Can Behavior Change Explain Increases in the Proportion of Genital Ulcers Attributable to Herpes in Sub-Saharan Africa?

A Simulation Modeling Study

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Background: **The proportion of cases of genital ulcer disease attributable to herpes simplex virus type 2 (HSV-2) appears to be increasing in sub-Saharan Africa.**

Goal: **To assess the contributions of HIV disease and behavioral response to the HIV epidemic to the increasing proportion of genital ulcer disease (GUD) attributable to HSV-2 in sub-Saharan Africa.**

Study Design: **Simulations of the transmission dynamics of ulcerative sexually transmitted diseases (STDs) and HIV with use of the model STDSIM.**

Results: **In simulations, 28% of GUD was caused by HSV-2 before a severe HIV epidemic. If HIV disease was assumed to double the duration and frequency of HSV-2 recurrences, this proportion rose to 35% by year 2000. If stronger effects of HIV were assumed, this proportion rose further, but because of increased HSV-2 transmission this would shift the peak in HSV-2 seroprevalence to an unrealistically young age. A simulated 25% reduction in partner-change rates increased the proportion of GUD caused by HSV-2 to 56%, following relatively large decreases in chancroid and syphilis.**

Conclusion: **Behavioral change may make an important contribution to relative increases in genital herpes.**

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THE DISTRIBUTION OF CAUSES of genital ulcer disease (GUD) differs widely between countries within Africa. The proportion of GUD attributable to herpes simplex virus type 2 (HSV-2) appears to be higher or increasing in countries with severe HIV epidemics.[1–3] For example, the proportion of GUD cases that were herpes-culture–positive increased from 11% in 1986–1988 to 21% in 1990–1992 among HIV-positive cases in Rwanda[4]; from 3% before 1981 to 14% in 1994 among gold miners in Johannesburg, South Africa[5]; and from 7% in 1984 to 40% in 1998 in Durban, South Africa.[2] Increases have also been reported in the occurrence of genital herpes as a proportion of new diagnoses of sexually transmitted diseases (STDs) in Durban (from 7% in 1989 to 11% in 1997) and Harare, Zimbabwe (from 6% in 1982 to 10% in 1997). Moreover, GUD appears to constitute a larger proportion of STD diagnoses in the countries of sub-Saharan Africa (SSA) with severe HIV epidemics than in West Africa.[6]

Several explanations have been proposed for the apparent increase in HSV-2 as a cause of GUD in SSA. Immunosuppression during advanced HIV disease can increase the duration, severity, and incidence of herpetic recurrences, leading to an increased herpes ulcer load.[7,8] This effect may be enhanced if the increased herpes ulcer load in HIV-infected patients increases the transmission of HSV-2. Decreases in the prevalence of bacterial causes of GUD, in particular chancroid, may induce a relative increase in HSV-2 as a cause of GUD. Bacterial GUD can decrease because of selective HIV-attributable mortality among high-risk groups[9] and behavior change as a result of HIV control programs promoting safer sex.[10–13] Improved management of bacterial STDs may also contribute to decreases in bacterial GUD.[2,14–16] Finally, apparent increases in genital herpes may reflect changes in detection rather than true shifts in GUD etiology.[2,17] Improved HSV-2 detection could result from increased awareness among clinicians and patients of herpes as a cause of GUD, as well as improved diagnostic choices such as the use of polymerase chain reaction as a complement to viral culture and clinical appearance.[1]

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The data obtained to date cannot directly enable epidemiologists to distinguish between these explanations. However, their implications about the burden of disease and the control of ulcerative STD and possibly HIV in SSA may differ. This article presents simulations of the influence of these possible causes on the epidemiology of ulcerative STD. We used the stochastic microsimulation model STDSIM[9,18,19] to simulate the spread of ulcerative STD and HIV for a typical SSA population with a severe HIV epidemic. Comparing simulation outcomes with empirical data, we discuss the likelihood and importance of the suggested explanations.

Methods

Microsimulation Model STDSIM

STDSIM simulates the natural history and transmission of multiple STDs and HIV in a population of individuals with assigned characteristics that change over time. The formation and dissolution of heterosexual partnerships and transmission of STDs during contacts between sexual partners are modeled as stochastic events.[9,18,19] Recently the model was adapted to include the simulation of genital infection with HSV-2 and effects of HIV infection on the natural history and transmission of STDs, including HSV-2, allowing us to study the epidemiology of HSV-2 in relation to that of other ulcerative STDs and HIV disease.

Simulated Population

Assumptions about demography, sexual behavior, and health care were chosen to reflect conditions in a typical SSA city with a severe and advanced HIV epidemic. For this, we adapted a previous model representation of a population in rural Tanzania,[9] by specifying a higher frequency of prostitute visits by men (25% more than in the Tanzania simulation), a higher frequency of client contacts per prostitute (an average of two per week), and an earlier time of introduction of HIV (1980). To adequately reproduce HSV-2 seroprevalence patterns observed in SSA cities,[20,21] we further adapted the representation of sexual behavior by specifying (1) larger age differences between sexual partners (with males being an average of 3.3 years older than their spouses) and (2) an increase in the mean age of sexual debut to 18 years for men and a corresponding decrease to 15 years for women.

