ORIGINAL RESEARCH ARTICLE

Determinants of generalized herpes simplex virus-2 epidemics: the role of sexual partner concurrency

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Summary: Little is known as to why some populations develop generalized herpes simplex virus 2 (HSV-2) epidemics. Sexual network-level factors, such as the proportion of partnerships that run concurrently, are plausible explanations. In this ecological analysis, we used Spearman's correlation coefficients to assess if there is an association between population prevalence of point-concurrency and HSV-2 in a number of national and subnational populations. We found that there is an association between prevalence of point-concurrency and female HSV-2 prevalence between different countries (Spearman's rho = 0.715; $P = 0.020$), and within different races and ethnic groups within countries. In addition, there was a strong association between peak HIV and HSV-2 prevalence in 40–44-year-old women at an international level (Spearman's rho = 0.720; $P = 0.0001$). This could be indicative of populations with high HIV and HSV-2 prevalence rates having extensively connected sexual networks which puts them at increased risk of spread by both these sexually transmitted infections (STIs). No country with an HSV-2 prevalence of under 20% in their 20–24-year-old women had a generalized HIV epidemic. Thus, HSV-2 prevalence in adolescents may be a useful marker of how risky a local sexual network is for STI spread and may provide a useful early indicator of the success or failure of behavior change initiatives.

Keywords: sexual networks, ecological analysis, sexually transmitted infections, STI transmission, concurrency, HIV, herpes simplex virus 2, HSV-2

INTRODUCTION

Herpes simplex virus 2 (HSV-2) spreads via sex networks. If individual level risk factors such as the number of lifetime sexual partners, condom utilization or circumcision cannot explain why only some populations are afflicted by generalized HSV-2 epidemics (GHEs), then network level factors are likely candidates.[1] In this paper, we use a female HSV-2 prevalence in 40–44-year-olds of 50% or higher as a proxy for GHEs. Sexual networks characterized by a larger proportion of relationships running concurrently offer an interconnected pathway for the spread of sexually transmitted infections (STIs). Evidence has emerged of the importance of concurrency in the spread of various STIs.[2–5] The high long-term concurrency rates in Southern and Eastern Africa are believed by some, but not all,[6] to be key to the genesis of the generalized HIV epidemics in this region.[2,7] We could not find any published work investigating the effect of network-level factors on HSV-2 spread.

In order to evaluate if network-level factors could play a role in GHEs, in this paper we explore various data-sets to assess the relationships between HIV, HSV-2 and concurrency.

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METHODS

HSV-2 – concurrency comparisons

There are numerous limitations in the available data on HSV-2 and concurrency, which make comparisons difficult. For both concurrency and HSV-2, population-based representative prevalence surveys have only been conducted in a limited number of populations worldwide. Comparisons of concurrency rates suffer particularly from the range of definitions used to define concurrency in different studies.[8] Agreement has only recently been reached on what measure of concurrency is best to use. A UNAIDS reference group on concurrency determined that concurrency should be defined as overlapping sexual partnerships where sexual intercourse with one partner occurs between two acts of intercourse with another partner. Furthermore concurrency should be measured as the point-concurrency of 15–49-year-olds six months prior to the survey.[9] Point-concurrency best captures differences in long-term concurrency rates that have been shown to be the measure of concurrency correlating most closely with HIV at a population level.[8] We limited our analyses to data sources that measured point-concurrency at the time of the survey. To ensure that comparisons were valid we only compared populations where point-concurrency prevalence rates were obtained by the same methodology within single studies. We used concurrency prevalence at the time of the survey rather than six

months prior to the survey as the available data-sets had more complete data on this variable and recent studies have argued that it is a preferable indicator of concurrency prevalence.[10,11]

We could find only two data-sets that measured both concurrency and HSV-2 prevalence – the Carletonville Youth Survey (CYS) and the Four Cities Study. For the other studies, we were forced to obtain HSV-2 prevalence from other population-based HSV-2 surveys.

