**World AIDS**

# Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials

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Two randomised controlled trials of sexually transmitted disease (STD) treatment for the prevention of HIV-1 infection, in Mwanza, Tanzania, and Rakai, Uganda, unexpectedly produced contrasting results. A decrease in population HIV-1 incidence was associated with improved STD case management in Mwanza, but was not associated with STD mass treatment in Rakai. Some reductions in curable STDs were seen in both studies. These trials tested different interventions in different HIV-1 epidemic settings and used different evaluation methods; the divergent results may be complementary rather than contradictory. Possible explanations include: differences in stage of the HIV-1 epidemic, which can influence exposure to HIV-1 and the distribution of viral load in the infected population; potential differences in the prevalence of incurable STDs (such as genital herpes); perhaps greater importance of symptomatic than symptomless STDs for HIV-1 transmission; and possibly greater effectiveness of continuously available services than of intermittent mass treatment to control rapid STD reinfection. Implications of the trials for policy and future research agenda are discussed.

## Introduction

The global burden of curable sexually transmitted diseases (STDs) is enormous, with an estimated total of more than 300 million new cases of syphilis, gonorrhoea, chlamydia, and trichomoniasis each year.[1] Because of their many serious complications and sequelae, particularly among women, STDs are one of the leading causes for the loss of healthy years of life. Even in the absence of HIV-1 infection, STDs account for a larger number of disability-adjusted life-years lost in women of childbearing age than any other group of diseases apart from maternity-related disorders.[2] Effective control of STDs was therefore a pressing global health priority even before their role as a cofactor in HIV-1 transmission was recognised.

During the past decade, overwhelming evidence has accumulated that some STDs enhance the transmission of HIV-1. Proving that STDs were indeed a cofactor was initially difficult, because HIV-1 and STDs share a mode of transmission, so associations seen in epidemiological studies may well have resulted from the confounding effect of risky sexual behaviour.[3] Moreover, in cross-sectional studies, the time sequence of infections is difficult to establish. Longitudinal studies provided stronger evidence, and showed substantial relative risks for HIV-1 infection associated with various STDs.[4-7] Further evidence has come from studies showing that viral shedding in the genital tract of HIV-1-infected men and women is substantially increased if they have an STD, and that treatment of the STD decreases viral shedding.[8-10]

Towards the end of the 1980s, Pepin and colleagues[11] suggested that STD control could be used as an indirect strategy to reduce HIV-1 transmission. On the basis of this hypothesis, WHO promoted improved STD treatment services, together with behavioural risk reduction, as essential components of national AIDS control programmes,[12] and this strategy has since been adopted in many countries. However, the impact of this approach is difficult to predict because it depends on the size of the cofactor effect, the prevalence of STDs in HIV-1-discordant partners, the proportion of treatable compared with untreatable STDs, and the effectiveness of control measures in reducing STD prevalence, none of which are easy to estimate.

Two types of investigation have collected empirical evidence on the effectiveness of an STD control strategy for HIV-1 prevention: uncontrolled intervention studies among sex workers, and community-based randomised controlled trials in general populations. These studies were done in sub-Saharan Africa, the region most severely affected by the HIV-1 pandemic, and where high prevalences of treatable STDs have been recorded in many countries. In former Zaire and Côte d'Ivoire, the introduction of effective and accessible STD treatment services for sex workers, with condom promotion and provision, was followed by a substantial and significant reduction in STD and HIV-1 incidence.[13,14] The effects remained after adjusting for condom use in the analysis, but residual confounding cannot be excluded and it is therefore difficult to disaggregate the effects of STD treatment from those of condom use. A further study in a mining community in South Africa showed that monthly presumptive STD treatment of sex workers reduced the prevalence of STDs not only in this high risk group, but also in the surrounding population of miners.[15] However, the effect on HIV-1 transmission was not measured directly in this study.

