

## Interpretation of the Mwanza and Rakai STI trials

**Editor** – In addition to discussing sexual behaviour aspects of the Mwanza and Rakai trials of interventions against sexually transmitted infection (STIs), Christopher Hudson also raises a number of points relating to STI control in developing countries that warrant further discussion. Hudson states that low prevalences of infection with HIV and herpes simplex virus (HSV), as in Mwanza, may mark the early stages of an HIV epidemic, and that high prevalences of these two viruses indicate a mature epidemic (1). However, data from the Mwanza study population show that the prevalence of HSV-2 antibodies, adjusted for age and sex, is high and very similar to the mature HIV epidemics in Rakai and Masaka referred to by Hudson (2). Also Hudson states that there was no association between HIV and HSV in an earlier study in Durban whereas, in fact, HSV was identified as a significant risk factor for HIV early on in the epidemic, particularly in young women (3).

Hudson suggests that the Rakai trial should in some way be termed the gold standard. However, there are still some points about the Rakai trial that remain uncertain. Firstly, there must be some doubt about whether or not subjects actually took the mass treatment. Antibiotic levels were not tested in either blood or urine. Although medication was administered through direct observation, the question remains whether tablets could have been “pocketed” by study subjects either to be used later on if they became symptomatic or sold as a source of revenue. The cost of 1 g of azithromycin alone at the time of the trial would have been in the region of US\$ 10, more than the weekly wage for the majority of the trial participants. Many of those in the trial would have been in stable monogamous relationships at very low risk of STI and HIV and would see little point in taking unnecessary medication and risking possible side-effects.

Secondly, as Michel Alary points out in the accompanying commentary (4), mobile high-risk individuals may have

been missed in Rakai. Coverage of the study was less than 80%, and one is reminded of the 80/20 rule that states that 20% of the population contributes at least 80% of the net transmission potential of infectious agents (5). If the subjects in the trial did not include these 20% high-risk core group transmitters it would not be surprising that the trial had little effect on STIs and HIV. Furthermore, the treatments took one month per cluster to complete which would have allowed plenty of time for new infections or reinfection from an untreated contact.

Hudson also states that more basic studies should have been done looking at the efficacy of single dose ciprofloxacin and azithromycin in curing chronic gonorrhoea. Differentiation of gonorrhoea into acute and chronic stages is not usually recognized by current STI textbooks and WHO STI treatment algorithms. Chronic gonorrhoea is, however, a common diagnosis in countries of the former Soviet Union and Mongolia where non-specific urethritis/chlamydia has not always been recognized (6). Azithromycin is accepted as an effective treatment for chlamydia.

The point that Hudson raises about behaviour change as a factor in reducing STI prevalence in Mwanza is an important one. While the Mwanza study reported on numbers of sexual partners, it may be that other sexual behaviours not recorded in Mwanza — such as continuing to have sex despite the presence of genital lesions or other symptoms — might be relevant in driving large-scale heterosexual HIV epidemics (7).

What the Mwanza and Rakai studies have shown is that improving STI control for HIV prevention is not straightforward and requires different approaches in different populations. Any search for a “magic bullet” is likely to be a lengthy one and should be viewed with scepticism. Perhaps a return to the basic principles of STI control, involving comprehensive case management to be implemented wherever STI treatments are dispensed, might be a more appropriate overall STI control strategy and one that could be adapted to local conditions. ■

## Nigel O'Farrell

Consultant, Pasteur Suite  
Ealing Hospital, Uxbridge Rd  
London UB1 3HW, England  
(email: ofarrell@postmaster.co.uk)

1. **Hudson CP.** Community-based trials of sexually transmitted disease treatment: repercussions for epidemiology and HIV prevention. *Bulletin of the World Health Organization*, 2001, **79**: 48–58.
2. **Obasi A et al.** Antibody to herpes simplex virus type 2 as a marker of sexual risk behaviour in rural Tanzania. *Journal of Infectious Diseases*, 1999, **179**: 16–24.
3. **O'Farrell N, Windsor I, Becker P.** Risk factors for HIV-1 in attenders at a sexually transmitted diseases clinic in Durban, South Africa. Paper presented at Sixth International AIDS Conference, June 1990, San Francisco (Abs FC 604).
4. **Alary M.** More community-based trials of STD control or more appropriate interventions: which is the priority for preventing HIV-1 infection in developing countries? *Bulletin of the World Health Organization*, 2001, **79**: 59–60.
5. **Woolhouse ME et al.** Heterogeneities in the transmission of infectious agents: implications for the design of control programmes. *Proceedings of the National Academy of Science*, 1997, **94**: 338–341.
6. **O'Farrell N.** *Mission report on visit to Mongolia, Dec 1998.* Manila, WHO Regional Office for the Western Pacific (unpublished document).
7. **O'Farrell N et al.** Sexual behaviour in Zulu men and women with genital ulcer disease. *Genitourinary Medicine*, 1992, **68**: 245–248.

## Interpretation of the Mwanza and Rakai STD trials

**Editor** – There has been considerable discussion of the contrasting results of the Mwanza and Rakai trials of interventions against sexually transmitted diseases (STDs). The Mwanza trial showed that improved STD treatment services as recommended by WHO led to a 38% reduction in HIV incidence (1), while in the Rakai trial mass treatment for STDs failed to reduce HIV infection (2). Several thoughtful reviews have discussed these findings, and in June last year scientists from the two trials combined forces to present their views (3). A number of explanations have been put forward: STDs may play a less important role in HIV spread in mature HIV epidemics; incurable STDs,

including herpes, may have been more common in Rakai; and rounds of mass treatment in Rakai may have been followed by rapid reinfection.