The CYS consisted of a random sample of 723 men and 784 women between the ages of 14–24 living in a township outside of Carletonville – a gold mining town in South Africa. Households were selected via a two-stage random sampling technique. The sampling scheme was arranged so as to be self-weighting. The response rate was 89%. Respondents were questioned about sexual partnerships and tested for HSV-2 type specific IgG antibodies via a quantitative enzyme-linked immuno assay (ELISA) (MRL Diagnostics, Los Angeles, CA, USA). For a more detailed description of the survey methodology see Auvert *et al*.[12]

The Four Cities Study was a cross-sectional population-based study conducted in two high and two low HIV prevalence African cities.[13] It was designed to explain differences in the rate of HIV spread in Africa. Representative samples of around 2000 15–49-year-olds were obtained in each city. Respondents had detailed sexual histories taken and HSV-2 testing was done with a HSV-2 type specific IgG EIA (Gull Laboratories, Bad Homburg, Germany). The point prevalence of concurrency was derived from questions that asked which of each relationship was ongoing at the time of the interview.

International comparisons

WHO/GPA behavioral surveys: In order to ascertain the practices underpinning the differential spread of HIV globally, the WHOs Global Programme on AIDS (GPA) embarked on a series of standardized sexual behavior surveys in different populations around the world. Eleven countries performed these surveys between 1989 and 1990 and included questions on concurrency and these are evaluated here.[14,15] All these surveys followed WHO/GPA protocols. These included that national probability samples of the general populations aged 15–49 should be utilized. In two cases, Manila and Rio de Janeiro, the samples were representative of these large cities rather than being nationally representative. A two-stage sampling strategy was the norm for the 11 countries, with census enumeration areas as the first stage and households as the second. The sample sizes were typically 1000–3000 men and women. Response rates were high in all cases. The variable for concurrency was derived from the question 'Do you now have one or more than one spouse/regular partner?' The dependant variables we used in our analysis were the percentage of 15–49-year-old men who had more than one sexual partnership active at the time of the survey. We only considered men as the concurrency data were available for all 11 countries for men, but only seven countries for women.

The comparative HSV-2 prevalence data for these populations were obtained from two systematic reviews of global HSV-2 incidence and prevalence.[16,17] These reviews were conducted in 2002 and 2005. Both restricted the data they present to that from peer-reviewed articles that used a type-specific serological methodology for the detection of HSV-2. Only articles that detailed age-specific rates were included and sample sizes were required to be greater than 20 per age group. Looker KJ, Garnett GP and Schmid GP kindly provided us with detailed tables of HSV-2 prevalence rates broken down by age for all the countries reviewed in their article. Unfortunately, neither HSV-2 review paper included standard errors for the measured HSV-2 prevalence in their results.

The two reviews did not include HSV-2 prevalence rates from three countries evaluated in the GPA surveys – Ivory Coast, Lesotho and Singapore. One of the findings of both reviews was that HSV-2 prevalence rates were close to uniformly high throughout sub-Saharan Africa. This was corroborated by the findings of the Four Cities Study. The HSV-2 prevalence rates in the 40–44-year-old women in Cotonou and Yaounde, the two West African cities in the Four Cities Study, were 57 and 78%, respectively. The only other West African country reflected in the HSV-2 reviews was Nigeria, which had an HSV-2 prevalence of 62% in the 35–44-year-old women.[18] We used this mid-range figure of 62% for the Ivory Coast. In the case of Lesotho, we used the figure of 66% which was taken from a survey of 40–49-year-old rural women in Zimbabwe.[19] For Singapore, the only HSV-2 survey we could find was one of patients at an STI clinic, which found that 32% of female attendees were HSV-2 positive.[20] We used this figure even though it is likely a significant overestimate.

The indicator we used for HSV-2 prevalence was the percentage of women 40–44-years-old who are HSV-2 seropositive. The rationale for choosing this indicator is that HSV-2 seroprevalence increases monotonically with age at different rates depending on both gender and the population concerned – being considerably faster in females and in populations with GHEs. The data for age groups above 45 years are, however, incomplete. HSV-2 prevalence in 40–44-year-old women is thus an indicator for which the available data are relatively complete and an indicator that will most likely exhibit differences in HSV-2 prevalence between populations.

