

# Sexually Transmitted Diseases and the Increased Risk for HIV Transmission: Implications for Cost-Effectiveness Analyses of Sexually Transmitted Disease Prevention Interventions

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**Summary:** We estimated the annual number and cost of new HIV infections in the United States attributable to other sexually transmitted diseases (STDs). We used a mathematical model of HIV transmission to estimate the probability that a given STD infection would facilitate HIV transmission from an HIV-infected person to his or her partner and to calculate the number of HIV infections due to these facilitative effects. In 1996, an estimated 5052 new HIV cases were attributable to the four STDs considered here: chlamydia (3249 cases), syphilis (1002 cases), gonorrhea (430 cases), and genital herpes (371 cases). These new HIV cases account for approximately \$985 million U.S. in direct HIV treatment costs. The model suggested that syphilis is far more likely than the other STDs (on a per-case basis) to facilitate HIV transmission. This analysis provides a framework for incorporating STD-attributable HIV treatment costs into cost-effectiveness analyses of STD prevention programs. **Key Words:** HIV/AIDS—Sexually transmitted diseases—Prevention—Bernoulli model.

Sexually transmitted diseases (STDs) can have serious long-term health consequences such as cervical cancer, infertility, and adverse outcomes of pregnancy (1). Because of the substantial health and economic effects of these complications, interventions designed to control STDs and their associated sequelae are often considered cost-effective expenditures of public health resources (2–8). In some cases, these programs can actually pay for themselves (5,8).

Because STDs can facilitate sexual transmission of HIV (9–59), control and treatment of STDs also can reduce HIV incidence. Reductions in HIV incidence through STD control have been observed (60), and mathematical transmission models suggest that a considerable portion of HIV infection is attributable to infection with other STDs, particularly in developing countries (61–65). Even in developed countries with low STD prevalence rates, the effect of STDs on HIV transmission can be substantial (65).

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The cost-effectiveness of STD prevention programs will be understated if the effect of STDs on HIV transmission is ignored (61). The averted treatment costs of prevented HIV cases should therefore be included when evaluating the cost-effectiveness of STD interventions. For example, the HIV-related treatment costs averted by eliminating syphilis-associated HIV transmission in the United States would likely be sufficient to offset the costs of a nationwide syphilis elimination campaign (66).

In this paper, we present a model that can be used to estimate the number of STD-attributable HIV infections and associated costs for any given STD. These estimates can be used to enhance and improve cost-effectiveness evaluations of STD control programs. After describing the model, we apply it to four common STDs: syphilis, chlamydia, gonorrhea, and genital herpes.

## METHODS

We used a Bernoullian model of HIV transmission (67–72) to estimate the probability that a given case of STD infection would facilitate HIV transmission (because of increased infectiousness or susceptibility) from an HIV-infected person to his or her partner. In this model of sexual HIV transmission, each act of sexual intercourse has two possible outcomes: HIV transmission or no transmission. For example, the

cumulative probability that a woman who is not infected with HIV will contract HIV after  $N$  unprotected sex acts with an HIV-infected man can be expressed as  $1 - (1 - R_{MF})^N$ , where  $R_{MF}$  is the per-act probability of male-to-female HIV transmission for an unprotected sex act. For simplicity,  $N$  represents the number of unprotected sex acts, as our model does not include protected sex acts. For a woman and a man of unknown HIV infection status, the cumulative probability that the woman will contract HIV after  $N$  sex acts with the man can be expressed as:

$$P_W = M(1 - W)[1 - (1 - R_{MF})^N], \quad [1]$$

where  $M$  is the a priori probability that the male is HIV-infected, and  $W$  is the a priori probability that the woman is HIV-infected. Similarly, the man's cumulative probability of contracting HIV after  $N$  sexual acts with the same woman can be expressed as:

$$P_M = W(1 - M)[1 - (1 - R_{FM})^N], \quad [2]$$

where  $R_{FM}$  is the per-act probability of female-to-male HIV transmission. The combined probability that HIV will be transmitted from one partner to the other after  $N$  acts is the sum of these two probabilities:

