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Association between *Schistosoma haematobium* Exposure and Human Immunodeficiency Virus Infection among Females in Mozambique

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Abstract. Recent evidence suggests an association between human immunodeficiency virus (HIV) and female genital schistosomiasis (FGS) in sub-Saharan Africa, especially in Mozambique, South Africa, Tanzania, and Zimbabwe. Women with FGS have increased numbers of HIV target cells and cell receptors in genital and blood compartments, potentially increasing the risk of HIV transmission per sexual exposure, and the association may explain the high female:male ratio of HIV prevalence unique to sub-Saharan Africa. We investigate this association in Mozambique by linking two georeferenced, high-quality secondary data sources on HIV prevalence and *Schistosoma haematobium*: the AIDS Indicator Survey, and the Global Neglected Tropical Diseases (GNTD) open-source database, respectively. We construct a schistosomiasis exposure covariate indicating women reporting "unimproved" daily drinking water sources and living no more than 2–5 km from high-endemic global positioning system (GPS) coordinates in the GNTD. In logistic regression analyses predicting HIV-positive status, we show that exposure increases the odds of HIV-positive status by three times, controlling for demographic and sexual risk factors.

Accumulating scientific evidence suggests a potential association between human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) in sub-Saharan Africa and the neglected tropical diseases, which infect over 1.4 billion people living in poverty, particularly women and children. There is considerable geographic overlap between areas of high neglected tropical disease prevalence and high HIV/AIDS prevalence, and two decades of studies indicate that HIV/AIDS can be exacerbated by neglected tropical disease coinfections through weakening the immune system, increasing susceptibility to other infections, and decreasing the effectiveness of antiretroviral therapy.[1] Although some have found the mostly observational evidence for these effects to be variable and inconclusive,[2] a randomized, double-blind, placebo-controlled trial found that treatment of helminths was associated with decreased HIV viral loads and increased $CD4^+$ T-cell counts,[3] and viral load is a strong predictor of sexual HIV transmission.[4] Also, helminth infection is associated with increased risk of maternal-to-child HIV transmission.

Although in most parts of the world HIV/AIDS infection rates are higher in men, in sub-Saharan Africa, 60% of infections are in women, and among women in rural areas with limited access to clean water, HIV prevalence peaks at younger ages than in urban regions.[5,6] One theory is that the parasitic infection female genital schistosomiasis (FGS) places young women at increased risk both by compromising the vaginal mucosal barrier and through systemic immunologic effects increasing susceptibility to infection and rate of disease progression. Exposure is through contaminated freshwater—swimming, bathing, fishing, and domestic chores can all place women at risk for contracting FGS. Schistosomiasis affects 261 million people worldwide, and more than 700 million people live in endemic areas.[5,7] In most of sub-Saharan Africa, schistosomiasis (especially *Schistosoma haematobium*) is endemic, with primary exposure occurring before the age of 5 years and prevalence peaking between age 10 and 20 years. *Schistosoma haematobium* was renamed "urogenital schistosomiasis" because it affects both the urinary and genital tracts in up to 75% of infected individuals.

A comprehensive review provides evidence that FGS may be a risk factor for HIV infection.[5] The World Health Organization (WHO) claims "urogenital schistosomiasis is also considered to be a risk factor for HIV infection, especially in women"[8] and recommends annual preventive chemotherapy for school-aged children in high-endemic areas. Further, complex co-associations and synergisms between HIV and schistosomiasis indicate opportunities for combined control in co-endemic regions, beginning in childhood.[9] Kleppa and others found higher frequencies of monocytes and frequencies of $CD4^+$ T cells expressing the HIV co-receptor CCR5 in blood samples taken from FGS+ South African women, both of which decreased after antischistosomal treatment.[10] In field studies in Zimbabwe, South Africa, and Tanzania,[11–13] women with patches of compromised tissue on vaginal exam were about three times as likely as their neighbors to be infected with HIV. A study of 345 women in rural Tanzania near Lake Victoria, where *Schistosoma mansoni* is hyperendemic, found that HIV prevalence was higher among women with more intense *S. mansoni* infection and schistosome intensity was higher in HIV-positive women.[14] Schistosomiasis is possibly the most important cofactor in Africa's AIDS epidemic, and 70 million African children could be dewormed twice a year for 10 years at a cost of $112 million, which is far less than the $38 billion U.S. President's Emergency Plan for AIDS Relief will spend on AIDS in that period.[12,15,16]