## Mwanza and Rakai trials

### Mwanza

A randomised trial in Mwanza region, Tanzania (map), between 1991 and 1994, tested the hypothesis that improved treatment services for STDs, integrated within the existing primary health-care system, would reduce HIV-1 transmission in the general population.[16,17] The intervention comprised training of health workers in syndromic case management as recommended by WHO,

provision of inexpensive but effective drugs, regular supervisory visits to health facilities, and village campaigns to improve treatment-seeking behaviour. The intervention was designed to be sustainable and affordable. Its impact was assessed in six pairs of large rural communities. Within each pair, one community was randomly allocated to receive the intervention, whereas in the comparison communities the existing unimproved services were maintained. The improved services were subsequently implemented in the comparison communities after completion of the trial. The two study groups were similar with respect to baseline STD and HIV-1 prevalences and other factors.[18]

To assess the effect of the intervention, a cohort of randomly selected adults (about 1000 from each community) was followed up for 2 years. For ethical reasons, all cohort members with a positive syphilis test (rapid plasma reagin) were treated at baseline in both groups. Key results of the trial are summarised in the panel. At follow-up, after adjustment for confounding factors, HIV-1 incidence was 38% lower in the intervention group than in the comparison communities, and this difference was highly significant.[17,19] Furthermore, the prevalence of seromarkers consistent with a diagnosis of active syphilis (positive *Treponema pallidum* haemagglutination assay/rapid plasma reagin titre $\geqslant 1:8$) was 29% lower, the incidence of active syphilis was 38% lower, and the prevalence of symptomatic male urethritis was 49% lower in the intervention group than in the comparison communities.[20] The syphilis seroprevalence results were significant; the other differences reached borderline significance. Reported sexual behaviour showed no difference between the two trial groups or over time. The investigators concluded that the observed effect on HIV-1 incidence was due to the STD intervention, and not due to behaviour change in the intervention group. The prevalence of symptomless male urethritis and the incidence of self-reported STD symptoms showed no significant reduction between trial groups or over time. Disappointingly, there was no effect on the prevalence of reproductive tract infections in pregnant women, as shown through two consecutive cross-sectional surveys in the same communities.[20]

### Rakai

Another community-based randomised trial was done in the Rakai district, Uganda (map), between 1994 and 1998.[21,22] This trial tested the concept that repeated rounds of mass treatment for STDs, delivered to trial participants in their homes, would reduce STD rates and HIV-1 transmission. The intervention comprised directly-observed treatment of all individuals every 10 months with highly effective single-dose oral antibiotics, and treatment of individuals who were positive for syphilis by toluidine red unheated serum test (TRUST) with intramuscular penicillin. In the comparison group, single-dose mass treatment with vitamins, iron, folic acid, and anthelminths was provided, and individuals who were positive for syphilis and all those with STD symptoms were referred for treatment. At trial completion the comparison group also received home-based mass treatment for STDs. The trial was carried out in 56 rural communities, which were



**Mwanza field team preparing to cross Lake Victoria to survey island communities**

grouped into ten clusters, five of which were randomly selected to receive the intervention. Care was taken to identify social networks, and this information was used to define the study clusters to reduce contamination. STD and HIV-1 prevalences at baseline were similar in the two study groups.

Effect of the intervention was measured through surveys of the entire population aged 15–59 years in the study communities every 10 months. In this open cohort, the number of participants was just over 14 000. Key results are summarised in the panel. The trial was stopped prematurely after 3 rounds of mass treatment, because no effect on HIV-1 incidence was seen, either overall or in subgroups including initially discordant couples or pregnant women. However, the prevalence of seromarkers consistent with active serological syphilis (positive *T pallidum* haemagglutination assay/TRUST titre $\geqslant 1:4$) was 20% lower and that of trichomoniasis 41% lower in the intervention group at follow-up, and both differentials were significant. The prevalence of these infections decreased over time in both treatment groups, but the reduction was significantly greater in the intervention group. There was no significant effect on the incidence of new cases of syphilis. The sample sizes for the measurement of gonococcal and chlamydial infections were small. These infections did not show a significant difference between trial groups at follow-up, but prevalence had decreased over time in the intervention arm by 40–60%, although no change was seen in the comparison group. No effect was seen on self-reported symptoms. Among pregnant women, prevalences of trichomoniasis, bacterial vaginosis, gonorrhoea, and chlamydia were 30–70% lower in the intervention group at follow-up, and these differences were significant. As in the Mwanza trial, there was no indication that results were confounded by differential sexual behaviour in the two study groups.

## Contradictory or complementary results?

The results of the Mwanza trial had a major influence on HIV-1 prevention policies in many countries around the world. However, the unexpected results of the Rakai trial have resulted in uncertainty among policy-makers and donor agencies. We believe that the differences in the trial results are not contradictory but complementary, that they can assist rather than confuse policy decisions, that they make a major contribution to our understanding of interactions between STDs and HIV-1, and that they lead to a number of well-defined research questions that need to be addressed urgently.