$$P = M(1 - W)[1 - (1 - R_{MF})^N] + W(1 - M)[1 - (1 - R_{FM})^N]. \quad [3]$$

The probability of HIV transmission is greater when another STD, such as syphilis, is present in the partnership, whether in the HIV-infected partner (because of increased infectiousness of HIV due to syphilis) or in the HIV-noninfected partner (because of increased susceptibility to HIV infection due to syphilis). If infectious syphilis is present in one or both of the partners, and if the presence of infectious syphilis increases the per-act probability of HIV transmission (both male-to-female and female-to-male) by a factor of  $\theta$ , then the cumulative probability that HIV will be transmitted from one partner to the other may be expressed as:

$$P_s = M(1 - W)[1 - (1 - \theta R_{MF})^N] + W(1 - M)[1 - (1 - \theta R_{FM})^N]. \quad [4]$$

Finally, the probability  $\bar{P}$  that a syphilis-attributable HIV transmission will occur is the difference between Equations 4 and 3:

$$\bar{P} = M(1 - W)[(1 - R_{MF})^N - (1 - \theta R_{MF})^N] + W(1 - M)[(1 - R_{FM})^N - (1 - \theta R_{FM})^N]. \quad [5]$$

In other words,  $\bar{P}$  represents the amount by which the probability of HIV transmission would be reduced if the infectious syphilis had been prevented. Thus,  $\bar{P}$  can be thought of as the "attributable risk" due to syphilis since it reflects the increased risk of HIV transmission due to the presence of syphilis. In particular,  $\bar{P}$  is the difference between the risk of HIV transmission in the presence of infectious syphilis (Eq. 4) and the corresponding risk in the absence of infectious syphilis (Eq. 3).

Same-sex partnerships are not considered in this paper, although

Equation 5 and its parameters could be modified to incorporate such partnerships. For simplicity, we treat everyone as heterosexual, an assumption which likely produces a conservative estimate of  $\bar{P}$ , due to the higher per-act probability of male-to-male HIV transmission and the higher HIV prevalence rates in men who have sex with men.

We used the following incidence estimates: syphilis, 42,000 new cases; gonorrhea, 650,000; chlamydia, 3,000,000; and genital herpes, 1,000,000 (73). The incidence estimates are based on national surveillance reports (syphilis, gonorrhea, and chlamydia) and national surveys (herpes) and are adjusted for underreporting (73). The estimated syphilis incidence assumes that primary, secondary, and early latent syphilis account for 60 per cent of all syphilis cases (74). We included secondary and early latent syphilis cases in the syphilis incidence estimates because these secondary and early latent cases reflect cases that recently were in the primary stage.

To estimate the total number of new HIV cases attributable to syphilis, gonorrhea, chlamydia, and genital herpes in 1996, we multiplied  $\bar{P}$  (calculated separately for each STD according to Eq. 5) by the estimated number of new cases of each of these STDs in the United States in 1996. Thus, for example, the estimated number of new HIV infections attributable to syphilis was: new HIV infections =  $\bar{P} \times 42,000$ , where  $\bar{P}$  is calculated for syphilis according to Equation 5, and 42,000 represents the estimated number of new syphilis cases in 1996. To calculate the expected STD-attributable HIV treatment cost per case of STD, we multiplied the probability of a new HIV infection attributable to a given STD infection (i.e.,  $P$ ) in 1996 by a published estimate (\$195,000 U.S., in 1996 dollars) of the discounted lifetime direct medical cost (including combination therapy) per case of HIV (75).

### Estimation of $N$

We estimated the expected number of unprotected sex acts during which STD-facilitated HIV transmission might occur ( $N$ ; see Eq. 5) by multiplying the estimated number of days during which an STD-infected person would be infectious ( $D$ ) by the estimated number of acts of unprotected sex per day ( $A$ ). Because syphilis, gonorrhea, and chlamydia (unlike herpes) are curable, treatment for these diseases will affect  $N$ . We therefore stratified the analysis into three groups, allowing  $D$  or  $A$  (and therefore  $N$ ) to vary across these groups. Group one consists of those who curtail sexual activity after the onset of STD symptoms. Group two consists of those who seek treatment for their STD symptoms but do not cease sexual activity between the onset of symptoms and STD treatment. Group three consists of those who do not seek STD treatment, including those with asymptomatic infections.

