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SHORT REPORT

HIV and herpes simplex virus type 2 epidemiological synergy: misguided observational evidence? A modelling study

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ABSTRACT

Objectives To investigate whether observational studies of HIV and herpes simplex virus type 2 (HSV-2) infections have the capacity to assess the HIV/HSV-2 epidemiological synergy.

Methods An individual-based Monte Carlo model was used to simulate HIV/HSV-2 epidemics in two scenarios: no HIV/HSV-2 biological interaction and HSV-2 seropositivity enhancing HIV acquisition. Cross-sectional observational studies were simulated by sampling individuals from the population to assess resulting crude and adjusted ORs of the HIV/HSV-2 association. Meta-analyses were conducted to estimate the pooled mean ORs. Impact of under-reporting of sexual behaviour and miscapture of high-risk individuals was assessed through sensitivity analyses.

Results Assuming no HIV/HSV-2 biological interaction, the crude HIV/HSV-2 OR ranged between 1.38 and 9.93, with a pooled mean of 6.45 (95% CI 5.81 to 7.17). Adjustment for the number of sexual partners over last year, over lifetime and for both partner numbers simultaneously reduced the mean OR to 5.45 (95% CI 4.90 to 6.06), 3.70 (95% CI 3.32 to 4.12) and 3.54 (95% CI 3.17 to 3.94), respectively. Assuming HIV/HSV-2 biological interaction, the crude OR ranged between 3.44 and 9.95, with a pooled mean of 8.05 (95% CI 7.14 to 9.07). The adjustments reduced the mean OR to 7.00 (95% CI 6.21 to 7.90), 3.76 (95% CI 3.32 to 4.25) and 3.68 (95% CI 3.25 to 4.17), respectively. Under-reporting of partners reduced the confounder-adjustment effects. Miscapture of high-risk individuals considerably lowered the estimated ORs.

Conclusions It is difficult to control for sexual-behaviour confounding in observational studies. The observed HIV/HSV-2 association appears more consistent with two infections sharing the same mode of transmission, rather than with HSV-2 enhancing HIV acquisition.

INTRODUCTION

The biological interactions and epidemiological synergy between HIV and herpes simplex virus type 2 (HSV-2) infections have been intensely investigated.[1] There is ample observational evidence for a strong HIV/HSV-2 association, and that HSV-2 enhances HIV acquisition.[2–4] Mathematical models incorporating this synergy estimated that HSV-2 has been a major contributor to the HIV epidemic in sub-Saharan Africa (SSA).[1 5]

Nevertheless, HIV and HSV-2 share the same sexual mode of transmission and propagate on the same sexual networks. It is 'natural' for these two infections to be strongly associated regardless of any HIV/HSV-2 biological interaction. Observational studies attempted to control for this confounding factor by adjusting the measured associations for sexual behaviour, often by controlling for the number of self-reported sexual partners.[4] As adjusted associations were still positive and strong, this supported the existence of a biological interaction, and consequently an epidemiological synergy, between these two infections.[4] As most self-reported sexual data are egocentric, network effects could not be adjusted for in these observational studies.

The difficulty of controlling for network effects, however, limits the validity of these observational studies. The risk of acquiring an STI depends not only on a person's behaviour, but also on the "ecology" of the person within the sexual network, including the partners and partners' partners behaviour, past and present.[6–11] Sexual networks, therefore, play a critical role in determining STI patterns.[6 8 12] For example, it has been hypothesised that concurrency is a main driver of the generalised HIV epidemics in SSA.[13–15]

Several clinical trials were conducted to target the HIV/HSV-2 epidemiological synergy, by suppressing HSV-2 reactivation to reduce HIV acquisition and transmission, but these trials reached negative outcomes.[16–18] Different explanations have been advanced for these negative results, such as ineffective HSV-2 suppression, insufficient dose or therapy duration, and poor adherence.[16–19] It is natural, however, to also question the very existence of this epidemiological synergy—that is, the observed HIV/HSV-2 association could be a spurious association not reflecting a genuine biological effect; it arose from intrinsic biases in study design due to failure to adequately control for confounding by sexual behaviour.

Here we investigate two related questions: Can observational studies adequately control for confounding by sexual behaviour? Is the observed association consistent with an absence of epidemiological synergy? We addressed these two questions through mathematical modelling by first simulating HIV/HSV-2 transmission in diverse sexual networks assuming no HIV/HSV-2 biological interaction. We

then simulated HIV/HSV-2 transmission assuming HIV/HSV-2 biological interaction with an effect size as that reported in observational studies.[2–4] Subsequently, we simulated the conduct and analysis of observational studies on the simulated epidemics, that is, we cross-sectionally sampled individuals from the population and estimated sample associations by logistic regressions.