Representation of Herpes Simplex Virus Type 2

Figure 1 shows the model representation of HSV-2 infection; the corresponding parameter values are given in Table 1. Infection starts with a primary ulcer episode of an average 3 weeks' duration.[22–26] The incubation period is ignored because it is short[23,24] and unlikely to influence HSV-2 transmission dynamics.

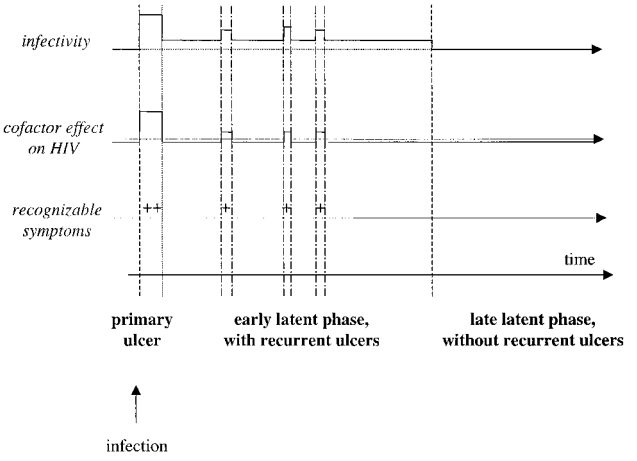

Fig. 1. Diagrammatic representation of the natural history of genital herpes simplex virus type 2 infection in the STDSIM model. Drawing not to scale. Corresponding parameter values are given in Table 1.

After the primary episode, patients progress to a long *early latent* phase, during which ulcers can recur. In the remainder of this article, the terms *ulcer* and *recurrence* denote both recognized and unrecognized genital lesions. The frequency of recurrences is known to decrease over the first years after primary infection.[25,27–33] Since no studies involving long-term follow-up have been conducted, it is however unknown whether recurrences stop after a certain period or continue at a much lower frequency. Comparisons of age-profile data for clinical presentations of herpetic recurrences and GUD (which peak between ages 30 and 40 years[29–32,34–38]), HSV-2 seroprevalence (which peaks at an older age[39,40]), and HSV-2 incidence (which peaks between ages 20 and 30 years[22,41]) suggest that the majority of symptomatic recurrences occur within 15 to 20 years after infection.

Among clinic patients, frequencies of five to eight recurrences annually are reported as typical,[29,31,32,36,38,42] but studies likely oversampled individuals with relatively severe and frequent recurrences.[38,43] Follow-up studies of HSV-2-infected persons sampled from general populations showed recurrence frequencies of two to four annually.[38,44] In line with these observations, we estimated that the early latent phase during which ulcers recur lasts for an average of 15 years, during which ulcers recur at a mean interval of 6 months. To reflect the large heterogeneity between individuals,[32] we assumed that the duration of the early latent phase and the interval between recurrences varies randomly between episodes within individuals, according to exponential distributions. After the early latent phase, simulated patients progress into a *late latent phase*, during which they remain HSV-2 seropositive but no longer have recurrences.

Recurrences were specified to last for an average of 1 week. Because this duration appears to be relatively homo-

TABLE 1. STDSIM Representation of Natural History and Transmission of Ulcerative Sexually Transmitted Disease

Disease, Stage	Mean Duration*	Transmission Probability†		Cofactor Effect on HIV Transmission†‡	% of Ulcers That Are Recognized	
		F	F→M		M	F
HSV-2						
Primary ulcer	3 weeks	0.30	0.15	25×	30	30
Early latent	15 years§‖	0.005‖	0.0025‖	NA‖	NA‖	NA‖
Recurrent ulcer	1 week§; interval between ulcers: 6 months§	0.20	0.10	10×	15	7.5
Late latent	Lifelong	0	0	NA	NA	NA
Syphilis						
Infectious	6 months	0.30	0.20	10×	80	50
Latent	15 years	0	0	NA	NA	NA
Chancroid	10 weeks	0.20	0.15	25×	90	70
HIV infection						
Primary	10 weeks	0.045	0.015	NA	NA	NA
Asymptomatic	3 or 5 years¶	0.00225	0.00075	NA	NA	NA
Symptomatic	4 or 2 years¶	0.00225	0.00075	NA	NA	NA
AIDS	40 weeks	0.01125	0.00375	NA	NA	NA

*Individual stage durations were sampled from a Weibull distribution function with shape parameter 2, except for the duration of the early latent stage of HSV-2 and the interval between recurrent HSV-2 ulcers, which used exponential distributions.
†Per contact; equal for recognized and unrecognized ulcers.
‡For both susceptibility (HIV-negative partner) and infectivity (HIV-positive partner).
§In scenarios 1 and 3 (of no effects of HIV on the natural history of HSV-2) and in scenario 2, only for individuals not symptomatic with HIV. In scenario 2a, values of these parameters for symptomatic HIV patients are 30 years, 2 weeks, and 3 months; in scenario 2b, 60 years, 4 weeks, and 1.5 month. See also Methods (Scenarios of Effects of HIV on the Natural History of HSV-2).
‖Except during recurrent ulcers.
¶For scenarios 1, 2a, and 3, asymptomatic phase is 5 years and symptomatic phase is 2 years; for scenario 2b, asymptomatic phase is 3 years and symptomatic phase is 4 years (see also Methods section on scenarios, noted above).
F = females; M = males; NA = not applicable.

geneous,[22,23,28,35,38] we assumed a Weibull distribution with shape parameter 2. Patients who have ulcers are considered to be infectious; a proportion of patients recognize symptoms. On the basis of their relative clinical severity,[22,26] we infer that rates of infectiousness and symptom-recognition are higher in association with primary ulcers than with recurrences.