This analysis combines two secondary data sources to investigate this association in Mozambique. The 2009 National Survey on Prevalence, Behavioral Risks and Information about HIV and AIDS in Mozambique (INSIDA)[17] provides nationally and provincially representative data on HIV prevalence and information on a number of HIV risk factors as well as household drinking water source. Although it provides no direct information on schistosomiasis prevalence,

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WHO has identified five countries with prevalence exceeding 50%: Madagascar, Mozambique, Tanzania, Ghana, and Sierra Leone. Second, Swiss and Danish scientists in collaboration with African ministries of health have recently developed an open-source framework for the mapping, control, and surveillance of neglected tropical diseases.[18] Initiated by the European Union–funded "multidisciplinary alliance to optimize schistosomiasis control and transmission surveillance in sub-Saharan Africa" project, the Global Neglected Tropical Diseases (GNTD) database was designed to foster epidemiological research and to obtain up-to-date disease risk estimates. The database is populated with survey data obtained from peer-reviewed publications and "grey literature," using a standardized approach, and directly from contributors. Regularly updated, at the beginning of 2011, it included more than 12,000 georeferenced survey locations (mainly on *S. haematobium* and *S. mansoni* in Africa). Database entries are searchable and freely downloadable.

In this analysis, we geospacially linked cluster-level data on HIV prevalence from the INSIDA datasets to point-prevalence data from the GNTD. We used the Stata (College Station, TX) user-written command geonear[19] to identify, using geodetic distances, nearest neighbor individuals in the INSIDA datasets to high-endemic survey points in the GNTD database. In the absence of a direct measure of FGS, we constructed a schistosomiasis exposure covariate indicating women reporting both "unimproved" daily drinking water sources and living within what could be considered concentric zones around high-endemic (> 50% point prevalence for infection with *S. haematobium*) global positioning system (GPS) coordinate points in the GNTD. "Unimproved" daily drinking water sources include an unprotected spring, an unprotected dug well, a cart with a small tank or drum, a tanker truck, surface water, bottled water,† and "other" sources.[20] Zone 1 was defined as the area nearest to a high-endemic point, that is, within a 2- (for urban clusters) or 5- (for rural clusters) km radius of that point. Zone 2 was defined as living within a 3- (urban) or 7.5- (rural) km radius of a high-endemic point, while Zone 3 was defined as living within a 5- (urban) or 10- (rural) km radius. Thus, the unexposed group was defined as reporting daily exposure to improved daily drinking water or to unimproved drinking water but not living in close proximity to a high-endemic *S. haematobium* GPS site. In multivariate weighted logistic regression models of HIV prevalence, we varied the distances from the high-endemic point prevalence locations in the construction of the exposure covariate, to demonstrate effect attenuation as distances increased. Control variables included standard demographic and sexual behavior variables associated with HIV prevalence from the INSIDA: age, urban/rural residence, employment status, highest level of education, wealth quintile, marital status, religion, and lifetime number of sexual partners.

Table 1 shows summary statistics for variables included in final model, overall and by drinking water source. Of the 8,847 total female respondents, slightly under half reported an unimproved source of daily drinking water. A total of 1,006 respondents (11%) were HIV positive, and a significantly higher percentage of those reporting an improved water source was HIV positive (13.7% versus 8.8%, $P < 0.001$). However, when stratifying for the geographical zones around high-endemic schistosomiasis points (with unprotected water), the central zones have more HIV cases (Table 2). Respondents reporting an improved water source were more likely to live in urban settings, as noted in Table 1, and data from the INSIDA indicate higher HIV prevalence rates among women aged 15–24 years in urban settings—14.3% in urban versus 9.2% in rural regions. When stratified by urban versus rural residence, the significant association between an improved water source and HIV-positive status becomes nonsignificant (data not shown). Those reporting an unimproved daily water source were slightly older, more likely to be working, much less educated, much poorer, and more likely to be married or living together with their partner. There were no significant differences in those reporting more than two lifetime sexual partners.

