 2000; Ndibazza et al., 2010; WHO, 2006). Furthermore, health professionals, including primary health care nurses and gynaecologists, could be trained and given tools with which to diagnose and treat FGS (UNAIDS, 2020b; WHO, 2006).

Although this study found a significant association of schistosomiasis with HIV, it could not generate a specific summary estimate for FGS. Few studies have directly examined women for FGS and study designs varied considerably, which precluded more robust analysis. A further limitation was that only three studies provided longitudinal designs that permitted documentation of schistosome infection status prior to acquisition of HIV. FGS is not routinely diagnosed because it requires a colposcope and trained healthcare workers to identify the clinical manifestations of the disease in the vaginal/cervical epithelium (WHO, 2015). No studies of schistosomiasis and HIV reported FGS as a specific outcome. The testing methods for schistosomiasis also varied between studies, and some studies did not differentiate between schistosome species (Table 1). Urinary *S. haematobium* among women was the closest proxy of FGS. Therefore, the summary estimate that were generated likely underestimated the association between HIV and FGS, but the findings are nonetheless relevant in understanding the relationship between HIV and FGS and corroborate recent findings (Zirimenya et al., 2020). In rare instances, *S. mansoni* has caused the genital lesions of FGS, thus these outcomes were included as well.

This systematic review also highlights knowledge gaps and presents a research agenda. Many of the authors of this manuscript participated in a workshop entitled *State of the Science at the Intersection of Helminth and HIV Infection*, which was sponsored by the National Institutes of Allergy and Infectious Diseases of the U.S. National Institutes of Health in November 2017. In September of 2019, the Coalition for Operational Research for Neglected Tropical Diseases convened a meeting focused on FGS, with a breakout session dedicated to linkages with HIV. Together, the meetings and the systematic review have enabled operational research to be identified that would improve understanding of the association between schistosomiasis and HIV infection and facilitate effective public health program integration to address both diseases in vulnerable populations. This is the only group to develop a research agenda and suggest actionable items to address this syndemic based on the results of this analysis.

AGYW are a priority population for HIV prevention and receive comprehensive HIV programming in sub-Saharan Africa through a significant investment by the global public health community (Saul et al., 2018). It is believed that these efforts could be undermined if factors that facilitate HIV infection are not addressed. Thus, it is felt that it is important to offer AGYW comprehensive sexual and reproductive health services, including prevention, diagnosis and treatment of schistosomiasis (UNAIDS, 2020b). Investing in high-quality

integrated programs can improve the long-term health and well-being of AGYW and may reduce gender inequalities, thus ensuring their dignity and well-being for years to come.

Acknowledgement

We would like to thank Mohamed Albirair, MBBS, MPH for his contribution to this paper.

Funding

No additional funding was required for this review and analysis.

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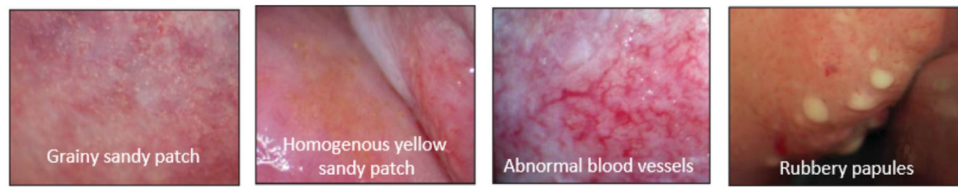


Figure 1.
Intra-vaginal lesions caused by female genital schistosomiasis. Images by Elisabeth Klepp, Eyrun Kjetland, Hashini Galappaththi-Arachchige, and Bodo Randrianasolo.