A number of important differences between the Mwanza and Rakai studies that could influence the measurable impact of STD interventions are highlighted in the panel, and the geographical distributions of the participating communities are shown in the map. Clearly, the two trials tested different interventions, and used different methods for effect evaluation, in different epidemiological environments. The results are therefore not directly comparable but these differences give rise to several hypotheses that may explain the observed discrepancy in trial outcomes.
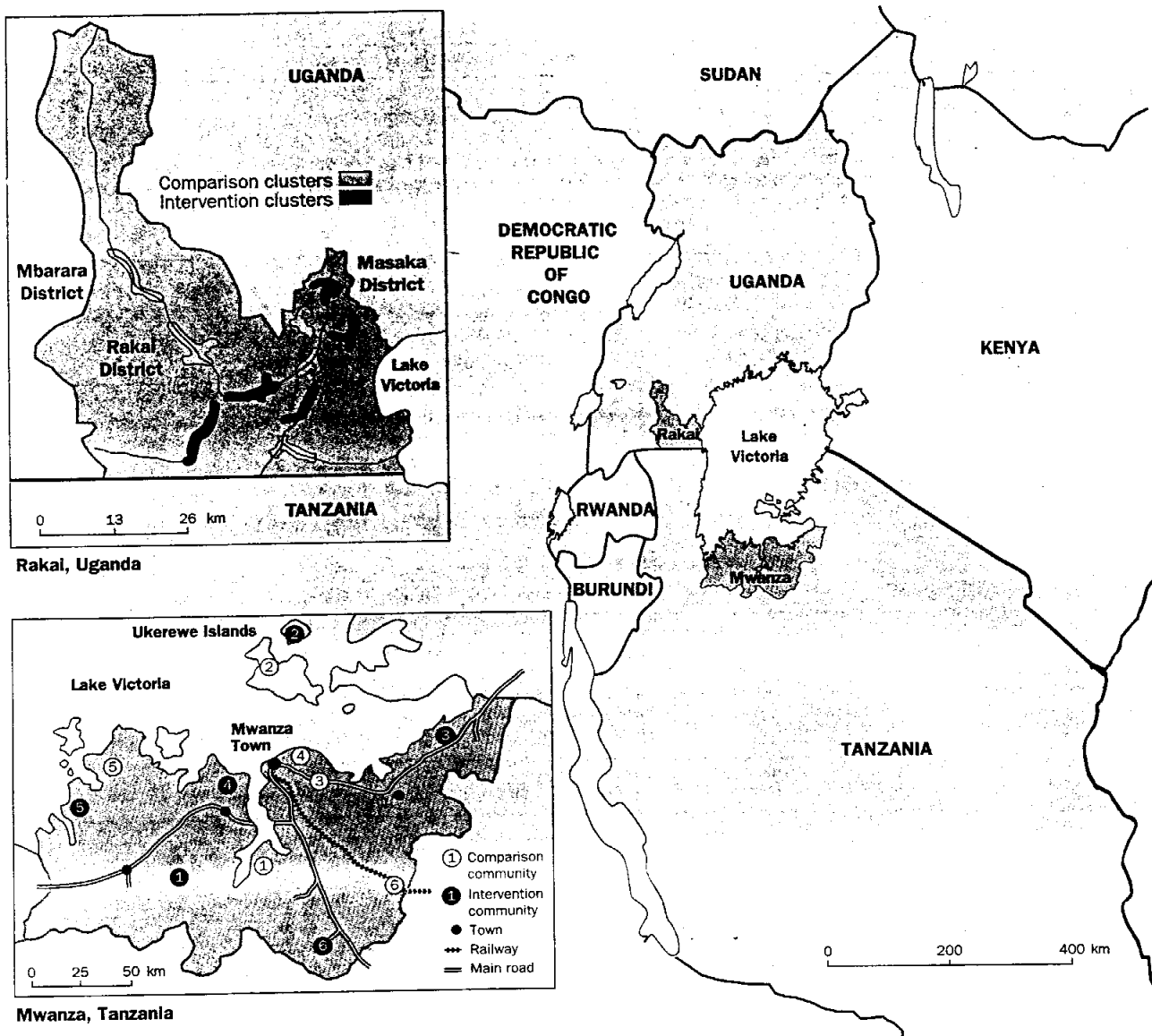
**Map of the study sites**

