Using Sexually Transmitted Disease Incidence as a Surrogate Marker for HIV Incidence in Prevention Trials

A Modeling Study

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Background: **Because many of the sexual behaviors that place individuals at risk of acquiring HIV are the same as those that place them at risk for other sexually transmitted diseases (STDs), researchers and policymakers have called for the use of non-HIV STDs as surrogate markers for HIV infection.**

Goals: **This study examined the epidemiologic conditions under which changes in STD incidence are associated with changes in HIV incidence.**

Study Design: **A mathematical model of HIV/STD transmission was applied to empirical data from a large HIV prevention intervention. The association between participants' HIV infection risk reduction scores and their STD risk reduction scores was measured with use of the Pearson product-moment correlation. The authors examined how the strength of association varied across different epidemiologic parameters and heterosexual behaviors.**

Results: **Moderate to strong associations were noted when the infectivity of the STD was similar to the infectivity of HIV. The association was attenuated for larger STD infectivity values. The prevalence of STD infection was a less important determinant of the strength of association. Stronger associations were obtained when the number of sex partners was large or the number of sex acts was small.**

Conclusions: **Easily transmitted STDs, such as gonorrhea, are unsuitable for general use as surrogate markers for HIV infection. Hepatitis B, syphilis, and chlamydial infection have more promising epidemiologic profiles. Careful studies of STD infectivity are needed to aid in the identification of potential marker STDs.**

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RIGOROUS EVALUATION is needed to assess the effectiveness of sexual risk reduction interventions. The most appropriate measure of effectiveness depends on the goal of the intervention.[1–3] For instance, the goal might be to change intervention participants' sexual behaviors by increasing condom use or decreasing the number of partners with whom they have sex. This goal acknowledges that particular behaviors, such as having unprotected sex with casual partners, are associated with a host of adverse outcomes, including infection with HIV or other sexually transmitted diseases (STDs) and unplanned pregnancies. Consistent with this goal, behavior change intervention programs can be evaluated by assessing the extent to which participants have reduced their risk behaviors. However, behavior change is seldom promoted for its own sake. Instead, the usual goal of sexual behavior change interventions is to reduce participants' pregnancy and/or STD risk, often with an emphasis on HIV prevention.

The best way to evaluate an intervention's effectiveness against a particular STD is to examine temporal changes in STD incidence. Unfortunately, this strategy poses considerable difficulties for evaluating HIV prevention interventions. Because the incidence of HIV infection in the United States is relatively low,[4] using HIV seroincidence as a primary intervention outcome is seldom feasible. To achieve adequate statistical power to detect an intervention effect would require recruiting an extremely large sample of high-risk individuals, at substantial cost. Consequently, most interventions aimed at prevention of HIV infection are evaluated by assessment of changes in risk behaviors,[5] sometimes augmented by mathematical modeling to estimate the epidemiologic impact of the interventions.[6]

Although the Consensus Development Conference on Interventions to Prevent HIV Risk Behaviors concluded that

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"the weight of the scientific evidence to date suggests that properly administered self-reports... can yield reasonably accurate [information],"[3,5] some researchers remain skeptical about the validity of self-reported measures of sexual behavior change.[7–9] Because many of the behaviors that place individuals at risk of acquiring HIV are the same as those that place them at risk for other STDs, researchers and policymakers have called for the use of non-HIV STDs as surrogate markers for HIV infection.[8,10–12] STD incidence recently has been used as a primary or secondary endpoint in several HIV prevention trials in the United States and United Kingdom.[13–21]

However, the relationship between particular sexual behaviors, HIV incidence, and the incidence of other STDs is complex, and thus far no empirical relationship between reductions in the incidence of HIV and any specific STD has been demonstrated.[1,2,5,11] The use of STD incidence as a primary intervention outcome relies on the assumption that "if there is a change in risk behaviors of the population, then the incidence of all STDs will be similarly affected."[7] But under what conditions is this assumption justified?

To examine this issue, we applied a mathematical model of HIV/STD transmission to empirical data from a large intervention to prevent HIV infection (Project Light) to determine the characteristics of an ideal marker STD. The main question we sought to address was, under what conditions are changes in STD incidence associated with changes in HIV incidence?

