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Beyond the barrier: Female Genital Schistosomiasis as a potential risk factor for HIV-1 acquisition

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ABSTRACT

Female genital schistosomiasis (FGS) results from egg-deposition in the female reproductive tract primarily by the waterborne parasite *Schistosoma (S.) haematobium*, and less commonly by *Schistosoma (S.) mansoni*. FGS affects an estimated 20-56 million women worldwide, mostly in sub-Saharan Africa. There is cross-sectional evidence of increased HIV-1 prevalence in schistosomiasis-infected women, but a causal relationship between FGS and either HIV-1 acquisition or transmission has not been fully established. Beyond the pathognomonic breach in the cervicovaginal barrier caused by FGS, this narrative review explores potential mechanisms for a synergistic relationship between *S. haematobium* infection, FGS, and HIV-1 acquisition through vaginal inflammation and target cell recruitment.

1. Introduction

There are an estimated 82 million African women living with *Schistosoma* infections (Lai et al., 2015). Though the risk factors for human immunodeficiency virus-1 (HIV-1) and *Schistosoma haematobium* are different, these two conditions share a substantial geographic overlap (Figure 1A and 1B). Worldwide, 53% of people living with HIV-1 reside in Eastern and Southern Africa, where the HIV-1 epidemic disproportionately affects young women (UNAIDS 2018). In 2017, 52% of the 36.9 million people living with HIV-1 were women aged 15 years and over (UNAIDS 2018). The synergy of many co-factors present in Africa increases the risk of heterosexual HIV-1 acquisition, namely high prevalence of bacterial vaginosis and sexually transmitted infection (STI) (Cohen et al., 2012), low uptake of circumcision in adult men (Kaul et al., 2015), baseline immune activation, and endemic co-infections (Modjarrad, 2010). In addition, schistosome infection in women (Downs et al., 2012), and more specifically, female genital schistosomiasis (FGS), has been associated with prevalent HIV-1 infection (Kjetland et al., 2006; Downs et al., 2011).

This review will focus on FGS and its causative agent, the parasite *S. haematobium*, which requires an aquatic environment and a freshwater snail vector to complete its life-cycle (Colley et al., 2014). When fertilized *S. haematobium* eggs are shed in human urine and enter fresh water, the miracidia hatch and penetrate a snail host. After 4-6 weeks, cercariae penetrate human skin and enter the bloodstream (Colley et al., 2014). *S. haematobium* eggs are often laid in the vesicular plexus where proximity to the pelvis' venous drainage provides circulating eggs access to male and female urogenital tissues. FGS occurs when circulating *S. haematobium* eggs lodge in the reproductive organs. FGS has been associated with poor reproductive health outcomes including ectopic pregnancy (Helling-Giese et al., 1996), abortion (Helling-Giese et al., 1996), and infertility (Kjetland et al., 2010), likely as a consequence of parasite egg deposition and inflammation in reproductive tissues. It is hypothesized that the relationship between FGS and HIV-1 acquisition is causal, with the mucosal breach caused by FGS allowing HIV-1 access to susceptible submucosal target cells. However, there have been no longitudinal studies investigating the mechanistic links between FGS and HIV-1 acquisition. This review explores potential mechanisms for the relationship between *S. haematobium*, FGS, and HIV-1 acquisition beyond a breach in cervicovaginal mucosal barrier function.

2. Methods

2.1. Search Criteria

References for this narrative review were identified through searching PubMed and Medline databases up to February 4, 2020 with

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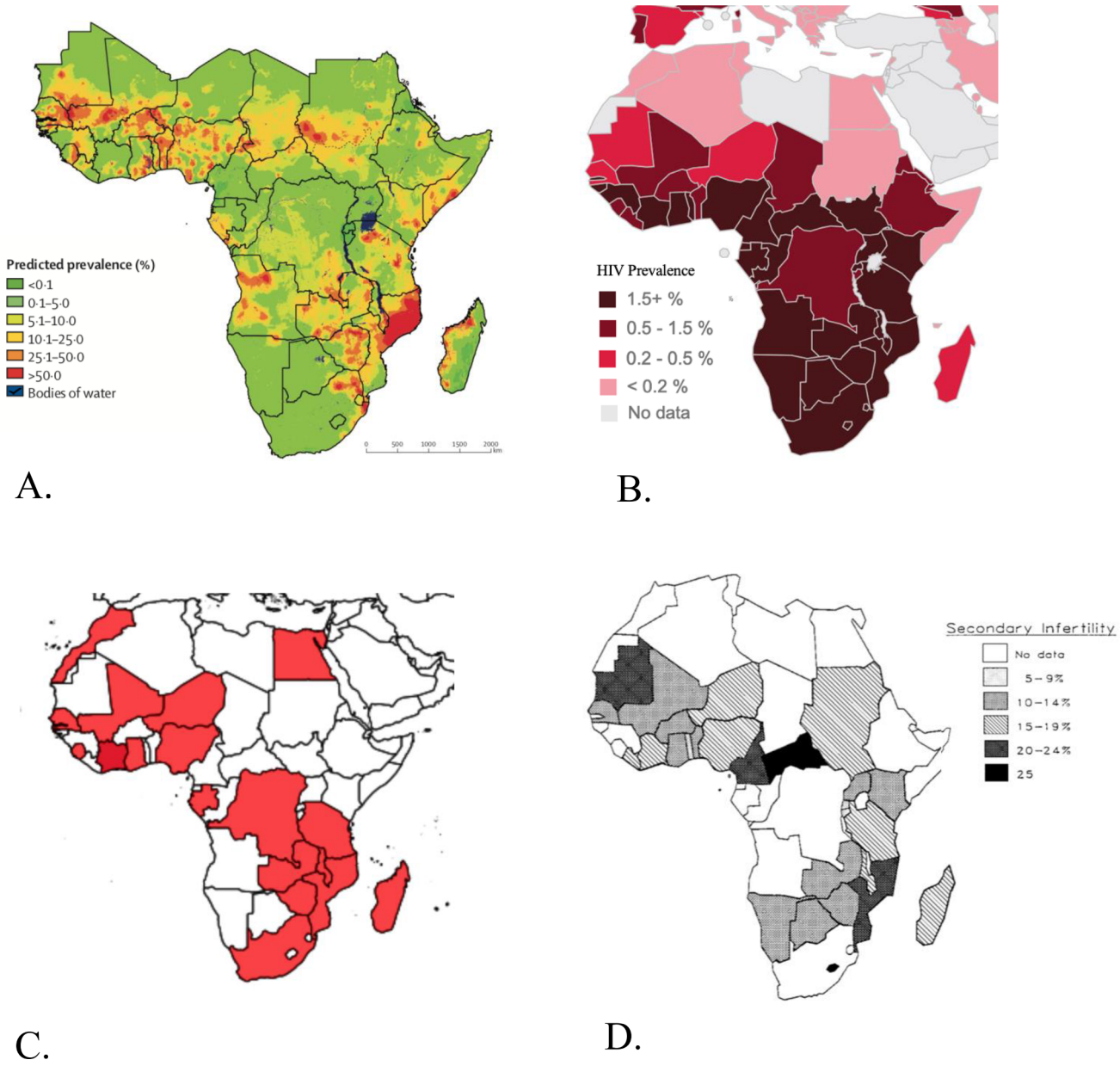