Table 1 summarizes the estimated percentages of STD patients in each group and the estimated number of acts while infectious. For group one, we assumed  $A = 0$  and therefore  $N = 0$ . The probability that an STD-infected individual would be in group one was calculated by multiplying the probability that the STD infection would be symptomatic ( $S$ ) by the estimated probability that a symptomatic person

TABLE 1. Estimates of the number of unprotected sex acts while infectious with an STD<sup>a</sup>

	Syphilis			Gonorrhea			Chlamydia		
	Percentage in group	Days (D)	Acts (N)	Percentage in group	Days (D)	Acts (N)	Percentage in group	Days (D)	Acts (N)
Group one: ceases sexual activity, seeks treatment	68	—	0	76	—	0	40	—	0
Group two: continues sexual activity, seeks treatment	11	6	2.34	13	6	2.34	7	6	2.34
Group three: continues sexual activity, no treatment	21	90	35.1	11	90	35.1	53	180	70.2

<sup>a</sup> For genital herpes, we did not stratify by groups, and  $N$  was set to 10.92.

would cease sexual activity until the STD is treated (0.80) (76). Our baseline values of S for syphilis, gonorrhea, and chlamydia are 0.85, 0.95, and 0.50, respectively. These baseline values are based on average estimates of the value of S for males and females (1).

For groups two and three, we used 0.39 as our baseline value of A (number of acts of unprotected sex per day), based on the reported sexual activity of heterosexuals at high risk for or a history of acquiring STDs (77–80). For group two, we assumed 6 days of STD infectiousness ( $D = 6$ ), based on studies of the average duration of STD symptoms before the patient visited an STD clinic (76,81–83). The probability that an STD-infected person would be in group two was calculated as the product of the following three probabilities: S, the probability of continuing sexual activity after the onset of symptoms (0.20) (76), and the estimated probability that an STD-infected person would seek treatment on his or her own initiative (0.66) (84).

For group three, we assumed that untreated syphilis, gonorrhea, and chlamydia would remain infectious for 90, 90, and 180 days, respectively. These baseline values of D represent one-half the expected duration of infectiousness in the absence of treatment (85). We used one half (rather than all) of the duration to reflect the possibility that the individuals in group three (who do not actively seek treatment) might nevertheless receive treatment for their STDs, perhaps through an STD screening program or through inadvertent treatment with antibiotics prescribed for another purpose. The probability that an STD-infected person would be in group three was calculated as  $(1-S) + (S)(0.2)(0.34)$ , which is the probability that the infection would be asymptomatic, plus the probability that the infection would be symptomatic but that the individual would continue sexual activity and not seek treatment.

For genital herpes, we did not stratify our estimate of  $N$  into three groups as we did for the curable, bacterial STDs. During primary genital herpes infection, lesions usually last about 18 days from onset to disappearance, followed by recurrences at a median rate of 0.33 per month (86). We assumed  $D = 28$  (to reflect the primary infection and one recurrence) and applied the baseline value of A (0.39) used above, yielding  $N = 10.92$  for those with herpes. This baseline value of  $N$  is likely conservative, since the median number of recurrences in the first year of infection is 4 for women and 5 for men (86). We also note that one study found a median of 24 sexual contacts between partners before the transmission of genital herpes (87).

These estimates of  $N$  do not depend on the number of partners of the STD-infected person, who might engage in one sexual act with each of  $N$  partners, or  $N$  acts with 1 partner only, or some other combination of  $N$  total acts. For simplicity, however, when  $N$  was applied in Equation 5, we assumed that all the  $N$  acts involved the same partner.

## Other Model Parameters

Additional model parameters are summarized in Table 2. The per-act probabilities of HIV transmission ( $R_{MF}$ ,  $R_{FM}$ ) are based on published epidemiologic studies (41,88). The remaining parameter estimates depend on the particular STD (syphilis, gonorrhea, chlamydia, or genital herpes) being evaluated. Although there is strong evidence that STDs increase the probability of HIV transmission, the exact magnitude of the cofactor effect ( $\theta$ ) is not known with certainty (12).

