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Does Partner Selection Mediate the Relationship Between School Attendance and HIV/Herpes Simplex Virus-2 Among Adolescent Girls and Young Women in South Africa: An Analysis of HIV Prevention Trials Network 068 Data

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Abstract

Objective: School attendance prevents HIV and herpes simplex virus-2 (HSV-2) in adolescent girls and young women, but the mechanisms to explain this relationship remain unclear. Our study assesses the extent to which characteristics of sex partners, partner age, and number mediate the relationship between attendance and risk of infection in adolescent girls and young women in South Africa.

Design: We use longitudinal data from the HIV Prevention Trials Network 068 randomized controlled trial in rural South Africa, where girls were enrolled in early adolescence and followed in the main trial for more than 3 years. We examined older partners and the number of partners as possible mediators.

Methods: We used the parametric g-formula to estimate 4-year risk differences for the effect of school attendance on the cumulative incidence of HIV/HSV-2 overall and the controlled direct effect (CDE) for mediation. We examined mediation separately and jointly for the mediators of interest.

Results: We found that young women with high attendance in school had a lower cumulative incidence of HIV compared with those with low attendance (risk difference = −1.6%). Partner age difference (CDE = −1.2%) and the number of partners (CDE = −0.4%) mediated a large portion of this effect. In fact, when we accounted for the mediators jointly, the effect of schooling on HIV was almost removed, showing full mediation (CDE = −0.3%). The same patterns were observed for the relationship between school attendance and cumulative incidence of HSV-2 infection.

Conclusion: Increasing school attendance reduces the risk of acquiring HIV and HSV-2. Our results indicate the importance of school attendance in reducing partner number and partner age difference in this relationship.

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Results: We found that young women with high attendance in school had a lower cumulative incidence of HIV compared with those with low attendance (risk difference = −1.6%). Partner age

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difference (CDE = −1.2%) and the number of partners (CDE = −0.4%) mediated a large portion of this effect. In fact, when we accounted for the mediators jointly, the effect of schooling on HIV was almost removed, showing full mediation (CDE = −0.3%). The same patterns were observed for the relationship between school attendance and cumulative incidence of HSV-2 infection.

Conclusion: Increasing school attendance reduces the risk of acquiring HIV and HSV-2. Our results indicate the importance of school attendance in reducing partner number and partner age difference in this relationship.

Key Words: South Africa, adolescent girls and young women, HIV, HSV-2, education, mediation

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INTRODUCTION

Young South African women have an extremely high burden of HIV and herpes simplex v-II (HSV-2). The prevalence of HIV in adolescent girls and young women (AGYW) aged 15–26 years is 16%,[1] and the prevalence of HSV-2 is 29%.[2] Most interventions to prevent sexually transmitted infections in AGYW have focused on modifying sexual risk behaviors and have had limited success.[3–5] However, there is now a large body of evidence showing that attending school and staying in school protect against HIV and HSV-2 infection.[6–10] Our analysis from South Africa showed that low school attendance and school dropout were associated with over twice the risk of both incident HIV and incident HSV-2.[11] Yet, the mechanisms underlying the relationship between attending school and sexually transmitted infections are not understood.

HIV and HSV-2 are most commonly transmitted sexually. Therefore, for schooling to affect acquisition of HIV and HSV-2, schooling must influence behavioral factors that can affect the likelihood of transmission such as exposure to infection through a sexual partner.[12] Researchers have hypothesized that the effect of education on HIV risk, including both educational attainment and school attendance, may be a result of changes in social networks, self-efficacy, socioeconomic status (SES), or sexual risk behaviors. However, there is limited empirical evidence investigating pathways between education and HIV or HSV-2 infection.[3] Because of associations between school attendance and both partner age difference and partner number and theories on the importance of sexual networks in individual acquisition of HIV, we chose to examine the mediating effect of characteristics of sex partners in the association between school attendance and HIV risk reduction.[7,13–16]

Our hypothesis is based on the idea that the structure of partnership networks is important in influencing young women's HIV risk.[17,18] Social control theory and the routine/time use perspective state that behavior (in this case sexual behavior) can be limited by social forces and that activities that involve structured, supervised time will limit adolescent deviant or risky behavior.[19–24] We theorized that the supervised, structured environment of school would lead to fewer partners as AGYW are occupied and to younger partners (who are less likely to have HIV), as students spend more time socializing with individuals in their peer group. Our previous study from South Africa showed that the girls who attend school have partners closer in age to themselves and fewer partners.[16] Therefore, it is possible that AGYW in school are less likely to become infected with HIV and HSV-2 because school attendance shapes their sexual network by influencing the types of partners they choose. No studies have directly examined if sex partners mediate the relationship between school attendance and HIV acquisition.