Table 2 shows results from logistic regression models using survey weights available in the INSIDA datasets and predicting HIV-positive status from potential *S. haematobium* exposure, by age groups, among respondents reporting an unimproved source of daily drinking water. In models controlling for all covariates, HIV-positive status was significantly associated with living in Zone 1. This association held for the all ages group (odds ratio [OR] = 2.71, 95% confidence interval [CI] = 1.56–4.71), as well as for those aged 15–24 years (OR = 2.31, 95% CI = 1.28–4.19) and those aged 25–59 years (OR = 2.97, 95% CI = 1.66–5.32). Women in the exposed group were between 2.3 and 3.0 times more likely to be HIV positive compared with those in the unexposed group. As distances between clusters in the INSIDA and coordinates in the GNTD increased (Zones 2 and 3) in the models with exposure plus all covariates, the associations remained positive but were nonsignificant.

Figure 1 shows first that the provinces with the highest female-to-male HIV prevalence rate ratios are Gaza, bordering South Africa and Zimbabwe; Tete, bordering Zambia, Zimbabwe, and Malawi; Niassa, bordering Tanzania; and Zambezia. These provinces all include several major rivers or lakes. Second, the GPS coordinate points representing highest prevalence rates of *S. haematobium* are concentrated in Zambezia, the location of the Zambezi River delta. Close proximity or overlap of these GPS coordinate points and the points indicating clusters with high HIV prevalence are locations of likely coinfection (red circles and blue squares). These sites occur in multiple provinces but are concentrated in Zambezia, and they tend to be located on or near rivers. Finally, plotting these data together provides some suggestive evidence of a geographic association or overlap between provinces with higher female:male ratios of HIV prevalence among youth aged 15–24 years and locations where there are likely to be higher rates of coinfection. The high prevalence of *S. haematobium* in the northern provinces agrees with findings from Augusto and others, who surveyed 83,331 schoolchildren in Mozambique to provide updated and accurate prevalence rates of schistosomiasis at the district level.[21]

A limitation of this study is the indirect assessment of *S. haematobium* exposure, and perhaps future AIDS Indicator Surveys/Demographic and Health Surveys will include

†Per reference 20: "Bottled water is considered to be improved only when the household uses drinking-water from an improved source for cooking and personal hygiene; where this information is not available, bottled water is classified on a case-by-case basis."

TABLE 1
Summary statistics for variables included in final model, by drinking water source

	Total	Drinking water source*		*P* value
		Unimproved	Improved	
n	8,847	4,180	4,667	
Dependent variable				
HIV positive, *n* (%)	1,006 (11.4)	367 (8.8)	640 (13.7)	< 0.001
Demographic variables				
Age in years, mean (SE)	33.1 (0.22)	34.1 (0.29)	32.3 (0.28)	< 0.001
Urban residence	2,826 (31.9)	555 (13.3)	2,271 (48.7)	< 0.001
Working	7,449 (84.2)	3,753 (89.8)	3,696 (79.2)	< 0.001
Education				
None	2,274 (25.7)	1,214 (29.0)	1,060 (22.7)	
Primary	5,172 (58.5)	2,692 (64.4)	2,481 (53.2)	
Secondary+	1,401 (15.8)	275 (6.6)	1,126 (24.1)	< 0.001
Wealth quintile				
Poorest	1,688 (19.1)	1,465 (35.0)	222 (4.8)	
Poorer	1,747 (19.8)	1,191 (28.5)	556 (11.9)	
Middle	1,760 (19.9)	767 (18.3)	994 (21.3)	
Richer	1,731 (19.6)	585 (14.0)	1,146 (24.6)	
Richest	1,922 (21.7)	173 (4.1)	1,749 (37.5)	< 0.001
Marital status				
Never married	1,151 (13.0)	295 (7.1)	855 (18.3)	
Married or living together	6,494 (73.4)	3,371 (80.7)	3,123 (66.9)	
Widowed, divorced, or not living together	1,203 (13.6)	514 (12.3)	689 (14.8)	< 0.001
Religion				
Catholic	2,860 (32.3)	1,551 (37.1)	1,310 (28.1)	
Protestant	1,933 (21.8)	778 (18.6)	1,155 (24.8)	
Muslim	1,668 (18.8)	763 (18.3)	905 (19.4)	
None/other	2,386 (27.0)	1,089 (26.0)	1,297 (27.8)	
Sexual behavior variable				
> 2 lifetime sex partners	3,846 (43.5)	1,747 (41.8)	2,099 (45.0)	