Subnational comparisons

To explore if variations in HSV-2 prevalence between different ethnic/racial groups within countries co-vary with concurrency rates, we explored this relationship in two countries – the USA and South Africa

USA: For the USA, the concurrency data were derived from the 1992 National Health and Social Life Survey (NHSLS).[3] This was a cross-sectional study that used a nationally representative stratified random sample of 3432 women and men between the ages of 18 and 59. The survey response rate was 82%. It included a detailed sexual behavior questionnaire. The adult (14–49 years) HSV-2 prevalence rates were derived from the National Health and Nutrition Examination Survey (NHANES) III (1988–1994). This was a nationally representative stratified sample of approximately 40,000 individuals. A random subset of 8262 men and women aged 20–59 were tested for HSV-2 seropositivity. The response rate was 83%.[21]

South Africa: The data on point-concurrency was taken from the Cape Area Panel Survey (CAPS), wave 3, which was conducted in 2005 and included a detailed sexual behavior questionnaire. CAPS utilized a representative longitudinal study design of 14–22-year-olds living in Cape Town, South Africa. A total of 3536 individuals were sampled in Wave 3 – a 75% response rate.[22] For the purposes of comparing HSV-2

prevalence by ethnic group in South Africa, the most representative HSV-2 prevalence data that we could obtain that included all ethnic groups were derived from a random sample of 200 HIV-negative blood donors sampled in 2005.[23]

All HSV-2 surveys were done utilizing type-specific HSV-2 antigen (IgG2) ELISA assays, or equivalent.

HSV-2–HIV prevalence comparisons

We assessed if there was any association between population-level HSV-2 and HIV prevalence. We obtained the HSV-2 prevalence rates from the two HSV-2 reviews detailed above. Since these reviews have been published a number of high-quality HSV-2 surveys have been published. We included three of these from Brazil, Malawi and Turkey that were all large, population-based HSV-2 surveys and that used type-specific HSV-2 serological testing.[24–26] All countries with population-based female HSV-2 prevalence in either the 20–24- or 40–44-year-old age groups were included (see Table 2). These HSV-2 prevalence rates were compared with peak adult HIV prevalence rates (15–49-year-olds), which we derived from the estimates of country-level HIV prevalence rates from 1990 to 2009. These country estimates were obtained from the Global Health Observatory Data Repository of the World Health Organization (http://apps.who.int/ghodata/#).

Statistical methods

The statistical significance of the correlations between HSV-2, HIV and concurrency were assessed using Spearman's correlation coefficient. The analysis was performed using STATA 10 software (Stata, East College Station, TX, USA). For the network-level correlations all the South African data were age-standardized to the 2001 national census.

RESULTS

As shown in Table 1, HSV-2 prevalence co-varies fairly closely with concurrency levels, but not with number of sex partners at both a national and subnational level. Populations with GHEs such as Cotonou, Yaounde, Kisumu, Ndola, the Central African Republic, Brazil, Côte d'Ivoire, Kenya, Lesotho, Zambia, blacks in South Africa and the USA all have high concurrency rates (point-prevalence of male concurrency of 8% or above). All the populations without GHEs have a point-prevalence of male concurrency of 3% or lower. The exception, with 7%, is Brazil which has an intermediate HSV-2 prevalence – 30% in 40–44-year-old women. In the WHO/GPA survey, Spearman's rank correlation coefficient for the relationship between point-concurrency and HSV-2 prevalence was 0.715 ($P = 0.020$) (see Figure 1).

When HSV-2 and sexual risk factor rates are broken down by ethnic group within these locales, HSV-2 co-varies fairly closely with concurrency prevalence but not lifetime number of sex partners (see Table 1). This is true for the differences in HSV-2 prevalence rates between whites and blacks in the USA and South Africa (Table 1) as well as the different ethnic groups in the Carletonville area.

