

New Information on the Risks of HIV Transmission in Mwanza, Tanzania

To the Editor—A recent article by Todd et al. provides at least 3 insights into HIV transmission from a 1991–1995 Mwanza trial exploring whether improved treatment of sexually transmitted infections (STIs) can reduce the incidence of HIV infection [1]. Their article also raises a long-unanswered question.

The first insight, which they stressed, is that herpes simplex virus type 2 (HSV-2) appears to have been an important cofactor for HIV transmission through heterosexual coitus. The second insight is that medical injections appear to have contributed to HIV transmission. Using data they report, I calculate a significant association between incident HIV infection and receipt of any injections during follow-up, with an odds ratio (OR) of 1.55 (95% confidence interval, 1.24–1.93) and a crude population-attributable fraction (PAF) of 20.4%. Using their reported adjusted ORs, I calculate an adjusted PAF of 26.6% (finding that 21.3% and 15.4% of incident infections among men and women, respectively, were associated with hospital and clinic injections and that 6.0% and 10.4% of incident infections among men and women, respectively, were associated with injections received elsewhere). Todd et al. missed this second insight by analyzing the association separately for subgroups of case patients and control subjects defined by sex and source of injection, which reduced the statistical power of the tests for association. They also speculated that “[r]everse causation and confounding may partially explain” [1, p. 465] the association. However, adjustment for HSV-2 infection and other variables increased their reported ORs for the incidence of HIV infection associated with injections. Other evidence supports the concept that the injections were not reliably safe; notably, surveys conducted at a random sample of public health facilities throughout the Mwanza region during 1991–1993 reported that supposedly sterile syringes and needles were contaminated at 22%–44% of facilities, that sterilization and storage facilities for sterilized equipment were often inadequate, and that injection procedures were often unsafe [2].

The third insight is that improved treatment of bacterial STIs in the intervention arm of the Mwanza trial very likely cannot explain the reported 38% lower incidence of HIV infection in the intervention arm than in the control arm [3]. Because “reported STI and HSV-2 status were strongly correlated” [1, p. 460], it is likely that HSV-2 was responsible for an important proportion of symptomatic STIs. If so, antibiotics administered to treat symptomatic STIs often had no impact. In this article, Todd et al. reported that HSV-2 infection was associated with 65% of HIV infections among men and 59% among women. Even if these PAFs are inflated because of unadjusted confounding (e.g., for injections), there is likely not enough HIV transmission remaining that is not associated with HSV-2 infection, injections, and/or having an HIV-positive spouse to allow treatment of bacterial STIs to explain the much lower incidence of HIV infection in the intervention arm. It is relevant here that the Mwanza study team hypothesized that the intervention reduced the duration and, thereby, the prevalence of symptomatic STIs.

Finally, Todd et al.’s recent report raises a question: how much of the observed lower incidence of HIV infection in the intervention arm can be explained by the subjects in that study arm receiving safer injections? Notably, the design of the Mwanza trial of the use of STI treatment to reduce the incidence of HIV infection included a de facto injection-safety intervention: in the intervention arm, the project provided benzathine penicillin and sterile injection equipment for treatment of genital ulcers [5]. The authors noted that “[b]efore the … intervention … short acting penicillin and tetracycline were the only antibiotics available” [5, p. 427] — a situation that presumably continued in the control arm throughout the trial. Hence, persons with genital ulcers in the intervention arm who reported to clinics received 1 injection of benzathine penicillin via more reliably sterile equipment, whereas persons with genital ulcers in the control arm likely received more injections via less reliably sterile equipment.

The Mwanza study team reported that the incidence of HIV infection was strongly and significantly associated with reported genital ulcers in the control arm (ORs of 11.1 and 6.7 for men and women, respectively) but not in the intervention arm (ORs of 2.3 and 0.0 for men and women, respectively) [4]. Setting aside issues of cost and time, it would be very difficult for ethical reasons to design a ran-
domized controlled trial of injection safety for the prevention of HIV infection. However, the trial may have already been done. I await data and analyses of the incidence of HIV infection associated with injections in the intervention and control arms of the Mwanza trial separately.

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References

Reply to Gisselquist
To the Editor—As noted by Gisselquist [1], our data confirm the importance of herpes simplex virus type 2 (HSV-2) infection as a risk factor influencing the incidence of HIV infection [2]. The population-attributable fractions (PAFs) that we calculated for rural Mwanza are consistent with those reported in a recent review by Freeman et al. that suggests that HSV-2 infection could be responsible for a substantial proportion of new HIV infections in sub-Saharan Africa [3].

We reported risk factors separately for men and women, because associations differed between the sexes for some factors. Using the same analytical methods as in the article [2], we have reanalyzed the combined data on men and women. Table 1 shows the effects of reported sexually transmitted infection (STI) syndromes and reported injections during the past 2 years, adjusted for sex, age group, residence stratum, treatment arm, HSV-2 serostatus, and the HIV serostatus of the marital partner. There was no confounding by other factors (data not shown). Results are shown both for all 12 communities and for the 6 comparison communities (the control arm) and the 6 intervention communities (the intervention arm) separately.