Given that attending school is one of the few factors that is strongly preventative against HIV and HSV-2 infection for adolescent girls, understanding the pathways through which school reduces the risk is important to improve our

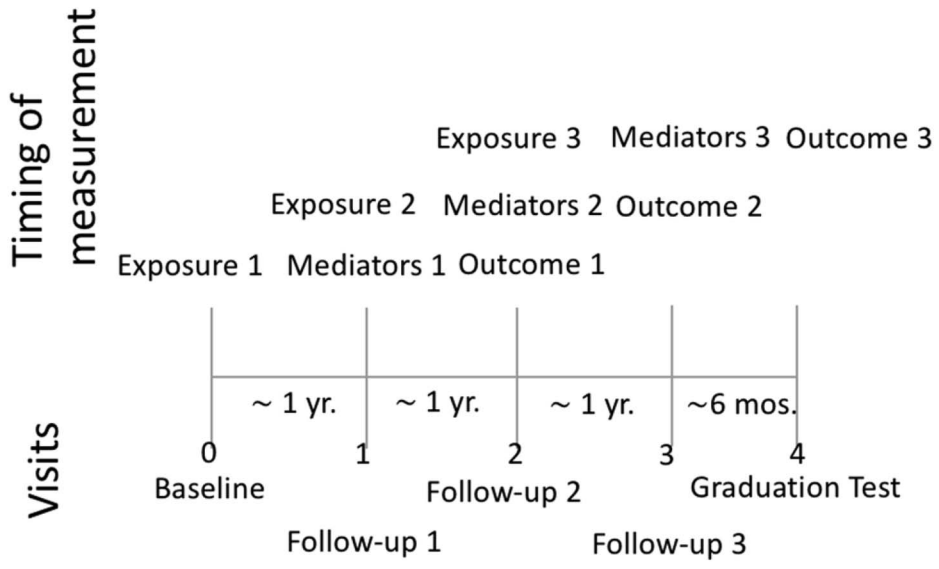

FIGURE 1. Timing and measurement of exposure, outcome, and mediators in a participant with all possible visits.

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prevention response. Our study explores if partner age difference or the number of partners mediate the relationships between school attendance and incident HIV and HSV-2 infection among AGYW.

METHODS

Study Population

We used data from the HIV Prevention Trials Network (HPTN) 068 study, a phase III randomized trial to determine whether providing cash transfers, conditional on school attendance, reduced the risk of HIV acquisition in young women.[25,26] Details of the behavioral questionnaire and laboratory data are available in the parent publication of the trial.[26] The study included young women living in 28 villages within the MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt) in rural Mpumalanga Province, South Africa. The study enrolled 2533 young women aged 13–20 years in high school grades 8, 9, 10, or 11. Young women who were pregnant or married at enrollment or had no parent/guardian in the household were excluded. To assess incident HIV infection and mediation, we only included young women who had at least 2 follow-up visits and were HIV negative at enrollment and at the first follow-up visit (Fig. 1). We did so to ensure that school attendance was measured before the potential mediators, and the mediators were measured before the outcome. For incident HSV-2 infection, we further excluded prevalent cases of HSV-2 at enrollment or the first follow-up.

Young women were seen annually from baseline until study completion or expected graduation from high school. Each annual study visit included an audio computer-assisted self-interview with the young woman and HIV and HSV-2 testing for those who were negative at the previous visit. Up to 4 assessments of the young women were conducted between 2011 and 2015, at baseline and roughly every 12 months thereafter. Young women were in different grades at enrollment and could have had fewer than 4 visits if they were expected to graduate before the end of the study period. An additional HIV and HSV-2 test was conducted for some girls around the time of expected graduation from high school or when the study was completed to capture more person time in the study if eligibility was met (termed the graduation test). This test was typically around 6 months after the previous annual visit.