HIV = human immunodeficiency virus; SE = standard error.
*Based on World Health Organization/United Nations Children's Emergency Fund classification of drinking water sources. "Unimproved" sources include an unprotected spring, an unprotected dug well, a cart with a small tank or drum, a tanker truck, surface water, bottled water, and "other" sources. "Improved" sources include piped water into dwelling, piped water to yard or plot, public tap or standpipe, tube well or borehole, protected dug well, protected spring, and rainwater. *P* values are calculated from Pearson survey design-based χ^2 tests for between-group differences in proportions of respondents reporting each characteristic or, for categorical variables, between-group differences in the proportions of respondents across categories. For the continuous variable age, an adjusted Wald test statistic is used to test between-group differences in means.

direct assessment of neglected tropical diseases. However, the combined definition of exposure used in the context of a country with national prevalence rates exceeding 50% makes the probability of exposure high. Also, the INSIDA randomly displaces GPS coordinates (i.e., randomly alters the precise coordinates to protect respondents from being located) for individuals tested for HIV, although displacement is normally confined to within 2 km (urban) and 5 km (rural). In this analysis, displacement is treated as random noise, which would make it more difficult to demonstrate an association via proximity. Although the exact household coordinates are unknown, they fall within the defined proximity range in which a significant association is detected, and further, they represent a reasonable walking travel distance to the unimproved water sources that would be the source of exposure. Also, the association could be an artifact of settlement patterns along water bodies causing both diseases to be proximal, but we are unaware of similar point-proximity patterns between HIV and other waterborne diseases, nor as clear a mechanism explaining a potential nonartifactual association. Although age ranges are provided in the GNTD, *S. haematobium* prevalence rates are not age adjusted. Because prevalence rates vary by age and most prevalence data are collected in children, while HIV acquisition

TABLE 2
Logistic regression models predicting HIV-positive status from potential *Schistosoma haematobium* exposure, by age groups (N = 8,847)

		INSIDA cluster proximity to high-endemic GPS coordinate in GNTD					
		Zone 1		Zone 2		Zone 3	
		Within 2 km for urban clusters and 5 km for rural clusters		Within 3 km for urban clusters and 7.5 km for rural clusters		Within 5 km for urban clusters and 10 km for rural clusters	
Population	Independent variables	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
All ages	Exposure*	1.98 (1.00–3.96)	0.051	1.07 (0.53–2.15)	0.852	1.00 (0.52–1.95)	0.991
	Exposure plus covariates†	2.71 (1.56–4.71)	< 0.001	1.62 (0.86–3.06)	0.138	1.55 (0.80–3.02)	0.191
Age 15–24 years	Exposure	1.76 (0.92–3.37)	0.086	1.09 (0.53–2.23)	0.817	1.06 (0.59–1.92)	0.847
(N = 2,689)	Exposure plus covariates	2.31 (1.28–4.19)	0.006	1.56 (0.66–3.67)	0.305	1.51 (0.75–3.04)	0.250
Age 25–59 years	Exposure	2.16 (0.95–4.90)	0.066	1.07 (0.50–2.28)	0.859	0.98 (0.46–2.10)	0.955
(N = 6,159)	Exposure plus covariates	2.97 (1.66–5.32)	< 0.001	1.68 (0.86–3.29)	0.131	1.59 (0.75–3.38)	0.226

HIV = human immunodeficiency virus; GPS = global positioning system; GNTD = Global Neglected Tropical Diseases; INSIDA = National Survey on Prevalence, Behavioral Risks, and Information about HIV and AIDS in Mozambique.
*Exposure defined as spatial proximity to survey points with *S. haematobium* prevalence ≥ 50% among those reporting unimproved drinking water sources.
†Covariates include age, highest education level, wealth index, marital status, religion, and self-reported number of lifetime sexual partners.