No data are available on per-contact transmission probabilities for HSV-2. Genital shedding, a likely correlate of infectivity, is higher during symptomatic episodes than asymptomatic or in-between episodes and higher during primary episodes than recurrences.[22,23] Because it is not known how shedding levels translate into transmission probabilities, the latter were chosen from a range of estimates for other ulcerative STDs.[45–47] Transmission was assumed to be twice as efficient from males to females than from females to males.[48–50] To account for episodes of viral shedding in the absence of clinical signs,[32,34,51–53] a continuous low level of infectiousness throughout the early latent phase (i.e., in between recurrences) was specified.

Between 10% and 50% of HSV-2-seropositive individuals in Western settings report a history of genital herpes,[54,55] and symptoms are more common in men than in women.[27,56,57] In a Tanzanian population, 28% and 8% of HSV-2-seropositive men and women reported having ulcers in the past, as compared with 3% and 2% of HSV-2-seronegative men and women; over the previous year, ulcers were reported by 11% and 6% of HSV-2-seropositive men and women, as compared with 1% and 2% of seronegative men and women.[57] On the basis of these data, we estimated that 30% of primary herpetic ulcers and 15% and 7.5% of recurrent herpetic ulcers in men and women, respectively, are recognized in SSA populations. Recognition was assumed to occur randomly and independently over different episodes and individuals, i.e., recognition at one episode did not influence recognition at subsequent episodes.

Scenarios of Effects of HIV on the Natural History of Herpes Simplex Virus Type 2

HIV disease is associated with threefold to fourfold increases in the number of HSV-2 culture–positive days[58–61] and the incidence of clinical ulcers.[62] The level of HSV-2 shedding during symptomatic ulcers increases with a decreasing CD4 cell count.[58,63] In addition, herpetic recurrences may last longer and be more severe in HIV-infected patients.[3,60,64]

Translating these effects into model parameters is not straightforward. It is unknown how shedding levels and clinical signs quantitatively translate into infectivity, symptom recognition, and cofactor effects. Studies likely oversample HIV-infected patients in the later, symptomatic

stages of disease. No prospective studies of the duration of untreated recurrences in relation to HIV status have been reported. To reflect these uncertainties, we simulated several scenarios. In scenario 1, HIV was assumed not to affect the natural history of HSV-2. In scenario 2a, HIV doubled the duration and the frequency of herpetic recurrences in patients with AIDS and in the last 2 years of the AIDS incubation period. In addition, the (remaining) duration of the early latent phase was doubled from the onset of symptomatic HIV. This ensured that most simulated HIV-infected patients continued to have recurrent ulcers until their deaths associated with AIDS. Thus, HSV-2–infected patients with HIV disease in this simulation suffered herpetic ulcers for an average of 8 weeks per year, as compared with a mean of 2 weeks for patients not infected with HIV. In scenario 2b, stronger biologic effects were assumed: HIV quadrupled the duration and frequency of recurrences and the (remaining) duration of the early latent phase in AIDS and the last 4 years of the AIDS incubation period. This corresponds to an average ulcer load of 32 weeks annually.

Representation of HIV, Syphilis, Chancroid, and STD Treatment

The STDSIM representations of syphilis, chancroid, and HIV disease (Table 1) were based on the scientific literature. Syphilis was represented by two consecutive stages, with the first, the *infectious stage*, corresponding to primary and secondary syphilis.[65] For computations of ulcer incidence, we assumed that each syphilis infection causes two ulcers during the infectious stage. Chancroid was represented as a continuous ulcerative episode lasting an average of 10 weeks.[66,67] Transmission probabilities were specified at a lower level (15–20%; Table 1) than the single available empirical estimate (43%, for male-to-female transmission[45]). This was done in order to have the model predict a realistic prevalence level and a realistic fraction of ulcers attributable to chancroid (see Results). To allow for the effects of HIV disease on the HSV-2 natural history described above, the AIDS incubation period was divided into three phases: *primary HIV disease, asymptomatic pre-AIDS, and symptomatic pre-AIDS*.

It was assumed that throughout the simulation period, 5% of symptomatic episodes of chancroid and the first syphilis stage were cured with antibiotic treatment, which reduced the episode duration to 2 weeks.

STD Cofactor Effects on HIV Transmission

We assumed that the presence of ulcers enhances the infectivity of HIV and the susceptibility to HIV. Because of the lack of data on STD cofactor magnitudes from controlled experimental studies, we estimated these magnitudes on the basis of data from observational studies of prostitutes and their clients in Nairobi (Table 1).[68,69] In line with their relative clinical severity, herpetic recurrences were attributed a lower cofactor effect (10-fold per contact) than were primary HSV-2 and chancroid (25-fold per contact). For the infectious stage of syphilis, during which several ulcer episodes may occur,[65] an average cofactor effect of 10-fold was applied throughout. Identical cofactor effects were assumed for recognized and unrecognized ulcers.