Methods

Description of Sample

The Project Light intervention was conducted at seven United States sites, beginning in 1989.[17,18] A total of 3706 high-risk participants, 74% of whom were self-identified as black, were recruited from STD clinics, primary care clinics, and other health service organizations. Participants were randomized to one of two intervention groups. Those in the main intervention group attended seven 90- to 120-minute small-group risk reduction counseling sessions that emphasized motivation, skills, and self-efficacy related to HIV infection risk reduction. Participants in the control intervention attended a single, one-hour AIDS education session in which they viewed a videotape on HIV prevention and engaged in a question-and-answer exchange.

Sexual behavior surveys were conducted at baseline and at 3, 6, and 12 months after the conclusion of the intervention. Each survey elicited information about participants' sexual behaviors in the preceding 3-month period, including the number of male and female sex partners and the number of acts of unprotected and condom-protected vaginal and anal intercourse. The results of the main outcome analysis indicated that both intervention groups reduced their sexual risk behaviors, but participants in the seven-session cognitive-behavioral intervention engaged in fewer unprotected sex acts, used condoms more frequently, and were more likely to use condoms consistently over the 12-month follow-up period than were participants in the comparison (video) intervention.[18]

The present analysis focuses on the baseline and 12-month follow-up data and includes only individuals for whom 12-month follow-up information was available. The final sample included 1859 women (918 in the seven-session intervention and 941 in the video intervention) and 1162 strictly heterosexual men (583 and 579, respectively). Table 1 summarizes the sexual behavior (number of partners and number of acts of unprotected and protected vaginal and anal intercourse) reported by this sample. Because of the paucity of available estimates of the infectivity of anal intercourse for any STD other than HIV, vaginal and anal intercourse were combined in the present analyses. Overall, anal intercourse accounted for approximately 4% of the total number of acts of intercourse reported by the men and women in the sample.

Mathematical Modeling

A Bernoulli mathematical model of STD/HIV transmission was used to translate participants' self-reported sexual behaviors into estimates of their risk of contracting STDs and the change in STD risk from baseline to the 12-month follow-up. (For this analysis, all intervention participants are assumed to be equally susceptible to infection.) In this model, STD risk is a function of the sexual behavior of the individual (number of acts of unprotected and condom-protected intercourse and number of sex partners); the STD prevalence among intervention participants' sex partners; the per-act STD transmission probabilities (infectivity) associated with unprotected insertive and receptive vaginal intercourse; and the effectiveness of condoms at preventing STD transmission.

The Bernoulli model is described in detail elsewhere.[22–24] As an example, the cumulative probability of STD infection for a woman who engages in n acts of unprotected vaginal intercourse and k acts of protected vaginal intercourse with each of m partners is approximately

$$P = 1 - \{(1 - \pi) + \pi(1 - \alpha)^n(1 - (1 - \phi)\alpha)^k\}^m, \quad (1)$$

where π is the prevalence of STD infection among her sex partners, α is the per-act transmission probability of unprotected receptive vaginal intercourse, and ϕ denotes the effectiveness of condoms in preventing STD transmission. The incidence of infection over the 3-month assessment period can be estimated by multiplying the average infection probability by the number of participants.[6]

Separate STD risk estimates were calculated on the basis of Project Light participants' sexual behavior during the

TABLE 1. Sexual Behavior Data

Intervention Condition	No. of Partners	No. of Vaginal Intercourse Acts		No. of Anal Intercourse Acts	
		Unprotected	Protected	Unprotected	Protected
Women: 7-session (n = 918)					
Baseline	2.4	23.8	4.9	0.5	0.1
12-month follow-up	1.4	12.2	9.1	0.3	0.1
Women: video (n = 941)					
Baseline	2.5	22.5	5.0	0.6	0.1
12-month follow-up	1.4	16.5	6.8	0.9	0.1
Men: 7-session (n = 583)					
Baseline	4.7	25.9	8.8	1.4	0.8
12-month follow-up	1.9	11.5	12.1	0.4	1.0
Men: video (n = 579)					
Baseline	4.3	23.7	6.0	1.4	0.4
12-month follow-up	1.9	15.6	7.0	0.5	0.2

previous 3 months, reported at baseline and follow-up. The difference between these estimates is a measure of the extent of risk reduction (or risk increase), and the mean change is an indicator of the expected reduction in STD incidence (infections per 3-month period) among participants.