In light of known limitations to observational evidence, namely under-reporting of sexual behaviour and miscapture (undersampling) of high-risk individuals in surveys, we repeated our analyses factoring in these limitations. Our study thus furnishes a 'microscopic' assessment, from first principles, of one of the most controversial factors in HIV epidemiology.

METHODOLOGY

We used a recently constructed individual-based Monte Carlo simulation model[6] to simulate sex partnering, birth/death and HIV/HSV-2 transmission in a population. The model was applied in two scenarios. First, HIV/HSV-2 transmission was simulated assuming no HIV/HSV-2 biological interaction. Second, HIV/HSV-2 transmission was simulated assuming that HSV-2 seropositivity increases the risk of HIV acquisition by 2.5-fold—the relative risk effect size as estimated from observational studies.[2–4] In the latter scenario, we lowered the overall average level of sexual risk behaviour so that both scenarios had similar HIV prevalence levels. Accordingly, the second scenario can be seen as a 'positive control' of the first scenario.

The model was parameterised with representative natural history and transmission parameters,[1 6] listed in online supplementary table S1. Since observational studies suggest that the effect size of the HIV/HSV-2 association varies between populations, such as the general population versus high-risk populations,[3] we assessed the association in diverse sexual networks to accommodate for potential variability in effect size by type of population/sexual network.

The sexual networks were simulated based on the range of population-based sexual behaviour data in SSA,[20] as derived from 25 Demographic and Health Surveys (DHS) data.[21] Marital partnerships formed/dissolved at a rate derived from DHS current-marriage age-specific data.[6 21] Non-marital partnerships formed/dissolved in unmarried (premarital sex) and married (extramarital sex) persons, but at different DHS-derived rates.[6 20] Sexual behaviour parameters were sampled (randomly) from the empirical distributions[20] to generate a diversity of sexual network statistics such as number-of-partners mean and variance, degree correlation, clustering coefficient, and concurrency—accommodating for variation by marital status and age.[6]

We simulated 100 HIV/HSV-2 epidemics on 100 different sexual networks, with initial population sizes of 2000, for each scenario—numbers sufficient to be representative of the diversity of the (stochastic) epidemics we see for these two infections. Each simulation was seeded with 10 HIV/HSV-2 infections, and was run with a 'burn-in' time of 200 years to reach equilibrium. Although the model allows assessment of the HIV/HSV-2 association temporally and by epidemic phase, we only assessed the association at endemic equilibrium to control for potential temporal effects on the association.

We cross-sectionally sampled all individuals 15–65 years of age from each of the 100 simulated epidemics/populations. In each sample, we assessed the HIV/HSV-2 association. Different univariable and multivariable logistic regression analyses were conducted to calculate crude and adjusted ORs of HIV infection with HSV-2 seropositivity. The following independent predictors were selected a priori because of relevance to the research questions: number of sexual partners over the last year (continuous variable), number of lifetime partners (continuous variable), age (continuous variable) and marriage (categorical variable), in addition to HSV-2 serostatus (categorical variable). Different regression models were used to adjust for the number of sexual partners over the last year, number of lifetime partners, both numbers of partners, and both numbers of partners, age and marriage. The latter analysis was done to reflect common adjustment variables in observational studies.[4] ORs of the 100 simulated studies were pooled using a DerSimonian-Laird random-effects model to calculate pooled effects.

For sensitivity analyses, we repeated the above analyses for each scenario, but after reducing (randomly) the *reported* number of partners over the last year, for individuals with >1 partners, by an average of 10%, 25% and 50%, to simulate under-reporting of sexual behaviour. We also repeated the above analyses, but after excluding individuals with the highest 10%, 25% and 50% number of partners over the last year, to simulate miscapture of high-risk individuals.

RESULTS

Table 1 shows the results of the regression analyses assuming no HIV/HSV-2 biological interaction. In the baseline scenario of no under-reporting and no miscapture, the crude OR ranged between 1.38 and 9.93, with a pooled mean of 6.45 (95% CI 5.81 to 7.17). Adjustment for the number of partners over last year, over lifetime and for both numbers of partners reduced the mean OR to 5.45 (95% CI 4.90 to 6.06), 3.70 (95% CI 3.32 to 4.12) and 3.54 (95% CI 3.17 to 3.94), respectively. Adjustment for age and marriage in addition to partner numbers yielded an OR of 4.93 (95% CI 4.41 to 5.52). The sensitivity analyses assuming under-reporting and miscapture yielded similar patterns.