Scenario of Changing Sexual Behavior

Several SSA countries have documented recent reductions in risk behavior, including decreases in casual sex and in prostitution and increases in condom use.[10–13,70–73] We assessed the influence of such behavioral changes on the proportion of GUD attributable to herpes in scenario 3, with a 25% reduction in the proportion of men visiting prostitutes, combined with a 25% reduction in relationship-formation rates, after 1990. This type and magnitude of behavior change provided good fit against survey data from Uganda.[10–12,72,74]

Simulation Design

To reduce random fluctuations associated with stochastic simulations, 100 simulation runs were conducted for each scenario. All outcomes are reported as averages over 100 runs and focus on the general adult population (aged 15–49 years). In univariate sensitivity analyses, simulations were rerun for a set of alternative quantifications in which the values of HSV-2 biomedical parameters were doubled and halved.

RESULTS

Herpes Simplex Virus Type 2 Epidemiology Before the HIV Epidemic

The model provided a reasonable fit to data on HSV-2 seroprevalence by age and sex in Ndola, Zambia (Fig. 2), and other SSA populations.[20,21] Seroprevalence among women exceeds that among men, especially in the youngest age group. This reflects that (1) women become sexually active at younger ages than men; (2) women typically have older sex partners (whereas men have younger partners[75,76]) and thus more often meet HSV-2-infected partners; and (3) male-to-female transmission is more efficient than female-to-male transmission.[48–50] This sex difference was somewhat smaller in the model than that evident in the data, perhaps partly because simulated age differences between partners (e.g., a mean of 3.3 years in marriages) may have been less than in reality.[77,78]

The simulated incidence of primary herpetic ulcers was 2.6 and 2.7 per 100 person-years among men and women, respectively (in the total population, including both HSV-2–positive and HSV-2–negative persons), with corresponding peaks in the age groups of 20 to 24 years and 15 to 19 years. For recurrences, including unrecognized episodes,

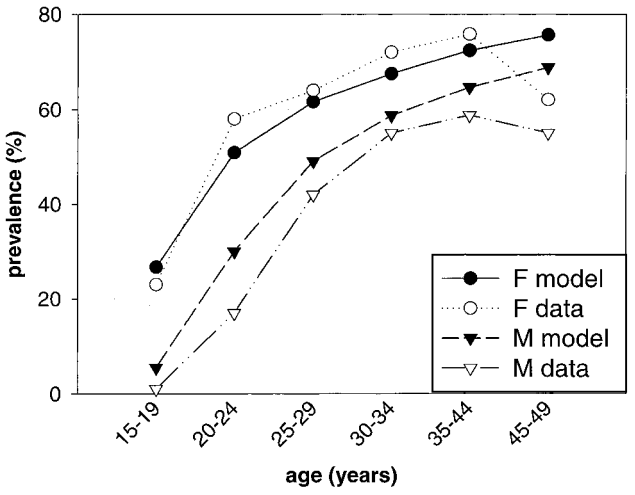

Fig. 2. Simulated herpes simplex virus type 2 seroprevalence (%) in the general population, by age and sex, in a hypothetical city in sub-Saharan Africa (SSA) in the year 1980. In the absence of empirical data on HSV-2 seroprevalence from general SSA populations in the 1980s, we used data from Ndola, Zambia, in 1997 for comparison.[21]

simulated incidence was 41 and 53 per 100 person-years among men and women. Recurrences peaked at age 25 to 34 years for men and 20 to 29 years for women. The overall simulated incidence of recognized herpetic ulcers was 5.9 per 100 person-years.

Ulcer Etiology Before the HIV Epidemic

Based on simulated incidence of herpetic ulcers, syphilis and chancroid, we derived a distribution of aetiologies of incident ulcers. Of all incident ulcers in 1980, 72% were attributable to HSV-2, 24% to chancroid and 4% to syphilis. For comparison with proportions reported in surveys or seen in STD clinics, we also derived the distribution for recognized ulcers only. Among recognized ulcers, 28% were attributable to HSV-2, reflecting the specified relatively poor recognition of herpetic recurrences (Table 1); 64% and 8%, respectively, were caused by chancroid and syphilis.

Trends in Ulcer Epidemiology During the HIV Epidemic

The simulated HIV epidemic reached a prevalence of 31% in 2000, allowing a clear illustration of the possible effects of HIV on the epidemiology of HSV-2 and GUD.

When it was assumed that HIV had no enhancing effect on HSV-2 (scenario 1), the simulated incidence of recognized herpetic ulcers was stable between 1980 and 2000, at approximately six per 100 person-years (Fig. 3). The proportion of recognized ulcers attributed to HSV-2 remained roughly stable at 28%. HSV-2 seroprevalence decreased from 48% to 43% because of the higher HIV-related mortality in high-risk groups (Fig. 4). Because of this same effect, the incidence of chancroid also fell during the HIV epidemic, and the proportion of recognized GUD attributable to chancroid decreased from 64% in 1980 to 59% by 2000. For syphilis, incidence and the contribution to GUD were fairly stable over time.

