

# Community-based trials of sexually transmitted disease treatment: repercussions for epidemiology and HIV prevention

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This paper reviews the scientific basis for trials exploring the relation between sexually transmitted diseases (STDs) and human immunodeficiency virus (HIV) infection in Mwanza in the United Republic of Tanzania and Rakai and Masaka in the Republic of Uganda. The importance of a study's location and explanations for the divergent results of these trials are discussed. The modest effect on STDs seen in the trial of syndromic management in Mwanza, in contrast to the 38% reduction in the incidence of HIV, casts doubt on the underlying hypothesis that treating STDs alone slows the transmission of HIV-1. According to the Piot-Fransen model, the trial in Rakai, which offered treatment of STDs to all subjects irrespective of symptoms ("mass" treatment), should have been more effective both in reducing the prevalence of STDs and the incidence of HIV. However, the Rakai trial was stopped because there was no difference in the incidence of HIV between the intervention and control arms.

If Mwanza is seen as the trial that needs explaining, another paradigm becomes relevant. In rural East Africa, where all trials have been conducted, networks of concurrent sexual partnerships are a source of infection with both STDs and HIV. Because of their shorter latency periods, STDs may prompt attendance at a clinic before the early signs of HIV-1 infection appear. Part of the management of STDs is to recommend abstinence or the consistent use of condoms until treatment is completed. This recommendation may cover the earliest period of viraemia during primary HIV-1 infection. This paradigm appears to explain the results from Mwanza and Rakai, emphasizing behavioural aspects of syndromic management.

**Keywords:** sexually transmitted diseases, complications; HIV, transmission; HIV infections, therapy; comorbidity; randomized controlled trials; Republic of Uganda; United Republic of Tanzania.

**Mots clés:** maladies sexuellement transmissibles, complications; VIH, transmission; infections à VIH, thérapeutique; comorbidité; essai clinique randomisé; Ouganda; République-Unie de Tanzanie.

**Palabras clave:** enfermedades sexualmente transmisibles, complicaciones; infecciones por VIH, transmisión; infecciones por VIH, terapia; comorbilidad; ensayos controlados aleatorios; Uganda; República Unida de Tanzania.

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## Introduction

In many ways, the public health response to AIDS has been more "scientific" than the responses to other diseases. The epidemic has coincided with moves towards practising evidence-based medicine and the now dominant use of randomized controlled trials in medical research. Thus, it would have been surprising if randomized trials of treatment for sexually transmitted diseases (STDs) had not been performed in the search for a better understanding of

HIV transmission. There were specific reasons (1–3) why the two trial trials exploring the relation between STDs and HIV infection in Mwanza in the United Republic of Tanzania, and Rakai in the Republic of Uganda, were conducted (4, 5). However, there was no expectation that the results would diverge. An additional, similar trial will soon be completed in Masaka, Uganda, but this was planned long before publication of the divergent findings.

In Mwanza, the trial of STD treatment produced a 38% reduction in the incidence of HIV-1 infection despite there being only a modest effect on infection with STDs; in Rakai a trial of mass treatment of STDs produced no effect on the incidence of HIV-1 infection but there was a more

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marked, but still modest, effect on the incidence of STDs compared to Mwanza (3). Although more trials are planned or in progress, this paper argues that the Mwanza and Rakai trials provide enough information to revise the paradigm of the interaction between STDs and HIV. Because basic science and observational studies have already been comprehensively reviewed (3), this analysis focuses on the trials and discusses scientific method, the prevention of HIV transmission, and syndromic management.

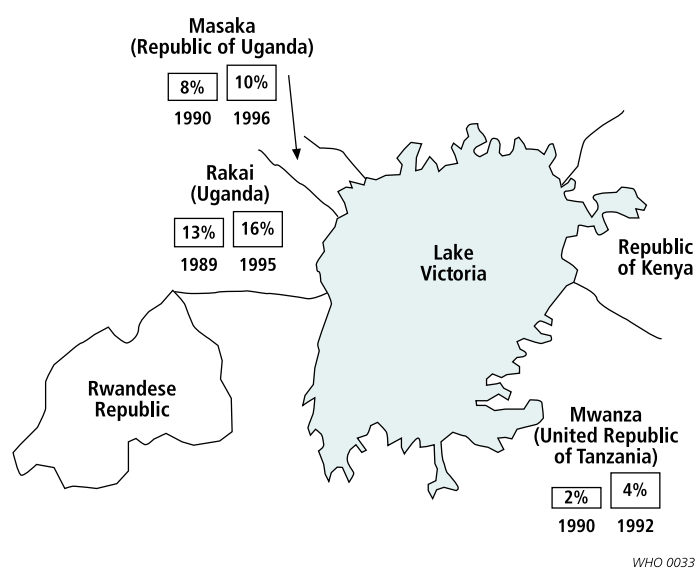
## Mwanza, Rakai and Masaka: three trials in East Africa

Between late 1989 and mid-1993 three randomized trials were designed to look at the interaction between STDs and HIV at the population level (2). The Mwanza trial began in 1992 and the other two — taking place less than 300 km away (Fig. 1) — started before the results of the Mwanza trial had been published.

The trial of improved syndromic management of STDs in Mwanza was designed to discover whether, at a population level, individuals infected with STDs are more likely to become infected with, or transmit, HIV (1) and to answer the practical question of how to improve the management of STDs in developing countries (2). The trial in Rakai was also a biomedical trial — that is, there were no new behavioural interventions. The authors did not try to improve the management of STDs but instead sought to determine whether providing mass treatment in communities where there was a high incidence of HIV transmission, such as roadside settlements, has a beneficial effect on rates of infection with STDs and the incidence of HIV infection. The third trial, in Masaka, compares the effect of health education alone with a “Mwanza plus” package (syndromic management of STDs plus health education) (2).

The hypothesis of the Mwanza trial was that inflammation associated with a symptomatic STD increased both infectiousness (person with STD and HIV positive but partner HIV negative) and susceptibility (person with STD and HIV negative but partner HIV positive). There was an impressive body of mostly epidemiological evidence at the time the Mwanza trial was designed (1). Recently, substantial basic science data have also accumulated (3). However, the hypothesis underlying the Rakai trial — that asymptomatic carriage of a bacterial STD has a similar effect on HIV transmission — is based on very limited evidence, at least in men. In women, data on the association between an asymptomatic STD and infectiousness is mostly qualitative (6, 7); additionally, data on viral load in genital secretions (8) are not as clear as data on men with a symptomatic STD (9). The scientific basis for the Masaka trial was the same as for Mwanza, with the added hypothesis that synergy exists when efforts to change sexual behaviour are conducted simultaneously with improved management of STDs.