TABLE 1. Baseline Characteristics of Young Women Aged 13 to 20 Without Prevalent HIV Infection and at Least Follow-Up Visits in Agincourt, South Africa From March 2011 to December 2012 (N = 2086)*

	n (%)
Young women's age at baseline (yr)	
13–14	717 (34.4)
15–16	913 (43.8)
17–18	384 (18.4)
18–20	72 (3.5)
Household wealth	
Low	540 (25.9)
Middle to low	566 (27.2)
Middle	489 (23.5)
High	488 (23.4)
CCT randomization arm	1091 (52.3)
Partner 5 or more years older	105 (5.1)
Ever pregnant or had a child	150 (7.3)
Prevalent HSV-2 infection	73 (3.5)
Any alcohol use	173 (8.3)
Double or single orphan	1314 (30.2)
Children's depression inventory score ≥7	369 (17.7)
Revised children's manifest anxiety score ≥7	570 (27.3)
Partner number	
0	1626 (78.9)
1	344 (16.7)
≥2	92 (4.5)

*Missing data in observed: age, 0; SES, 3; age difference, 5, pregnant, 23; HSV-2 status, 2; alcohol, 3; orphan, 98; depression, 0; anxiety, 0; partner number, n = 24.
CCT, Conditional Cash Transfer.

Exposure, Outcome, and Mediator Ascertainment

The exposure of school attendance was constructed using school attendance registers collected directly from high schools. School attendance was defined as the average percentage of days attended in the months of February, May, and August between surveys, as these months were most representative of normal attendance because of the absence of holidays or examinations. School attendance was dichotomized as high (≥80% of school days) versus low (<80% of school days) attendance as per the original cash transfer study.[26]

The mediator of "having an older partner" was defined as having had at least 1 sexual or nonsexual partner 5 or more years older at each follow-up visit. Partners with whom there was no reported sexual relationship were included to account for potential misreporting about sexual behaviors. The mediator of the "number of sexual partners" was defined as having zero, 1 or >1 sex partners in the past 12 months at each visit. The outcomes of incident HIV and HSV-2 infection were defined as new cases after the first follow-up visit, as described by testing procedures in the main article.[26] We include incident cases from the second visit onward to ensure that all infections occurred after the mediator and exposure ascertainment.

Statistical Analysis

We used the potential outcomes framework to define the total effect as the risk difference (RD) comparing the 4-year cumulative incidence of HIV or HSV-2 had all young women had high attendance to the 4-year cumulative incidence of HIV or HSV-2 had all young women had low attendance. Likewise, the controlled direct effect (CDE) was defined as the RD (high versus low attendance) that would have been observed if attendance was prevented from affecting each of the mediators.[27,28] Specifically, our study explored if partner age difference or the number of partners were mediators in the relationship between school attendance and incident HIV/HSV-2 infection by estimating the CDE of

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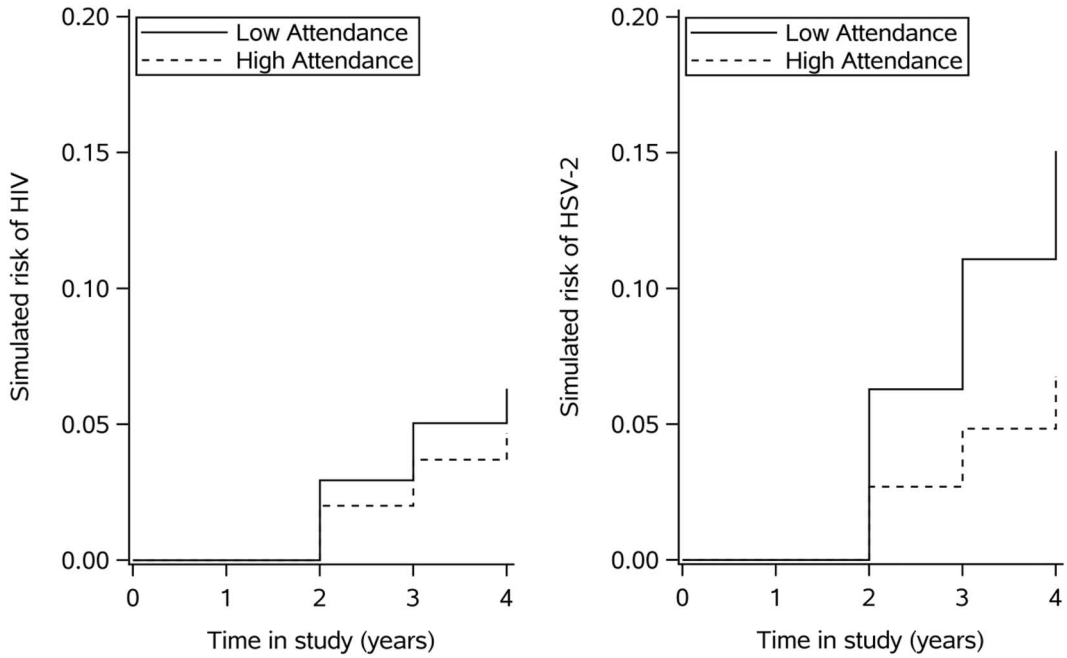