Estimates of the epidemiologic parameters were obtained from the literature. For the base-case analysis, condom effectiveness was set at 90%.[25] In the sensitivity analyses, condom effectiveness was varied from a low of 67%[26,27] to 100%[28] to examine the impact of uncertainty in this parameter. The same condom effectiveness value was used for HIV and all other STDs; therefore, these analyses apply only to STDs that are not easily transmitted by skin-to-skin contact. The per-act infectivity of HIV for receptive intercourse was set at 0.001 and the infectivity for insertive intercourse was set at 0.0006.[29–31] Holmberg's synthesis of HIV prevalence estimates suggests that approximately 2% of all high-risk heterosexuals in major United States metropolitan areas are infected with HIV.[4] In the base-case analysis we assumed that 2% of the participants' sex partners are HIV-infected. Sensitivity analyses were conducted for all main parameters, including HIV prevalence.

Measures of Association

To assess the strength of association between reductions in STD risk and reductions in HIV risk as a result of the intervention, we calculated Pearson product-moment correlations between participants' HIV risk reduction scores and their STD risk reduction scores. The square of the correlation coefficient, which is known as the *coefficient of determination* and is denoted R^2, indicates the strength of association. The coefficient of determination can be interpreted as the proportion of variance in HIV risk reduction associated with reductions in STD risk.

Infectivity Estimates

Estimates of the infectivity of several STDs are available in the literature. These estimates generally were obtained from observational studies of heterosexual couples, and most take the form of per-partnership rather than per-act transmission probabilities. Available estimates of the per-partnership transmission probability for syphilis range from 0.15932 to 0.682.[32] Cates and colleagues[33] summarized the results of five studies[34–38] and arrived at an overall average of 0.413. Because of the variety of sources for syphilis infectivity estimates, it is difficult to convert the per-partnership values to equivalent per-act values. For example, if the 0.413 estimate were the result of 10 acts of intercourse, then the equivalent per-act infectivity would be 0.05, whereas if it arose from 100 acts of intercourse, the per-act infectivity would be closer to 0.005. Unfortunately, no information about the number of acts in these studies is available.

The per-partnership probability of chlamydia transmission has been estimated at 0.323 for female-to-male transmission and 0.395 for male-to-female transmission, on the basis of transmission rates for STD clinic clients and their partners.[39] The per-act infectivity could be much smaller, depending on the number of acts of intercourse on which these estimates were based. It is possible to infer a per-act infectivity value from a study of chlamydia acquisition by prostitutes.[40] Three of 20 susceptible women became infected as a result of a total of 939 acts of intercourse. If a 3.5% prevalence of infection among their male partners is assumed, the per-act transmission probability is approximately 0.1.

If it is assumed that each prostitute had sexual intercourse only once with each man, the cumulative probability of infection is

$$P = 1 - \{(1 - \pi) + \pi(1 - \alpha)^n\}^m \quad (2)$$
$$= 1 - (1 - \alpha\pi)^m,$$

where m = 939/20 = 46.95 is the mean number of partners per prostitute, $\pi = 0.035$ is the prevalence of chlamydia infection among the men,[40] and α is the unknown per-act transmission probability. There were three incident infections among 20 women, hence $P = 3/20 = 0.15$. Solving the equation for α implies that the per-act chlamydia infectivity for male-to-female transmission is 0.099.

Gonorrhea appears to be relatively easily transmitted. Estimates of the per-act infectivity range from approximately 0.241 to more than 0.5.[41–43] As with syphilis and HIV, male-to-female transmission of gonorrhea is more efficient than female-to-male transmission.[30,33,44,45]

Less is known about the infectivity of the hepatitis B virus. For homosexual anal intercourse, the per-contact transmission probability is estimated to be 10 times greater than the corresponding probability for HIV transmission.[46,47] Applying the same scaling factor to heterosexual transmission routes yields a per-act hepatitis B infectivity of approximately 0.01 for male-to-female intercourse and 0.006 for female-to-male intercourse.

Results

The main analysis focuses on the women in the cognitive-behavioral intervention (the women in the video intervention and the men in both intervention conditions are considered below). Figure 1 illustrates the relationship between reductions in STD risk and reductions in HIV risk for women in the seven-session intervention condition for a highly infectious STD such as gonorrhea and a less infectious one such as hepatitis B. For the analysis presented in Figure 1A, the STD infectivity was set at 0.2 and the STD prevalence was set at 0.05. This figure suggests that this STD would make a relatively poor marker for HIV infection. As shown, some of the women with the largest proportionate reductions in HIV risk experienced almost no change in their STD risk, and vice versa. This can be attributed to the very high infectivity of the STD. We would expect new STD infections in 20% of all women who had a single act of unprotected intercourse with an infected man and in 67% of the women who had unprotected intercourse with an infected man five or more times. Unless condoms are used for nearly ever act of intercourse, women who have sex with infected men are likely to become infected. Conversely, the much smaller infectivity of HIV permits a nearly linear relationship between increases in condom use and decreases in HIV risk.[48,49] Thus, by increasing their use of condoms, some women in the intervention reduced their HIV risk to a much greater (relative) extent than they did their STD risk. Therefore, given its high infectivity, it is not surprising that this gonorrhea-like STD makes a poor marker for HIV infection.