Figure 1. Overlapping geographical distributions of schistosomiasis infection, HIV-1 prevalence, reported cases of FGS, and infertility. (A) Prevalence of *S. haematobium* infection in school-aged children in Sub-Saharan Africa from 2000 onwards (from (Lai et al., 2015)); (B) HIV prevalence in African adults (15-49) (from (UNAIDS 2018)); (C) African countries with published reports of FGS (adapted from (Christinet et al., 2016)), FGS cases have been published by countries shaded in red; (D) Secondary infertility in Sub-Saharan Africa (from (Larsen 2000)).

the use of terms "Schistosomiasis" OR "*Schistosoma*" OR "Female Urogenital Schistosomiasis" OR "Genital or Urogenital Schistosomiasis" OR "Genital or Cervicovaginal Inflammation", AND "HIV or Human Immunodeficiency Virus". The references of relevant articles were also used to identify additional sources. No language restrictions were applied.

2.2. Selection Criteria

To be eligible for this narrative review (Gasparyan et al., 2011), studies must have included some proportion of women who had a definitive diagnosis of FGS, including either detection of *Schistosoma (S.)* DNA by molecular methods or through histopathologic diagnosis (eggs of either *S. haematobium* or *S. mansoni* detected in genital tissue). Studies were also eligible for inclusion if they contained a comparator group for both prevalent HIV-1 and FGS and were prospective (randomized or non-randomized) or cross-sectional studies in African populations. Initially, we searched for studies that evaluated the association between prevalent HIV-1 and FGS, but only identified two studies that fit these criteria (Supplementary Table 1). We therefore added an additional question regarding the association of *non-genital* schistosomiasis with prevalent HIV-1 in African populations, with analogous inclusion criteria to the first study question; however, with the requirement that some proportion of the study population have a measure of active schistosome infection (defined by positive microscopy or parasite circulating anodic antigen (CAA) or circulating cathodic antigen. We identified ten studies with relevant information on this question (Supplementary Table 2).

Beyond the study questions discussed above, where studies focusing on FGS were not identified, we include findings from publications reporting *S. haematobium* infection or urogenital schistosomiasis as a narrative synthesis. In circumstances where *S. haematobium* data were

not available, we reference literature relating to *S. mansoni*.

2.3. Data Extraction & Synthesis

One reviewer identified the eligible articles (A.S.) and two reviewers (A.S. and E.W.) extracted relevant data. We extracted study location, study design, participant ages, the author's definition of FGS, proportions of study participants with FGS/schistosome infection, proportion of study participants with HIV-1, method of *Schistosoma* egg detection, and the association between FGS/schistosome infection and HIV-1. Studies relating to our primary question of the association of FGS with HIV-1 are shown in Supplementary Table 1. Studies relating to the association of non-genital schistosome infection with HIV-1 are shown in Supplementary Table 2. Other articles identified in the search are referenced herein.

3. Female Genital Schistosomiasis – Definition, Clinical Presentation & Impact

3.1. Urinary schistosomiasis, genital schistosomiasis and their overlap

A working group from the World Health Organization coined the term "urogenital schistosomiasis" in 2009 to describe the frequent co-existence of *S. haematobium* ova in the urinary tract (urinary schistosomiasis) and the female genital tract (genital schistosomiasis) (World Health Organization 2009). Female Genital Schistosomiasis (FGS) refers therefore, to the presence of *S. haematobium* eggs, DNA, or characteristic clinical changes specifically in the genital tract (Figure 2), regardless of whether or not these are present in the urinary tract (Kjetland et al., 1996; Kjetland et al., 2005). Female Urogenital Schistosomiasis (FUS) refers more broadly to the deposition of schistosome eggs in either the female urinary or genital tracts, or both. FGS is caused most frequently by the parasite *S. haematobium*. *S. mansoni* eggs have, albeit rarely, also been found in genital tissue (Downs et al., 2011).

