Female Genital Schistosomiasis and HIV: Research Urgently Needed to Improve Understanding of the Health Impacts of This Important Coinfection

Daniel P. O'Brien, FRACP,[a,b,c] Nathan Ford, FRCPE,[d] Amadou G. Djirmay, MD,[e] Alexandra Calmy, MD,[f] Marco Vitoria, MD,[d] Tomas O. Jensen, FRACP,[g] and Vanessa Christinet, MD[h]

Abstract: Evidence suggests that there are important interactions between HIV and female genital schistosomiasis (FGS) that may have significant effects on individual and population health. However, the exact way they interact and the health impacts of the interactions are not well understood. In this article, we discuss what is known about the interactions between FGS and HIV, and the potential impact of the interactions. This includes the likelihood that FGS is an important health problem for HIV-positive women in *Schistosoma*-endemic areas potentially associated with an increased risk of mortality, cancer, and infertility. In addition, it may be significantly impacting the HIV epidemic in sub-Saharan Africa by making young women more susceptible to HIV. We call for immediate action and argue that research is urgently required to address these knowledge gaps and propose a research agenda to achieve this.

Key Words: female genital schistosomiasis, HIV, sub-Saharan Africa, research

(*J Acquir Immune Defic Syndr* 2019;80:489–493)

Schistosomiasis, a water-borne flatworm parasitic infection, is endemic to many countries mainly in Africa (90% of cases) but also in Asia, South America, and the Caribbean. It is estimated to affect more than 200 million people with deaths estimated between 24,067[1] and 200,000 globally yearly[2] and has the highest disease burden among the World Health Organization recognized neglected tropical diseases.[3,4] People are infected most commonly in childhood through skin contact with contaminated water, and depending on the species, the adult worms settle in different parts of the venous system where they live on average for 5–7 years. Pathological lesions resulting from inflammatory reactions to *Schistosoma* egg deposition in the tissues by female adult worms are known to be one of the major causes of chronic liver disease, portal hypertension, and bladder cancer in sub-Saharan Africa.

Schistosomiasis also affects the female genital tract (fallopian tubes, uterus, cervix, vagina, and vulva). Termed female genital schistosomiasis (FGS), it is usually caused by the species *S. haematobium* but also by other species including *S. mansoni*. Clinical features include hypertrophic and ulcerative lesions of the vulva, vagina, and cervix, as well as grainy sandy patches, abnormal blood vessels, and rubbery papules on the cervix or vaginal wall. Estimates suggest there may be 20 million cases of FGS worldwide,[5,6] with a prevalence in women ranging from 33% to 75% in some African endemic countries.[7–11] The diagnosis is challenging, requiring a gynecological examination by a trained clinician, and FGS can be mistaken for other pathologies such as cervical cancer or sexually transmitted infections (STIs).

The medication used to treat schistosomiasis, praziquantel (PZQ), is cheap, available, and effective in early infections[12–14] but likely ineffective once chronic calcified lesions have developed.[15] The best strategy to prevent FGS is to treat schistosomiasis rapidly after infection occurs. The World Health Organization recommends annual treatment with praziquantel for school-aged children in highly endemic areas to treat schistosomiasis[12,16,17]—an intervention that is relatively affordable, at about 40 US cents per person.[18]

Over the years, several studies have indicated an association between HIV prevalence and FGS. *Schistosoma haematobium* and HIV prevalences correlate in sub-Saharan Africa,[19] and in this region, a study across 43 countries found that each *S. haematobium* infection per 100 individuals was associated with a 2.9% (95% CI: 0.2% to 5.8%) increase in HIV prevalence.[20] In Zimbabwe, women with FGS had a higher prevalence of HIV than those without FGS (33% compared to 26%, $P = 0.05$), with an even stronger association in women older than 35 years (37.5% compared to 16.8%, $P < 0.001$).[21] In Mozambique, a study showed an

Received for publication September 3, 2018; accepted December 20, 2018.
From the [a]Manson Unit, Médecins Sans Frontières, London, United Kingdom; [b]Department of Infectious Diseases, University Hospital Geelong, Geelong, Australia; [c]Department of Medicine and Infectious Diseases, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; [d]HIV Department, World Health Organization, Geneva, Switzerland; [e]Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland; [f]HIV Unit, Division of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland; [g]Medical Department, Médecins Sans Frontières, Paris, France; and [h]Centre International de Recherches, d'Enseignements et de Soins en milieu tropical (CIRES), Akonolinga, Cameroon.
The authors have no funding or conflicts of interest to disclose.