For all 12 communities, HIV infection was significantly associated with reported injections in hospitals or clinics (odds ratio [OR], 1.81 [95% confidence interval [CI], 1.02–3.19]; P = .04) and in other settings (OR, 2.68 [95% CI, 1.16–6.16]; P = .02), giving an overall PAF of 21%. As was noted previously, this association may be explained partly by confounding or reverse causation.

Assuming that injections were causally related to the risk of HIV infection, Gisselquist postulates that the effect should have been stronger in the control arm than in the intervention arm, because safe injection practices were promoted in the lat-

Table 1. Selected risk factors influencing the incidence of HIV infection in rural Mwanza for both sexes combined, adjusted for age, sex, residence stratum, treatment arm, HSV-2 serostatus, and HIV serostatus of marital partner.

<table>
<thead>
<tr>
<th>Category, parameter</th>
<th>All communities (n = 12)</th>
<th>Comparison communities (n = 6)</th>
<th>Intervention communities (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>P</td>
<td>Value</td>
</tr>
<tr>
<td>Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no.</td>
<td>920</td>
<td></td>
<td>503</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>465 (50.5)</td>
<td>248 (49.3)</td>
<td>217 (52.0)</td>
</tr>
<tr>
<td>Reported an STI syndrome during preceding 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>.2</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>1.44 (0.83–2.50)</td>
<td>2.00 (1.02–3.92)</td>
<td>0.80 (0.28–2.32)</td>
</tr>
<tr>
<td>Reported an injection during preceding 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1</td>
<td>.03</td>
<td>1</td>
</tr>
<tr>
<td>In hospital or clinic</td>
<td>1.81 (1.02–3.19)</td>
<td>1.42 (0.70–2.89)</td>
<td>2.75 (1.03–7.40)</td>
</tr>
<tr>
<td>Elsewhere</td>
<td>2.68 (1.16–6.16)</td>
<td>2.24 (0.81–6.19)</td>
<td>3.97 (0.88–18.0)</td>
</tr>
</tbody>
</table>

NOTE. Data are odds ratios (95% confidence intervals), unless otherwise specified. P values were derived from the likelihood ratio test for differences in odds between categories. STI, sexually transmitted infection.

a Analysis was restricted to 920 subjects with complete data on modeled covariates.
ter during the trial. Table 1 shows that the opposite was the case, with a stronger association seen in the intervention arm than in the control arm, although the difference was not significant (test for interaction, $P = .34$). Estimated PAFs in this analysis were 31% and 17% in the intervention and control arms, respectively. These findings refute Gisselquist’s hypothesis that the impact on HIV incidence observed in the Mwanza trial was the result of improved injection practices in the intervention arm. Because most injections occurred at health facilities, the association between injections and the incidence of HIV infection observed in the intervention arm of this trial was most likely the result of reverse causation, whereby injections are given to treat HIV-related illnesses.

The association between reported STI syndromes and HIV infection shows a different pattern (table 1). After data on men and women were combined, there was no association between reported STIs and HIV infection in the intervention arm after adjustment for HSV-2 serostatus, but in the control arm the effect was large and significant (OR, 2.00 [95% CI, 1.02–3.92]; $P = .04$). These findings are consistent with the hypothesis that curable STIs were an important cause of HIV infection in the control arm, whereas this effect was largely absent in the intervention arm, where syndromic management reduced the duration and, hence, prevalence of curable STIs. Contrary to Gisselquist’s assertion, there was clear evidence that the intervention reduced the prevalence of some STIs, as has been reported previously [4].

Gisselquist points to the high PAFs observed for HSV-2 infection and for injections and questions whether this leaves enough HIV transmission attributable to curable STIs to explain the 38% reduction in HIV incidence observed in the trial [5]. However, PAFs require careful interpretation. It is incorrect to assume that PAFs for different risk factors sum to 100% or that they represent the breakdown of cases caused by different factors [6]. Their use in the analysis of risk factors for infectious diseases is also problematic [7]. The PAFs computed in our analysis represent the individual-level effects that risk factors have on the acquisition of HIV infection among HIV-negative subjects. However, STIs are also known to influence the infectivity of HIV-positive subjects. The population-level effect that an intervention has on an infectious disease may, therefore, considerably exceed that suggested by PAF calculations. Mathematical modeling can be used to project such population-level effects. Detailed models fitted to data from the Mwanza trial have shown that syndromic management at the coverage and clinical efficacy levels reported in the trial could result in a 30% reduction in the incidence of HIV infection, which is only slightly below the observed effect [8].

An important conclusion of the modeling research was that the effect that STI treatment has on HIV incidence would be expected to decrease in mature, generalized HIV epidemics. There is an urgent need for additional interventions to reduce HIV transmission in such settings. In addition to behavioral interventions, other measures that are currently being investigated include circumcision of males, vaginal microbicides, and control of HSV-2 infection. We agree with Gisselquist that measures to ensure the safety of health care practices, including blood transfusions and medical injections, must remain an essential component of all AIDS control programs.

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References

Potential conflicts of interest: none reported.

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