For syphilis, we applied a baseline cofactor effect of 30 (with a range of 10–50) based on an analysis of the effect of genital ulcers on heterosexually acquired HIV infections in commercial sex workers in Africa (89). We assumed a baseline cofactor effect of 10 for gonorrhea and 5 for chlamydia and herpes, consistent with the parameters used in other models of HIV transmission (90). Although the cofactor effects may vary over the course of the STD infection (for example, the cofactor effect is likely higher in primary syphilis than in early latent syphilis), we assumed that these cofactor effects were constant over the duration of infectiousness.

Based on a recent review of 34 studies, the overall HIV seroprevalence in people with syphilis is about 17.5 percent (91). HIV seroprevalence rates of about 3% have been detected among those without syphilis but at high risk for syphilis, such as men not infected with syphilis at an STD clinic during an outbreak of syphilis (92). Based on these estimates, and because HIV seroprevalence rates are higher in men, we assumed the a priori probability of HIV infection for men and women who either have or are at high risk for syphilis, was 0.13 and 0.09, respectively. Values of M and W for those with, or at risk for, gonorrhea were based on the estimated HIV seroprevalence in heterosexual, nonintravenous drug users seen at STD clinics (93). Baseline values of M and W for those with, or at risk for, chlamydia or genital herpes were based on HIV prevalence rates for the general population, which suggest that 0.78% of men and 0.16% of women in the 18- to 59-year-old age group are infected with HIV (94).

## Sensitivity Analyses

We performed multiple sensitivity analyses in which one or more parameter values were varied while holding other parameters at their baseline values. Ranges of the parameter values are summarized in Table 2. In examining the sensitivity of the model to the number of acts ( $N$ ), we varied  $N$  directly, rather than varying the parameters used to estimate  $N$ . Our lower bound value of  $N$  was one half of the baseline

TABLE 2. Parameter values<sup>a</sup>

Parameter					Baseline value (range)
HIV transmission probability					
Male to female ( $R_{MF}$ )					0.001 (0.0005–0.0015)
Female to male ( $R_{FM}$ )					0.0006 (0.0003–0.0009)
STD-specific parameters	Syphilis	Gonorrhea	Chlamydia	Genital herpes	
STD cofactor effect ( $\theta$ ) <sup>b</sup>	30 (10–50)	10 (5–15)	5 (3–15)	5 (3–15)	
Initial probability of HIV infection					
Male (M)	0.13 (0.05–0.20)	0.014 (0.01–0.05)	0.0078 (0.003–0.01)	0.0078 (0.003–0.01)	
Female (W)	0.09 (0.03–0.15)	0.01 (0.005–0.02)	0.0016 (0.001–0.01)	0.0016 (0.001–0.01)	

<sup>a</sup> Values for ( $N$ ), the number of unprotected sex acts while infectious with an STD are summarized in Table 1. The range of values for  $N$  is  $1/2 N$ –2  $N$ .

<sup>b</sup> The sexually transmitted disease (STD) cofactor effect represents the magnitude of the increased risk in the per-act probability of HIV transmission in the presence of another STD.

value of  $N$  as listed in Table 1, and our upper bound value of  $N$  was double the baseline value of  $N$ .

## RESULTS

Results of this analysis are presented in Table 3. According to the model, the probability that a new STD will facilitate a new case of HIV is 0.02386 for syphilis, 0.00066 for gonorrhea, 0.00108 for chlamydia, and 0.00037 for genital herpes. When multiplied by the \$195,000 U.S. lifetime cost of HIV treatment, these probabilities suggest that the STD-attributable HIV cost in U.S. dollars per new STD is \$4,653 for syphilis, \$129 for gonorrhea, \$211 for chlamydia, and \$72 for genital herpes. The model estimates suggest that in 1996 an estimated 5052 new HIV cases were attributable to the four STDs considered here: chlamydia (3249 cases), syphilis (1002 cases), gonorrhea (430 cases), and genital herpes (371 cases). To treat these cases of HIV disease would cost an estimated \$985 million ( $\$195,000 \times 5052$ ) over the course of the patients' lifetimes.