All authors have seen and approved the manuscript and have contributed significantly to the work. The article has not been published and is not being considered for publication elsewhere.
Correspondence to: Daniel P. O'Brien, FRACP, Department of Infectious Diseases, University Hospital Geelong, Geelong 3220, Australia (e-mail: Daniel.obrien@amsterdam.msf.org).

TABLE 1. Programmatic Actions for the Integration of FGS and HIV

Expand mass drug administration for schistosomiasis for school-aged children and women of reproductive age using a human rights approach, with emphasis on participation and informed community consent.
Expand integration of prevention, care, and treatment services to address HIV, cervical cancer, and FGS, and their impacts on reproductive health.
Improve awareness, education, and communication regarding FGS and HIV, with a focus on both communities and medical professionals.
Leverage HIV programs to expand knowledge of FGS, and integrate prevention services among affected communities and their health care providers.
Use existing health care delivery systems as a platform to expand FGS prevention, screening, and treatment. Address possible discrimination in health care settings and stigma attached to sexual and reproductive conditions.
Intensify efforts to advance gender equality and the sexual and reproductive health and rights of all girls and women.

association between high rates of schistosome exposure and increased rates of HIV infection in women.[22] Two case–control studies have also shown an up to 4 times increased odds of HIV infection in people with urogenital schistosomiasis.[23,24] The association between FGS and HIV seems clearer than the association between HIV and *S. mansoni* or *S. haematobium* infection in general. For example, some studies found increased odds of becoming HIV-infected if coinfected with *S. mansoni* compared with women who were not coinfected,[25,26] while other case–control studies did not find any association.[21,27–29]

These studies suggest that schistosomiasis may put women at a higher risk of acquiring HIV. FGS may lead to an increased susceptibility to HIV infection through damage to the mucosal barrier of the cervix and vagina by lesions.[11] In addition, susceptibility to HIV may increase through local[30–32] and systemic[33] immune modulation induced by the immunological reactions to egg deposition. This may explain the high rates of HIV in young women living in highly endemic rural areas such as along Lake Victoria in Tanzania[34] and KwaZulu-Natal.[35] Therefore, it is plausible that PZQ treatment programs aimed at the prevention, or if proved effective, treatment of FGS, could reduce HIV infection, especially in younger women.[36–39]

The effect of HIV on the frequency and severity of FGS has not been well described. It is not known, for example, if HIV-infected women are at an increased risk of becoming infected with schistosomes through reduced immunity and thus are at an increased risk of developing FGS. This possibility is supported by data from Tanzania showing that the intensity of *S. mansoni* infection was higher in HIV-positive women.[26] However, if FGS does develop in HIV-infected women, it may be associated with less severe disease forms because many of the pathogenic effects of schistosome infection are immune mediated, and therefore potentially less severe if one is immune suppressed. It has also been shown that urinary excretion of *S. haematobium* eggs is decreased or equivalent in HIV-positive women.[28,40–42] In addition, a reported sequelae of FGS is infertility, and it is possible that this risk is increased in HIV-infected women if their risk of FGS is increased.[43–46]

Another potential clinical concern is a further increase in the rate of cervical cancer in HIV-positive women, already at an increased risk of this malignancy due to HIV. The chronic inflammation associated with schistosome infection is known to cause bladder and liver cancer, and there are reports of an association with cervical cancer either as a direct effect of the schistosomiasis or by influencing persistence of high-risk subtypes of human papillomavirus (HPV).[47,48]

The effects of FGS on those infected with HIV are also not well understood. In a case–control study from Tanzania, those with schistosomiasis who recently acquired HIV had higher HIV viral loads compared with those who did not have schistosomiasis.[25] Furthermore, a study from Zimbabwe showed that treatment of schistosomiasis was associated with lower HIV viral loads and increased CD4 cell counts.[49] Therefore, schistosome infection, which leads to chronic immune activation, may increase HIV viral load[50] and, thus, the rate of HIV disease progression. On the other hand, a recent study from Tanzania showed that those with evidence of schistosome infection at the time of HIV seroconversion had an 82% reduction in the risk of their CD4 count falling to < 350 cells/mm^3 and/or death.[51] In addition, a further study from Tanzania found lower HIV viral loads in those with schistosome coinfection if the time of HIV infection was taken into account.[52] These studies suggest some protection against HIV disease progression by schistosome coinfection.