3.2. The burden of Female Genital Schistosomiasis

With up to 163 million Africans infected with *S. haematobium* or *S. mansoni* (Lai et al., 2015), schistosomiasis morbidity is an underestimated public health problem in many parts of sub-Saharan Africa (World Health Organization 2017). In the 2017 Global Burden of Disease Study, schistosomiasis was estimated to cause the loss of 1,440 million disability-adjusted life years (DALYs) (Global Burden of Disease DALYs and Hale Collaborators 2018). Many women acquired *S. haematobium* infection in childhood, and 30 to 75% of infected women may develop FGS (Leutscher et al., 1998; Kjetland et al., 2005). A study in Tanzania reported that 43% (53/122) of women with urinary schistosomiasis had concurrent FGS (diagnosed by cervical biopsy) (Poggensee et al., 1998). A cross-sectional study of girls aged 10-12 in KwaZulu-Natal, South Africa reported that significantly more girls with urinary *S. haematobium* infection reported gynecologic symptoms (bloody or foul-smelling vaginal discharge) and genital discomfort (prior to sexual debut and menstruation in 98.6% and 93.0%, respectively) (Hegertun et al., 2013). To our knowledge no clinical studies have evaluated cervicovaginal physical exam findings in school-aged girls. However, this study suggested that girls with urinary *S. haematobium* infection may develop the genital changes associated with FGS prior to sexual debut or the onset of menstruation. Since FGS may develop in childhood, it is surprising that with the prevalence of *S. haematobium* estimated at up to 25% in a survey of school-age children in a majority of sub-Saharan African countries (Lai et al., 2015), less than half of the countries (shaded red in Figure 1C) have formally published FGS case estimates. No population prevalence studies have been performed but best estimates are that 20 - 56 million women in sub-Saharan Africa may be living with FGS (World Health Organization 2017).

3.3. FGS morbidity and clinical presentation

Studies of FGS histopathology reported that women ultimately diagnosed with FGS initially sought care for vaginal bleeding, abdominal pain, or infertility (Swai et al., 2006). Frequently associated, but not

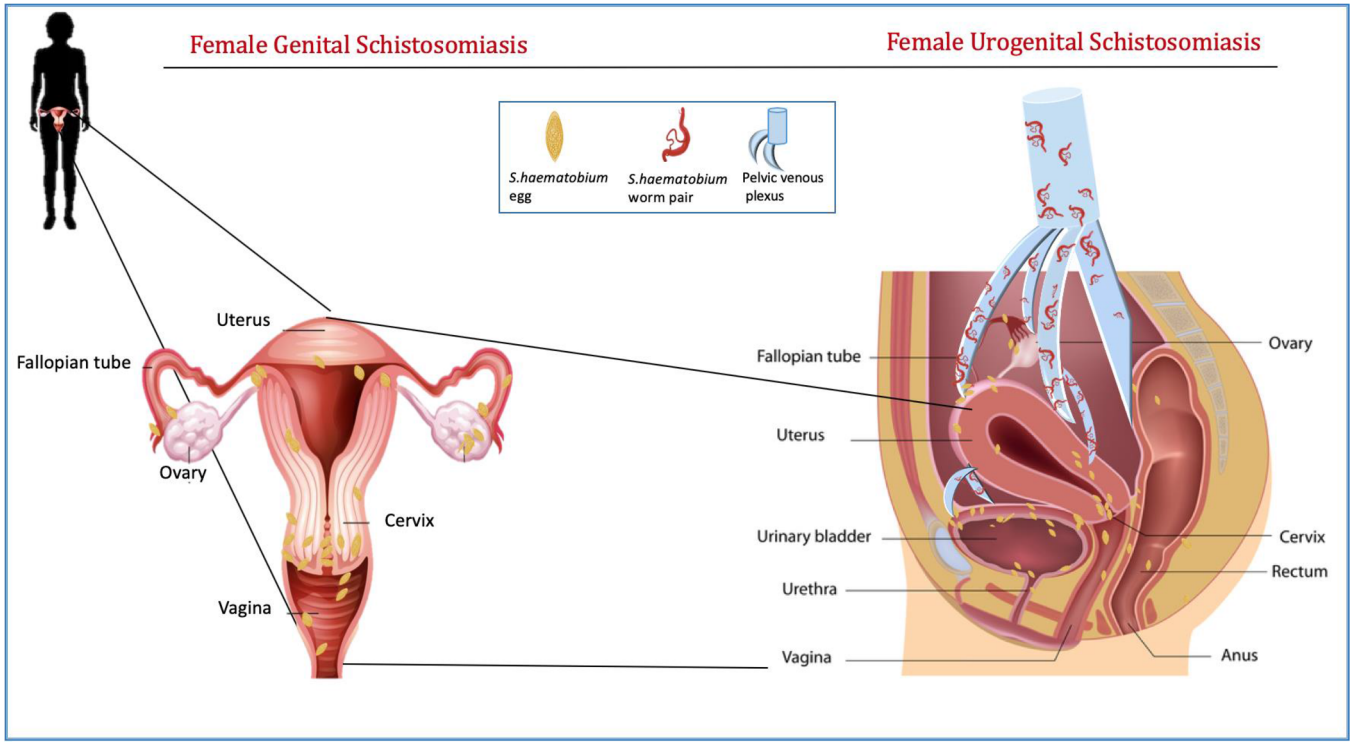

Figure 2. The anatomy of female genital and female urogenital schistosomiasis.