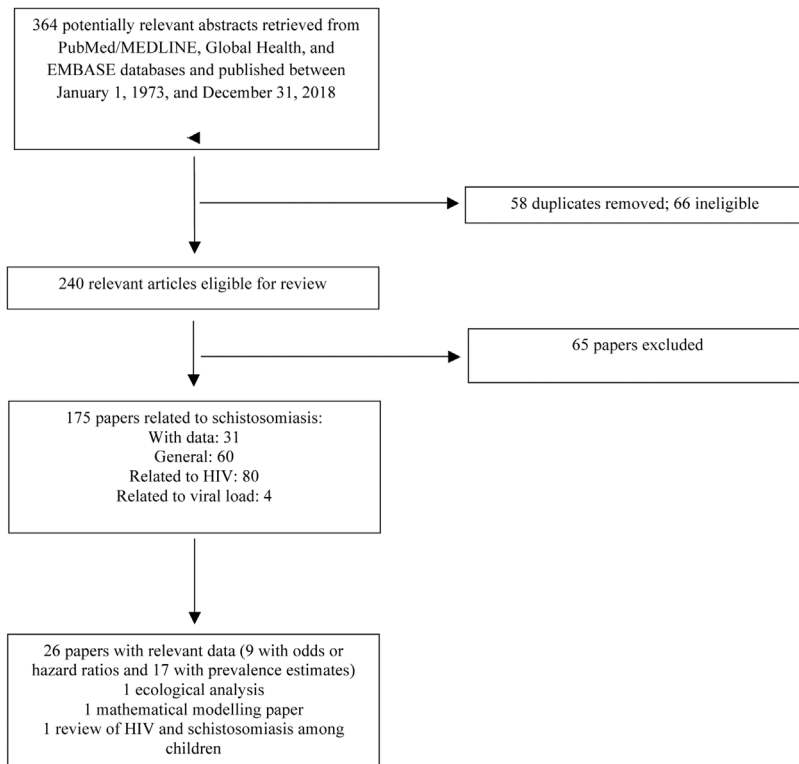


Figure 2. Selection of studies regarding schistosomiasis and HIV.

Schistosomiasis spp.

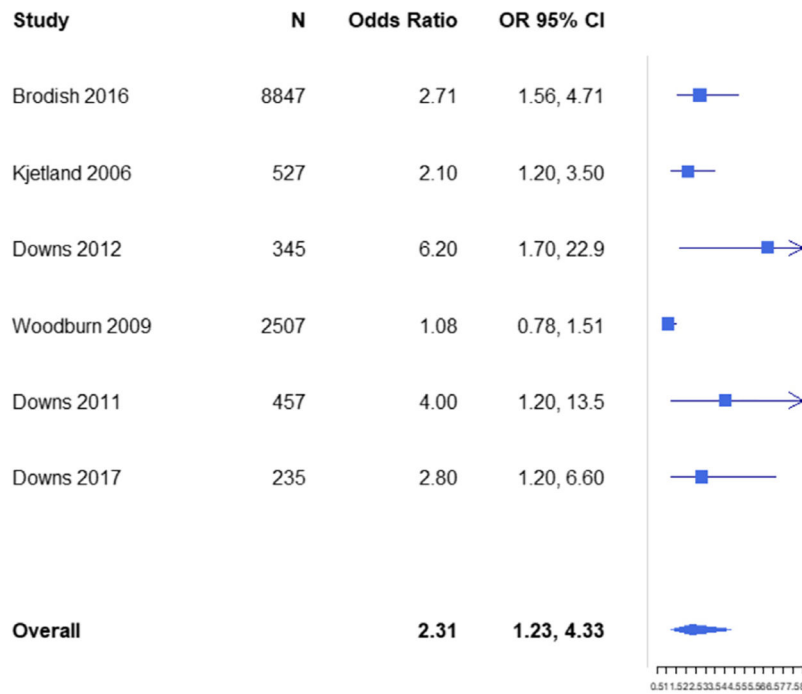


Figure 3. Pooled estimate of odds of HIV infection among women with *Schistosoma haematobium* or *Schistosoma mansoni* using data from six studies in sub-Saharan Africa.