Schistosomiasis may also significantly increase the risk of HIV transmission to sexual partners and from mother to child either due to increased viral load[53] or the presence of increased virus-carrying inflammatory cells in semen and vaginal fluids. A modeling study suggested that for every 100 HIV-infected people, each suffering one episode of schistosome infection, there were 8.5 (2.7%–97.5%: 0.2–38.6) excess onward HIV-1 transmission events attributable to schistosome coinfection.[54]

Importantly, it is not known if there is an effect on mortality in HIV-infected women affected by FGS. However, it is plausible that it may be increased through genitourinary related sepsis from inflamed and ulcerated mucosa. It is known that severe bacterial sepsis is a frequent cause of mortality in HIV-infected patients, especially when immune suppression is severe.[55] Mortality rates are also increased in HIV-infected people with other illnesses associated with the breakdown of protective surfaces such as skin in patients with Buruli ulcer.[56] If a true increase in mortality risk was found, it would demand increased attention to the prevention, screening, and treatment of FGS in HIV populations.

There may also be significant treatment effects to consider for coinfected patients. First, it is possible that the effectiveness of FGS treatment with PZQ, which is already in question,[15] may be further reduced compared to non–HIV-infected women, either due to immune suppression from HIV infection, or through interactions with antiretroviral drugs to treat HIV, as PZQ is metabolized by the cytochrome P450 group including CYP 3A4 and CYP2C19.[57] This metabolism pathway may result in increased treatment failure or

TABLE 2. Proposed Research Agenda for FGS and HIV

Research Question	Study Design
Epidemiology	
What is the prevalence of FGS in HIV-infected women in schistosomiasis-endemic regions and is it increased compared to HIV-uninfected women?	Epidemiological surveillance; cross-sectional studies
Is there an association of HIV with severity of FGS disease? Is the severity influenced by the level of HIV-related immune suppression?	Observational studies (case–control and prospective cohort)
Is FGS associated with an increased risk of HIV infection, either through primary acquisition or through secondary transmission to others?	Population-based cohort study; case–control studies
Are rates of mortality, infertility, and cervical cancer increased in those coinfected with HIV and FGS?	Observational studies (case–control and prospective cohort)
Diagnosis	
What is the accuracy of emerging point-of-care diagnostic tests for FGS?	Diagnostic accuracy studies
What is the feasibility of integrating FGS diagnosis with diagnostic tests for STIs?	Implementation science
Treatment	
What is the effectiveness of PZQ in treatment of FGS in HIV-infected women compared with HIV-negative women in terms of cure, recurrence, mortality and infertility rates?	Comparative prospective cohort study
Does ART improve outcomes of FGS (such as cure, recurrence, and infertility rates) in coinfected patients?	Observational studies (case–control and prospective cohort)
Is ART associated with an increased incidence of FGS-associated IRIS reactions? If so, how severe are they and what are the effects, and how can they be managed?	Observational studies (case–control and prospective cohort)
Can regular treatment with PZQ in school-aged young women reduce incidence of HIV?	Cluster randomized trial
Service delivery	
What are the optimal approaches to integrating FGS care for HIV-infected women into health programs?	Implementation science

recurrence rates.[58] PZQ doses may need to be increased or prolonged, but these issues have not been adequately studied. It has also been reported that schistosome coinfection is associated with a reduced immunological response to ART.[59] Furthermore, it is possible that ART initiation may lead to immune reconstitution inflammatory syndrome associated with FGS.[60,61] If severe, the resulting tissue damage could lead to increased long-term FGS complications, including infertility, and this could justify screening for FGS before ART initiation.