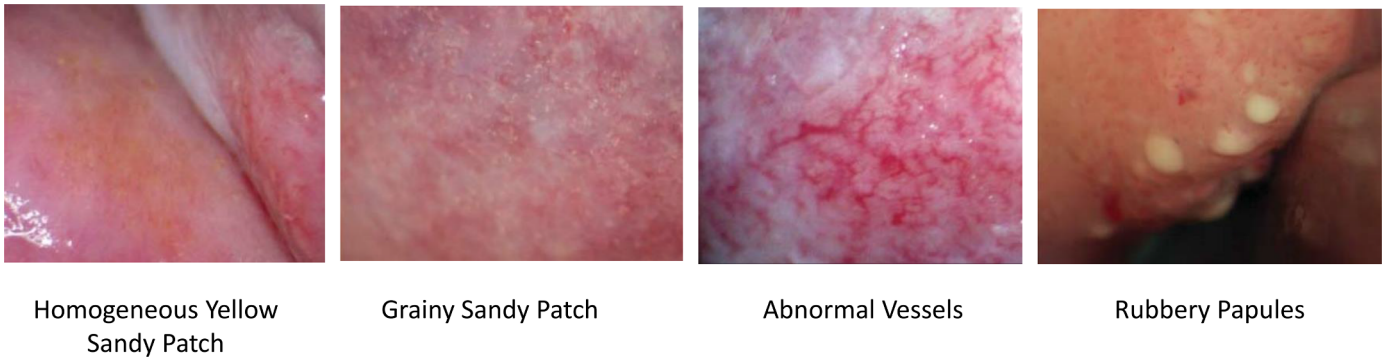

Figure 3. Visual findings suggestive of Female Genital Schistosomiasis, from World Health Organization (2015).

pathognomonic, symptoms included haematuria, dyspareunia, and post-coital bleeding (Kjetland et al., 1996). FGS has characteristic clinical findings: grainy sandy patches (representing ova near the mucosal surface) (Kjetland et al., 1996), homogenous yellow sandy patches (Kjetland et al., 2005), and rubbery papules (Figure 3). These lesions are associated with neovascularization (Kjetland et al., 1996; Kjetland et al., 2005) and contact bleeding (Kjetland et al., 1996; Kjetland et al., 2005). Common sites for egg visualization in adult females were the cervix (Kjetland et al., 2005), vagina (Kjetland et al., 2005), and vulva (Kjetland et al., 1996) while women under the age of 20 commonly presented with vulvar lesions (Helling-Giese et al., 1996; Swai et al., 2006). The difference in presentation may be related to anatomic, hormonal, and vascular changes associated with puberty (Helling-Giese et al., 1996).

3.4. Treatment of S. haematobium infection and FGS with praziquantel

Currently the World Health Organization (WHO) recommends praziquantel (PZQ) mass drug administration (MDA) to control *S. haematobium* disease and reduce morbidity. Data on the effect of PZQ on FGS lesion reversibility are scarce and subject to limitations. To date, three studies of adult women with FGS followed after treatment with PZQ have been conducted in Zimbabwe (n = 338), Tanzania (n = 33), and Malawi (n = 9). All three suggested that, following treatment with at least 40mg/kg of PZQ, a proportion of cervicovaginal lesions are irreversible with variation by lesion type, duration of follow-up, and praziquantel dose provided (Richter et al., 1996; Kjetland et al., 2006; Downs et al., 2013). Data from Zimbabwe suggested that women treated for schistosomiasis prior to the age of 20 had significantly lower prevalence of sandy patches and contact bleeding than untreated women (Kjetland et al., 2008). PZQ administration prior to the age of 21 has also been associated with lower rates of sub-fertility (Miller-Fellows et al., 2017). Thus, it is critical that schistosomiasis treatment occurs early, prior to the development of FGS lesions. Further well-designed clinical trials are required to investigate this question.

In addition to its role in schistosomiasis morbidity reduction, mathematical modelling suggests that PZQ treatment of women and school-aged children in *S. haematobium* high-risk communities could reduce HIV-1 prevalence (Gibson et al., 2010; Mushayabasa and Bhunu 2011; Ndeffo Mbah et al., 2013; Ndeffo Mbah et al., 2014). This finding highlights the need for further research into the use of PZQ for HIV-1 prevention. Other effective HIV-1 prevention methods include antiretroviral therapy and pre-exposure prophylaxis (PrEP). However, even with the use of linkage strategies, PrEP (Mugwanya, 2018) and ART uptake (Bor et al., 2018) and coverage are substantially less than 100% (Granich et al., 2015), and PrEP adherence in both men and women is imperfect (Koss et al., 2017). These limitations outline the need for a comprehensive approach to HIV-1 prevention, and further research is needed to evaluate praziquantel's role.

3.5. The impact of FGS on reproductive health

Due to its ability to affect both the upper and lower female reproductive tract, FGS has been implicated in poor reproductive health outcomes. However, data are mostly limited to pathology and case reports. Pathology reports described the presence of severe scarring (Swai et al., 2006) and inflammation (Wright et al., 1982; Swai et al., 2006) in the fallopian tubes related to the presence of *S. haematobium* eggs. Case reports described poor pregnancy outcomes in FGS, including stillbirth (Helling-Giese et al., 1996), ectopic pregnancy (Helling-Giese et al., 1996; Odubamowo et al., 2014) and spontaneous abortion (Helling-Giese et al., 1996; Friedman et al., 2007). The negative impact of FGS on reproductive health is most likely mediated through the histologic and mechanical effect of tissue destruction caused by schistosome eggs (Kjetland et al., 2010), but more research is urgently needed to understand the detrimental implications of FGS for a woman's sexual and reproductive health. Additional adverse outcomes attributed to *S. haematobium* infection in pregnancy include anemia, preterm labor, intrauterine growth restriction, and low birth weight (Friedman et al., 2007).