The comparison of HSV-2 and HIV prevalence rates revealed a fairly tight correlation between the two (see Figures 2a and 2b). Spearman's rank correlation coefficients were 0.677 and 0.720 for HSV-2 in 20–24- and 40–44-year-old women, respectively. The P values for both were less than 0.0001. If we define a generalized HIV epidemic as one where adult (15–49-year old) HIV prevalence exceeds 5%, then no country with a HSV-2 prevalence of under 20% in the 20–24-year-old group had a generalized HIV epidemic. The commensurate figure for the 40–44-year-old HSV-2 prevalence was 50%.

DISCUSSION

The relationship between HSV-2 and concurrency

There are multiple methodological reasons why it is difficult to demonstrate a relationship between concurrency and STI transmission.[8] A key reason is that concurrency's major impact on enhancing STI transmission is via increasing a sexual network's connectivity.[7] This is a network-level property that cannot be easily assessed via the individual-level variables collected in traditional behavioral surveys. Being a network-level phenomenon, it is appropriate to assess the relationship between concurrency and STIs at an ecological level. All the data-sets we have examined here exhibit evidence of a relationship between concurrency and HSV-2 prevalence at an ecological level. In the 11 countries in the GPA surveys, the relationship between HSV-2 and concurrency exhibits a non-linear relationship with evidence of a critical threshold effect. Above a point-concurrency prevalence of around 5%, HSV-2 prevalence increases very rapidly and then levels off (see Figure 1).

There are a number of limitations to our study. The ecological nature of the analysis demonstrates an association but is susceptible to the ecological inference fallacy and cannot by itself establish proof or direction of causality. There are very few data-sets available that collect information on both HSV-2 serostatus and sexual partner concurrency. We were thus forced to use different data-sets for parts of our analysis. We tried to limit the negative effects of this as far as possible. In particular, we limited the sources of the concurrency data to high-quality studies that measured point-concurrency at the time of the survey. We then only compared groups from within the same studies where the same methodology was used to ascertain concurrency rates. The relationship we found could however be confounded by other variables such as condom use or co-infections.

There are notable gaps in the availability of data pertaining to HSV-2 prevalence rates for parts of the world's population. In the case of a country such as Singapore, for example, we were forced by one such gap to use what is in all likelihood a significant overestimate of HSV-2 prevalence based on attendees of a STI clinic. HSV-2 prevalence rates in East and South East Asia are much lower than those in sub-Saharan Africa,[16,17] but it is noticeable how even this likely overestimate of the HSV-2 prevalence is considerably lower than the general population prevalence rates from sub-Saharan Africa.

A further problem was the difference in dates when the HSV-2, HIV and sexual behavior surveys were performed (see Table 2). An alternative methodology would have been to use the HIV prevalence at or near the time of the HSV-2/sexual behavior survey, instead of the peak HIV prevalence. This methodology, however suffers, from the serious problem of arbitrarily assigning HIV severity based on the year that the survey of the independent variable is performed.[27] If the South African HSV-2 survey had been done in 1990, for example, then the HIV prevalence used would been 0.7%.[28] We believe that the peak HIV prevalence of 18.1% (1994) is a more meaningful and accurate

Table 1 **Population-level comparison of HSV-2 prevalence with point-concurrency and lifetime number of sexual partners**