FGS can be diagnosed clinically through identification of the pathognomonic lesions associated with *S. haematobium* infection in the female genital tract—mucosal grainy sandy patches linked to egg granulomas.[11,62] However, this requires gynecological examination equipment and trained clinicians. Diagnosis can also be made by visualization of eggs in lesions, but this requires access to histopathology services, which are uncommon in most endemic countries, and unless excluding malignancy, biopsying lesions is best avoided, as the biopsy site may temporarily increase HIV infection risk. FGS lesions have the potential to be misdiagnosed as cancer without histopathology, potentially leading to unnecessary cancer surgery.[63] Research, therefore, needs to be undertaken to develop better diagnostic tools for FGS, especially focused on point of care. An example would be health clinic diagnosis using self-administered vaginal swabs, as a positive *Schistosoma*-specific PCR in vaginal lavage fluid can detect genital lesions,[64] although the sensitivity for detection with current tools is low.[65] Perhaps, multiplex-based polymerase chain reaction technology could be applied to combine the detection of *Schistosoma* DNA in gynecological samples with the detection of STIs such as HPV, herpes simplex virus (HSV), chlamydia, gonorrhoea, and syphilis.

Currently screening for FGS is uncommonly performed in HIV-infected women in schistosomiasis-endemic areas. This is likely related to a number of factors including the lack of awareness and understanding of the significance of FGS in HIV-coinfected women, a lack of capacity in HIV services to perform adequate gynecological examinations, unclear cost-benefit, a lack of training of staff in how to diagnose FGS, and the absence of an easy to use point-of-care diagnostic test.

For programs wanting to address the burden of FGS and at the same time cervical cancer screening, the HIV-infected population is an appropriate group to include as a prioritized population because they seem to have a higher burden of both diseases than the non–HIV-infected population—therefore, targeting HIV-positive women will likely allow access to large numbers of women with these diseases. In addition, they are also likely to have a greater risk of adverse clinical outcomes from FGS than in non–HIV-infected women meaning addressing this issue is particularly urgent in this population. However, there is a need to increase awareness among clinicians and program managers about the importance of FGS in this population, and strategies need to be designed to incorporate FGS screening, prevention, and treatment into the care of HIV-positive women (Table 1). Models of care need to be explored to ensure this is performed efficiently and appropriately. Options could include combining them with HPV prevention and cervical cancer screening or STI services, either introduced into HIV clinics, or established in female-specific health services. Operational research needs to be undertaken to pilot and assess the feasibility and effectiveness of the different models of care.

The paucity of data regarding the impact of FGS and HIV coinfection points to an urgent need for clinical research

TABLE 3. Potential Important Health Interactions Between FGS and HIV

Potential Effects of HIV on FGS	Potential Effects of FGS on HIV
Increased susceptibility to FGS	Increased risk of primary HIV infection
Increased risk of cervical cancer secondary to FGS	Increased risk of HIV transmission to others
Increased risk of infertility secondary to FGS	Enhancement of HIV disease progression
Reduced effectiveness of FGS treatment	Increased mortality
Increased severity of FGS due to IRIS reactions on ART	Reduced effectiveness of ART

to better understand the extent and significance of these concerns. Summarized in Table 2, we propose a research agenda that aims to address many of these important information gaps and stimulate interest and support. Answering these questions would help to inform the development of approaches for the management of FGS/HIV coinfection, which are currently lacking. In combination with the proposed research agenda, more emphasis needs to be put into increasing the knowledge and awareness of communities, clinicians, program managers, and local, regional, and national programs around the important issues relating to FGS/HIV coinfection. Support from funding agencies will be needed to make the resources available required to turn the research agenda into reality.

In conclusion, the likely increased prevalence of HIV in women infected with FGS means that FGS is an important health problem for HIV-positive women in schistosomiasis-endemic areas. FGS may have significant effects on those infected with HIV including more rapid disease progression, increased HIV transmission to others, and potentially increased mortality (Table 3). Furthermore, FGS may make young women more susceptible to HIV and be significantly impacting the HIV epidemic in sub-Saharan Africa. In addition, it is possible that HIV may have a significant effect on FGS outcomes such as disease severity, risk of cervical cancer and infertility, and response rates to PZQ treatment. Therefore, there is an urgent need for research (clinical and operational) around FGS/HIV coinfection to answer the significant gaps in current knowledge. There is also an important need to increase awareness about the issues and provide guidance for clinicians and program managers caring for HIV/FGS-coinfected women.