Infertility, a known consequence of upper reproductive tract pathology, is another reproductive health outcome that is associated with *S. haematobium* (Woodall and Kramer 2018). A 44% prevalence of subfertility (higher than worldwide averages of 8-12%) has been reported in women living in an area of high *S. haematobium* endemicity (60-85% prevalence in school-age children) (Miller-Fellows et al., 2017). FGS, defined in this study as the finding of *S. haematobium* ova in Papanicolau smears, was associated with primary infertility, defined as the inability to conceive after four years of regular sexual activity (OR 3.6; 1.0 – 12.0, p = 0.04) (Kjetland et al., 2010). The distribution of secondary infertility (infertility after giving birth to a child) overlaps substantially with the distribution of FGS in sub-Saharan Africa (Figure 1A and 1D).

4. Female Genital Schistosomiasis and HIV-1 co-infection

4.1. S. haematobium and HIV-1 – epidemiology and an ecological association

In addition to biologic plausibility supporting the association between an entity that causes cervicovaginal barrier disruption and HIV-1 acquisition, ecological associations have been reported between *S. haematobium* and HIV-1 (Mbah et al., 2013; Brodish and Singh 2016). The epidemiology of both schistosomiasis and HIV-1 may be influenced by interactions between the two infections, but individual studies have reported disparate conclusions regarding egg excretion, infection intensity, and association of schistosome infection with HIV-1. Ten studies that evaluated the association of non-genital schistosomiasis with HIV-1 met our inclusion criteria. Four studies with varied methodologies suggested an association between schistosome infection (genital

infection status was not reported) and HIV-1 (N'Zoukoudi-N'Doundou et al., 1995; Ndhlovu et al., 2007; Downs et al., 2012; Downs et al., 2017) albeit the association in two studies was only seen within sub-groups (Ndhlovu et al., 2007; Downs et al., 2017). Of note two of the studies found an association with HIV-1 evaluate *S. haematobium* (N'Zoukoudi-N'Doundou et al., 1995; Ndhlovu et al., 2007) and two studies measured CAA (Downs et al., 2012; Downs et al., 2017), which suggests active schistosome infection but cannot differentiate between *S. haematobium* or *S. mansoni* species. Conversely, six cross-sectional or case-control studies identified in our search evaluated the association between schistosome infection and HIV-1 did not show an association between schistosome and HIV-1 infection (Fontanet et al., 2000; Kallestrup et al., 2005; Mazigo et al., 2014; Sanya et al., 2015; Ssetaala et al., 2015; Downs et al., 2017), of note, none of these studies described FGS or *S. haematobium* infection in isolation. Meaningful comparison across studies was limited by variations in diagnostic methods and definitions of schistosome infection and many studies did not report analyses stratified by sex. In those that did, associations between schistosome infection and HIV-1 prevalence (Downs et al., 2012), increased acquisition (Downs et al., 2017), or transmission (Wall et al., 2018) were commonly (although not universally) seen in females but not in males. In females, cervicovaginal schistosome egg-containing tissue is exposed to semen containing HIV-1. The prostate and seminal vesicles are commonly affected by *S. haematobium* in men (Kayuni et al., 2019), internal structures that are not exposed during sexual contact. Authors finding a difference in the association between schistosomiasis and HIV-1 infection by sex hypothesize that this may be due to differential contact of egg-containing tissues in female versus male genital tissues during sexual contact (Downs et al., 2017).

4.2. FGS as a risk factor for the heterosexual acquisition of HIV-1

While the majority of studies examine the association between schistosome infection and HIV-1, our search identified only two studies that evaluate a definition of FGS that includes egg deposition in genital tissue, and its association with prevalent HIV-1 (Supplementary Table 1). Data from these two cross-sectional studies suggested that women with FGS have increased odds of having HIV-1 (Kjetland et al., 2006). One study performed in rural Zimbabwe, found that 41% (29/70) of women with FGS (diagnosed by *S. haematobium* eggs in Papanicolaou, wet smear, or genital biopsy) were HIV-1 positive, compared with 26% (96/375) in the egg negative group (OR 2.1, 95% CI 1.2-3.5; p = 0.008) (Kjetland et al., 2006). A study in Tanzania investigated HIV-1 prevalence among women with FUS (defined as either urinary *S. haematobium* egg excretion (16/23 participants) or egg detection in genital tissue (7/23 participants)), found that of the 23 women with FUS, 4 (17.4%) were HIV-1 infected compared with 23 (5.3%) of 434 women without FUS (OR 4.0, 95% CI 1.2–13.5) (Downs et al., 2011). This study was limited by small numbers, a low number of women with eggs detected in genital tissue, and the use of a broad FUS definition.

4.3. Schistosomiasis as a risk factor for HIV-1 incidence and transmission

To our knowledge, published data evaluating the association of FGS with HIV-1 incidence or transmission are lacking, although a small number of studies have evaluated the association of schistosome infection with HIV-1 (but genital infection status was not reported in these studies) (Downs et al., 2017; Wall et al., 2018). A retrospective analysis of a longitudinal cohort study of HIV-1 incidence in anti-retroviral therapy (ART) naïve, heterosexual HIV-1 serodiscordant couples in Zambia examined the association of baseline schistosome antibody status (as a proxy for previous or current infection) with incident HIV-1 acquisition and transmission (Wall et al., 2018). The presence of *S. haematobium* antibodies in 482 HIV-1 negative women was associated with increased risk of HIV-1 acquisition (Wall et al., 2018). However, limitations include the absence of information on the timing of the index partner's HIV-1 infection, the use of *Schistosoma* serology, which does not differentiate between past or present infection, and missing data on ART initiation. Research is needed to evaluate the association of FGS with HIV-1 incidence and transmission in the era of universal ART.