Table 2 shows the results of the regression analyses assuming increased HIV acquisition with HSV-2 seropositivity. In the baseline scenario of no under-reporting and no miscapture, the crude OR was higher with a range of 3.44–9.95 and a pooled mean of 8.05 (95% CI 7.14 to 9.07). Adjustment for the number of partners over last year, over lifetime and for both numbers of partners reduced the mean OR by larger margins than those with no HIV/HSV-2 biological interaction—the mean OR was reduced to 7.00 (95% CI 6.21 to 7.90), 3.76 (95% CI 3.32 to 4.25) and 3.68 (95% CI 3.25 to 4.17), respectively. Adjustment for age and marriage in addition to partner numbers yielded an OR of 4.71 (95% CI 4.15 to 5.35). The sensitivity analyses assuming under-reporting and miscapture yielded similar patterns.

Adjustments for the lifetime number of partners always had larger effects on the OR than those for the last-year number of partners (tables 1 and 2). The simultaneous adjustment for both numbers of partners resulted in a larger effect on the OR, although not much larger than that for only the lifetime number of partners. Under-reporting of partners reduced the adjustment effects for both numbers of partners. Miscapture of high-risk individuals considerably lowered the estimated ORs.

DISCUSSION

Our results demonstrate the difficulty of adequately controlling for sexual-behaviour confounding. While the ORs were closer to 1 after adjustment for numbers of partners, they remained well above 1 despite absence of any biological interaction in the first modelling scenario. The lifetime-partner-number adjustment was also more effective, probably because it captured better the exposure risk to both infections over lifetime.

Table 1 Association between HIV infection and HSV-2 infection in 100 simulated cross-sectional observational studies, assuming no HIV/HSV-2 biological interaction

				Studies	Sample size	Crude OR	Adjusted OR	Pooled OR across all simulations*
				N	n†	Range	Range	Mean (95% CI)
Baseline scenario‡		Crude OR (95% CI)		100	1755	1.38–9.93		6.45 (5.81 to 7.17)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1755	1.38–9.93	1.34–8.78	5.45 (4.90 to 6.06)
			For number of lifetime sexual partners	100	1755	1.38–9.93	1.29–7.34	3.70 (3.32 to 4.12)
			For number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	1.23–6.96	3.54 (3.17 to 3.94)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	0.27–10.91	4.93 (4.41 to 5.52)
Under-reporting§	50% under-reporting	Crude OR (95% CI)		100	1755	1.38–9.93		6.45 (5.81 to 7.17)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1755	1.38–9.93	1.43–8.80	5.58 (5.02 to 6.21)
			For number of lifetime sexual partners	100	1755	1.38–9.93	1.14–8.10	4.39 (3.94 to 4.88)
			For number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	1.23–7.42	4.06 (3.65 to 4.53)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	0.27–11.12	5.59 (5.00 to 6.26)
	25% under- reporting	Crude OR (95% CI)		100	1755	1.38–9.93		6.45 (5.81 to 7.17)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1755	1.38–9.93	1.24–8.93	5.57 (5.01 to 6.19)
			For number of lifetime sexual partners	100	1755	1.38–9.93	1.31–8.13	4.46 (4.01 to 4.97)
			For number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	1.24–7.58	4.13 (3.71 to 4.60)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	0.27–11.79	5.71 (5.10 to 6.38)
	10% under- reporting	Crude OR (95% CI)		100	1755	1.38–9.93		6.45 (5.81 to 7.17)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1755	1.38–9.93	1.28–8.82	5.56 (5.00 to 6.18)
			For number of lifetime sexual partners	100	1755	1.38–9.93	1.06–7.72	4.47 (4.01 to 4.97)
			For number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	1.00–7.75	4.14 (3.72 to 4.62)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1755	1.38–9.93	0.26–11.33	5.75 (5.14 to 6.43)
Miscapture¶	50% miscapture	Crude OR (95% CI)		100	877	0.00–23.02		4.84 (4.23 to 5.54)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	877	0.00–23.02	0.00–24.37	4.41 (3.85 to 5.06)
			For number of lifetime sexual partners	100	877	0.00–23.02	0.00–17.25	2.98 (2.58 to 3.44)
			For numbers of sexual partners over the last year and lifetime	100	877	0.00–23.02	0.00–18.12	2.98 (2.58 to 3.43)
			For age, marriage and the numbers of sexual partners over the last year and lifetime	100	877	0.00–23.02	0.00–25.44	3.57 (3.06 to 4.16)
	25% miscapture	Crude OR (95% CI)		100	1316	0.00–13.21		4.31 (3.84 to 4.84)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1316	0.00–13.21	0.00–14.24	3.97 (3.54 to 4.46)
			For number of lifetime sexual partners	100	1316	0.00–13.21	0.00–13.55	2.60 (2.30 to 2.94)
			For number of sexual partners over the last year and lifetime	100	1316	0.00–13.21	0.00–13.89	2.59 (2.29 to 2.92)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1316	0.00–13.21	0.00–19.91	3.17 (2.80 to 3.59)
	10% miscapture	Crude OR (95% CI)		100	1579	1.44–9.22		4.71 (4.22 to 5.25)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1579	1.44–9.22	1.37–10.26	4.29 (3.85 to 4.79)
			For number of lifetime sexual partners	100	1579	1.44–9.22	0.23–8.02	2.68 (2.39 to 3.01)
			For number of sexual partners over the last year and lifetime	100	1579	1.44–9.22	0.23–8.12	2.66 (2.37 to 2.98)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1579	1.44–9.22	0.14–9.16	3.43 (3.05 to 3.86)