Fig. 1. Geographical location of the three major sexually transmitted disease/acquired immunodeficiency syndrome prevention trials and HIV prevalence in these locations. The HIV prevalence is the first available prevalence estimate from a community-based study and the baseline survey for the intervention trial



## Design and trial implementation

The designs of the three trials in East Africa are compared in Table 1 and baseline data (10–13) are shown in Table 2. The trials in Mwanza and Masaka had input from researchers based at the London School of Hygiene and Tropical Medicine. It is therefore not surprising that these two trials are similar in design, and hopefully the results may be pooled for a meta-analysis. The Rakai and Masaka trials evolved independently despite being conducted in adjacent districts (Fig. 1), starting in the same year, and having head offices that are less than 100 m apart (at the Uganda Virus Research Institute in Entebbe). Attempts to tabulate results of the trials in a comparative way have been hampered by the lack of common indicators other than HIV prevalence and incidence (8, 12). Even the approach to syphilis serology testing has been different: the Rakai trial used the toluidine red unheated serum test (TRUST test) for screening and then the *Treponema pallidum* haemagglutination assay (TPHA) for confirmation, whereas the Mwanza study used the rapid plasma reagin (RPR) and TPHA tests on all specimens.

## Can results be compared?

Table 3 shows those results from Mwanza and Rakai that are directly comparable. The prevalence of active syphilis at the end of each study is shown: it is the most relevant public health measure. Table 2 includes both old cases and treated cases with low titres, thus giving a better picture of the history of syphilis in each population (14). The burden of syphilis was similar at the three trial sites at the start of the trials. Table 3 shows that the similarity in prevalence in Mwanza and Rakai persisted throughout the studies.

Table 1. Design of the three major community-based trials of sexually transmitted disease treatment in East Africa

| Characteristic                              | Clinical trial                                   |   |   |
|---|--|---|---|
|   | Mwanza (2, 4)                                    | Rakai (2, 5)                            | Masaka (2)  |
| Intervention (all trials had a control arm) | Improved management of STD                       | Mass STD treatment at each survey round | IEC <sup>a</sup> (one arm) and IEC plus syndromic management <sup>b</sup> |
| Units of randomization                      | 6 pairs of clinics                               | 5 pairs of communities                  | 6 pairs of clinics <sup>c</sup>   |
| Cohort for evaluation                       | 1000 adults per catchment area (random sampling) | All adults in selected communities      | All adults in villages near clinics                                       |
| Type of cohort                              | Closed (newcomers not included)                  | Open (newcomers included)               | Closed  |
| Follow up interval                          | 2 years  | 2 periods of 10 months                  | 2 periods of 18 months  |

<sup>a</sup> Information, education and communication.

<sup>b</sup> Treatment regimens are similar to those used in Mwanza.

<sup>c</sup> As there are three arms (two intervention and one control) in the Masaka trial, clinics were matched in triplets but analysis will be within pairs, e.g. IEC intervention clinic versus control clinic summed over 6 pairs of clinics.

Table 2. Baseline data for the three trials in East Africa

| Characteristic                           | Sex    | Clinical trial  |           |                 |
|--|--------|-----------------|-----------|-----------------|
|  |        | Mwanza (4, 8)   | Rakai (5) | Masaka (8, 10)  |
| Age range                                |        | 15–54           | 15–59     | ≥ 13            |
| Participation                            | male   | NA <sup>a</sup> | NA        | 64              |
|  | female | NA              | NA        | 75              |
| HIV prevalence (%)                       | male   | 4               | 14        | 9               |
|  | female | 4               | 19        | 11              |
| Herpes simplex virus type 2 serology (%) | male   | 12              | 31        | 57 <sup>b</sup> |
|  | female | 36              | 61        | 74 <sup>b</sup> |
| Syphilis <sup>c</sup> (%)                | male   | 8               | 10        | 11              |
|  | female | 9               | 10        | 11              |

<sup>a</sup> Not available (85% both sexes combined in Mwanza).

<sup>b</sup> Data from a rural area of Masaka district not in the trial and using Western blot analysis (11) instead of enzyme-linked immunosorbent assay (ELISA) (other two studies).

<sup>c</sup> RPR<sup>+</sup>/TPHA<sup>+</sup>, except for Masaka (RPR<sup>+</sup>/TPHA outstanding); TPHA, *Treponema pallidum* haemagglutination test (specific test); RPR, rapid plasma reagin (non-specific test).

Table 2 and Table 3 highlight the importance of measuring several STDs to gain a picture of the stage of the HIV epidemic. Although rates of syphilis appear to have been similar in Mwanza and Rakai for some years, the relatively low prevalence of infection with HIV and herpes simplex virus type 2 (HSV-2) in Mwanza may mark the early stages of an HIV epidemic, and the high prevalence of these two viruses in Rakai may indicate a “mature” epidemic. The high prevalence of HSV-2 infection in Masaka, albeit measured by a now out-of-date methodology and only in two villages (11), indicates that Masaka and

Rakai are at a similar stage of the epidemic. This is borne out by the similarity in mortality from HIV-related causes (15, 16). In Mwanza the lower mortality among HIV-positive adults and lower awareness of AIDS deaths in the general population corroborate the assessment of the area as being in the early stages of an epidemic (17). However, the incidence of HIV and the prevalence of urethritis in the control arm of the study were half that found in Rakai, indicating that the potential for a large epidemic is limited.

## Reconciling Rakai with Mwanza: conventional wisdom

Although comparing results from Mwanza and Rakai has been difficult, there is no mistaking that there was no difference in HIV incidence between the intervention and control communities in Rakai and there was about a 40% reduction in Mwanza. Most commentators on these studies believe that Mwanza is the gold standard and the Rakai results must be “explained” (3, 18). The issues raised in the most recent review (12) are discussed here.