The moderately strong effects of HIV on HSV-2 (scenario 2a) increased the incidence of recognized herpetic ulcers from 5.9 to 7.4 per 100 person-years between 1980 and 2000. Combined with the relatively large decrease in the incidence of chancroid due to selective AIDS-related mortality, these effects increased the proportion of recognized

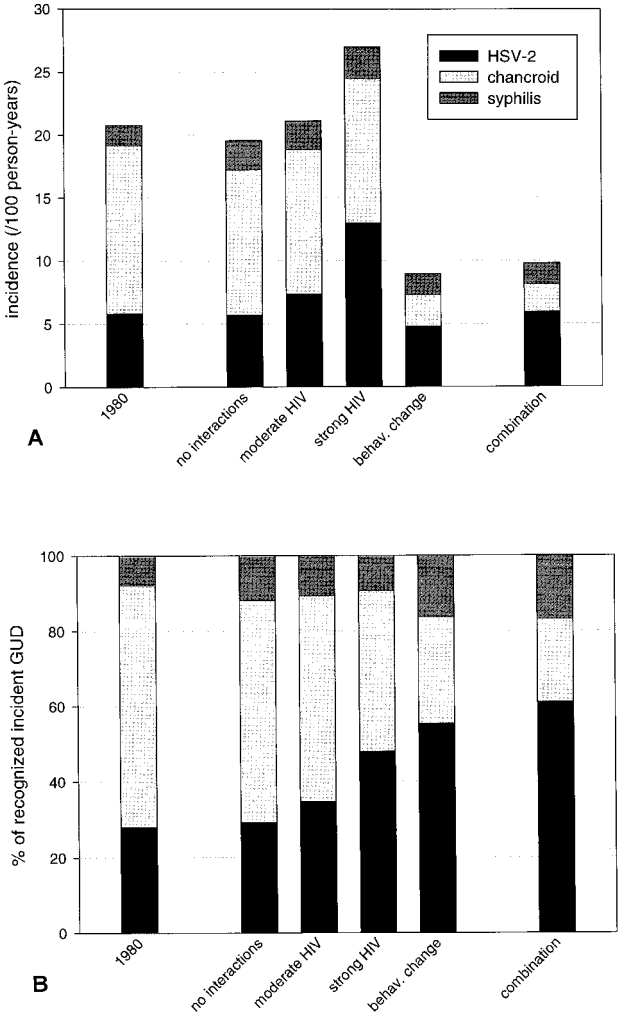

Fig. 3. Simulated incidence of recognized ulcers in the general population (aged 15–49 years), by etiology, in 1980 (leftmost bar) and 2000 (right bars): (A) Absolute incidence (per 100 person-years). (B) Proportional contribution (%) to genital ulcer disease (GUD). Scenario 1: no interactions; scenario 2a/moderate HIV: moderately strong effects of HIV on the natural history of herpes simplex virus type 2; scenario 2b/strong HIV: very strong effects of HIV on the natural history of HSV-2; scenario 3: behavior change, starting in 1990; scenario 4: combination of behavior change and moderately strong effects of HIV on HSV-2. For complete descriptions of scenarios, see Methods.

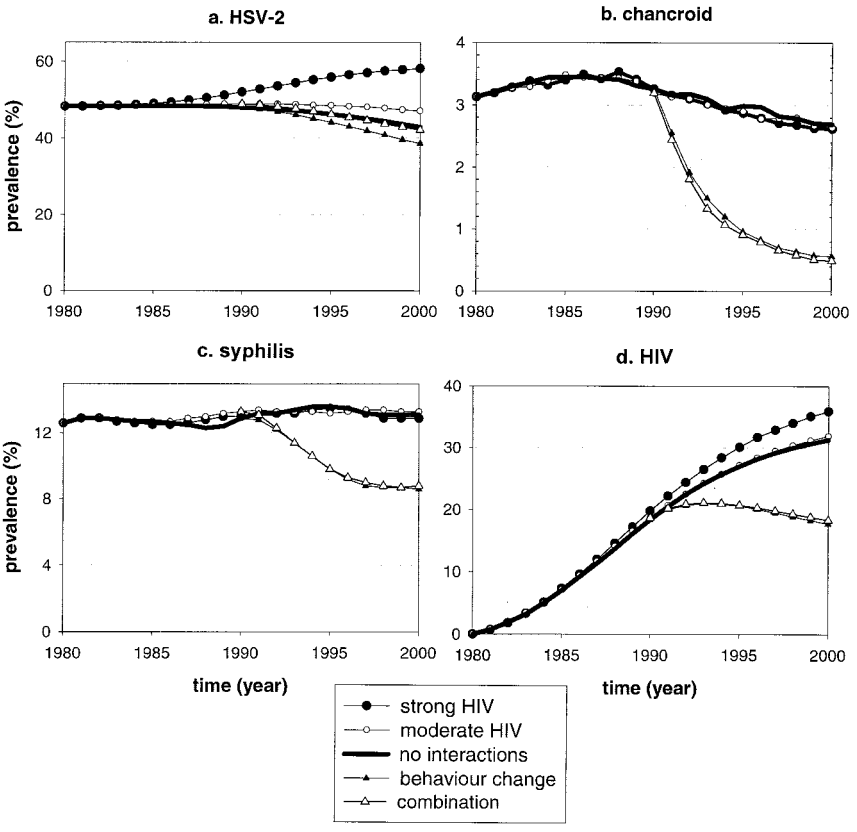

Fig. 4. Simulated prevalence (%) in the general population (15–49 years) over time of (A) herpes simplex virus type 2; (B) chancroid; (C) syphilis (ulcerative and nonulcerative stages combined, corresponding to serological syphilis); and (D) HIV in alternative scenarios. For complete descriptions of scenarios, see Methods.