Malawi's Schistosomiasis and HIV Incidence

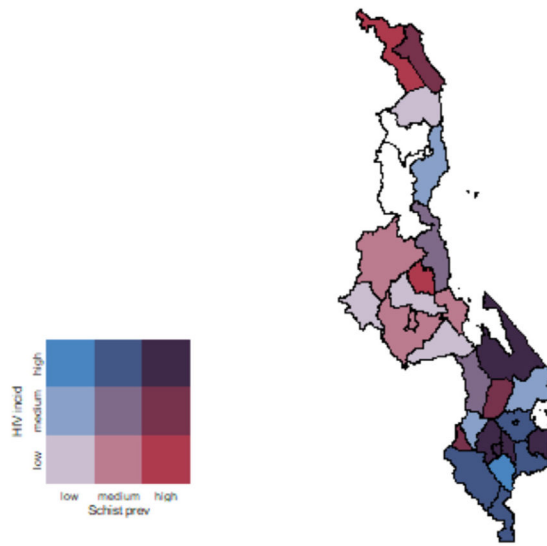


Figure 4. District mapping of HIV incidence among young women (15–24 years) and *Schistosoma haematobium* prevalence in Malawi.

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Table 1

Summary of studies that reported prevalence estimates and odds ratios for schistosomiasis and HIV.

HIV and schistosomiasis measure	Country	Organism	Sample size	Numerator	Denominator	Prevalence (%)	95% CI	Type of schistosome testing
<i>Prevalence - Schistosomiasis among HIV-positive people</i>								
Colombe et al. (2018)	Tanzania	<i>Schistosoma</i> spp.	20,000	63	172	36.6		serum antigen
Noormahomed et al. (2014)	Mozambique	<i>Schistosoma</i> spp.	601	139	601	23		serum antibody
Stete et al. (2018)	Tanzania	<i>Schistosoma</i> spp.	461	88	461	19.1		serum antigen
Sanyaolu et al. (2016)	Nigeria	<i>Schistosoma</i> spp.	1080	1	65	1.5		microscopy
Costiniuk et al. (2012)	Toronto	<i>S. mansoni</i> and <i>S. haematobium</i>	97	7	97	7.4		serum antibody
Sadlier et al. (2013)	Europe	<i>S. mansoni</i> and <i>S. haematobium</i>	90	7	90	8		serum antibody
Efraim et al. (2013)	Tanzania	<i>S. mansoni</i> and <i>S. haematobium</i>	364	97	364	27.6		microscopy and urine antigen
Lar et al. (2016)	Nigeria	<i>S. mansoni</i>	205	34	205	16.5		microscopy
Tegegne et al. (2017)	Ethiopia	<i>S. mansoni</i>	223	2	223	0.9		microscopy
Marti et al. (2017)	Tanzania	<i>S. mansoni</i>	305	30	305	19.7		urine antigen
Olusegun et al. (2011)	Nigeria	<i>S. haematobium</i>	2000	6	2000	0.3		microscopy
<i>Prevalence - HIV among people with schistosomiasis</i>								
Downs et al. (2017b))	Tanzania	<i>S. mansoni</i> and <i>S. haematobium</i>	674	38	429	5.8		microscopy and serum antigen
Kallestrup et al. (2005)	Zimbabwe	<i>Schistosoma</i> spp.	287	130	227	57.3		microscopy
Mazigo et al. (2014)	Tanzania	<i>S. mansoni</i>	1785	125	854	6.29	3.59–11.04	microscopy
Kleppa et al. (2015)	South Africa	<i>S. haematobium</i>	792	123	765	16.1		microscopy
Mwanakasale et al. (2003)	Zambia	<i>S. haematobium</i>	544	73	507	14.4		microscopy
Ndhlovu et al. (2007)	Zimbabwe	<i>S. haematobium</i>	544	72	216	33.3		microscopy
<i>Odds ratio</i>								
Brodish and Singh (2016)	Mozambique	<i>S. haematobium</i>	8847	Population		Odds Ratio	95% CI	
Kjetland et al. (2006)	Zimbabwe	<i>S. haematobium</i>	527	women		2.71	1.56–4.71	
Downs et al. (2012)	Tanzania	<i>S. mansoni</i>	345	women		2.1	1.2–3.5	
Woodburn et al. (2009)	Uganda	<i>S. mansoni</i>	2507	women		6.2	1.7–22.9	
Sanya et al. (2015)	Uganda	<i>S. mansoni</i>	538	women		1.08	0.78–1.51	
Ssetaala et al. (2015)	Uganda	<i>S. mansoni</i>	200	both		1.04	0.74–1.47	
Downs et al. (2011)	Tanzania	<i>S. mansoni</i> and <i>S. haematobium</i>	457	both		1.23	0.3–5.7	
				women		4.0	1.23–2.57	