REFERENCES

1. WHO. *Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015*. Geneva, Switzerland: World Health Organization; 2016.
2. WHO Expert Committee. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. *World Health Organ Tech Rep Ser.* 2002; 912:i–vi, 1–57, back cover.
3. van der Werf MJ, de Vlas SJ, Brooker S, et al. Quantification of clinical morbidity associated with schistosome infection in sub-Saharan Africa. *Acta Trop.* 2003;86:125–139.
4. *WHO. Neglected Tropical Diseases*; 2018. Available at: http://www.who.int/neglected_diseases/diseases/en/. Accessed August 30, 2018.
5. Hotez P, Whitham M. Helminth infections: a new global women's health agenda. *Obstet Gynecol.* 2014;123:155–160.
6. Christinet V, Lazdins J, Stothard J, et al. Female genital schistosomiasis (FGS): from case reports to a call for concerted action against this neglected gynaecological disease. *Int J Parasitol.* 2016;46:395–404.
7. Renaud G, Devidas A, Develoux M, et al. Prevalence of vaginal schistosomiasis caused by Schistosoma haematobium in an endemic village in Niger. *Trans R Soc Trop Med Hyg.* 1989;83:797.
8. Leutscher P, Ravaoalimalala VE, Raharisolo C, et al. Clinical findings in female genital schistosomiasis in Madagascar. *Trop Med Int Health.* 1998;3:327–332.
9. Poggensee G, Kiwelu I, Weger V, et al. Female genital schistosomiasis of the lower genital tract: prevalence and disease-associated morbidity in northern Tanzania. *J Infect Dis.* 2000;181:1210–1213.
10. Talaat M, Watts S, Mekheimar S, et al. The social context of reproductive health in an Egyptian hamlet: a pilot study to identify female genital schistosomiasis. *Soc Sci Med.* 2004;58:515–524.
11. Kjetland EF, Ndhlovu PD, Mduluza T, et al. Simple clinical manifestations of genital Schistosoma haematobium infection in rural Zimbabwean women. *Am J Trop Med Hyg.* 2005;72:311–319.
12. Toure S, Zhang Y, Bosque-Oliva E, et al. Two-year impact of single praziquantel treatment on infection in the national control programme on schistosomiasis in Burkina Faso. *Bull World Health Organ.* 2008;86: 780–787, A.
13. Richter J, Poggensee G, Kjetland EF, et al. Reversibility of lower reproductive tract abnormalities in women with Schistosoma haematobium infection after treatment with praziquantel—an interim report. *Acta Trop.* 1996;62:289–301.
14. Kjetland EF, Ndhlovu PD, Kurewa EN, et al. Prevention of gynecologic contact bleeding and genital sandy patches by childhood antischistosomal treatment. *Am J Trop Med Hyg.* 2008;79:79–83.
15. Kjetland EF, Mduluza T, Ndhlovu PD, et al. Genital schistosomiasis in women: a clinical 12-month in vivo study following treatment with praziquantel. *Trans R Soc Trop Med Hyg.* 2006;100:740–752.
16. Crompton DWT. *Preventive Chemotherapy in Human Helminthiasis: Coordinated Use of Anthelminthic Drugs in Control Interventions: A Manual for Health Professionals*. Geneva, Switzerland: World Health Organization;2006.
17. WHO. *Schistosomiasis Strategy*; 2018. Available at: http://www.who.int/schistosomiasis/strategy/en/. Accessed August 30, 2018.
18. Hotez PJ, Fenwick A, Kjetland EF. Africa's 32 cents solution for HIV/AIDS. *PLoS Negl Trop Dis.* 2009;3:e430.
19. Mbabazi PS, Andan O, Fitzgerald DW, et al. Examining the relationship between urogenital schistosomiasis and HIV infection. *PLoS Negl Trop Dis.* 2011;5:e1396.
20. Ndeffo Mbah ML, Poolman EM, Drain PK, et al. HIV and Schistosoma haematobium prevalences correlate in sub-Saharan Africa. *Trop Med Int Health.* 2013;18:1174–1179.
21. 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;101:433–438.
22. Brodish PH, Singh K. Association between Schistosoma haematobium exposure and human immunodeficiency virus infection among females in Mozambique. *Am J Trop Med Hyg.* 2016;94:1040–1044.
23. 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;84:364–369.
24. Kjetland EF, Ndhlovu PD, Gomo E, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. *AIDS.* 2006;20: 593–600.
25. Downs JA, Dupnik KM, van Dam GJ, et al. Effects of schistosomiasis on susceptibility to HIV-1 infection and HIV-1 viral load at HIV-1 seroconversion: a nested case-control study. *PLoS Negl Trop Dis.* 2017;11:e0005968.
26. Downs JA, van Dam GJ, Changalucha JM, et al. Association of Schistosomiasis and HIV infection in Tanzania. *Am J Trop Med Hyg.* 2012;87:868–873.
27. 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;20:1190–1195.