4.4. The intersection of FGS and host HIV-1 susceptibility

S. haematobium egg deposition in the female reproductive tract leads to a histological microenvironment that may enhance HIV-1 vulnerability. HIV-1 susceptibility is influenced by multiple factors but ultimately requires the presence of susceptible host cells (commonly in the vagina or cervix) (Kaul et al., 2015). HIV-1 fusion with and entry into susceptible target cells (T-lymphocytes, monocyte/macrophages or dendritic/Langerhans cells) requires the expression of the principal CD4 receptor and a chemokine co-receptor (CCR5 or CXCR4) (Kaul et al., 2015). These target cells and their chemokine co-receptors are found in the human genital tract (Kaul et al., 2015). HIV-1 susceptibility in the host is influenced by the overall number (Secor et al., 2003), density, and expression of the chemokine co-receptors on target cells that can be utilized by HIV-1 for cellular entry (Kaul et al., 2015). Certain CD4+ subsets are more susceptible to HIV-1 infection (McKinnon et al., 2011) and thus the availability, activation status, and phenotype of mucosal target cells influence HIV-1 susceptibility (Secor et al., 2003; McKinnon and Kaul 2012). In women with FGS, cervical tissue containing *S. haematobium* eggs has an increased density of CD4+ lymphocytes and macrophages compared to cervical tissue not containing eggs (Jourdan et al., 2011). On a histological level, cervical tissue containing *S. haematobium* eggs is also more vascularized (Jourdan et al., 2011) potentially allowing increased vascular access to HIV-1 target cells. Thus, the granuloma environment in *S. haematobium* infection theoretically encourages a milieu of cellular populations necessary to establish HIV-1 infection.

Compared to egg negative men, egg-positive *S. mansoni* infection in Kenyan males was associated with a higher density of CCR5 and CXCR4 co-receptors in the peripheral blood (Secor et al., 2003). Such data are not available in *S. haematobium* infection and are hypothesis-generating regarding the association between schistosome infection and HIV-1 status. Limited data exist regarding the influence of FGS on co-receptor expression. A small study conducted in KwaZulu-Natal, South Africa followed 14 women aged 15 – 23 years with FGS (defined by a suggestive clinical exam) for 8 months (Kleppa et al., 2014). Flow-cytometry was performed from peripheral blood and cervical cytobrush samples before and after praziquantel treatment. Compared to FGS negative women, participants with FGS had increased expression of the CCR5 co-receptor on plasma CD4 cells and vaginal CD14+ monocytes and increased frequencies of systemic monocytes (Kleppa et al., 2014). Increased frequencies of HIV-1 target cells and co-receptor expression are plausible mechanisms for increased HIV-1 vulnerability in women with FGS, but given the small sample size and the lack of histologic or laboratory diagnosis of FGS, additional research is needed.

5. Does FGS behave like an STI or bacterial vaginosis in heterosexual HIV-1 acquisition? Mechanistic hypotheses for the role of FGS in HIV-1 vulnerability

Although the association between FGS and HIV-1 has been hypothesized to be a direct result of FGS-associated lesions in the female genital tract (Feldmeier et al., 1994; Kjetland et al., 2005), the mechanism of the HIV-1 vulnerability has not been fully described. In ulcerative STIs (e.g. syphilis or herpes simplex virus (HSV)), damage to the protective cervicovaginal barrier is associated with increased risk of HIV-1 transmission (Gray et al., 2001) and acquisition (McKinnon and Kaul 2012). In this section we put forth several hypotheses (Figure 4) for how FGS may influence mechanisms associated with HIV-1 acquisition. In addition to causing barrier dysfunction, STIs, and perhaps also FGS, increase the risk of HIV-1 transmission through their contribution

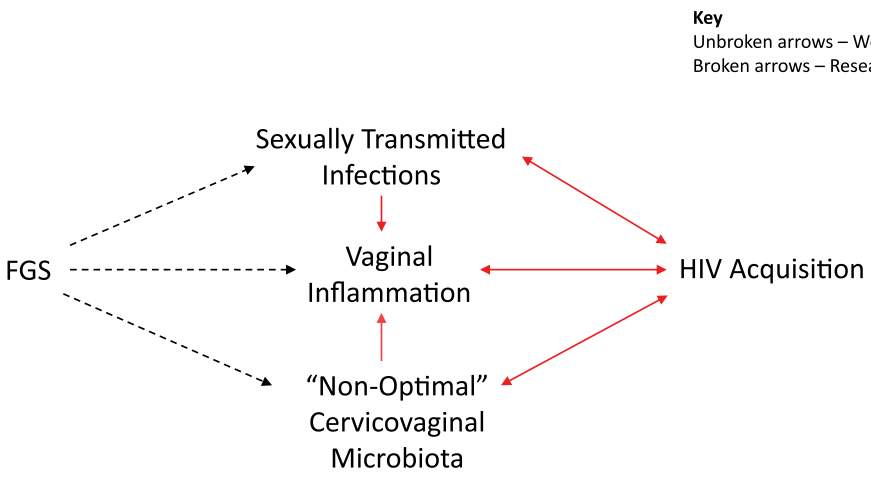

Figure 4. Conceptual pathway describing the potential contribution of FGS to vaginal inflammation and the association of FGS with sexually transmitted infection and "non-optimal" cervicovaginal microbiota (McKinnon et al., 2019).

to genital HIV-1 replication (Cohen et al., 1997) and HIV-1 acquisition through genital inflammation (Masson et al., 2014; Masson et al., 2015) and HIV-1 target cell recruitment (Masson et al., 2014).