Without doubt a major reason for the discrepant findings was the stage of the epidemic at the different study sites. The data from Rakai (19) confirm earlier predictions (20, 21) that the role of STDs in HIV transmission in the late stages of epidemics will be small compared to transmission in HIV-discordant couples (one partner HIV positive and the other HIV negative). Also associated with the stage of the HIV epidemic is the rise in HSV-2 infection (22) and, on the basis of serological testing, this common cause of genital ulcer disease would now appear to be a risk factor for HIV infection in Africa (23, 24). However, it could be that infection with HIV promotes transmission of HSV-2 (25) rather than the other way around. Although the viral load of HIV-1 rises when there are also ulcers caused by HSV-2 (26), those who have ulcers might abstain from sex once the lesions become painful sores. One study showed that there was no association between infection with HSV-2 and HIV, but an earlier survey at the same clinic found that there was an association (27). It may be that, like syphilis (22), the epidemiology of HSV-2 and HIV-1 diverge once a high HIV-1 prevalence/low HIV-1 incidence state has been reached at the population level. This is in keeping with findings from two villages in Masaka where there was no incidence of HIV-1 infection despite a high incidence of HSV-2 infection (11).

The lack of difference in treatment effects between men and women in the two trials (5, 28) is evidence that HSV-2 infection (note the large sex differences in serology in Table 2) and bacterial vaginosis did not act as confounders. The increased risk of HIV associated with bacterial vaginosis (if it is a genuine effect) is thought to operate by increasing susceptibility in women (29). However, among pregnant women in Rakai, in whom prevalence of bacterial vaginosis was 39% in the intervention group

and 53% in controls, HIV-1 incidence was higher in women in the intervention group despite the significantly reduced incidence of bacterial vaginosis (5). The high rate of bacterial vaginosis in Mwanza (12) also militates against the idea that this condition contributes to the difference between the trials.

A major difference between the two trials was the way symptomatic STDs were managed. However, a high proportion of study participants in Rakai had symptomatic STDs (Table 3). If STDs have an important role in HIV transmission during chronic HIV infection (as opposed to acute primary HIV infection) some effect would have been expected in Rakai, provided reinfection rates were small. Wawer et al argued that reinfection is unlikely to be a sufficient reason for the negative findings of HIV incidence (5). Furthermore, reinfection is likely to have been a problem in Mwanza, given that only 25–35% of index patients referred their partners for STD treatment (30, 31). Finally, while the small population attributable fraction (PAF) for STDs in HIV transmission in Rakai (32) is consistent with the negative result, the difference in the PAF in Mwanza between the intervention and control arms is only half the observed treatment effect (28). If the effect of the intervention in Mwanza had been mediated solely through treatment of STDs, the absolute difference in the PAF between treatment arms (23%) should have been similar to the effect on incidence of HIV-1.

The final explanation commonly given for the discrepant trial results is chance (8, 12). This relates to the imprecision of the estimates of intervention effect (the 95% confidence intervals), which in turn relate to sample size, study design, and imbalance of risk factors or prevalence of HIV and STDs in intervention-comparison pairs at baseline (matching of communities). The Rakai trial could have used six community pairs as in the other two trials but the awkward shape and topography of the region made this difficult. The reason for wide confidence intervals in the trials was the imbalance between the trial arms at baseline, which may have had a greater effect than originally thought (33). However, we should be wary of ascribing differences to chance just because the results of both trials conflict with the original hypotheses.

## Mwanza and causality

The hypothesis of the Mwanza trial was that infection with an STD makes it easier for HIV to be transmitted. In the terminology of Rothman (34), STDs are intermediaries in the causal pathway of infection (Fig. 2). For individuals to become infected with HIV through sexual exposure they must have sexual contact with someone who is infected (the “necessary cause”). The risk of transmission is increased if a co-factor (the “component cause”) is present. However, there may be more than one component cause that, when combined with exposure, results in inevitable transmission (so that “sufficient cause” is met). This model suggests that an intervention aimed at an

Table 3. Results from the Mwanza and Rakai randomized clinical trials<sup>a</sup>

| Characteristic   | Clinical trial |                |                          |
|--|----------------|----------------|--------------------------|
|  |                | Mwanza (4, 13) | Rakai (5)                |
| Follow-up syphilis prevalence (%) (TPHA <sup>+</sup> , RPR > 1/4) <sup>b</sup> | Intervention   | 5.0            | 5.6                      |
|  | Control        | 7.0            | 6.8                      |
| Urethritis symptoms in year prior to follow-up visit (%) <sup>c</sup>          | Intervention   | 1.8            | 6.4                      |
|  | Control        | 3.2            | 5.7                      |
| Follow-up prevalence of urethritis (%) <sup>d</sup>                            | Intervention   | 1.6            | 3.2                      |
|  | Control        | 2.5            | 5.2                      |
| Annual HIV incidence (%)   | Intervention   | 0.6            | 1.3 and 1.8 <sup>e</sup> |
|  | Control        | 0.9            | 1.3 and 1.8 <sup>e</sup> |

<sup>a</sup> Indicators are those that allow direct comparison between the two trials, i.e. same or similar laboratory test performed or question asked and results presented on the same population group.

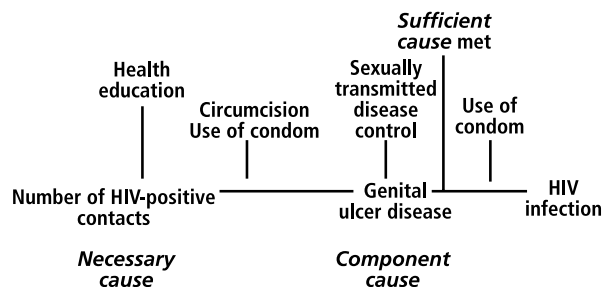
<sup>b</sup> TPHA, *Treponema pallidum* haemagglutination test (specific test); RPR, rapid plasma reagin (non-specific test).

<sup>c</sup> Previous 10 months in Rakai trial.

<sup>d</sup> As measured by leucocyte esterase dipstick testing of urine. This was done for all men in Mwanza and a sub-sample in Rakai.

<sup>e</sup> The two follow-up periods have been listed separately. Overall incidence was 1.5%.

Fig. 2. Causal pathway for HIV infection



intermediary in the causal pathway must be more effective in eliminating that co-factor than in reducing the occurrence of the disease. In other words, Mwanza should have achieved a greater reduction in STD rates than in HIV incidence (35, 36).

Some may argue that after adjusting for baseline differences, a 49% reduction was achieved in the prevalence of symptomatic urethritis, and this is greater than the 38% reduction in HIV incidence. There are four responses to this. Firstly, the concept of causality implies large differences in the observed effect between the intermediary and the end result. Secondly, the reduction in urethritis was only a reduction relative to the control arm: the absolute prevalence went up when compared with baseline (37, 38). Thirdly, the basic scientific evidence for STD as a co-factor is for gonorrhoea (9), so symptomatic urethritis may not be the best measure. Some would add trichomoniasis to gonorrhoea on the list of causes of urethritis that affect HIV transmission (39).