It is logical to assume that the best marker STD would be one that is similar to HIV in transmission characteristics.

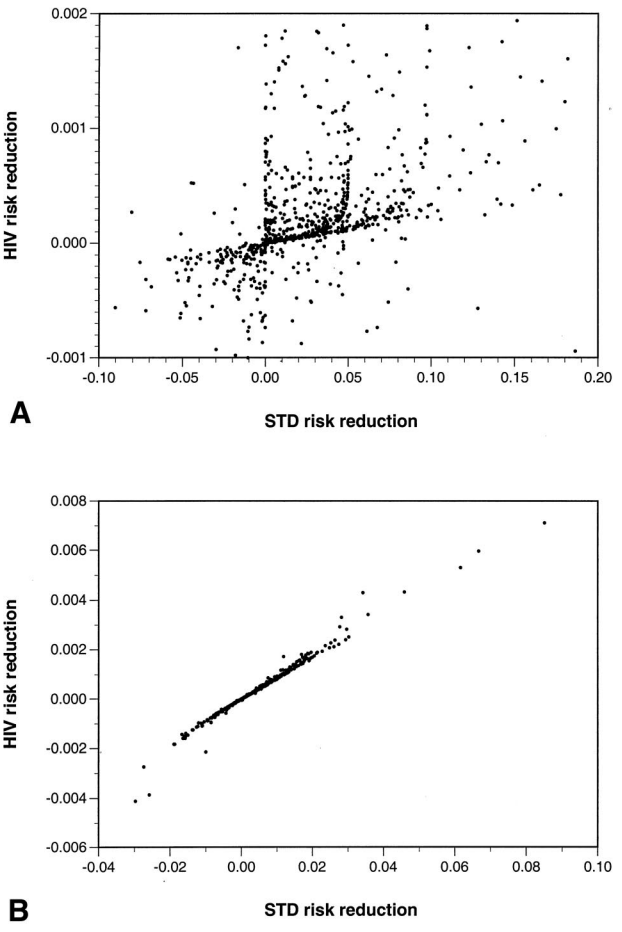

Fig. 1. Sexually transmitted disease (STD) risk reduction versus HIV risk reduction for women in the seven-session intervention condition, for (A) a highly infectious STD, such as gonorrhea, or (B) a much less infectious STD, such as hepatitis B.

Figure 1B demonstrates that this assumption is correct. This scatterplot shows the relationship between STD and HIV infection risk reduction for an STD with a per-act infectivity of 0.005 and a prevalence of 5% (the corresponding values for HIV are $\alpha = 0.001$ and $\pi = 2\%$). An almost perfect correlation ($R^2 = 0.98$) is obtained for this less infectious, hepatitis B–like STD.

Additional analyses were conducted to examine how the strength of association varies across STD prevalence and infectivity values. Figure 2 shows the degree of association between STD risk reduction and HIV infection risk reduction—as reflected in the R^2 value—for the women in the seven-session intervention condition, as a function of the infectivity and prevalence of the STD. As this figure illustrates, the infectivity of the STD is a critical determinant of the strength of the association between HIV infection risk reduction and STD risk reduction. The association is strongest when the per-act STD transmission probability for receptive vaginal intercourse is near 0.001, which is the assumed per-act HIV transmission probability. However,