5.1. Impaired cervicovaginal barrier function

In the female genital tract, the cervicovaginal immune defences are physical and immunological (Selhorst et al., 2017). An intact vaginal mucus layer, antimicrobial peptides, an acidic pH, and optimal vaginal microbiota combined with a preserved cervicovaginal epithelium provide an effective barrier, the first defence against HIV-1 acquisition (Selhorst et al., 2017). STIs are a classic example of how compromised cervicovaginal barriers increase susceptibility to HIV-1 acquisition. Like STIs, the characteristic lesions of FGS represent a breach in the intact cervicovaginal mucosal barrier and are hypothesized to be an entry point for HIV-1 (Feldmeier et al., 1995). At a population level, non-ulcerative STIs may be more important given their higher incidence and prevalence. And unlike many bacterial STIs which resolve with appropriate treatment, a proportion of FGS genital lesions may persist despite treatment with praziquantel (see section 3.4) (Downs et al., 2013). Further research is needed to evaluate if, similar to HSV ulcers, healed FGS lesions are associated with persistent localized inflammation, including HIV-1 target cells (Zhu et al., 2009).

5.2. The role of vaginal inflammation in HIV-1 acquisition. Could FGS contribute?

Inflammation and immune activation are central to HIV-1 pathogenesis and acquisition. Biological mechanisms that are influenced by vaginal inflammation and contribute to male-to-female heterosexual HIV-1 acquisition include mucosal target cell recruitment (McKinnon and Kaul 2012) and impaired cervicovaginal barrier function (Arnold et al., 2016). Initiation of the inflammatory cascade functions to recruit immunologic cellular mediators. In an escalating onward cascade, the presence of vaginal inflammation recruits the very cells needed to establish HIV-1 infection (Arnold et al., 2016). HIV-1 can infect T-lymphocytes, macrophages, and dendritic cells present in the cervicovaginal tissue (McKinnon and Kaul 2012). Elevated genital cytokines affect the expression of proteins associated with the cervicovaginal epithelium's integrity (Arnold et al., 2016). Compromise of this physical barrier occurs in FGS and provides a rich supply of activated and available subepithelial HIV-1 target cells.

S. haematobium infection has been associated with altered levels of systemic (Lyke et al., 2006; Erikstrup et al., 2008), seminal fluid (Leutscher et al., 2005), and vaginal cytokines (Dupnik et al., 2018). Raised vaginal concentrations of chemotactic (Morrison et al., 2014) and inflammatory cytokines are a risk factor for HIV-1 acquisition (Masson et al., 2015). In a study of 58 female HIV-1 seroconverters in South Africa, women with elevation of more than 5 out of 9 inflammatory cytokines had increased odds of HIV-1 acquisition (OR 3.2, 95% CI 1.3-7.9) (Masson et al., 2015). Mechanistically, the association has biological plausibility, as the production of inflammatory cytokines can influence expression of biomarkers of tissue remodelling and integrity (Arnold et al., 2016), modulate HIV-1 replication through transcription factor expression (Masson et al., 2014), or indirectly influence the differentiation, proliferation, and activation of HIV-1 target cells (Masson et al., 2014). Further research is needed to evaluate if FGS is associated with the genital inflammatory cytokines that are also associated with HIV-1 infection (Masson et al., 2015).

5.3. HIV-1 RNA concentrations, schistosomiasis, and HIV-1 transmission

Treatment of bacterial STI with antibiotics significantly decreases the concentration of HIV-1 RNA in seminal plasma (Cohen et al., 1997). Similarly, African men with genital schistosomiasis showed a decline in the concentration of HIV-1 RNA in seminal plasma after treatment with praziquantel (Midzi et al., 2017). Immunologically, egg-positive schistosome infection induces a strong Th2 bias (Pearce et al., 1991). Limited data suggest that HIV-1 replicates preferentially in activated CD4 Th0/Th2 cells (Maggi et al., 1994). Thus, there is immunologic plausibility to a hypothesis linking schistosomiasis with HIV-1 transmission. Practically, this may manifest as altered plasma and genital HIV-1 RNA concentrations among those who are dually infected with HIV-1 and schistosomiasis. Understanding the effect of schistosome infection on HIV-1 viral loads is critical given that schistosome infection in both women and men has been associated with HIV-1 transmission (Wall et al., 2018). However, the data regarding the association of schistosomiasis with elevated plasma viral loads are conflicting (Downs et al., 2017; Colombe et al., 2018; Bochner et al., 2019) and there may be a species-specific effect of *Schistosoma* on viral load (Bochner et al., 2019). In a study of HIV-1 seroconversion, participants with *S. haematobium* had higher set point plasma viral loads (+0.33 $\log_{10}$ copies, 95%CI -0.07-0.73, p = 0.11) compared to uninfected individuals, while participants with *S. mansoni* had lower set point HIV-1 viral loads (-0.34 $\log_{10}$ copies, 95% CI -0.58 to -0.09,p = 0.007) (Bochner et al., 2019). Recent longitudinal studies report both increased (Downs et al., 2017) and decreased (Colombe et al., 2018; Bochner et al., 2019) HIV-1 viral load set points in participants co-infected with HIV-1 and *S. mansoni.* Of note, FGS status was not evaluated in these studies (Downs et al., 2017; Colombe et al., 2018; Bochner et al., 2019). Differences in the results

highlight the need to adjust for ART use and duration of HIV-1 infection when evaluating HIV-1 viral load in the context of schistosomiasis (Downs et al., 2017; Colombe et al., 2018; Bochner et al., 2019).