Fourthly, the epidemiological evidence has always been stronger for genital ulcer disease as a co-factor, and the effect on this was modest.

### Mwanza: miracle or mirage?

Why did Mwanza work? There may be two answers: behaviour may have changed in relation to STD episodes and there may have been a decrease in the number of sexual partners. The Mwanza team may have missed a significant difference in sexual behaviour at follow-up by only interviewing a sample of 1 in 8 participants (40) and by only succeeding in interviewing 68% of those selected (28). Although the trial results were adjusted to account for differences in baseline variables (4), they could not be adjusted for important behavioural variables. It is possible that information campaigns in communities in the intervention arm resulted in women refusing new sexual partners. At baseline, 13% of women in the intervention group reported having had two or more sexual partners in the last year compared with 9% at the end of follow-up (4). In contrast, the proportion of women reporting two or more partners in the last year doubled in the control group from 7% at baseline to 14% at follow-up.

The rise in the number of partners may explain the apparent increase in the prevalence of STDs during the trial. Sexual behaviour in women, although under-reported, may be the most useful indicator of a population's risk of HIV (20, 41). It may have been the worsening economic circumstances in Mwanza (8) that put the population at increased risk. Alternatively, urban men may have begun seeking rural partners as a result of the visibility of AIDS in towns and the perception that rural areas had less of a problem (20). A study of factory workers in Mwanza town found that 79% knew someone infected with HIV (42); in the rural areas covered by the Mwanza trial only 7 of 73 deaths occurring among HIV-infected adults were recognized by relatives as being associated with HIV (17).

While sample size calculations were based on an annual estimate of HIV incidence of 1% (40), this assumed that HIV prevalence was destined to rise. In fact, as elsewhere in rural Africa (43), prevalence might have stabilized at 4% with a low incidence but for the changes in behaviour suggested above. Between 1989 and 1991, antenatal seroprevalence remained stable in Mwanza town (44), and trends in rural areas generally follow those in towns after a 2–3 year delay (45). The Mwanza researchers could have tested the hypothesis that treatment effect depended on an increase in unsafe behaviour in the control group by seeing if the intervention pairs that showed the largest effect were those initiated last (the trial used a staggered introduction of pairs).

The Mwanza trial could have failed if all communities had lived in roadside settlements, as

they did in Rakai. Fig. 3 shows the small impact of the intervention in the pair of roadside communities in Mwanza compared with the other community pairs (30). It seems that it is most difficult to intervene successfully in roadside communities, which are some of the most vulnerable and convenient communities in which to intervene (20). The benefit of intervening in roadside settlements may be felt chiefly in adjacent rural areas (20).

### The Piot–Fransen model

The Piot–Fransen model (2) is shown in Fig. 4. This presents the burden of disease in a community, the proportion of infected individuals that are symptomatic, the proportion of these that seek care, and the proportion that receive appropriate care. If asymptomatic STDs are important in HIV transmission it is clear that the Mwanza trial would never have succeeded. However, if only symptomatic STDs have effects as co-factors, the main concern should be the small number of symptomatic patients who are correctly treated. In a post hoc assessment of the Mwanza intervention it was concluded that only 38% of participants in the intervention arm would have been cured (46).

The basis for the Rakai trial was the Piot–Fransen model and the assumption that asymptomatic STDs have at least some effect in increasing HIV transmission. Rakai was a negative trial in terms of offering mass treatment as an intervention against STDs and in terms of preventing HIV transmission. With the exception of pregnant women (47), the effect on STD prevalence was marginal or, in the case of trichomoniasis, unimportant from a public health perspective (48). The widespread occurrence of asymptomatic urethral infections in men in Africa (39, 49) is in keeping with the view that repeated cycles of infection followed by imperfect treatment result in partial acquired immunity (50). The efficacy of mass treatment of STDs may depend on drug bioavailability in genital sanctuary sites (such as the prostate), and this may be impaired when there is minimal inflammation as a consequence of partial acquired immunity or the presence of scar tissue. Greater vascularity during pregnancy, with consequent drug penetration of genital mucosa, could perhaps explain the efficacy of the trial in pregnant women in terms of STDs.

### Is Rakai the gold standard?

When a trial fails to show a significant result there are a number of possible explanations: the hypothesis could have been faulty; the location of the study could have been inappropriate; the study could have been poorly designed; or the study could have inadequate statistical power. In the Rakai study, the hypothesis would appear to be faulty, and cure rates for ciprofloxacin and azithromycin were assumed rather than proven. The

decision to run the trial in an area where there is a “mature” epidemic — that is, one in which the incidence is low relative to the prevalence — has been heavily criticized. However, this scenario occurs in much of Africa, and thus this sort of trial could prove relevant to those making policy decisions, particularly in countries using azithromycin as preventive treatment for trachoma among the population.

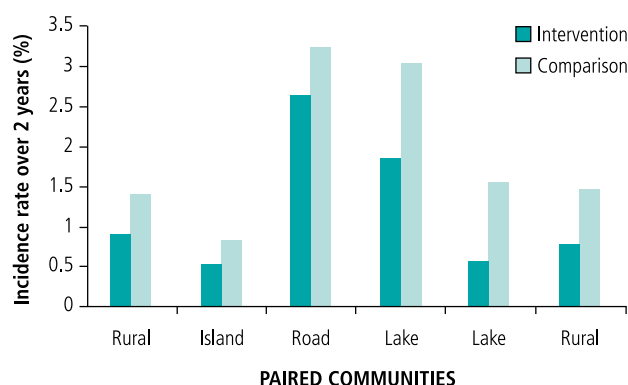
The proximity of the Masaka trial and the possibility of contamination from their information, education, and communication programme and improved STD treatment arms, in addition to the presence of a Médecins du Monde programme in Kakuuto county (51) — one of the areas included in the Rakai trial — have never been discussed. However, as pointed out by the Rakai researchers (5), few participants seemed to have used appropriate STD treatment services, and there was no evidence of behaviour change. The latter negative finding may be due to the difficulty of capturing “sexual networking” using brief questionnaires; a comparison of two other studies in Rakai found a decrease in the extent of sexual networking over time (52, 53).