	Lifetime sex partners (mean)*	% Concurrency (point-prevalence)† (%)	*n*	HIV prevalence‡ (%)	Peak HSV-2 prevalence§ (%)
Intra-national comparisons					
South Africa Black ethnic groups					
Men					
All	4.7	555	19.9	11.8	18.1
Sotho	5.3	87	13.7	13.6	20.2
Zulu	4.3	47	27.1	14.9	27.6
Xhosa	5.3	158	22.6	14.3	19.5
Tswana	4.1	234	18.4	8.1	14.0
Tsonga	4.1	14	22.0	14.3	53.2
Other	4.6	15	28.9	20	28.0
Women					
All	2.6	613	10.2	41.6	57.2
Sotho	3.2	118	9.4	40.5	50.5
Zulu	2.1	42	4.7	54.8	63.6
Xhosa	2.6	193	13.5	43.2	61.3
Tswana	2.4	221	7.5	35.9	55.5
Tsonga	4.1	14	34.5	57.1	78.6
Other	2.7	25	10.7	56	79.1
South Africa racial groups					
White	2.5	160	0.6	0.5	6.3
Coloured	2	1015	0.7	3.2	16.7
Black	2.4	1305	7.8	19.9	31.3
USA					
Men					
White	(10.4)	866	3.1	0.4	17.5
Black	(21.8)	164	11.3	2.3	42.8
Women					
White	(4.0)	1003	1.3	0.06	22.2
Black	(8.3)	259	3.7	1.1	64.8
International comparisons					
4 Cities study					
Cotonou					
Men	5	928	15.9 (10.1)	3.3	42
Women	2	1015	17.8 (0.6)	3.4	57
Yaounde					
Men	10	896	29.6 (27.5)	4.1	55
Women	3	1017	15.5 (10.2)	7.8	78
Kisumu					
Men	5	622	19.8 (14.2)	19.8	76
Women	2	893	17.2 (2.4)	30.1	84
Ndola					
Men	5	624	8.5 (6.5)	23.2	61
Women	2	910	3.6 (0.6)	31.9	69
WHO/GPA study					
Central African Republic	(2/1)	2431	20	10.1	82
Brazil	(10/1)	1341	7	0.4	66.7
Côte d'Ivoire	(9/1)	3001	36	7.5	62
Kenya	(4/1)	2967	13	10.5	56.7
Lesotho	(7/0)	1582	55	24.5	66
Philippines	(7/1)	1617	3	0.1	8.7
Singapore	(3/0)	2115	2	0.1	32
Sri Lanka	(0/0)	3012	2	0.1	26
Tanzania	(5/3)	1992	18	7.9	87
Thailand	(11/0)	2601	3	2.1	34.7
Zambia	(7/1)	1992	22	15	69

*Mean lifetime number of sex partners for all studies excluding 4 Cities where median value given. The NHSLS (USA data) and WHO/GPA studies did not report number of lifetime sex partners so therefore the data presented here are: for WHO/GPA, the percentage of men/women who reported five or more non-regular partners in the last 12 months is shown here, for the NHSLS, the percentage who report three or more sexual partners in total in the last 12 months is reported[46]

†Point-concurrency of all respondents at the time of interview. Values in parentheses for 4 Cities Study are point-concurrency percentages excluding those who are in exclusive polygamous marriage

‡Adult HIV prevalence is for 15–49-year-olds, excluding Carletonville where it is for 14–24-year-olds. South African HIV prevalence data by race from HSRC 2005 survey.[47] USA HIV prevalence data by race from CDC HIV/AIDS factsheet.[48] The HIV prevalence for the WHO/GPA study countries is the peak national 15–49-year-old HIV prevalence between 1990 and 2009 taken from the Global Health Observatory Data Repository of the World Health Organization

§HSV-2 prevalence is for 15–49-year-olds excluding USA (20–59-year-olds) and Carletonville (14–24-year-olds). For year of HSV-2 and HIV surveys see Table 2

Table 2 **Cross-national comparison of HSV-2 and HIV prevalence rates. (HSV-2 prevalence rates obtained from references 7 and 8. Peak HIV prevalence refers to the highest HIV prevalence in the 15–49-year-old age group between the years 1990 and 2009 as detailed in text)**