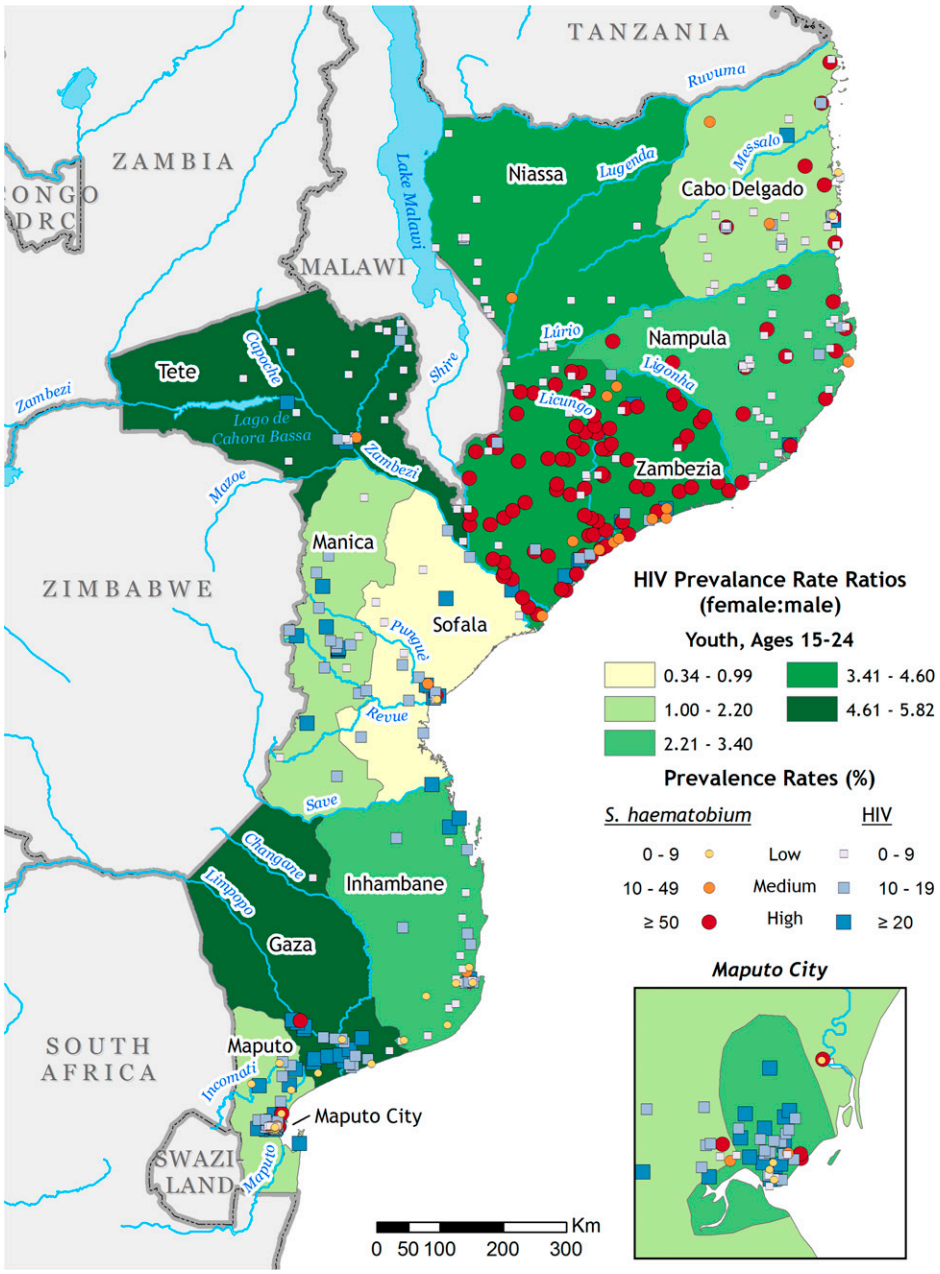

FIGURE 1. Map of Mozambique plotting *Schistosoma haematobium* and human immunodeficiency virus (HIV) prevalence rate categories at global positioning system coordinate points from the Global Neglected Tropical Diseases and National Survey on Prevalence, Behavioral Risks and Information about HIV and AIDS in Mozambique (INSIDA) datasets, HIV prevalence rate ratios by province, and major lakes and rivers.

presumably occurs after sexual debut, a geospatial analysis is problematic if persons exposed as children move away from the survey location before their sexual debut. Similarly, because some GNTD data were collected up to 60 years ago, conditions may have changed in a particular survey location, which were not captured by the covariates in our models. A further limitation is that the availability of mass drug administration in the various survey regions is unknown, but it would tend to make it more difficult to identify an association to the extent that treated persons were protected from HIV acquisition.

These results provide additional evidence supporting the claim that *S. haematobium* is a risk factor for HIV acquisition and transmission and the need to scale-up preventive chemotherapy and protected water access in Mozambique. Associations should be investigated in other countries where there is high co-endemicity. Preventive chemotherapy would be inexpensive and could be scaled up and targeted to these areas, focusing on communities lacking access to improved water sources, potentially averting millions of new HIV cases.

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