The design of the Rakai trial can be faulted for having intervention and control communities that were geographically too close together and for the fact that it did not include rural villages near to the study communities; these could have been a source of reinfection with STDs. The incidence of reinfection might also have been reduced if the interval between survey rounds had been shorter. However, as the Rakai researchers argued, reinfection is unlikely to have been a major factor (5). A better comparison of Mwanza, Masaka, and Rakai would have been possible if the Rakai trial had analysed data as a closed cohort study (excluding people seen in the second round who were not treated in the first). However, the negative outcome was not a case of missing a potentially significant difference (there is no problem with the study power): the trial was stopped early because incidence of HIV-1 was identical in both arms in both follow-up periods and the rate ratio was near 1 in all subgroup analyses (5). To be fair, the study could not have been performed to a higher standard.

## Reconciling Mwanza with Rakai: a new hypothesis

Could the confusion over Mwanza and Rakai be a consequence of seeing Mwanza as the gold standard? New possibilities emerge if we regard Mwanza as the trial with the inherent contradiction (having more effect on HIV than STD) and Rakai as the trial with the expected result (no evidence for a role of asymptomatic STDs in increasing HIV transmission). There is evidence that roadside settlements in rural East Africa are the conduit by which both STD and HIV reach remote villages (20); there is also compelling evidence that sexual networking involving concurrent partnerships also acts as a conduit

Fig. 3. HIV seroconversion over two years in six paired communities, Mwanza Region, United Republic of Tanzania



Source: ref. 22

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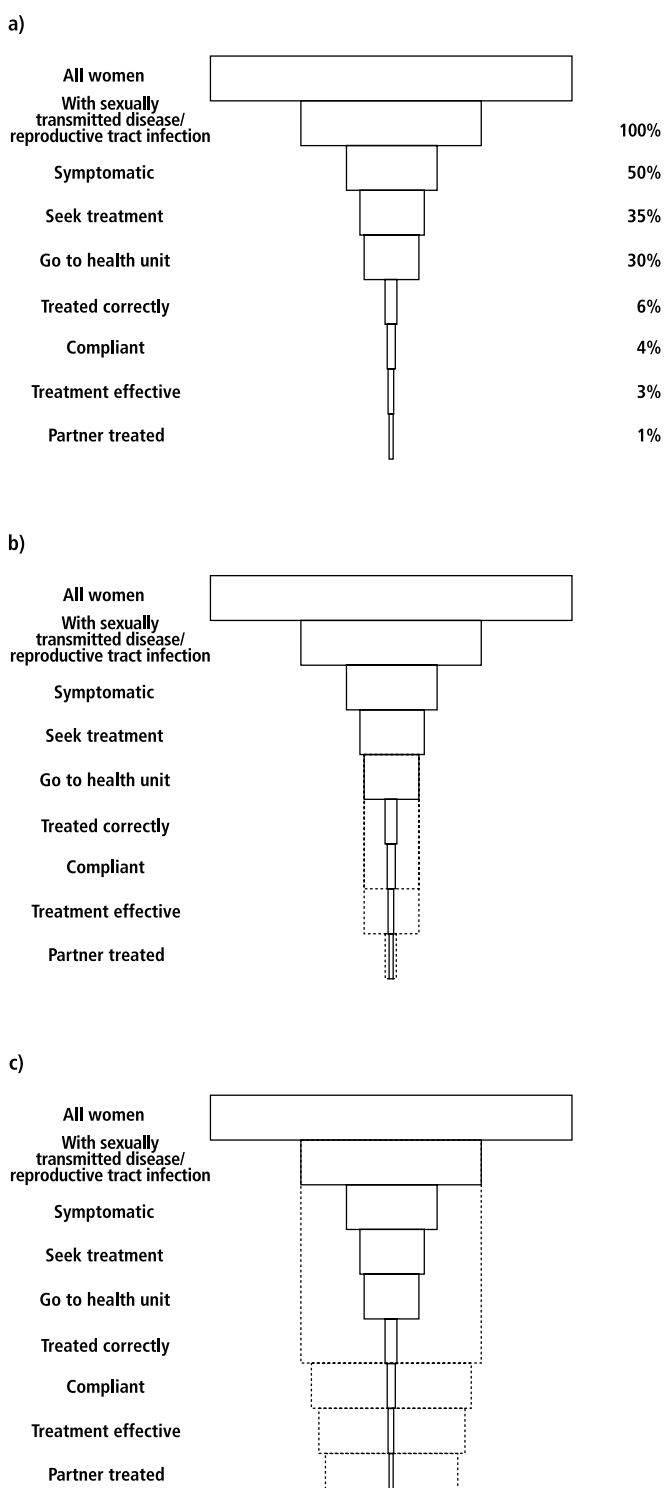
(52–54). Men living in villages regularly visit roadside settlements and have sex with women there before returning to their steady partner or partners. If these sexual networks are the source of both STD and HIV then some people will contract both at the same time (Fig. 5). Due to their shorter latency periods, STDs may prompt clinic attendance before the viraemia of primary HIV-1 infection is apparent; this is believed to be the force driving the epidemic in Africa (20).

Part of the management of STDs is to recommend abstinence or the consistent use of condoms until treatment is completed. This recommendation may cover the earliest period of viraemia during primary HIV-1 infection. However, the infected individual may have transmitted an STD to one or more partners before seeking treatment, ensuring that STD prevalence remains high and HIV-1 incidence is lower. This explanation of the Mwanza trial also shows why the groups who benefited most from the intervention were women aged 15–24 and men aged 25–34 (4); these are the groups most involved in sexual networking (20).

In both the Mwanza and Rakai trials there was a strong association between HIV transmission and genital ulcer disease among men who were HIV-negative at baseline and who later seroconverted (28, 32). Ulcers could be a marker for primary HIV-1 infection (55). It is possible that pathogen-negative urethritis is also a symptom of primary HIV-1 infection (56), and in one African study of couples discordant for HIV infection 2 of 4 seroconversions in men were associated with urethritis that responded to monotherapy with co-trimoxazole, which is an inadequate therapy (57). Thus, associations between the incidence of HIV-1 and symptoms in men but not women (28) may reflect differences in manifestations of primary HIV-1 infection.

Abstinence during episodes of genital ulcer disease not only diminishes transmission during some cases of primary HIV-1 infection but also reduces transmission from individuals with advanced HIV-1 infection who may have pathogen-negative ulcers (58). Awareness of secondary syphilis as an STD may result in abstinence during episodes of

Fig. 4. Piot–Fransen models for sexually transmitted diseases



Note  
 a) Piot–Fransen model of sexually transmitted disease management in rural women. The figure shows sexually transmitted disease/reproductive tract infection prevalence in the community, the steps needed to ensure effective treatment, and the percentage of sexually transmitted disease/reproductive tract infections effectively treated. Data are illustrative and based on studies in Uganda, Zaire, and the United Republic of Tanzania. b) Piot–Fransen model showing potential effect of syndromic sexually transmitted disease treatment services. c) Piot–Fransen model showing potential effect of mass STD treatment.