FIGURE 2. Cumulative incidence of HIV and HSV-2 by time since study enrollment and attendance in a Monte Carlo sample of 10,000, accounting for confounding.

attendance while intervening to fix (ie, control for) the mediators.[29–31] In our study, the CDE can be interpreted as the effect of school attendance on HIV and HSV-2 that occurs through mechanisms other than by reducing partner age and number. We chose to estimate the CDE for mediation rather than the natural direct or indirect effect because it does not require as many assumptions including the assumption that there is no mediator-outcome confounder that is affected by the exposure, which we cannot assume in this analysis.[32] Additionally, we examined the CDE under several different scenarios or "interventions" including (1) prevent young women from having any sexual partners and older sexual or nonsexual partners; (2) set women to have 1 sexual partner and prevent women from having any older sexual or nonsexual partners; (3) reduce the number of women with an older partner by 50%; (4) set young women to have fewer partners (those with ≥2 have 1 partner and those with 1 have 0 partners); and (5) set young women to have fewer partners and reduced the number of women with an older partner by 50%.

We estimated the total effect and CDE using the parametric g-formula, a generalization of standardization that allows us to account for time-varying confounding and accommodate interactions between school attendance and

TABLE 2. CDE of School Attendance on Incident HIV and HSV-2 by Different Levels of the Mediators Partner Number and Partner Age Difference

	HIV			HSV-2		
	Risk (%)	RD% (95% CI)	RR (95% CI)	Risk (%)	RD% (95% CI)	RR (95% CI)
Total effect						
High attendance	4.7	−1.6 (−2.3 to −1.0)	0.74 (0.66 to 0.83)	6.7	−8.3 (−9.1 to −7.5)	0.45 (0.41 to 0.49)
Low attendance	6.3	0	1.0	15.1	0	1
CDE: no older partners						
High attendance	4.6	−1.2 (−1.8 to −0.7)	0.79 (0.70 to 0.88)	6.3	−6.2 (−7.1 to −5.4)	0.51 (0.46 to 0.55)
Low attendance	5.8	0	1	12.6	0	1
CDE: no sexual partners						
High attendance	3.2	−0.4 (−0.9 to 0.1)	0.89 (0.77 to 1.03)	5.8	−6.9 (−7.8 to −6.1)	0.46 (0.41 to 0.50)
Low attendance	3.6	0	1	12.8	0	1
CDE: 1 sexual partner						
High attendance	7.0	−0.8 (−1.6 to −0.1)	0.89 (0.81 to 0.98)	8.2	−7.6 (−8.5 to −6.7)	0.52 (0.48 to 0.56)
Low attendance	7.8	0	1	15.8	0	1

RD, risk difference, RR, risk ratio.

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the mediators.[27,31,32] Details on using the parametric g-formula for mediation analysis have been described previously.[27,33–37] Briefly, we created a simulated version of our data set with no confounding in which we set variables to mimic interventions (see technical appendix for more detail) on school attendance and each mediator.