	Female HSV-2 prevalence 20–24-year-olds (%)	Female HSV-2 prevalence 40–44-year-olds (%)	Year of HSV-2 survey	Peak HIV prevalence (15–49-year-olds) (%)	Year of HIV peak
Australia	8.3	20	1995–1998	0.1	1990
Bangladesh	7.9		1996–1998	0.1	1990
Belgium	8.9	27.7	1999	0.2	1996
Benin	17	57	1997–1998	1.4	1997
Brazil	21.2	30	1996–1997	0.4	1990
Bulgaria	15	33	1999	0.1	1990
Burkina Faso	14.4		2000	4	1991
Cameroon	39	78	1997–1998	5.5	2002
Canada	7.5	28	2000–2001	0.2	1991
Central African Republic		82	1998–1999	10.1	1996
China		18	1995	0.1	1990
Costa Rica	17	47.7	1993–1994	0.3	2004
Czech Republic	4	9	1989	0.1	1990
Côte d'Ivoire		62*		7.5	1997
Denmark	19	33	1986	0.2	2006
Estonia	14.8	31.7	2000	1.2	2007
Finland	6	19	1997–1998	0.1	1990
France		16.9	1995	0.4	2003
Gabon		57.1	Pre-2003†	5.4	2002
Gambia	21	49	1998	2	2009
Germany	4.6	18.2	1997–1998	0.1	1990
India	7.5	13	2000	0.4	1996
Israel	2	6.3	2000	0.2	2003
Italy	1.1	4.8	1988	0.3	1990
Japan	0	3.6	1993	0.1	1990
Kenya	66	84	1997–1998	10.5	1996
Lesotho		66*	1998–1999	24.5	2000
Malawi	56	78	1998–2001	14.7	1997
Mexico	10.8	20.4	1994–1996	0.4	1990
Morocco	10.1	21.6	2000	0.1	1990
Netherlands	5	12	1996	0.2	1995
New Zealand	4.3		1993	0.1	1990
Nigeria	59	62	1999	4	1995
Norway	17	35	1992–1994	0.1	1990
Papua New Guinea		22	2001	0.9	2007
Peru	6	39	1991–1992	0.5	1992
Philippines	9	8.7	1991–1993	0.1	1990
Singapore		32	2005	0.1	1990
South Africa	78.3		1999	18.1	2004
Spain	3.6	3	1992–1993	0.5	1993
Sri Lanka	8.4	26	2000	0.1	1990
Sweden	12	37	1990–1993	0.1	1990
Switzerland	5.1	19.5	1997	0.4	2006
Syria	0	0	1995–8	0.1	2001
Thailand		34.7	Pre-2002†	2.1	1994
Turkey	2.1	8.1	Pre-2003†	0.1	0.1
Uganda	74	88	1990–3	10.7	1991
United Kingdom	12.5	13	2000	0.2	2002
United Republic of Tanzania	48	87	1992	7.9	1996
United States of America	17	27	1988–1994	0.6	2005
Zambia	58	69	1997–1998	15	1995
Zimbabwe	50	66	1998–1999	26.5	1997

Empty cells indicate that data were not available
*Derived data as explained in methodology section
†'Pre-2002' indicates that the study was published in 2002 but that study did not indicate when the HSV-2 survey was performed

measure of the South African sexual network's HIV transmissibility, even if it postdates the date of the HSV-2 survey by five years. Differences in the dates of collection of the variables of this scale pose problems for the validity for an ecological study. However, if it is agreed that peak HIV prevalence is the most appropriate variable to use, and it could be shown that HSV-2 and concurrency prevalence rates are fairly stable over the time course of the study then the methodology would be acceptable. As detailed below, the available longitudinal studies demonstrate that HSV-2 prevalence rates are fairly stable over time.[1,21,26] While there is evidence that concurrency rates have fallen in many African countries (preceding their drop in HIV incidence) the GPA surveys were performed prior to these changes.[29] The available evidence also indicates that concurrency rates remain considerably higher in sub-Saharan Africa than most other locales.[2,8,22]