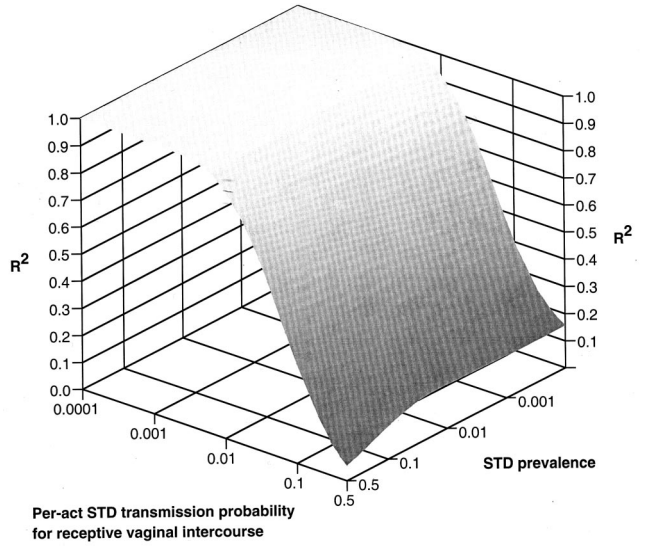

Fig. 2. Strength of association—as indicated by the coefficient of determination (R^2)—between sexually transmitted disease (STD) risk reduction and HIV risk reduction for women in the seven-session intervention condition, assuming a per-act HIV transmission probability of 0.001 and an HIV prevalence of 0.02.

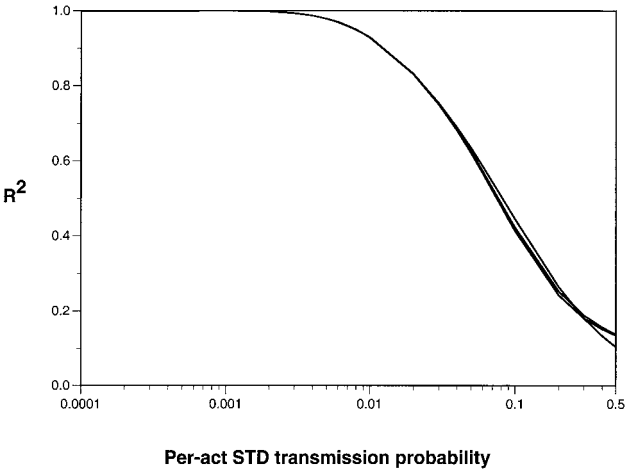

Fig. 3. Strength of association (R^2) between sexually transmitted disease (STD) risk reduction and HIV risk reduction for women in the seven-session intervention condition, as a function of the per-act STD transmission probability, for three STD prevalence values: π = 0.002, 0.02, and 0.2.

the association falls off as the infectivity increases from 0.001. For an STD with an infectivity of 0.2, R^2 is less than approximately 0.30, regardless of the STD prevalence. Thus, for gonorrhea and other highly infectious STDs with infectivities of 0.2 or greater, the variance in the women's STD risk reduction values accounts for less than 30% of the variance in their HIV infection risk reduction values. The association also is stronger when the prevalence of STD infection is close to the HIV prevalence. Indeed, the association is perfect (R^2 = 1.0) when the HIV and STD infectivities agree and the STD prevalence equals the HIV prevalence (0.02 in Figure 2).

Notably, the association between STD risk reduction and HIV risk reduction is relatively less affected by differences in HIV and STD prevalence than by differences in HIV and STD infectivity. This point is underscored in Figure 3, which illustrates how the coefficient of determination varies as a function of the per-act STD transmission probability for the women in the seven-session intervention condition. This figure demonstrates that the strength of association is greatest when the STD infectivity equals the HIV infectivity, dropping off sharply for transmission probabilities greater than 0.01. The STD prevalence is essentially immaterial; indeed, the three curves, which correspond to prevalence values of 0.002, 0.02, and 0.2, are nearly indistinguishable.

Other Populations

These results could depend on the particular dataset selected for this analysis or on the values assumed for various HIV-related epidemiologic parameters. Sensitivity analyses, described below, were conducted to address the second of these issues. To examine the first issue, we applied this model to a second subset of the Project Light dataset: men who have sex only with women. For this analysis the HIV infectivity of insertive intercourse was set at 0.0006.[50] As illustrated in Figure 4, the results for the men in the seven-session intervention condition were similar to those for the women, although for men the strength of association declined somewhat more rapidly as the STD infectivity value

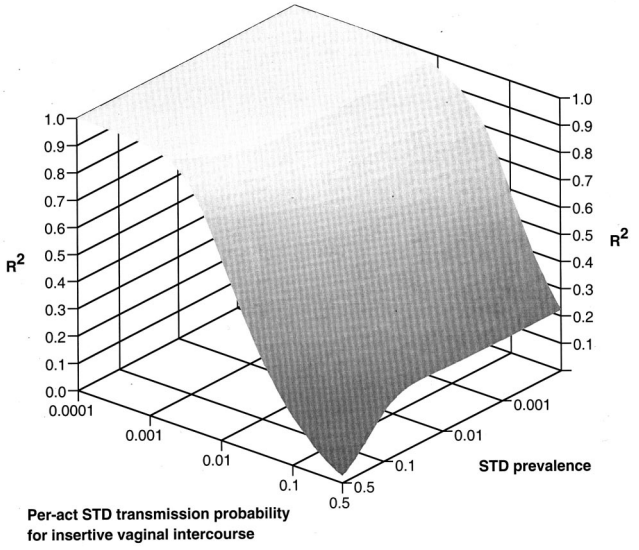

Fig. 4. Strength of association (R^2) between sexually transmitted disease (STD) risk reduction and HIV risk reduction for men in the seven-session intervention condition who have sex only with women.