HIV and schistosomiasis measure	Country	Organism	Sample size	Numerator	Denominator	Prevalence (%)	95% CI	Type of schistosome testing
Downs et al. (2017b)	Tanzania	<i>S. mansoni</i> and <i>S. haematobium</i>	235	women		2.8	1.2–6.6	
			131	men		0.7	0.3–1.8	
<i>Hazard ratio</i>	Zambia	<i>S. haematobium</i>	596	women		Hazard Ratio	1.23–2.57	
			599	men		1.38	1.01–1.87	
Wall et al. (2018)								

Table 2

Gaps in knowledge regarding HIV and schistosomiasis co-infection.

Gaps	Opportunities
<i>HIV susceptibility and transmission</i>	• Effect of schistosomiasis disease on the urogenital and/or gastrointestinal microenvironments and on mucosal integrity as it relates to risk of HIV infection
	• Extent of genital inflammation caused by female genital schistosomiasis (FGS) and risk of HIV infection
	• Effect of praziquantel treatment on cervical/mucosal lesions on immune activation and risk of HIV infection
	• Effect of pre-exposure prophylaxis (PrEP) in preventing HIV infection among adolescent girls and young (AGYW) with FGS
	• Effect of FGS and its treatment among pregnant women and vertical transmission of HIV
	• Effect of co-infection on HIV viral load and response to antiretroviral therapy
	• Effects of schistosomiasis on female susceptibility, female infectiousness, male susceptibility and male infectiousness
<i>HIV progression</i>	• Effect of praziquantel treatment to reduce spread of HIV in co-endemic communities
	• Effect of immunomodulation (T-cell upregulation) on viral suppression
	• Effect of immune activation on occurrence of opportunistic infections and comorbidities
	• Effect of praziquantel treatment on immune activation and HIV markers
	• Effect of treatment on reversal of immunomodulation and thus on progression
	• Effect of co-infection on susceptibility to cervical cancer and sexually transmitted diseases
	• Need for a point of care, non-invasive diagnostic test for FGS
<i>Additional considerations</i>	• Need for definitive prevention of FGS
	• Need for definitive curative treatment of FGS
	• Examination of mass treatment versus individual treatment
	• Need for healthcare worker training and curricula incorporating FGS
	• Need for post-graduate training for gynaecologists, medical doctors and nurses performing vaginal examinations
	• Need for community and school information programs
	• Effect of co-infection with HIV and antiretroviral therapy use on potential benefit of praziquantel treatment
	• Effect of human papillomavirus (HPV) vaccine among women with FGS and HIV on prevention of cervical cancer
	• Explore the pathogenic synergy of HIV, HPV and FGS and risk of cervical cancer
	• Effect of schistosomiasis on immunological response to HIV and HPV vaccines
	• Need for feasible, evidence-based schistosomiasis prevention interventions that incorporate the local environment and social context of at-risk populations
	• Need to develop a package of interventions addressing multiple related infections in AGYW, including HIV, HPV, other sexually transmitted diseases, and schistosomiasis
• Need for strong advocacy for neglected tropical diseases (NTDs), including schistosomiasis to leverage collaborators and resources to eradicate these NTD	

Gaps	Opportunities
	<ul style="list-style-type: none"> • Need for support of the inclusion of access to safe water, improved sanitation, hygiene education, and snail control as a part of prevention and control of schistosomiasis
<i>Policy needs</i>	<ul style="list-style-type: none"> • Operationalise policy for treatment of schistosomiasis beyond school-age children • Policy to improve global access of praziquantel for management of all at-risk groups • Policy to facilitate integrated public health programming to offer comprehensive care to AGYW • Policy to forge public-private partnerships and community engagement to advance integrated interventions • Policy for monitoring and evaluation of schistosomiasis-HIV in integrated sexual and reproductive health programs for AGYW • Policy to leverage existing surveillance systems to assess burden of co-infection with HIV and schistosomiasis