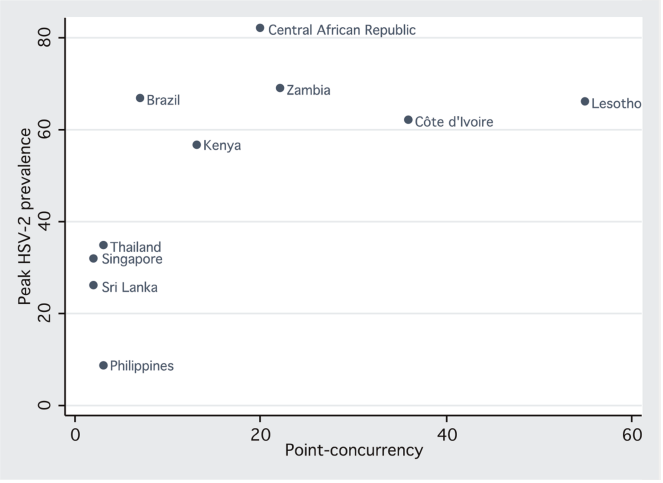

Figure 1 **The association of female HSV-2 prevalence (40–44-year-olds) and point-concurrency (15–49-year-olds) in the WHO/GPA surveys (Spearman's rho = 0.715; $P = 0.020$). HSV-2, herpes simplex virus-2**

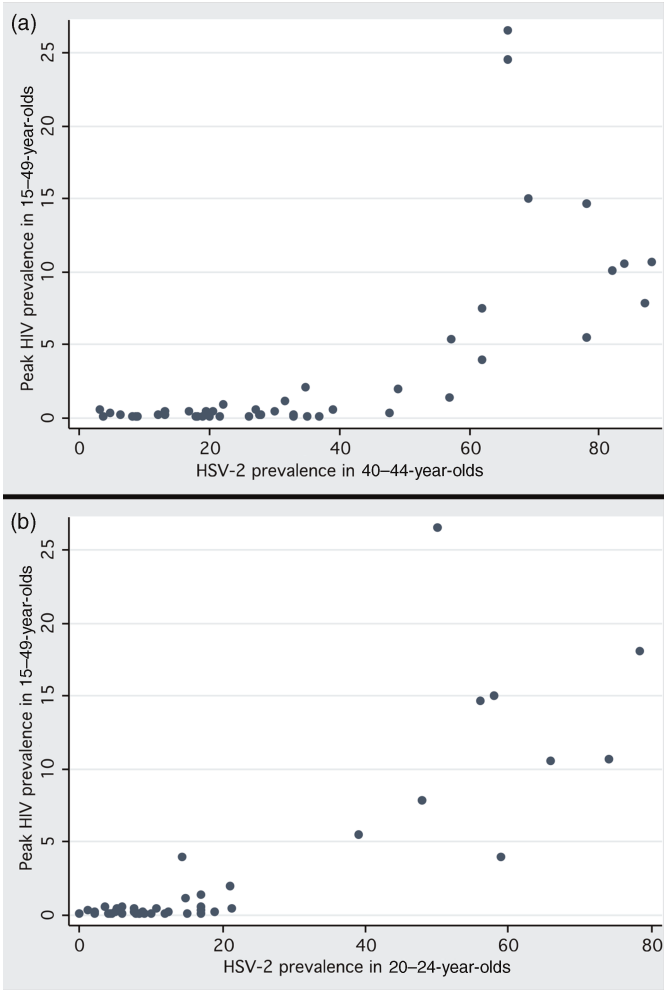

Figure 2 **National female HSV-2 prevalence at age 20–24-year-old (a) and 40–44-year-old (b) versus peak adult HIV prevalence (15–49-year-olds). HSV-2, herpes simplex virus-2**

The relationship between HIV and HSV-2

Studies to date exploring the co-variation in HIV and HSV-2 prevalence have typically favoured the explanation that HSV-2 is a potent risk factor for HIV transmission.[13,30] There is very little written as to why only certain populations have GHEs. One study claimed that HSV-2 and HIV fuel the spread of one another.[13] The available modelling[31] and longitudinal evidence, however, suggests that HIV epidemics are a poor explanation for GHEs. In the two locales where we have good quality long-term data on HSV-2 prevalence, the arrival of the HIV epidemics had little or no impact on HSV-2 prevalence.[1,26,32] Firstly, a study in Northern Malawi tracked population HSV-2 prevalence from 1988 to 2005 – a time when adult HIV prevalence increased from 4% to 12%.[26] During this time the age-adjusted HSV-2 prevalence did not increase. Secondly, HSV-2 prevalence has been closely followed in the USA since 1976 via the NHANES. Although HIV prevalence was extremely low at the time of the first survey, HSV-2 prevalence was high among the black population.[32] HIV has disproportionately affected the black population in the USA (adult HIV prevalence reaching 3% in Washington DC),[33] but this has not translated into any noticeable increase in HSV-2 (HSV-2 prevalence for black women 51% in 1976–1980 and 48% in 2005–2008).[1,32] These historical data provide a rebuttal to the argument that high HSV-2 prevalence rates are primarily due to HIV.