*Meta-analyses were conducted using a DerSimonian-Laird random-effects model.
†Average sample size of each cross-sectional observational study.
‡Sample was drawn randomly from the simulated population.
§Sample was drawn randomly from the simulated population, but after assuming under-reporting of the number of sexual partners over the last year.
¶Sample was drawn randomly from the simulated population, but after excluding individuals with the largest number of sexual partners.
HSV-2, herpes simplex virus type 2.

Table 2 Association between HIV infection and HSV-2 infection in 100 simulated cross-sectional observational studies, assuming that HSV-2 seropositivity increases the risk of HIV acquisition by 2.5-fold (relative risk=2.5)[2–4]

				Studies	Sample size	Crude OR	Adjusted OR	Pooled OR across all simulations*
				N	n†	Range	Range	Mean (95% CI)
Baseline scenario‡		Crude OR (95% CI)		100	1438	3.44–9.95		8.05 (7.14 to 9.07)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1438	3.44–9.95	3.42–9.60	7.00 (6.21 to 7.90)
			For number of lifetime sexual partners	100	1438	3.44–9.95	1.89–6.03	3.76 (3.32 to 4.25)
			For number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	1.96–5.88	3.68 (3.25 to 4.17)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	2.00–9.49	4.71 (4.15 to 5.35)
Under-reporting§	50% under-reporting	Crude OR (95% CI)		100	1438	3.44–9.95		8.05 (7.14 to 9.07)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1438	3.44–9.95	3.51–9.91	7.13 (6.32 to 8.05)
			For number of lifetime sexual partners	100	1438	3.44–9.95	2.45–7.01	4.85 (4.29 to 5.49)
			For number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	2.49–6.92	4.61 (4.08 to 5.22)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	2.36–10.71	5.72 (5.04 to 6.49)
	25% under- reporting	Crude OR (95% CI)		100	1438	3.44–9.95		8.05 (7.14 to 9.07)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1438	3.44–9.95	3.60–9.82	7.09 (6.28 to 8.00)
			For number of lifetime sexual partners	100	1438	3.44–9.95	2.90–8.20	5.01 (4.43 to 5.66)
			For number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	2.82–8.07	4.73 (4.19 to 5.35)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	3.09–12.3	5.86 (5.16 to 6.65)
	10% under- reporting	Crude OR (95% CI)		100	1438	3.44–9.95		8.05 (7.14 to 9.07)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1438	3.44–9.95	3.51–9.69	7.12 (6.31 to 8.03)
			For number of lifetime sexual partners	100	1438	3.44–9.95	2.69–7.69	5.03 (4.45 to 5.69)
			For number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	2.75–7.50	4.77 (4.22 to 5.39)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1438	3.44–9.95	3.22–12.09	5.27 (5.23 to 6.73)
Miscapture¶	50% miscapture	Crude OR (95% CI)		100	719	0.00–19.69		4.89 (4.22 to 5.65)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	719	0.00–19.69	0.00–19.69	4.56 (3.93 to 5.28)
			For number of lifetime sexual partners	100	719	0.00–19.69	0.00–17.93	3.03 (2.60 to 3.53)
			For number of sexual partners over the last year and lifetime	100	719	0.00–19.69	0.00–17.72	3.06 (2.62 to 3.56)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	719	0.00–19.69	0.00–21.31	3.42 (2.93 to 4.00)
	25% miscapture	Crude OR (95% CI)		100	1079	2.61–8.34		5.04 (4.44 to 5.72)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1079	2.61–8.34	2.44–9.00	4.75 (4.18 to 5.40)
			For number of lifetime sexual partners	100	1079	2.61–8.34	1.11–6.95	2.86 (2.50 to 3.26)
			For number of sexual partners over the last year and lifetime	100	1079	2.61–8.34	1.13–7.00	2.88 (2.51 to 3.29)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1079	2.61–8.34	1.57–8.89	3.32 (2.90 to 3.81)
	10% miscapture	Crude OR (95% CI)		100	1294	3.04–9.25		5.97 (5.28 to 6.74)
		Adjusted OR (95% CI)	For number of sexual partners over the last year	100	1294	3.04–9.25	2.93–9.28	5.50 (4.86 to 6.22)
			For number of lifetime sexual partners	100	1294	3.04–9.25	1.42–5.70	3.12 (2.74 to 3.54)
			For number of sexual partners over the last year and lifetime	100	1294	3.04–9.25	1.40–5.76	3.09 (2.72 to 3.51)
			For age, marriage and the number of sexual partners over the last year and lifetime	100	1294	3.04–9.25	1.77–8.38	3.76 (3.30 to 4.29)