Confounders were selected using a directed acyclic graph for the relationship between school attendance and HIV and for the relationship between school attendance and HSV-2. We included the exposure-outcome confounders of time, age at baseline, intervention assignment at baseline, SES at baseline (defined using quartiles of household assets), time-varying orphan status, time-varying alcohol use, time-varying children's depression inventory score,[38,39] and time-varying revised children's manifest anxiety score.[40] In addition, we included HSV-2 status in the model for the outcome of HIV. We also included the mediator-outcome confounders of depression, anxiety, and alcohol use in all models (all time varying). An interaction term between the mediators, partner age difference and partner number, was also included in the model, but we were unable to include an interaction term between exposure and mediators because of sparse data (see technical appendix). We examined SES defined using both household assets and parental educational attainment but ultimately chose assets because results were similar and assets had less missing data.

Risk of HIV and HSV-2 for each exposure pattern (the combination of interventions on exposure and mediators) was estimated using the complement of the Kaplan–Meier estimator extended to account for time-varying exposures.[33] We compared the risk of HIV and HSV-2 at the end of the study period (4 years to account for the extra graduation test) under each exposure plan using RDs and risk ratios. Ninety five percent confidence intervals (CI) were computed using the standard errors from 200 nonparametric bootstrap resamples. SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used for all analyses.

RESULTS

A total of 2086 young women who were HIV negative at baseline and at the first follow-up, and had at least 2 follow-up visits following baseline were included in our HIV cohort. For the HSV-2 cohort, we further excluded prevalent cases of HSV-2 at baseline and those who were missing HSV-2 status for a total of 1963 young women with 4192 visits over the study period. In the observed data, there were 74 incident HIV infections and 117 incident HSV-2 infections from follow-up visit 2 to the end of the study period. Of the 4450 visits with school attendance data, girls who were HIV negative at baseline had high attendance during 95.2% of visits (n = 4234). At baseline in the observed data, 5.1% (n = 105) had a partner 5 or more years older, 78.9% had zero partners (n = 1626), and 16.7% (n = 344) had 1 partner in the past 12 months (Table 1).

The risk of HIV at 4 years of follow-up time would be 6.3% if all young women had low school attendance and 4.7% if all young women had high attendance over the entire study period (Fig. 2 and Table 2). Cumulative incidence of HIV and HSV-2 estimated under no intervention on exposure or mediators (the "natural course") was similar to the cumulative incidence of the outcomes in the observed data (HIV 4.9%; HSV-2 8.1%; Appendix Figure 1, http://links.lww.com/QAI/B180). Table 2 shows the total effect of school attendance compared with the CDE of attendance when young women also do not have an older partner, when they have 1 partner and zero partners. The estimated RD at 4 years for the effect of high versus low school attendance on HIV was −1.6% (95% CI: −2.3% to −1.0%). The RD of −1.6% represents the total effect of school attendance on HIV operating through all pathways, including partner age and number. When we removed the effect of attendance on partner age by setting all girls to have a younger partner, the RD for the effect of school attendance on HIV was −1.2%