Source: ref. 2.

rashes, which are known to be associated with transient, high titres of HIV-1 and disease progression (59). The role of brief episodes of viraemia in

HIV-1 transmission should not be underestimated: in one small study the only marker of transmission risk in discordant couples was raised concentrations of suppressor T-cells (60). This finding was interpreted by the authors as indicating that there had been a recent episode of viraemia in the index case which had been controlled but not before transmission had taken place.

### Rakai and the interaction between primary HIV-1 infection and STDs

In the Rakai trial mass treatment would have occurred at all possible stages of the scenario illustrated in Fig. 5. If a man received treatment while incubating both an STD and HIV, his partner would have been protected from contracting the STD but she could still have been infected with HIV-1. If he received treatment after developing and transmitting an STD then the scenario described in Fig. 5 would apply, except that the woman would have been treated and would have no increased susceptibility at the time of her partner's viraemia. Thus, the incidence of HIV could remain high even though the incidence of STDs decreased.

### Lessons for epidemiology

The first lesson from Mwanza and Rakai is to be sure of your hypothesis before conducting a trial. More basic scientific studies should have been conducted on asymptomatic STD infection and HIV viral load and the efficacy of single dose ciprofloxacin and azithromycin in curing chronic infection with gonorrhoea. The second lesson is to always collect process data so that a confusing or equivocal result can be interpreted. The Mwanza trial has been criticized for not proving directly that the average duration of STD episodes was reduced (35, 61).

The third, and most important, lesson is that the timing and location of a study are of supreme importance. Most scientists and funding agencies favour conducting studies where there is infrastructure and a body of data on which to base sample size calculations. It is ironic that Mwanza was the successful trial as there was inadequate infrastructure and comparatively little data before the trial. Insights into the local epidemic were based on annual antenatal surveys (44) and a cross-sectional community-based study (62, 63). Because only prevalence data were available, sample size calculations for incidence were based on assumptions. In contrast, there was a wealth of data from Rakai before the trial started (64, 65). With the benefit of hindsight, the Rakai team paid the price for choosing to stay where they were rather than move to a new area that was at an earlier stage of the epidemic.

Finally, and perhaps controversially, epidemiologists need to listen to the participants in their studies, have more faith in focus groups, and

believe in behaviour change. The PAF of 10% calculated, at great expense, for the co-factor effect of STDs in the Rakai trial (32) is exactly the same as if it had been calculated on the basis of their pre-trial cross-sectional study, which relied on self-reports (41). Furthermore, focus groups in early 1990 indicated that there had recently been a drastic change in sexual behaviour (65) when compared with previous sexual networking (54). This should have warned the Rakai researchers that the high incidence they observed in pre-trial data (64) was likely to be due to transmission occurring in couples discordant for HIV (21) rather than the co-factor effect of STDs.

## Lessons for syndromic management

The rapid rise of tetracycline resistance in gonorrhoea cases from 35% to 96% in Mwanza should not be overlooked (30, 66). The monitoring of future interventions must incorporate susceptibility testing, and this must include the period after the trial has finished because standards of care may deteriorate. Follow-up studies in Rakai could define the risk to the future reproductive health of participants of untreated, asymptomatic STDs (the control arm of the trial). However, until and unless the follow-up of such patients confirms a substantial risk, the emphasis of syndromic management should be on providing counselling about abstinence and condoms and on contact tracing (22) rather than on obtaining the most expensive treatments and teaching staff how to use them.

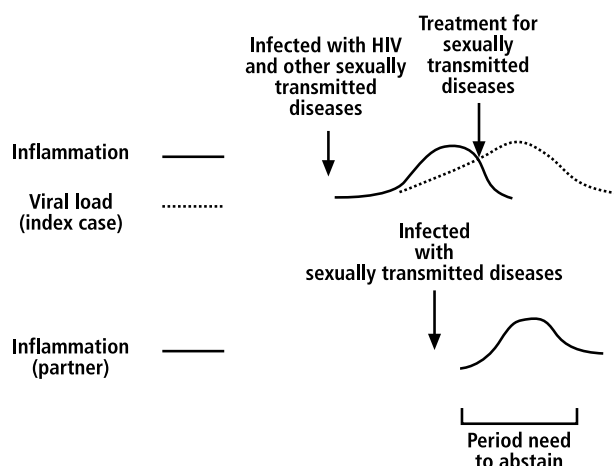
## Masaka: preparing for another negative result

Before they published their results, the Mwanza team outlined reasons why the trial might fail (40). Rather than waiting for a result and trying to explain it, this is the intellectually honest approach. This will be discussed using the sequence of issues raised by Hayes et al. (40), but the stage of the HIV epidemic and STD epidemic are added as key issues.

The slight upward trend in HIV-1 prevalence in Masaka (Fig. 1), the high seroprevalence of HSV-2 infection (Table 2), and the high HIV-related mortality (16) all indicated that there was a “mature” epidemic at the start of the intervention; there was, however, a lower prevalence of HIV-1 than in neighbouring Rakai. A natural history cohort outside the trial area has shown a significant decline in HIV-1 incidence (67), to well below the figure used in the calculations of sample size.

Contamination of the control group has occurred in Masaka. The original intention was to use a health intervention that was not associated with preventing HIV transmission (improving immunization coverage, malaria control, and sanitation) (8). However, there is now counselling available to those

Fig. 5. Interaction of primary HIV-1 infection and sexually transmitted diseases



Source: ref. 22

WHO 00342

that request it and testing for HIV and condom social marketing in all arms of the trial (68). Additionally, the intervention has been introduced slowly, and the cure rate for STDs is only 70%. Only 70% of the target population was enrolled, so bias is likely. The slow pace of the intervention may relate to previous friction between researchers and study communities (69).

## Conclusion

If the Masaka study yields a result that is not significant, the Mwanza study may remain the only trial of an intervention with a “successful” outcome. Yet the Mwanza trial may have been misinterpreted as confirming its hypothesis when it actually confirmed the behavioural component of syndromic management. A trial of improved counselling alone versus improved counselling and improved syndromic treatment is urgently required. Such a trial is needed in addition to ongoing studies.

Irrespective of the explanation for the success in Mwanza, the Rakai trial is bad news. In responding to the critics of the Rakai trial, Wawer et al. said: “It is unlikely that a syndromic approach would have had substantial effects on HIV-1 in Rakai, where most HIV-1 transmission occurred independent of symptoms or laboratory diagnoses” (61). Unfortunately, most of Africa has by now reached the same stage of the epidemic as Rakai had in 1994.