28. N'Zoukoudi-N'Doundou MY, Dirat I, Akouala JJ, et al. Bilharziasis and human immunodeficiency virus infection in Congo. *Med Trop (Mars).* 1995;55:249–251.
29. Thigpen MC, Filler SJ, Kazembe PN, et al. Associations between peripheral Plasmodium falciparum malaria parasitemia, human immunodeficiency virus, and concurrent helminthic infection among pregnant women in Malawi. *Am J Trop Med Hyg.* 2011;84:379–385.
30. Helling-Giese G, Sjaastad A, Poggensee G, et al. Female genital schistosomiasis (FGS): relationship between gynecological and histopathological findings. *Acta Trop.* 1996;62:257–267.
31. Kleppa E, Ramsuran V, Zulu S, et al. Effect of female genital schistosomiasis and anti-schistosomal treatment on monocytes, CD4+ T-cells and CCR5 expression in the female genital tract. *PLoS One.* 2014;9:e98593.
32. Jourdan PM, Holmen SD, Gundersen SG, et al. HIV target cells in Schistosoma haematobium-infected female genital mucosa. *Am J Trop Med Hyg.* 2011;85:1060–1064.
33. Secor WE, Shah A, Mwinzi PM, et al. Increased density of human immunodeficiency virus type 1 coreceptors CCR5 and CXCR4 on the surfaces of CD4(+) T cells and monocytes of patients with Schistosoma mansoni infection. *Infect Immun.* 2003;71:6668–6671.
34. Barongo LR, Borgdorff MW, Mosha FF, et al. The epidemiology of HIV-1 infection in urban areas, roadside settlements and rural villages in Mwanza Region, Tanzania. *AIDS.* 1992;6:1521–1528.
35. Kharsany AB, Mlotshwa M, Frohlich JA, et al. HIV prevalence among high school learners - opportunities for school-based HIV testing programmes and sexual reproductive health services. *World Health Popul.* 2012;13:43–50.
36. 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:e2346.
37. Ndeffo Mbah ML, Gilbert JA, Galvani AP. Evaluating the potential impact of mass praziquantel administration for HIV prevention in Schistosoma haematobium high-risk communities. *Epidemics.* 2014;7:22–27.
38. Mushayabasa S, Bhunu CP. Modeling schistosomiasis and HIV/AIDS codynamics. *Comput Math Methods Med.* 2011;2011:846174.
39. Gibson LR, Li B, Remold SK. Treating cofactors can reverse the expansion of a primary disease epidemic. *BMC Infect Dis.* 2010;10:248.
40. Mwanakasale V, Vounatsou P, Sukwa TY, et al. Interactions between Schistosoma haematobium and human immunodeficiency virus type 1: the effects of coinfection on treatment outcomes in rural Zambia. *Am J Trop Med Hyg.* 2003;69:420–428.
41. Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: implications of coinfection for excretion of eggs. *J Infect Dis.* 2005;191:1311–1320.
42. 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:e0119326.
43. Kjetland EF, Kurewa EN, Mduluza T, et al. The first community-based report on the effect of genital Schistosoma haematobium infection on female fertility. *Fertil Steril.* 2010;94:1551–1553.
44. Bullough CH. Infertility and bilharziasis of the female genital tract. *Br J Obstet Gynaecol.* 1976;83:819–822.
45. Woodall PA, Kramer MR. Schistosomiasis and infertility in east Africa. *Am J Trop Med Hyg.* 2018;98:1137–1144.
46. Miller-Fellows SC, Howard L, Kramer R, et al. Cross-sectional interview study of fertility, pregnancy, and urogenital schistosomiasis in coastal Kenya: documented treatment in childhood is associated with reduced odds of subfertility among adult women. *PLoS Negl Trop Dis.* 2017;11:e0006101.