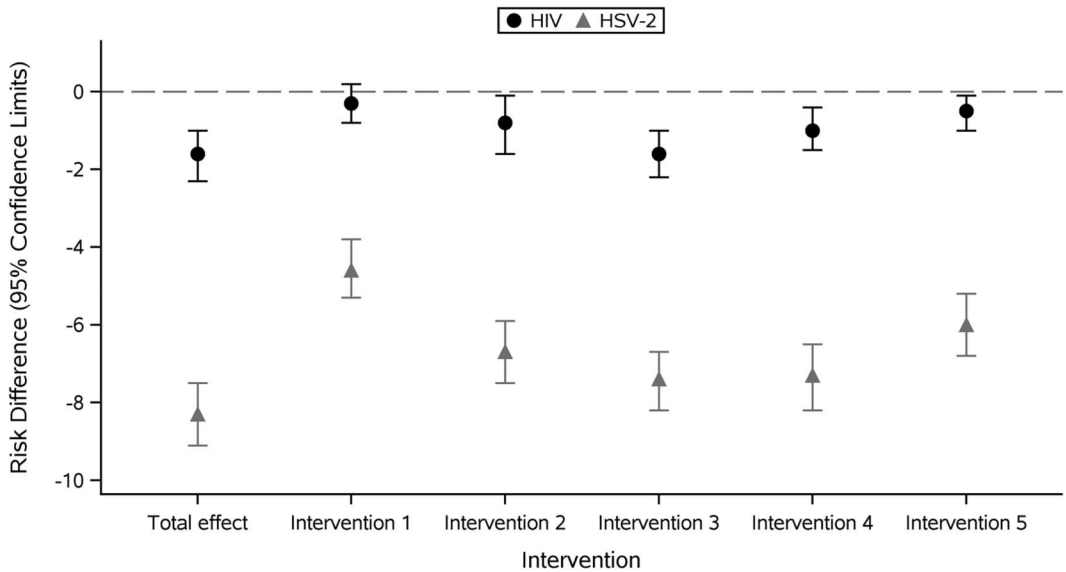

FIGURE 3. CDE of school attendance on incident HIV and HSV-2 with various interventions on the mediators partner age difference and partner number.

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(95% CI: −1.8% to −0.7%). When we removed the effect of school attendance on partner number by setting young women have 0 partners, the RD for the effect of school attendance on HIV was −0.4% (95% CI: −0.9% to 0.1%). When we set the number of partners to 1 partner (even those with 0 partners), the RD at 4 years was −0.8% (95% CI −1.6% to −0.1%).

The risk of HSV-2 at 4 years was 15.1% if all young women had low attendance and 6.7% if all young women had high attendance over the entire study period (Fig. 2 and Table 2). The estimated RD for the total effect of high versus low school attendance on HSV-2 was higher than that on HIV at −8.3% (95% CI: −9.1% to −7.5%) (Table 2). When we removed the effect of attendance on partner age, the RD at 4 years was −6.2% (95% CI: −7.1% to −5.4%) When all young women had 0 partners, the RD was −6.9% (95% CI: −7.8% to −6.1%). When we set the number of partners to 1, the RD at 4 years was −7.6% (95% CI: −8.5% to −6.7%).

Figure 3 shows the effect of school attendance on HIV and HSV-2 under 5 potential scenarios where we have jointly removed the effect of school attendance on both partner age difference and partner number. For incident HIV, the RD for the CDE of school attendance was attenuated from the total effect in all scenarios. Under intervention 1, the RD was almost zero (RD, −0.3%; 95% CI: −0.8% to 0.2%). Even under intervention 5 where we do not completely set behaviors, the effect of school attendance on HIV acquisition was almost removed (RD, −0.5%; 95% CI: −1.0% to −0.1%). For incident HSV-2 infection, the RD for the effect of school attendance on HSV-2 was again attenuated from the total effect in all scenarios, although the effect was never completely removed. The RD for the effect of school attendance on HSV-2 was closest to the null under intervention 1 when we intervened to set all young women to have younger partners and zero partners (RD, −4.6%; 95% CI −5.3% to −3.8%).

DISCUSSION

In this cohort of AGYW in rural South Africa, we found that partner age and partner number mediated the relationship between school attendance and HIV and HSV-2 acquisition. School attendance was associated with the risk of both incident HIV and HSV-2. The effect of school attendance on incident infection was nearly removed when also intervening on the number of older partners and partner number, suggesting that a large proportion of protective effect of school attendance on HIV acquisition in this cohort is the result of sexual partner characteristics. In fact, the effect of school attendance on HIV, although primarily driven by partner number, is null after accounting for partner selection.

Our results are compatible with the theory that young women who attend more school are at the lower risk of HIV and HSV-2 infection because of their sexual network structure.[7,16] Previous studies have reported a lower prevalence of HIV and HSV-2 in young men and women attending school and associations between school attendance, partner age difference, and number of partners.[7,16,41] We found that school attendance was associated with a reduced risk of HIV and HSV-2, and we add to the literature by formally assessing mediation to illustrate that partner age difference and partner number are mediators of these relationships. Although it may be impossible to do things like "prevent older partners" explicitly, these results are important because they show illustratively that school attendance naturally prevents HIV and HSV-2 by providing periods of structure and supervision in young adults' lives, which reduce opportunities for sexual activity and promote safer networks.[3,16,19]