Laga argued in her 1995 commentary (70) on the original paper that reported the results of the Mwanza trial that “rather than focusing our efforts on further quantifying the attributable risk of STD control, we should now put all our energies into determining how best to deliver STD care.” The response to Rakai has been worthy of the title of Randy Shilts’ book *And the band played on* (71): the progress of science depends on revising hypotheses to fit research findings, rather than ignoring findings that do not fit hypotheses. The band



must play on, but to a different tune: one that is behavioural not biomedical. ■

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### Résumé

#### Essais communautaires de traitement des maladies sexuellement transmissibles : répercussions sur l'épidémiologie et la prévention du VIH

Cet article examine les bases scientifiques des essais visant à explorer la relation entre les maladies sexuellement transmissibles (MST) et l'infection par le virus de l'immunodéficience humaine (VIH), réalisés à Mwanza (République-Unie de Tanzanie) et à Rakai et Masaka (Ouganda). L'importance de la localisation de l'étude est soulignée et les explications des divergences entre les résultats des essais sont passées en revue. La modestie de l'effet sur les MST dans l'essai de prise en charge syndromique réalisé à Mwanza, par opposition à la diminution de 38 % de l'incidence du VIH, jette un doute sur l'hypothèse selon laquelle le traitement des seules MST ralentirait la transmission du VIH-1. Suivant le modèle de Piot-Fransen, l'essai réalisé à Rakai, et qui consistait en un traitement de masse des MST, aurait dû être plus efficace pour réduire à la fois la prévalence des MST et l'incidence du VIH. Cet essai avait toutefois été arrêté du fait de l'absence de différence d'incidence du VIH entre les groupes d'intervention et les groupes témoins.

Si l'on considère l'essai de Mwanza comme l'essai aberrant nécessitant une explication, on se trouve face à un autre paradigme. Dans les régions rurales d'Afrique orientale où ces essais ont été conduits, les réseaux de partenaires sexuels multiples constituent la source d'infection à la fois par les MST et par le VIH. Du fait de leur plus courte période de latence, les MST peuvent amener le sujet à se rendre dans un dispensaire avant que les premiers signes d'une infection par le VIH-1 ne se manifestent. Dans le cadre de la prise en charge des MST, il est recommandé de s'abstenir de relations sexuelles ou d'utiliser systématiquement le préservatif jusqu'à la fin du traitement. Cette recommandation peut couvrir la période de virémie précoce lors d'une primo-infection par le VIH-1. Ce paradigme semble pouvoir expliquer les résultats des deux essais, ce qui souligne l'importance des aspects comportementaux dans la prise en charge syndromique de ces infections.

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### Resumen

#### Ensayos comunitarios del tratamiento de las enfermedades de transmisión sexual: repercusiones para la epidemiología y la prevención de la infección por el VIH

En el presente artículo se examina la base científica de los ensayos realizados para analizar la relación entre las enfermedades de transmisión sexual (ETS) y la infección por el virus de la inmunodeficiencia humana (VIH) en Mwanza (República Unida de Tanzania), y Rakai y Masaka (República de Uganda). Se examina la importancia que reviste el lugar elegido para el estudio, así como las discrepancias existentes entre los resultados de esos ensayos. El discreto efecto en las ETS observado en el ensayo del tratamiento sindrómico llevado a cabo en Mwanza contrasta con el 38% de reducción de la incidencia del VIH y cuestiona la hipótesis subyacente de que el tratamiento de las ETS por sí solo disminuye la transmisión del VIH-1. Según el modelo de Piot-Fransen, el ensayo de Rakai, donde se ofreció masivamente tratamiento contra las ETS, debería haber sido más eficaz en lo que respecta a reducir tanto la prevalencia de las ETS como la incidencia del VIH. Sin embargo, el ensayo de Rakai se interrumpió porque no se detectó ninguna

diferencia en la incidencia de infección por el VIH entre el grupo de intervención y el grupo testigo.

Si se considera que el ensayo anómalo es el de Mwanza, es posible concebir un mecanismo explicativo. En las zonas rurales de África oriental, donde se llevaron a cabo esos dos ensayos, las redes de parejas sexuales simultáneas son la fuente de contagio tanto de las ETS como del VIH. Dado su menor periodo de latencia, las ETS pueden llevar a la persona afectada a acudir al ambulatorio antes de la aparición de los primeros signos de infección por el VIH-1. Parte del manejo de las ETS consiste en recomendar la abstinencia o el uso sistemático del preservativo hasta el término del tratamiento, y esa recomendación puede abarcar el periodo inicial de viremia durante la primoinfección por el VIH-1. Este mecanismo parece poder explicar los resultados de los dos ensayos, y subraya los aspectos comportamentales del manejo sindrómico.

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## Commentaries

### STI care: one of many necessary approaches for prevention of HIV infection

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Challenging orthodoxy always has an appeal to some, and we must confess we are part of that group. In his article (1), Hudson is challenging a hastily built orthodoxy — derived from the results of the Mwanza trial — that spread rapidly and largely without question throughout the public health world. Following publication of the trial results, which seemed to indicate that management of sexually transmitted infection (STI) could result in significant reduction of HIV incidence, many were quick to conclude that an important AIDS-prevention tool was at hand (2). The fact that the original hypothesis of the study, linking STI management and HIV transmission, was not proven was eclipsed by an important decline in HIV incidence in Mwanza — at a time when the public health community needed hope. Perhaps STI prevalence did not decline as much as HIV incidence, reasoned the authors, because of the high prevalence of asymptomatic

infection among women. It is not possible to address asymptomatic infection with syndromic management, the main STI management strategy used in the Mwanza trial.

Enter the results of the Rakai trial, which was meant to address the problem of asymptomatic STI by presumptive mass treatment. However, for reasons made clear by Hudson and others (1, 3–5), the Rakai trial failed to reduce HIV incidence at all. Hudson suggests this failure may stem from a misreading of the results of the Mwanza trial. To assume that the link between STI management and HIV transmission was conclusively proven at Mwanza is to ignore the nuances and context of the trial: these must be considered in order to make sense of the complicated epidemiology of HIV/AIDS.