The results of the sensitivity analyses are summarized in Table 4, which shows the estimated HIV cases attributable to the four STDs when applying the lower bound and upper bound parameter values. The results were particularly sensitive to the cofactor effect ( $\theta$ ) and the number of acts ( $N$ ). When varying only one parameter value at a time, the estimated HIV cases attributable to the four STDs ranged from 2526 to 11,670. When multiple parameter values were varied simultaneously, an even greater range of estimates was obtained. For example, applying the lower bound values of  $M$ ,  $W$ , and  $\theta$  produced an estimate of 1085 STD-attributable HIV cases, whereas 22,331 HIV cases were attributed to the four STDs when applying the upper bound values of  $M$ ,  $W$ , and  $\theta$ .

## DISCUSSION

Results of this modeling exercise suggest that the number and cost of new HIV infections attributable to STD infections are considerable. Of the estimated 40,000 to 80,000 new HIV infections that occur each year

(94,95), as many as 5052 or more may result from facilitating effects of syphilis, chlamydia, gonorrhea, and genital herpes on HIV transmission. The direct medical cost associated with treating these cases of HIV/AIDS totals almost \$1.0 billion U.S. To put this figure into perspective, the estimated direct medical care cost of adult syphilis, chlamydia, gonorrhea, genital herpes, and pelvic inflammatory disease attributable to bacterial STDs in the United States totaled \$1.8 billion U.S. in 1996 (73). Thus, the \$1.0 billion U.S. annual STD-related HIV treatment cost represents a substantial portion of the medical costs of non-HIV STDs. The results suggested that syphilis reduction would be more beneficial (on a per-case basis) than the other STDs, since each new case of syphilis leads to an expected 0.024 new cases of HIV, far greater than the expected number of new cases of HIV associated with the other STDs.

Moreover, these estimates are likely to underestimate the true effects of STDs on HIV transmission, because of conservative assumptions about various parameter values, such as the number of unprotected sex acts ( $N$ ) engaged in while the STD patient is infectious. For example, our assumption that 80% of symptomatic STD patients cease sexual activity is likely an overestimate, especially when compared with estimates for adolescent populations (82). Our baseline values of the estimated HIV prevalence rates for men and women with, or at risk for, STDs are also conservative (Table 2). For example, a study of STD clinic patients in New York City in 1992 found HIV infection in more than 25% of individuals with primary and secondary syphilis, in 9% of those with gonorrhea, and in 14% of those with genital herpes (96). A study of patients at STD clinics in 10 American cities in 1994 found that 6% of genital ulcer patients were infected with HIV (97). In contrast, we assumed a 1.4% HIV prevalence for persons with, or at risk for, gonorrhea, and we applied general population HIV prevalence estimates for chlamydia and herpes. Our HIV prevalence estimates for persons with, or at risk for, syphilis are not quite as conservative, as there is less uncertainty about these estimates due to the relative abundance of studies of syphilis and HIV coinfection (91). In light of the stud-

**TABLE 3.** Estimated number of and cost of annual sexually transmitted disease (STD)-attributable HIV transmissions

	Syphilis	Gonorrhea	Chlamydia	Genital herpes	Total
Expected number of STD-attributable HIV infections, per case of STD <sup>a</sup>	0.02386	0.00066	0.00108	0.00037	—
Expected HIV cost per case of STD <sup>a</sup>	\$4,653	\$129	\$211	\$72	—
Annual HIV cases attributable to STD	1002	430	3,249	371	5052
Direct medical cost of HIV cases attributable to STD <sup>a</sup>	\$195.4 million	\$83.8 million	\$633.6 million	\$72.4 million	\$985 million

<sup>a</sup> Amounts shown in 1996 U.S. dollars.