An elevated genital HIV-1 viral load is a known risk factor for HIV-1 transmission (Baeten et al., 2011). An analysis of four prospective cohort studies in HIV negative persons in Kenya or Uganda who experienced HIV-1 seroconversion provided data regarding the association of schistosome infection with altered genital HIV-1 RNA concentrations. After adjusting for age, year of HIV-1 acquisition, and $\log_{10}$ plasma viral load, 8 women with *S. haematobium* infection who acquired HIV-1 were found to have lower cervical (ß = -0.59 [-1.11- -0.06], p = 0.029) and similar vaginal (ß = -0.09 (-0.65-0.46), p = 0.74) HIV-1 viral loads compared with participants who did not have schistosomiasis (Bochner et al., 2019). However, since the numbers were small, the estimates were not adjusted for multiple comparisons, and genital schistosomiasis status was not assessed, further research is needed to describe the association of FGS with genital HIV-1 RNA concentrations.

5.4. Vaginal microbiota in S. haematobium endemic countries and the risk of HIV-1 acquisition

Optimal vaginal microbiota are characterized by the presence of lactic acid and hydrogen-peroxide producing bacteria, often *Lactobacilli*. "Non-optimal" cervicovaginal microbiota (McKinnon et al., 2019) is not dominated by *Lactobacilli*. Bacterial vaginosis (BV) is one condition within this category (Cohen et al., 2012). BV involves the replacement of lactic acid producing bacteria by anaerobes, with bacterial species often clustering into distinct communities (McKinnon et al., 2019). Prevalence of BV is estimated to be high among women in sub-Saharan Africa (Cohen et al., 2012) and women of African descent. Although BV is seldom associated with clinically visible inflammation (McKinnon et al., 2019), it is consistently associated with elevated concentrations of pro-inflammatory immune proteins (Masson et al., 2014) and poor sexual and reproductive health outcomes, such as preterm delivery, miscarriage, pelvic inflammatory disease, and HIV-1 acquisition (Atashili et al., 2008). A meta-analysis of HIV-1 incidence studies reported that the presence of BV resulted in a 60% increased risk of HIV-1 acquisition (Atashili et al., 2008). Potential factors contributing to this increased risk include an increase in vaginal pH and upregulation of cytokines that promote HIV-1 replication (Masson et al., 2014). As a chronic and recurrent disruption of the genital tract environment, BV contributes a substantial population attributable fraction (PAF) of HIV-1 acquisition (Masese et al., 2015). Given the substantial risk for HIV-1 acquisition that BV poses in sub-Saharan Africa, it is critical to evaluate if FGS might also be associated with changes in the cervicovaginal microbiota. Since the cervicovaginal presence of FGS likely persists over time, FGS may, like BV, contribute a high PAF for HIV-1 acquisition.

Research on the role of the gut microbiota in persons with urinary *S. haematobium* suggested that the effect of urinary *S. haematobium* infection may be manifest in body compartments distinct from the location of egg deposition (Kay et al., 2015). The differential detection of microbes based on *Schistosoma* infection status extended into the urinary microbiota as well (Adebayo et al., 2017). That *S. haematobium* infection is associated with alteration in the gut and urinary microbiota lends plausibility to the hypothesis that FGS may alter the cervicovaginal microbiota. The composition of the vaginal microbiota played a role in HIV-1 acquisition, as demonstrated by a study of 236 South African women, 31 of whom acquired HIV-1 after a median 335 days of follow-up. This study illustrated that compared with *Lactobacillus crispatus* dominance, high-diversity vaginal bacterial communities with low *Lactobacillus* abundance was associated with HIV-1 acquisition (Gosmann et al., 2017), however FGS or schistosome infection was not evaluated. Women with anaerobic dominance were also found to have increased genital CD4+ T-cell numbers, concentrations of cytokines produced by activated CD4+ cells (Gosmann et al., 2017), and cytokines that have been associated with HIV-1 acquisition (Masson et al., 2015). Further research is needed to evaluate the potential mechanistic connection between the vaginal microbiota and FGS.

6. Female Genital Schistosomiasis – research priorities

This review highlights gaps in the literature and the need for revised research priorities that evaluate the mechanistic links between FGS and HIV-1 acquisition and transmission. Research regarding additional biological mechanisms for HIV-1 vulnerability in FGS is urgently needed and future research must explore the association of FGS with: 1) cervicovaginal HIV-1 concentrations 2) cytokines and chemokines associated with HIV-1 acquisition, and 3) vaginal microbial community composition.

7. Conclusion

FGS is a neglected gynaecological disease of poverty, affecting vulnerable women in sub-Saharan Africa. FGS may be an unmeasured regional risk factor that compounds biological and cultural covariates in a population at risk for HIV-1 acquisition and transmission. The clinical cervicovaginal findings of FGS demonstrate a breach in the physical epithelial barrier. This mechanical mucosal defect may allow greater access to the HIV-1 target cells in the sub-mucosa. However, the hypothesis that cervicovaginal barrier dysfunction in FGS is the sole mechanism linking FGS and HIV-1 acquisition is likely incomplete. The experience of STI and BV and their association with HIV-1 vulnerability includes consideration of additional co-factors: target cell recruitment, vaginal inflammation, and HIV-1 RNA concentrations. A more complete understanding of the association of FGS with HIV-1 will advance the research agenda on diagnostic, therapeutic and prevention strategies for this disabling disease, and its synergistic role in the HIV-1 epidemic.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actatropica.2020.105524.

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