Many facts argued for caution in interpreting the Mwanza results: the well-known observation that “first trials” commonly produce more positive results than subsequent trials; the fact that the original hypothesis was not really proved; and the seemingly inexorable drive to find a single intervention, a “magic bullet”, that will make control of the epidemic possible. It has long been known that no magic bullet exists nor is likely to for some time to come, and that a multiplicity of approaches is needed (6). One key approach must be to encourage behavioural change. Changing sexual behaviour, the first element of any public health programme to control HIV, is a strategy that often enjoys too little confidence in such programmes, despite the fact that there are no national examples in which the spread of HIV has

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been diminished or brought under control without behavioural change playing an important, if not the key role.

Efforts to prevent HIV infection by encouraging behavioural change are either being increasingly ignored (7) or are being forced to compete against other approaches for already insufficient resources. Successful interventions involving behavioural change, are — we know now — not notable for their sophistication, but rather for their consistency, intensity, and duration. More research is needed to determine if there are ways to achieve the same ends with less effort. Currently, however, we know how to prevent HIV infection, we lack only the will.

If the architects of these two key trials in Mwanza and Rakai can be blamed for anything, it is for paying insufficient attention to behaviour and behavioural change, either in their efforts to reduce sexual risk (8) or, as Hudson points out (1), by failing to consider important behavioural changes already taking place. If the interpreters of the Mwanza trial can be held accountable for anything, it is for overstating the results and trying to justify STI management through HIV control. STI care certainly has a role in HIV prevention, but it is also an important public health activity. Overselling STI management as the sole intervention for HIV control will only damage efforts to address an epidemic that has long preceded HIV/AIDS.

The history of public health efforts in AIDS prevention will undoubtedly show the folly of ignoring what we know in favour of what we might prefer. Hudson has reminded us (1), as we must be reminded frequently, it seems, that there is no single answer, that multiple approaches must be used probably everywhere, and that behavioural change remains a key component everywhere. To place undue effort on any one intervention is ill-advised and certainly not justified by the evidence produced to date. ■

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## More community-based trials of STD control or more appropriate interventions: which is the priority for preventing HIV-1 infection in developing countries?

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Much debate has followed the publication of the results of the Rakai trial in 1999 (1). Given the outcome of the Mwanza trial published a few years earlier (2), most of the AIDS scientific community was expecting positive results from Rakai. Indeed, how could periodic mass treatment for sexually transmitted disease (STD) fail to prevent HIV-1 transmission at the community level when a much more modest intervention (appropriate STD treatment for people with STD symptoms attending primary health care centres) had led to a 38% reduction in HIV-1 incidence?

The main reason evoked up until now for these discrepant results is the difference in the stage of the HIV epidemic at the study sites (3, 4). Indeed, as confirmed by a sub-analysis of the Rakai data (5), the population attributable fraction for STD in HIV-1 transmission will be quite low when the HIV epidemic reaches a high but stable prevalence with a low to moderate incidence. Other reasons put forward have been the increase in herpes simplex virus type 2 infection (an incurable STD) at the population level in mature epidemics, which could then contribute to further HIV-1 transmission; the possibility of reinfection occurring between mass treatment cycles; the possibility that symptomatic STDs play a more important role in HIV-1 transmission than asymptomatic STDs; and chance (4), with imbalance between the study arms at baseline resulting in wide confidence intervals (6).

In this issue of the *Bulletin of the World Health Organization*, Hudson presents new arguments (7), adding to the debate. He draws three main points: firstly, in contrast to most previous analyses, he considers that the Rakai trial should be considered as the gold standard, and it is the Mwanza results which need to be “explained”, mainly because reinfection between mass treatment rounds is unlikely to be a major factor accounting for the negative results from Rakai. Secondly, behavioural counselling, rather than STD treatment, could explain the Mwanza results, mainly because STD symptoms, in people contracting HIV-1 and an STD simultaneously, may prompt attendance at a clinic prior to manifestations of primary HIV-1 infection; this would lead to abstinence or consistent condom use during the earliest period of viraemia associated with primary

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infection. Thirdly, a community-based randomized trial of improved counselling alone versus improved counselling combined with improved syndromic management of STDs is urgently needed.

It is likely that the counselling component of STD syndromic management has a more important impact on HIV-1 transmission than the STD treatment per se. Indeed, the results of a recent mathematical modelling exercise mimicking an intervention which started in 1993 in Cotonou, Benin, suggest that increased condom use averted many more cases of HIV-1 infection than cases of STD treated (8). Additional data from Cotonou also suggest that simultaneous exposure to HIV and an STD is frequent, especially among female sex workers (9). However, I consider that STD management at the primary health care level should include both counselling and effective STD treatment. It is unacceptable to set these two interventions in opposition. STD treatment must reach the highest standards possible, even if only for the proper management of STDs, which have their own important impact on the population's health, especially that of women. The real urgency is to increase the scope of interventions that are currently far too modest. For instance, it is very likely that the impact of STD treatment on HIV-1 transmission would be more significant if interventions had greater intensity and population coverage (8). There is no need for more trials at the community level: instead, comprehensive interventions, taking into account the context in which they will be applied (e.g. urban versus rural settings; late versus early stage of the epidemic), should be designed, appropriately funded, implemented, and evaluated.

Furthermore, reinfection between mass treatment rounds could, in fact, explain the Rakai trial results. Both the surveys and the mass treatment interventions in Rakai were household based. This type of survey tends to miss people whose sexual behaviour puts them more at risk (e.g. female sex workers), because they also tend to be the most mobile or not to live in a standard household. We have recently shown that, although the coverage of the population in the Rakai trial was high, differential coverage of the low- and high-risk sectors of the population could well have led to a very pronounced decrease in the impact of the intervention, as a result of reinfection and persistent enhancement of HIV-1 transmission by untreated STDs in the high-risk group (10). This raises the issue of whether interventions should be targeted at the most vulnerable sectors of the population. Although the importance of "core groups" has been recognized since the early phase of the HIV-1 epidemic (11), interventions specifically targeting these sectors of the population have not been sufficiently promoted. In a recent extensive review of the data available from Cotonou, Benin, we have shown that most of the new HIV-1 cases in the general population were linked to sexual networks between female sex workers, their

clients, and the other, mostly regular, female sexual partners of the clients (9). Thus we, like others (12), strongly believe that interventions aimed at the prostitution milieu — including condom promotion, individual counselling and STD care — should be of the utmost priority for the control of the HIV-1 epidemic in developing countries. This is particularly important in places where the epidemic is increasing, as it is in Asia and still is in many countries of sub-Saharan Africa (e.g. West Africa). If there is one community-based randomized trial yet to be performed, it should aim to assess the impact of such interventions on HIV-1 transmission at the population level. ■

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