**TABLE 4.** Sensitivity analysis: estimated HIV cases attributable to four common sexually transmitted diseases when applying lower and upper bound parameter values

Parameter(s) varied	Syphilis		Gonorrhea		Chlamydia		Genital Herpes		Total	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
$R_{MF}$	749	1152	295	542	1968	4275	208	529	3220	6498
$R_{FM}$	866	1102	366	487	3071	3406	351	391	4653	5386
$\theta$	403	1347	204	626	1731	8458	187	1239	2526	11,670
M	614	1342	346	1183	1486	4058	168	464	2613	7047
W	832	1173	364	561	3108	5223	356	583	4660	7539
N	615	1405	232	742	1792	5371	188	719	2827	8237
$N, \theta$	219	1673	107	1023	925	11,079	95	2285	1345	16,060
$R_{MF}, R_{FM}$	612	1252	231	599	1789	4432	188	549	2821	6832
M, W	396	1471	279	1302	1343	6020	153	675	2171	9467
W, W, N	244	2067	151	2233	739	10,170	78	1312	1211	15,782
M, W, $\theta$	160	1980	133	1892	715	16,195	77	2265	1085	22,331
$R_{MF}, R_{FM}, \theta$	218	1567	106	849	924	10,195	95	1790	1343	14,401
$R_{MF}, R_{FM}, \theta, M, W, N$	45	2617	35	3794	197	24,117	20	5908	297	36,437

$R_{MF}$ , per-act probability of male-to-female HIV transmission;  $R_{FM}$ , per-act probability of female-to-male HIV transmission;  $\theta$ , STD cofactor effect on per-act probability of HIV transmission; M, initial probability that the man is HIV-infected; W, initial probability that the woman is HIV-infected; N, number of sex acts while STD patient is infectious.

ies mentioned above, it is likely that HIV prevalence rates in those with genital herpes or gonorrhea are substantially higher than the estimates we applied in our model, and therefore our estimates of the HIV cases attributable to genital herpes and gonorrhea may be far more conservative than our estimates for chlamydia. Therefore our results should not be used to gauge the relative importance of gonorrhea, chlamydia, and genital herpes as cofactors in the spread of HIV.

Our methodology of assessing the effects of STDs on the spread of HIV is also conservative because it ignores secondary transmissions of HIV. Each new HIV infection attributable to syphilis might eventually lead to HIV infections in others, who in turn might infect their partners, and so on. Another reason why our model might underestimate the number of HIV infections attributable to STDs is that our model includes unprotected sex acts only and ignores sex acts in which a condom is used. This bias is likely to be small, however, given that most cases of heterosexual HIV transmission probably result from unprotected intercourse (98).

In addition, our estimates of the number of STD-attributable HIV cases are conservative because our model assumes that the cofactor effect is eliminated at the time STD treatment is received. In reality, the heightened risk of HIV transmission may persist after treatment. For example, one study demonstrated that the viral load in the semen of HIV-infected men coinfective with urethritis may remain above preurethritis infection levels for weeks after treatment (57).

To examine the plausibility of our estimates, we can compare our results with other studies of the effects of STDs on HIV transmission. Mathematical models sug-

gest that most heterosexually acquired HIV cases in the United States could be prevented through the control of STDs (99). Although our model suggested a very low probability (on a per-case basis) that chlamydia will facilitate HIV transmission, we estimated that a substantial number of new HIV cases might be attributable to chlamydia due to its high prevalence. Our estimates of new HIV cases attributable to gonorrhea and genital herpes are considerably more conservative than our estimates for chlamydia, as described above. A recent analysis based on a simplified transmission model estimated that 1082 new, heterosexually acquired HIV cases could be attributed to syphilis each year (66), which is similar to the estimate of 1002 obtained here. A study of HIV seroconversion in STD clinic patients in Miami estimated that 18% of HIV seroconversions could be attributed to coinfection with syphilis (45). Another study, based on data from clinical records of >4000 HIV-infected STD clinic patients in eight U.S. cities, indicated that treatment of STDs could reduce new HIV cases by 44% (100). Assuming 40,000 to 80,000 new HIV infections per year in the United States, our estimates suggest that 1.3% to 2.5% of these new HIV cases are attributable to syphilis, and 6.3% to 12.6% of new HIV cases are attributable to syphilis, gonorrhea, chlamydia, and genital herpes combined. Compared with the results of previous research, our estimates appear plausible, although possibly conservative.

Our approach has limitations. First, many of the parameter values are uncertain, and the model results are sensitive to some of these parameters. The results are especially sensitive to the magnitude of the cofactor effect and to the number of acts that transpire while the

STD patient is infectious. Our conservative assumptions about the number of unprotected acts ( $N$ ) are intended to mitigate the uncertainty associated with (and the sensitivity of the results to) the parameter  $N$ . The sensitivity of the model to the cofactor effect is to be expected because the actual number of HIV cases attributable to STDs is strongly correlated with the actual magnitude of the cofactor effect. However, given the importance of the cofactor effect to our model, our baseline assumptions about the magnitude of the cofactor effect warrant further discussion.