GUD attributable to HSV-2 from 28% to 35%. In absolute terms, the increase in herpetic ulcer incidence counterbalanced the decrease in GUD incidence due to selective HIV-attributable mortality. As a result, HSV-2 seroprevalence and the overall incidence of GUD (of any etiology) remained stable between 1980 and 2000. Similar but more pronounced shifts in GUD etiology were predicted for scenario 2b, involving very strong effects of HIV. Here, the fraction of GUD attributable to HSV-2 increased to 48%. The absolute incidence of herpetic ulcers increased from six to 13 per 100 person-years, whereas the HSV-2 seroprevalence increased from 48% in 1980 to 58% in 2000.

Behavior change (scenario 3) reduced the incidence and prevalence of chancroid and syphilis considerably and rapidly (Figs. 3 and 4). The rates for chancroid decreased more markedly than those of syphilis because of its lower reproductive number.[47] Both HSV-2 seroprevalence and the incidence of herpetic ulcers decreased relatively little (from 48% to 39% and from 5.9 to 4.8 per 100 person-years, respectively). Since HSV-2 is a lifelong infection with a high baseline prevalence and recurrent nature, herpetic ulcerations can be reduced only by reductions in new infections in the youngest age groups. Therefore, it takes a long time for a decrease in HSV-2 transmission to have an impact on the incidence of herpetic ulcers at a population level. As a result of the large decrease in chancroid relative to the occurrences of herpes and syphilis, the proportion of recognized incident GUD attributable to HSV-2 increased from 28% in 1980 to 56% in 2000, whereas the proportion caused by chancroid decreased from 64% to 28%.

In a fourth scenario, combining behavior change and moderately strong effects of HIV, the incidence of herpetic ulcers remained unchanged over time, whereas that of chancroid and syphilis decreased, increasing the proportion of GUD attributable to HSV-2 to 61% by year 2000.

Figure 5 shows the age- and sex-specific seroprevalence of HSV-2 in year 2000 in the various scenarios. Effects of HIV on herpetic ulcerations increased HSV-2 seroprevalence, especially in the younger age groups. Very strong effects of HIV (scenario 2b) would shift the peak from the oldest group to a plateau from age 25 to 29 years onward for men and age 20 to 24 years for women, resulting in an unrealistic age pattern.[20,21] Behavior change, in contrast, slightly decreased HSV-2 seroprevalence in the younger age groups, who have the highest partnership-change rates. The age pattern in the combined scenario 4 resembled that in scenario 1, of no interactions.

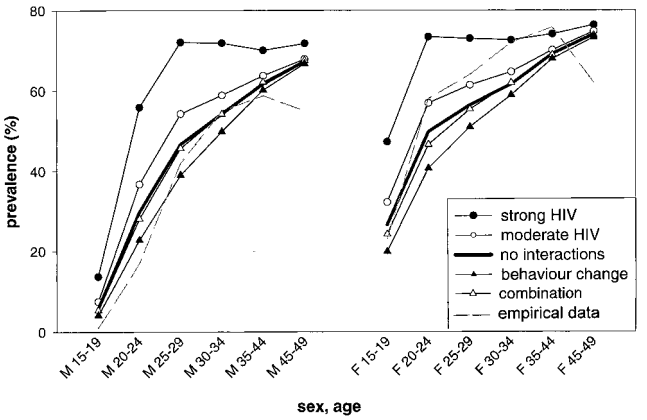

Fig. 5. Simulated herpes simplex virus type 2 seroprevalence (%), by age and sex, in 2000 in alternative scenarios. For complete descriptions of scenarios, see Methods. Empirical data, for comparison, are from Ndola, Zambia, in 1997.[21]

Sensitivity Analyses

To explore the robustness of the results, we assessed their sensitivity to variations in model assumptions on HSV-2 and its possible interactions with HIV.

Of the parameters tested, the average duration of the early latent phase, the probability distribution function assumed for this duration, and the interval between recurrent ulcers were the most important determinants of HSV-2 seroprevalence and ulcer incidence levels. Although halving durations considerably reduced HSV-2 seroprevalence, doubling them did not substantially increase seroprevalence, because of saturation. In all simulations, the gender difference in HSV-2 seroprevalence was insensitive to the relative efficiencies of male-to-female and female-to-male transmission, indicating that its population distribution is mainly determined by sexual behavior patterns. Across all quantifications, behavior change shifted GUD etiologic distributions much more than moderately strong biologic effects of HIV. Of the different possible effects of HIV, that on the frequency of herpetic recurrences had the greatest impact on GUD etiology. Of the two assumed components of behavioral change, a 25% reduction in relationship-formation rates had more of an impact on GUD etiology than did a 25% reduction in prostitute visits.

Discussion

Herpes Simplex Virus Type 2 Transmission Dynamics

In order to simulate both observed HSV-2 seroprevalences among adults in SSA (≥45%) and plausible frequencies of herpetic recurrences (<5 per 100 person-years), a high level of asymptomatic HSV-2 transmission had to be assumed. This finding supports the empirical evidence that a large proportion of herpetic ulcerations go unrecognized and that these contribute substantially to transmission.[49,54,55]

Simulated HSV-2 epidemiology and GUD etiologic distribution were robust against most uncertainties in the natural history of HSV-2 (sensitivity analysis). This corroborates findings with simpler transmission models, in which interventions that had an impact on HSV-2 infectivity and ulceration had little influence on seroprevalence levels.[79,80] The duration of the early latent phase, during which ulcers recur, and the variability of this duration within the population were critical, however. Better data about these parameters, from long-term follow-up studies of unselected populations, would improve understanding of the transmission dynamics of HSV-2.