TABLE 2. Base Case and Sensitivity Analyses: Coefficient of Determination (R^2) as a Function of STD Infectivity

	STD Infectivity			
Base Case or Sensitivity Analysis	0.005	0.05	0.1	0.2
Base case analysis*	0.98	0.61	0.43	0.29
HIV prevalence = 0.002	0.98	0.61	0.43	0.29
HIV prevalence = 0.2	0.98	0.61	0.43	0.28
Condom effectiveness = 100%	0.98	0.62	0.44	0.30
Condom effectiveness = 67%	0.98	0.61	0.43	0.29
Double number of acts	0.95	0.47	0.32	0.21
Double number of partners	0.99	0.77	0.60	0.43
Double number of acts and partners	0.98	0.63	0.45	0.30
HIV infectivity = 0.01	0.98	0.82	0.63	0.45
Women in video intervention condition	0.96	0.44	0.25	0.10
Men in 7-session intervention condition	0.98	0.74	0.56	0.39
Men in video intervention condition	0.98	0.74	0.57	0.40

These analyses are based on the assumption that the prevalence of STD (sexually transmitted disease) and the prevalence of HIV equal 0.02, unless otherwise noted.
*Condom effectiveness = 90%; HIV infectivity = 0.001; HIV prevalence = 0.02.

increased. Again, the infectivity of the STD seems to be much more important than the prevalence of infection in determining the strength of association, except when the STD infectivity is very large.

Although this analysis has focused on participants in the seven-session cognitive–behavioral intervention, qualitatively similar results were obtained for male and female participants in the video intervention (data not shown). As noted elsewhere, this control intervention also was effective at changing participants' risk behaviors[18]; hence, it is not surprising that this intervention produced similar results.

Summary of Base-Case Results

In sum, the general pattern appears to be fairly robust across Project Light populations (heterosexual women and men) and intervention conditions. The first main finding is that the association between HIV and STD risk reduction is strongest for STDs with infectivities that are similar to that of HIV. The association is attenuated for larger infectivity values. Second, STD prevalence influences the strength of association for STDs with very large infectivities but does not substantially affect the strength of association when the STD infection is moderate or small. In particular, for STD infectivity values similar to that of HIV—where the strength of association is strongest—the prevalence of STD is essentially immaterial.

Sensitivity Analyses

A further question is whether modeling assumptions, or the particular values assumed for the HIV epidemiologic parameters, might have affected the results obtained in the base-case analysis. We conducted sensitivity analyses to examine this issue. These analyses focus on the women who participated in the seven-session intervention.

The results of the base-case analysis and the sensitivity analyses are summarized in Table 2, which lists the R^2 value for several different STD infectivity values, under the assumption that the prevalence of the STD equals the prevalence of HIV. As shown, changing the condom effectiveness (from 90% to 67% or 100%) or HIV prevalence (from 0.002 to 0.2) had little effect on the results. The only manipulations that had a substantial effect on the results were doubling the number of acts of intercourse for all participants and doubling the number of partners. Doubling the number of acts of intercourse reduced the strength of association, especially for larger STD infectivity values. (As discussed above, for highly infectious STDs, transmission is likely if the number of acts of intercourse is sufficiently large; hence, increasing condom use and taking other risk reduction steps has relatively less effect on STD incidence than on HIV incidence.) In contrast, doubling the number of sex partners increased the strength of association. However, doubling *both* the number of acts and the number of partners produced results that were nearly identical to the base-case results. Finally, if the true infectivity of HIV were 10 times larger than the base-case value of 0.001, then the results would be shifted so that the strength of association is greatest when the STD infectivity also is 0.01, but otherwise the pattern is similar to that obtained in the base case (see Figure 5).

As indicated in Table 1, moderate to strong associations were obtained for STDs that have infectivity values of 0.05 or less. Indeed, solely on the basis of these epidemiologic considerations, hepatitis B could be a suitable marker for HIV infection (assuming that its true infectivity is close to 0.005). The association between HIV infection risk reduction and gonorrhea risk reduction is much weaker because of the high infectivity of this STD ($\alpha \geq 0.2$).