The close ecological correlation between HIV and HSV-2 prevalence is therefore most likely explained by their both being influenced by a common risk factor(s). Plausible candidates include sexual network level factors, the prevalence of circumcision and the prevalence of bacterial vaginosis (BV). Lack of circumcision and BV have both been linked with the risk of HIV and HSV-2 infection at an individual level.[34–37] At a population level the lack of circumcision is, however, an unlikely cause of GHEs as almost none of the populations with the lowest circumcision rates in the world (Latin America, Europe and non-Muslim Asia) have GHEs.[17,38] BV and HIV prevalence co-vary fairly closely (C Kenyon's unpublished data) but this relationship is confounded by the fact that both BV (author's unpublished data) and HIV prevalence[39] are associated with point-prevalence of male concurrency.

The findings presented here and elsewhere that BV, HSV-2 and HIV prevalence[39] are all strongly associated with point-prevalence of male concurrency suggest that high concurrency rates may be important in the genesis of both generalized HIV and HSV-2 epidemics.

This study is one of many that has argued that HSV-2 incidence and prevalence are a very useful measure of sexual behavior; they capture network dimensions that are difficult to capture with traditionally collected questions about sexual behavior.[31,40–42] As such, high HSV-2 prevalence may be a marker of the key factors that are difficult to monitor in traditional behavioral surveys. It may well be a composite marker of risk factors such as increased network connectivity and intergenerational sex. Network connectivity is difficult to assess in behavioral questionnaires as respondents are often not aware of, or are unsure of, if their partners have additional partners.[43] If HSV-2 prevalence is a useful composite marker of risk, then regular, relatively small, HSV-2 surveys of young persons could be done as a way of assessing network risk. The data presented here suggest that populations that have a 20–24-year-old HSV-2 prevalence of under 20% have a very low risk of a generalized HIV epidemic. It would be more

useful to know what is an 'acceptable' HSV-2 prevalence in slightly younger age groups. These data could then be used to interpret regular small HSV-2 surveys of adolescents aged 15–19 years to see if behavior change campaigns have been successful. A number of recent behavior change campaigns in other fields have demonstrated the utility of 'realtime' feedback of evidence of whether or not behavior change occurred on effecting behavior change.[44] In a similar way, HSV-2 prevalence data could be fed back to populations such as schools as an additional behavior change motivational strategy.

There are a number of plausible biological reasons that would support HSV-2 as a useful marker of network connectivity. A key one is that there are significant differences in the duration of high infectiousness for HIV and HSV-2. HSV-2 reactivates frequently, and therefore remains highly infectious, for years after infection compared with HIV whose main burst of infectiousness is in the relatively short period of acute HIV infection.[8,45] This would conceivably make HSV-2 a better marker of network connectivity than HIV in less densely connected networks. Above a particular threshold of connectivity (such as the 5% point-prevalence of concurrency mentioned above), HSV-2 prevalence may be relatively saturated and in this scenario HIV may be a more discriminating measure. The limitations in our methodology noted above mean that considerably more work needs to be done to confirm if HSV-2 surveys could be used as a marker of connectivity. The utility of HSV-2 surveys likely transcends this consideration. The emerging evidence of the strong correlations between the prevalence rates of HSV-2 with HIV and with other STIs suggests that HSV-2 surveys of late adolescents could be a useful early warning system to detect populations at high risk for generalized STI epidemics – regardless of what the exact mediating variables are.

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