*Meta-analyses were conducted using a DerSimonian-Laird random-effects model.
†Average sample size of each cross-sectional observational study.
‡Sample was drawn randomly from the simulated population.
§Sample was drawn randomly from the simulated population, but after assuming under-reporting of the number of sexual partners over the last year.
¶Sample was drawn randomly from the simulated population, but after excluding individuals with the largest number of sexual partners.
HSV-2, herpes simplex virus type 2.

These findings highlight how HIV or HSV-2 exposure risk in a sexual network cannot be captured by simply numbers of partners, but depends on an array of network properties, including variance of number of partners, concurrency and clustering /assortativeness.[6 22]

As expected, the ORs were larger in the positive-control analyses where HSV-2 seropositivity increased the risk of HIV acquisition (table 2). However, these ORs were not as large as one may have expected given the biological interaction. The adjustments for the sexual-behaviour confounding yielded also larger reductions in the ORs compared with the 'null' scenario of no interaction (table 2 vs table 1). These outcomes testify to the complexity of the HIV/HSV-2 overlapping epidemiology. AIDS mortality, for example, had a differential effect based on HSV-2 serostatus (with the higher risk of acquiring HIV for those HSV-2 seropositive), thereby lowering the values of the ORs.

Our results demonstrate how the ORs depend on complex interplays between the HIV/HSV-2 biological interaction, sexual behaviour and networking, HIV/HSV-2 background prevalence, demography, and AIDS mortality. This lack of a one-to-one correspondence between 'true' and observed ORs further increases the challenge of disentangling a biological interaction between HIV and HSV-2 from methodological biases.

This study has limitations. Our findings could conceivably be dependent on our model. While we studied this association across a diversity of sexual networks and HIV/HSV-2 epidemics, other factors, not accounted for here, may also affect the epidemiological observations, such as potential variation of this association by risk population, sex or biological route of exposure (eg, men who have sex with men versus heterosexual populations). Our results may not also explain the observed HIV/HSV-2 synergy in serodiscordant couples.[3] Having said so, the evidence from serodiscordant couples for an association appears inconclusive.[3] Lastly, while our results cast doubt on an effect for HSV-2 on enhancing HIV acquisition, they do not strictly preclude an HSV-2 effect on enhancing HIV infectiousness.

In conclusion, can observational studies adequately control for confounding by sexual behaviour? Our findings demonstrate that it is challenging to assess the existence of an HIV/HSV-2 biological interaction in observational studies, as it is difficult (if not impossible) to fully control for the sexual-behaviour confounding using egocentric partners' data. Is the observed association consistent with an epidemiological synergy or confounding? The answer to this question remains unsettled, but our findings suggest that the empirically observed HIV/HSV-2 association appears to be more consistent with two infections sharing the same mode of transmission—HSV-2's effect on HIV acquisition may be weaker than thought, perhaps even absent.

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