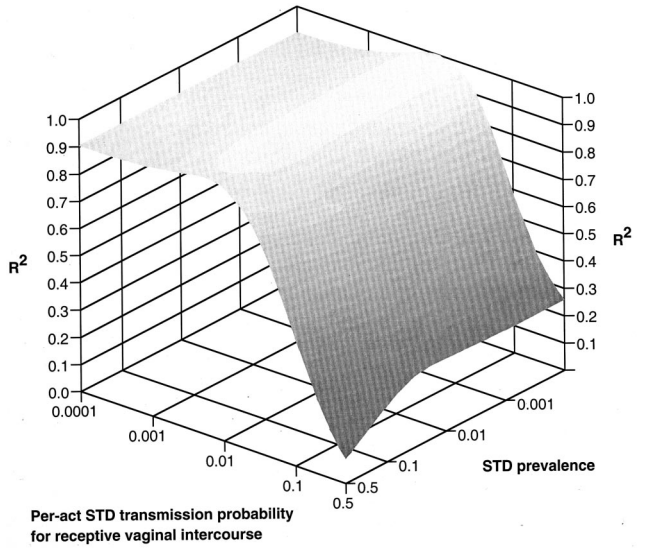

Fig. 5. Strength of association (R^2) between sexually transmitted disease (STD) risk reduction and HIV risk reduction for women in the seven-session intervention condition, with assumption of a per-act HIV transmission probability of 0.01 and an HIV prevalence of 0.02.

Discussion

For changes in STD incidence to serve as a surrogate for changes in HIV incidence, STD risk reduction must be strongly associated with HIV infection risk reduction. The analyses presented here indicate that the strength of association between HIV risk reduction and STD risk reduction critically depends upon the infectivity but not the prevalence of the STD. Strong associations were noted for STDs with infectivities of approximately 0.05 or less, and moderate associations were noted with infectivities of less than approximately 0.2 (Figure 3). In contrast, STDs with infectivities greater than 0.2 produced weak associations.

There is limited evidence about the infectivity of common STDs.[51,52] However, estimates of the infectivity of hepatitis B and (possibly) syphilis and chlamydial infection suggest risk reduction associations in the moderate to strong range. In contrast, easily transmitted STDs such as gonorrhea appear to be unsuitable for use as surrogate markers of HIV infection. More information is needed about the true infectivity of these and other STDs to aid in the identification of potential marker STDs. Information also is needed to characterize interpersonal variability in infectiousness and susceptibility to infection, as well as infectivity differences due to stage of infection (e.g., primary versus secondary syphilis infection).

In these analyses, the prevalence of STD infection among sex partners was not an especially important factor in determining the strength of association. For STDs with suitably low infectivities, the prevalence of infection was essentially immaterial. However, the prevalence of infection is likely to be more important for populations in which the number of partners is greater than it was for the heterosexual participants in Project Light and for homosexual populations, because of the substantially greater infectivity of receptive anal intercourse in comparison with receptive vaginal intercourse.

These analyses indicate that stronger HIV–STD associations will be obtained when the observation period for incident STD infections is kept relatively short. The base case results were with an assumed 3-month clinical follow-up, limiting the potential number of sex acts and partners. The sensitivity analyses show that doubling the number of partners strengthens the association between STD and HIV infection risk reduction, whereas doubling the number of acts diminishes the association by diluting the impact of condom use, which is greater for HIV than for other STDs because of the greater infectivity of the latter.[24] However, doubling both acts and partners produces results that are almost identical to those obtained in the base case. Although many people are likely to engage in twice as many acts of intercourse in 6 months as in 3, few individuals will have twice as many sex partners. Therefore, on balance, we would expect a 6-month follow-up schedule to produce weaker associations than a 3-month schedule.

The simple Bernoulli model used in this analysis is both a strength and a limitation. This transmission model is easily described and manipulated, requires few parameters, has high biologic plausibility, and has been empirically verified in an HIV seroconversion study in Africa.[53,54] However, this simple model omits important STD transmission dynamics, including nonrandom mixing patterns, selective condom use (e.g., with new partners but not with steady partners), sexual contact network characteristics, and concurrent partnerships.[8,55–63] These complexities could introduce unknown errors into the analyses. For example, this analysis might underestimate the utility of a marker STD that "inhabits" the same networks as HIV (this is discussed further below). In addition, there is evidence that the per-act Bernoulli model may underestimate or overestimate risk in some situations.[64,65] These concerns are ameliorated somewhat by the use of the model in the present context, in which *changes* in HIV risk are compared with *changes* in STD risk.