47. Kjetland EF, Ndhlovu PD, Mduluza T, et al. The effects of genital Schistosoma haematobium on human papillomavirus and the development of cervical neoplasia after five years in a Zimbabwean population. *Eur J Gynaecol Oncol.* 2010;31:169–173.
48. Petry KU, Scholz U, Hollwitz B, et al. Human papillomavirus, coinfection with Schistosoma hematobium, and cervical neoplasia in rural Tanzania. *Int J Gynecol Cancer.* 2003;13:505–509.
49. Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: effect of treatment of schistosomiasis on CD4 cell count and plasma HIV-1 RNA load. *J Infect Dis.* 2005;192:1956–1961.
50. Secor WE. Interactions between schistosomiasis and infection with HIV-1. *Parasite Immunol.* 2006;28:597–603.
51. Colombe S, Machemba R, Mtenga B, et al. Impact of schistosome infection on long-term HIV/AIDS outcomes. *PLoS Negl Trop Dis.* 2018;12:e0006613.
52. Colombe S, Corstjens P, de Dood CJ, et al. HIV-1 viral loads are not elevated in individuals Co-infected with Schistosoma spp. after adjustment for duration of HIV-1 infection. *Front Immunol.* 2018;9:2005.
53. Blaser N, Wettstein C, Estill J, et al. Impact of viral load and the duration of primary infection on HIV transmission: systematic review and meta-analysis. *AIDS.* 2014;28:1021–1029.
54. 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;68:594–598.
55. Ford N, Shubber Z, Meintjes G, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. *Lancet HIV.* 2015;2:e438–e444.
56. Christinet V, Comte E, Ciaffi L, et al. Impact of human immunodeficiency virus on the severity of buruli ulcer disease: results of a retrospective study in Cameroon. *Open Forum Infect Dis.* 2014;1:ofu021.
57. Li XQ, Bjorkman A, Andersson TB, et al. Identification of human cytochrome P(450)s that metabolise anti-parasitic drugs and predictions of in vivo drug hepatic clearance from in vitro data. *Eur J Clin Pharmacol.* 2003;59:429–442.
58. Kigen G, Edwards G. Drug-transporter mediated interactions between anthelminthic and antiretroviral drugs across the Caco-2 cell monolayers. *BMC Pharmacol Toxicol.* 2017;18:20.
59. Efraim L, Peck RN, Kalluvya SE, et al. Schistosomiasis and impaired response to antiretroviral therapy among HIV-infected patients in Tanzania. *J Acquir Immune Defic Syndr.* 2013;62:e153–6.
60. Lawn SD. Immune reconstitution disease associated with parasitic infections following initiation of antiretroviral therapy. *Curr Opin Infect Dis.* 2007;20:482–488.
61. Goovaerts O, Mwinzi PNM, Muok EMO, et al. Aberrant plasma MMP and TIMP dynamics in Schistosoma—immune reconstitution inflammatory syndrome (IRIS). *PLoS Negl Trop Dis.* 2018;12:e0006710.
62. WHO. *Female Genital Schistosomiasis: A Pocket Atlas for Clinical Health-Care Professionals*; 2015. Available at: http://apps.who.int/iris/handle/10665/180863. Accessed August 30, 2018.
63. Swai B, Poggensee G, Mtweve S, et al. Female genital schistosomiasis as an evidence of a neglected cause for reproductive ill-health: a retrospective histopathological study from Tanzania. *BMC Infect Dis.* 2006;6:134.
64. Randrianasolo BS, Jourdan PM, Ravoniarimbinina P, et al. Gynecological manifestations, histopathological findings, and schistosoma-specific polymerase chain reaction results among women with Schistosoma haematobium infection: a cross-sectional study in Madagascar. *J Infect Dis.* 2015;212:275–284.
65. Galappaththi-Arachchige HN, Holmen S, Koukounari A, et al. Evaluating diagnostic indicators of urogenital Schistosoma haematobium infection in young women: a cross sectional study in rural South Africa. *PLoS One* 2018;13:e0191459.