Numerous studies have suggested that persons with STDs have at least a twofold to fivefold increase in risk for HIV infection (9,12). However, these studies cannot provide an estimate of the per act cofactor effect of a given STD given that these odds ratios are based on the result of a number of sexual exposures over time, including exposures during the time in which the STD was not present (89). Thus, the actual per-act cofactor effect is likely to be substantially higher than the twofold to fivefold increase indicated in previous studies (66,89). To our knowledge, only one study (89) has attempted to quantify the per-act cofactor effect and this study estimated that the presence of genital ulcer disease increases the per-act risk of male-to-female sexual transmission of HIV by a factor of 10 to 50, and the female-to-male risk by a factor of 50 to 300. Based on this study, we assumed a baseline value of 30 and a range of between 10 and 50 for the cofactor effect of syphilis, and we applied more conservative estimates for the nonulcerative STDs (gonorrhea and chlamydia) and as well as for genital herpes, under the assumption that genital herpes might not always cause lesions. Although great uncertainty exists about the exact magnitude of the cofactor effect, our baseline values reflect conservative best guesses based on the information currently available, and we applied a wide range of values of the cofactor effect in the sensitivity analysis to reflect this uncertainty.

A second limitation concerns our assumption that each STD-infected person has only 1 partner rather than several while the STD is infectious. However, because the number of assumed acts is very small, and the per-act probability of HIV transmission is low, the impact of this assumption is apt to be slight. Another limitation of our model is that it does not capture the possibility that an individual might have more than one non-HIV STD at a given time, such as coinfection with gonorrhea and chlamydia. A more complex transmission model is needed to examine the effect of multiple STD infections, secondary HIV transmissions, and other dynamic factors.

Because our model is based on a simplified per-act approach, it may be more suitable for examining HIV

transmission in casual sexual contacts rather than in main, steady partnerships, for which a per-partnership approach might be more suitable (101,102). However, we note that those acquiring STDs are more likely to have multiple partners than the general non-STD population. Further, any bias introduced by the per-act approach should be limited by our assumption that each person with an STD has at most 1 sexual partner while the STD is infectious.

Additional limitations of our approach, such as assumptions regarding the lifetime costs of HIV treatment, the use of HIV prevalence rates to estimate the a priori probability of HIV infection, and assumptions regarding sexual mixing patterns are discussed more thoroughly elsewhere (66).

These results have implications for assessing the cost-effectiveness of STD prevention programs. Economic analyses of such programs should incorporate all identifiable costs and benefits, including reductions in STD-attributable HIV transmission and associated medical treatment costs. The estimated HIV treatment cost per STD case provided in Table 3 can be used to estimate the total savings in averted HIV-related medical costs due to preventing STDs. For example, a program that prevents 10 cases of syphilis would be expected to save \$46,530 U.S. ( $10 \times \$4,653$  U.S.) in syphilis-attributable HIV costs. Alternatively, rather than applying our baseline estimates of the expected HIV costs per case of STD, a cost-effectiveness analyst could apply the simplified model presented in this paper, substituting population-relevant parameter estimates (such as higher values of HIV prevalence for interventions in high-risk urban populations) in place of the baseline parameter values assumed in this analysis, thereby generating more appropriate estimates of the expected HIV costs averted by preventing STDs in the given population.

We estimated that 5052 cases of HIV were attributable to four common STDs in the United States in 1996. In the basic sensitivity analysis, estimates ranged from 2526 to 11,670 new HIV cases, although a wider range of estimates was found when multiple model inputs were varied simultaneously. The baseline estimate of 5052 new HIV cases represents direct medical costs of almost \$1.0 billion U.S., and suggests that 6.3% to 12.6% of new HIV cases in 1996 were attributable to these STDs. This analysis provides a framework for incorporating STD-attributable HIV treatment costs into cost-effectiveness analyses of STD prevention programs.

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