The results for mediation of the effect of school attendance on HIV differed slightly from the results for HSV-2. Partner selection can almost entirely explain the relationship between school attendance and HIV. However, removing the effect of school attendance on partner age and partner number removed only some of the effect of school attendance on HSV-2. These results indicate that there are likely other mechanisms that are additional mediators of the relationship between school attendance and HSV-2. For example, because HSV-2 is more transmissible than HIV, condom use to reduce efficiency of transmission per contact might be an important determinant of infection that is linked to schooling.[42,43] It is also possible, given the higher prevalence of HSV-2 in general, that younger men are more likely to have HSV-2, making network patterns different than HIV.[44]

It should be noted that information on sexual behaviors was self-reported, and there may have been some misreporting in the study despite the use of audio computer-assisted self-interview to minimize reporting bias.[25] Misreporting about sexual behaviors is apparent in the remaining risk of HIV/HSV-2 infection after we fix all young women to have zero partners (we would expect that girls would not get infected if they do not have sex). We do show that even if young women had 1 partner overall or if they had 50% fewer older partners and fewer partners overall, the effect of school attendance on the incidence of infection would still be much smaller. A sensitivity analysis was done setting all HIV cases in girls with 0 partners to have 1 partner and to have 2 partners (Appendix Table 2 and Table 3, http://links.lww.com/QAI/B180) and we found similar results. However, the total effect and the mediation by partner number were larger, and mediation by partner age difference was not as pronounced. It is likely that girls who misreport sexual activity would also misreport partner age, as they may not have included the ages of any partners on the survey. Moreover, when we assumed that girls who were HIV positive and had 0 partners also had older partners, we found again similar results and mediation by partner age difference (Appendix Table 3, http://links.lww.com/QAI/B180).

In addition, the assumption of no unmeasured confounding is a strong assumption that is impossible to assess in the data.[31] It is possible that there are confounders we did not measure or include in our models. However, we did explore measured confounding by examining the effect of adding and removing different variables to our models. We also used the CDE instead of the indirect and natural direct effects for mediation to avoid the assumption of no mediator-outcome confounders affected by prior exposure. Second, the parametric g-formula assumes that the parametric models used to predict our variables are correctly specified. This assumption is not testable, but covariate distributions and cumulative incidence functions in the predicted natural course were a close fit to the

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observed data, suggesting that the models were adequately specified.[33] Finally, one benefit of using causal inference methods for mediation is to include exposure-mediator interactions; however, we were unable to do so in our analysis because of sparse data (see technical appendix). Therefore, our analysis assumes that the effects of exposure and mediators are multiplicative.

It should be noted that the data are from a randomized controlled trial where all young women were already enrolled in school at study enrollment. Previous analyses of the data have shown potential selection bias where young women in the study may have been more likely to attend school than the underlying population and a Hawthorne effect where young women in the trial were less likely to drop out of school because of trial participation.[45] However, we would expect the relationship between schooling and HIV/HSV-2 to remain similar.

We found that school attendance was associated with both incident HIV and HSV-2 infection and are the first to show that partner age difference and the number of partners mediate the relationships between school attendance and incident HIV and HSV-2 infection. These findings are significant as education has been one of the factors that is most consistently associated with preventing HIV in AGYW and we provide a better understanding about how that relationship operates.[3,8,46,47] Our study shows illustratively that school attendance naturally reduces the risk HIV and HSV-2 acquisition among AGYW by providing periods of structure and supervision in young adults' lives, which encourage younger and fewer partners. Changes in these partnership factors will ultimately reduce opportunities for sexual activity and promote safer networks where girls are not exposed to infection. Interventions to prevent infections in young women should focus on keeping girls in school and creating other environments like school that constructively occupy time and provide a safe space where young women can associate with their peers. Alternatively, given the importance of partner age and number to adolescent HIV acquisition, efforts to provide biomedical interventions like Pre-Exposure Prophylaxis to girls who are sexually active, out of school, or who have older partners may help to prevent new infections. Schooling is one of the strong preventative interventions for HIV and HSV-2 among AGYW. Evidence that this effect operates through partner selection should encourage interventions to keep girls in school and the development of interventions that emulate this supervised and structured environment, potentially changing sexual networks and norms.

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