In a recent contribution to the *Bulletin*, Dr Hudson puts forward an alternative view (4), arguing that the trial results failed to demonstrate that STD treatment reduces HIV transmission, and that the HIV effect seen in Mwanza was due instead to behavioural change. Unfortunately, while we welcome open debate, we do not think Hudson's paper will do much to illuminate the present controversy, since most of his assertions are inconsistent with published data.

Hudson argues that the HIV effect in Mwanza could not have been due to improved STD treatment because the effect on STDs was only "modest". However, the prevalence of symptomatic urethritis was cut by half, and newly acquired syphilis by at least 40% (5). The prevalence of chancroid was not measured, but the syphilis data suggest that the prevalence of genital ulcer disease (GUD) was reduced very substantially. There is now overwhelming evidence that GUD plays a key role in HIV spread in Africa, and it seems very likely that the reduction in GUD in Mwanza made an important contribution to the observed decrease in HIV incidence. Interestingly, the Rakai intervention had no effect at all on newly acquired syphilis. The reported effect on syphilis refers to the prevalence of positive serology, and this fell due to treatment of positives at mass treatment rounds. However, most of these were low titre cases, probably representing latent infections that are of little relevance to HIV transmission.

Hudson suggests the HIV impact in Mwanza resulted from behavioural change due to counselling of STD patients at clinics or to information campaigns in the villages. The latter focused on informing the community about the improved treatment services, and it seems very unlikely that this would have had a measurable effect on sexual behaviour. Hudson identifies one variable in the published data that seems to show a difference between the intervention and comparison communities in women, but this is an isolated and non-significant finding and is not borne out in other variables or in men. The overwhelming impression from the many behavioural variables examined was that there was no difference

between the trial arms. Promoting sexual abstinence or condom use until treatment is complete is an important component of STD case management. However, the idea that this could have a substantial impact on the overall level of HIV transmission in the community, even if some patients were in the viraemic phase of primary HIV infection, seems fanciful. Moreover, condom uptake in these rural areas at the time of the trial was extremely low, despite counselling, and only 0.9% of STD patients accepted free condoms.

Finally, Hudson misinterprets recently published data from Mwanza on population-attributable fractions (PAF) of HIV due to symptomatic STDs (6). The fact that in the comparison arm 40% of HIV seroconversions in men were attributable to self-reported STD syndromes, but only 12% in the intervention arm, strongly supports the hypothesis that reductions in symptomatic STDs led to a reduction in HIV. Calculations show that this difference would explain nearly 80% of the observed effect on HIV (6). The striking contrast between the strong association of GUD and HIV in the comparison arm (OR = 14.8) and lack of association in the intervention arm (OR = 1.1) is very difficult to explain other than through an effect of treatment on GUD duration and hence on HIV acquisition. Data from Rakai showed a much lower PAF due to treatable STDs.

Hudson suggests a trial of counselling of STD patients alone versus counselling and improved STD treatment. This is ethically unacceptable as it would mean actively withholding care for harmful infections from patients attending improved facilities in the control communities.

Drs O'Reilly & Gerbase, in their accompanying commentary (7), stress that STD treatment is not a "magic bullet", but one of many approaches needed for HIV prevention. We fully agree. As stated in the original Mwanza report: "Educational interventions, aimed at modifying risk behaviour ... remain an important priority for national AIDS control programmes. However, our results suggest the importance of complementing these activities with improvements to STD treatment services" (1). That STDs are an important risk factor for HIV transmission is beyond question. Effective STD management has been identified as

a fundamental component of primary care, not only because of the effect of STDs on HIV but their many other adverse effects. While continuing to promote behavioural change, AIDS control programmes must continue to ensure that this basic provision is available to all. ■

### Richard Hayes

Professor of Epidemiology and International Health

### Heiner Grosskurth

Senior Lecturer in Infectious Disease Epidemiology

### David Mabey

Professor of Communicable Diseases  
London School of Hygiene and Tropical Medicine,  
Keppel Street, London WC1E 7HT, England  
(email: richard.hayes@lshtm.ac.uk)

1. Grosskurth H et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet*, 1995, **346**: 530–536.
2. Wawer MJ et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. *Lancet*, 1999, **353**: 525–535.
3. Grosskurth H et al. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet*, 2000, **355**: 1981–1987.
4. Hudson CP. Community-based trials of sexually transmitted disease treatment: repercussions for epidemiology and HIV prevention. *Bulletin of the World Health Organization*, 2001, **79**: 48–58.
5. Mayaud P et al. Improved treatment services significantly reduce the prevalence of sexually transmitted diseases in rural Tanzania: results of a randomised controlled trial. *AIDS*, 1997, **11**: 1873–1880.
6. Orroth K et al. Syndromic STD treatment reduces the proportion of incident HIV infections attributable to these diseases in rural Tanzania. *AIDS*, 2000, **14**: 1429–1437.
7. O'Reilly KR, Gerbase AC. STI care: one of many necessary approaches for prevention of HIV infection. *Bulletin of the World Health Organization*, 2001, **79**: 58–59.