The HIV infectivity values used in the current study, which were estimated from transmission rates for long-term HIV-serodiscordant couples,[29–31] may fail to capture the brief period of very high viral load—and presumably highly elevated infectiousness—that occurs soon after initial infection and before the development of an effective immune response. Predictions from mathematical models suggest that a substantial proportion of all HIV transmission occurs during this brief period of primary infection,[66,67] which lasts a few weeks to several months. During this time, HIV acts more like a high-infectivity STD than a low-infectivity STD. Consequently, the utility of highly infectious STDs as markers for HIV will be greater in situations in which there

is a nonnegligible probability of encountering a partner who was recently infected with HIV—for example, in populations with high partner-change rates. A related issue concerns the facilitative effect on HIV transmission of infection with non-HIV STDs.[68–70] If the same people who are at risk for HIV infection are also at risk for other STDs, which is a fundamental assumption underlying the use of non-HIV STDs as surrogate markers of HIV, then the "effective" infectivity of HIV is likely to be increased in at-risk populations, because of STD in one partner or the other. However, it is not clear how large this "cofactor effect" is likely to be or to what proportion of the population it applies.

Additional limitations of this study include the use of self-reported behavior in the modeling exercise and uncertainty in the HIV and STD infectivity estimates.[29] Notably, the Project Light intervention data were used here to provide a concrete illustration of the relationship between HIV infection risk reduction and STD risk reduction; therefore, slight distortions of the data due to self-reporting bias are of minimal consequence. Although quantitatively the results of the analysis are sensitive to the infectivity estimates, qualitatively the main finding appears robust: namely, that the best marker STD is one with an infectivity near that of HIV. This result was anticipated by Aral and Peterman, who proposed that "for trends in one STD to serve as a good biomarker for another STD, the two STDs need to be identical or very similar" in terms of epidemiologic and other characteristics.[7]

The results of this analysis can be used to guide the selection of STD markers for use in HIV prevention trials. However, they also suggest the need for caution in interpreting the results of trials employing surrogate markers. Transmission of HIV and other STDs is differentially sensitive to such factors as partnership acquisition rates and frequency of condom use. Behavioral changes that affect the incidence of a marker STD might not be the same as those that would reduce the incidence of HIV, and vice-versa. Therefore, the failure to detect a measurable reduction in STD incidence does not necessarily imply that an HIV prevention trial has failed to achieve its stated objective of reducing HIV infection risk.[1] Conversely, interventions that successfully decrease STD incidence could have both direct and indirect HIV prevention benefits: first by reducing participants' behavioral risk and second by diminishing the facilitative effect of STDs on HIV transmission.[71,72]

There also are practical obstacles to the use of STDs as surrogate markers of HIV infection risk. This study assumed perfect diagnosis of incident STDs. Existing diagnostic tests for STDs have imperfect sensitivity and specificity,[11] which would impair the performance of the STD as a surrogate for HIV infection risk. Some STDs are readily curable, so between follow-up visits for a study, a participant might become infected with an STD, experience symptoms, receive treatment, and be cured. If the infection was not detected on the subsequent visit, this would be equivalent to a false-negative test result, which would reduce the performance of the marker STD. Another factor that could influence the performance of an STD as a surrogate for HIV infection risk is the distribution of the STD in the population, compared with the distribution of HIV. If an STD was concentrated in the same subgroups of the population as HIV, its utility as a marker for HIV infection risk would be enhanced, whereas if the STD and HIV had different distributions, the performance of the STD as a surrogate would be diminished. For some STDs, acquired immunity could also affect their performance as markers for HIV.

The current analysis focused on HIV and STD acquisition by individuals rather than on the spread of these pathogens throughout a population. As noted above, dissemination of an STD within a population is affected not only by the behavioral characteristics of the individuals who make up that population but also by such factors as the extent of mixing between different risk strata and nonuniform distribution of infection. Population-level models that take these complexities into account are needed. However, because STDs may be differently affected by various network and population-level factors, caution will be required when interpreting the results of these analyses, just as caution is needed here.

This analysis is a first step toward the goal of identifying a suitable marker STD. Further research is needed to better quantify the infectivity of HIV and other STDs and to develop more sophisticated transmission models to examine the complex relationship between HIV and STD risk reduction.

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