GUD Incidence and Etiology

The model showed that realistic prevalences of HSV-2 and syphilis are consistent with an incidence of recognized GUD as high as 20 per 100 person-years. The simulated fraction of the population with recognized GUD in the last year, in contrast, was only 9% (scenarios 1 and 2), corresponding with proportions reported for SSA populations.[20,37] The difference between the incidence rate and the proportion with ulcers is the result of recurrence of ulcers (such as for HSV-2) and reinfections (such as for chancroid), as well as of clustering of ulcers caused by different STD, because of shared risk factors.

The simulated etiologic distribution of recognized GUD in 1980 (Fig. 3) matched data from the 1980s from SSA cities. Chancroid was the predominant cause of GUD.[2,4,81–86] The observed proportions should be viewed with caution, however, because diagnosis was based on either culture methods with limited sensitivity (likely resulting in underestimation) or clinical appearance (possibly causing overestimation).[82,83,87] The simulated 28% attributable to HSV-2 is higher than values reported for Nairobi (2–16%),[82–85] Kigali (11–19%),[4,86] and Durban and Johannesburg (3–7%).[2,5] These values, however, are from older studies in which culture was used to diagnose herpes.[1] The low simulated proportion attributable to syphilis (8%) matches proportions found in Nairobi (3–10%)[82,85] and Zimbabwe (6%).[81] Studies in Johannesburg and Rwanda showed proportions of 15% and 19%,[4,88] but because these diagnoses were based on serology (which remains positive for years after the disappearance of ulcers),[1,65,89] these may be overestimates.

Behavioral Change Versus Biologic Effects of HIV

In both scenario 2b and scenario 3, the proportion of GUD attributable to HSV-2 increased considerably during the HIV epidemic (from 28% to 48% and 56%, respectively), resulting in GUD etiologic distributions in year 2000 (Fig. 5) in the range of those observed in advanced HIV

epidemics. In Uganda, 75% to 85% of reported ulcers of which the cause was known were attributable to HSV-2, 6% to 9% were due to chancroid, and 4% to 17% were due to syphilis.[37,64] In Malawi, the three infections accounted for about equal proportions of GUD.[90] In rural Zimbabwe, 32% of diagnosed ulcers were attributable to HSV-2, 47% to chancroid, and 22% to syphilis.[91]

Seemingly very strong biologic effects (scenario 2b) had to be assumed to explain a shift in GUD etiology approaching that caused by apparently realistic magnitudes of behavior change (scenario 3), and only in scenario 2b would HSV-2 seroprevalence and GUD incidence increase in absolute terms. The limited sensitivity of HSV-2 epidemiology in the general population to enhancement of herpetic ulceration in HIV-infected patients is first explained by the fact that not all HSV-2–infected patients are infected with HIV. Even in a severe HIV epidemic, not all HSV-2–infected patients contract HIV, and those who do contract it die earliest, which limits the combined prevalence. Second, the majority of partners of patients infected with HSV-2 or HIV are already infected with HSV-2; thus, increased infectivity does not always increase transmission in the population. Long-term follow-up studies in HIV-positive and HIV-negative populations could help determine whether HIV truly enhances herpetic ulceration as strongly as assumed here.

We may have overestimated the increase in the proportion of GUD attributable to HSV-2 because the simulation did not allow for a possible enhancement by HIV disease of chancroidal ulceration.[7] Because of its low reproductive number,[47] the latter effect could markedly increase the spread of chancroid during HIV epidemics. It should also be noted that the simulated HIV epidemic was, at a prevalence of 31% in 2000, more advanced than in many SSA populations. For less severe epidemics, increases in herpetic ulceration due to HIV would be less. Furthermore, we assumed sexual activity to be unaffected by symptoms. If many patients with ulcers were to temporarily abstain or reduce the frequency of intercourse,[64,92] we may have overestimated the influence of herpetic ulceration on HSV-2 transmission. Conversely, we ignored an effect of HIV on the severity of herpetic ulcers, which might lead HIV-infected patients to more often recognize these. This may have caused our model to underestimate the shift in GUD etiology possible among clinical cases in severe, advanced HIV epidemics.

The simulated shifts in GUD etiology in scenarios 2b and 3 were mediated through different mechanisms, which had opposing effects on HSV-2 seroprevalence and the absolute incidence of herpetic ulcers, chancroid, and syphilis (Figs. 3, 4, and 5). Does comparison of these predicted concomitant effects with empirical data allow inference as to which scenario best reflects reality?

No data are available on HSV-2 seroprevalence over time periods spanning the course of SSA HIV epidemics.[2] One study showed an increase in seroprevalence in urban and rural Zaire between 1959 and 1985 (from 21% to 60% and from 6% to 32%, respectively).[39] But sampling for these surveys was among young men in 1959[93] and in undefined general populations in 1985, circumstances leaving doubts about their comparability in terms of age and risk profile. Moreover, this putative time trend occurred largely before the HIV epidemic in this region. For herpetic ulcer incidence, longitudinal data allowing assessment of time trends in SSA are also lacking. The contrast between scenarios 2b and 3 in their effect on the absolute incidence of herpetic GUD and HSV-2 seroprevalence therefore does not allow proper validation. Future population-based surveillance on trends in these indicators may help to solve this issue.

Data on time trends in bacterial ulcerative and nonulcerative STDs in several SSA settings are available, and some match the simulated reduction in rates of syphilis, chancroid, and recognized GUD in scenario 3. For example, the number of chancroid diagnoses decreased sevenfold in Harare between 1990 and 1998[2]; prevalences of gonorrhea, chlamydia, and syphilis decreased twofold to threefold among women in Nairobi between 1992 and 1997[94]; in Malawi there were 1.1-fold to twofold decreases in the prevalence of syphilis, trichomoniasis, gonorrhea, and genital ulcers between 1990 and 1996[95]; and factory workers in Mwanza, Tanzania, reported 35% less GUD in 1994 than in 1991.[70]

Comparison between empirical data and simulations on age patterns in HSV-2 seroprevalence suggests that the true effect of HIV on herpetic ulceration is less strong than assumed in scenario 2b. The simulated saturation of HSV-2 seroprevalence at ages 20 to 29 years in this scenario (Fig. 5) is inconsistent with available data from SSA populations. For example, in Ndola, Harare, and Kisumu, HSV-2 seroprevalence peaked above age 45 or 35 years for both sexes.[20,21] This inconsistency was apparent in spite of conservative assumptions about the relation between ulceration and infectivity, since we specified a nonzero infectivity throughout the early latent phase in between recurrences and ignored a possibly higher infectivity with the occurrence of recognized (more severe) ulcers than with unrecognized episodes. If HSV-2 infectivity in SSA populations would correlate more strongly with (recognized) ulcers than in these simulations, the specified strong effects of HIV would result in even more unrealistic age patterns. Behavior change, in contrast, did not produce unrealistic age patterns in HSV-2 seroprevalence, although the limited available epidemiologic data did not allow us to check whether this scenario fit better for populations with recorded behavior change than for populations without. For Ndola, the simulated decrease in HSV-2 seroprevalence among the young after reduction of risk behavior improved the fit for males but worsened it for females (Figs. 2 and 5). For this advanced HIV epidemic, scenario 4 (combining behavior change with moderately strong effects of HIV) fit observed age patterns in

HSV-2 seroprevalence as well as scenario 1 (with no interactions) did.

Other Explanations?

The large influence of behavior change can explain why increases in HSV-2 as a cause of GUD are also pronounced in developing countries without severe HIV epidemics, such as Southeast Asia.[96–98] For example, in Thailand the incidence of clinical syphilis and chancroid decreased threefold and 20-fold between 1987 and 1993,[98] the period of the 100%-condom-use program that successfully constrained the spread of HIV.[99]

The simulated reduction in partner-change rates is not the only form of behavior change that can underlie relative increases in herpes. With increased condom use, the shift in GUD etiology could be even more marked than with partner reduction, because condom efficacy is likely lower against HSV-2—which can cause lesions outside the condom-protected genital area—than against bacterial STDs.

Behavior changes have not been noted in all countries in which the etiology of GUD has changed, not in, e.g., South Africa.[2,14–16,100] Also, the only published reports on absolute increases in genital herpes—which, according to our simulations, could result in advanced HIV epidemics if biologic effects of HIV are strong and there are no behavioral responses—come from Singapore and India.[101,102] Because Singapore and India at the time of these studies did not have advanced HIV epidemics, these absolute increases cannot be explained by HIV-related immunosuppression. This suggests that risk reduction and, in severe HIV epidemics, HIV-related immunosuppression are not the main explanations of (relative) increases in HSV-2 in all countries. Increased detection of genital herpes because of greater awareness may well be another important factor.

Finally, improved antibiotic management of STDs may have contributed to relative increases in herpes, through decreases in syphilis and especially chancroid. Improved care for STDs probably contributed to GUD epidemiologic shifts in more developed (e.g., Southeast Asian) countries.[101] For SSA populations, whose treatment facilities, symptom recognition, and treatment-seeking behavior are much poorer,[103] it is questionable whether STD treatment has so far played an important role. However, improvement of STD treatment, coupled with population-based health education to improve clinic attendance, certainly has the potential to enhance ongoing trends in GUD epidemiology in this region.

Conclusion and Implications

Our results suggest that seeming increases in genital herpes in SSA are mainly relative—or artifacts reflecting changes in detection—rather than absolute. Even in severe HIV epidemics, the overall incidence of GUD and HSV-2 seroprevalence are unlikely to increase in absolute terms, because the effects of HIV-related enhancement of herpetic ulceration are at a population level easily offset by factors causing GUD to decrease, such as HIV-attributable mortality. Behavioral response to the HIV epidemic is a particularly potent cause of relative increases in herpes among patients with GUD, through rapid and large decreases in chancroid.

The increasing proportion of HSV-2 as a cause of GUD in patients presenting to clinics implies that, as long as antiviral therapy for HSV-2 is not evident in developing countries, education on the prevention of transmission and on avoiding possible consequences of ulcers, including enhanced transmission of HIV (e.g., through temporary abstinence or condom use), becomes an increasingly important component of STD management.

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