*Stage of the HIV-1 epidemic*

The epidemic in Rakai had reached a mature generalised stage, with high HIV-1 incidence (about 1·5–2·0 per 100 person-years) and a stable prevalence of around 16% in the study population. By contrast, HIV-1 incidence in Mwanza was about 1 or less per 100 person-years and prevalence was comparatively low (4%) but rising.[23] Computer models suggest that, at the population level, the contribution of STDs to HIV-1 transmission decreases as HIV-1 epidemics mature.[24] This decline may occur because HIV-1 infection then extends beyond high-risk groups in which HIV-1 and other STDs tend to coincide, and because a substantial proportion of new infections in mature epidemics occur among the spouses and regular partners of HIV-1-infected individuals, in whom frequent exposure may lead to high transmission rates even in the absence of cofactors. In Rakai, HIV-1 infection was more prevalent than most other STDs, including gonorrhoea, chlamydia infection, or syphilis. Where HIV-1 is so prevalent relative to other infections, the proportion of HIV-1 transmission due to other STDs may be quite limited.[22] Recent analyses from Rakai show that HIV-1 viral load in the infected individual was the main determinant of transmission risk, and suggest that in discordant couples, the effect of viral load on transmission is substantially greater than that of STD symptoms in either partner.[25] The proportion of people with high HIV-1 viral load may differ substantially by duration of the HIV-1 epidemic.

*Role of genital herpes*

Serological studies have shown high rates of infection with herpes simplex virus type 2 (HSV-2) in the general population in both Tanzania and Uganda.[22,26] In Rakai, HSV-2 was detected by PCR in 45% of genital ulcers. The cause of genital ulcers was not assessed in the Mwanza cohort, but limited data, based on an enzyme immunoassay (less sensitive than the PCR test used in Rakai), from the STD clinic in Mwanza town suggest that less than 10% of ulcers in STD patients in Mwanza are attributable to herpes. The cofactor effect of HSV-2 lesions on HIV-1 transmission may be substantial, and increased genital shedding of HIV-1 has been reported in their presence.[27] In mature HIV-1 epidemics the incidence of symptomatic episodes of herpes is likely to increase, due to

## Design and results from Mwanza and Rakai trials

| Mwanza | Rakai |
|---|---|
| **Epidemiological background** | |
| ● HIV-1 prevalence 4% and rising | ● HIV-1 prevalence 16% and stable |
| ● HIV-1 incidence in comparison areas 0·9% | ● HIV-1 incidence in comparison areas 1·5% |
| ● Intermediate stage of HIV-1 epidemic | ● Mature, generalised stage of HIV-1 epidemic |
| ● HSV-2 seroprevalence 20% in men, 50% in women aged 15–29 years | ● HSV-2 seroprevalence 31% in men, 61% in women aged 15–29 years |
| ● <10% of ulcers due to HSV-2 in Mwanza town | ● 43% of ulcers due to HSV-2 |
| **Trial design** | |
| ● Community-based RCT, closed cohort | ● Community-based RCT, open cohort |
| ● Unmasked study population | ● Single-masked study population |
| ● Communities separated by large distance (>50 km) | ● Communities separated by sexual network and geographical boundaries (swamps, hill ranges) |
| **Intervention design** | |
| ● Improved STD case management and campaigns to improve treatment seeking | ● Periodic mass treatment |
| ● Continuous availability of services | ● Intervention delivery every 10 months |
| ● People with reinfection and mobile population had continuous access to services when they sought treatment | ● People with reinfection and mobile population advised to seek treatment from government clinics stocked with penicillin |
| ● Intervention in comparison group: no change to routine practice | ● Intervention in comparison group: mass treatment with anthelminths, vitamins and folic acid |
| ● RPR-positive cohort members in comparison group offered treatment for syphilis | ● TRUST-positive participants in comparison group referred for free syphilis treatment |
| **Trial implementation** | |
| ● 50–75% of symptomatic STD patients in catchment areas used STD services | ● 70% of censused population received mass treatment (85% of those eligible and present) |
| ● 85% of censused population recruited to cohort, 71% of cohort seen at follow-up | ● 77% of censused population recruited to cohort, 74% of cohort seen at follow-up |
| ● Follow-up interval 24 months (1 follow-up round) | ● Follow-up interval 2×10 months (2 follow-up rounds) |
| **Effect on HIV-1 incidence (differences between trial groups at follow-up)** | |
| ● 38% reduction (95% CI 15–55) | ● 3% reduction (95% CI −16 to 19) |
| **Effect on STDs in general population (differences between trial groups at follow-up)** | |
| ● 31% reduction in syphilis (TPHA+) seroincidence (not significant) | ● 35% reduction in syphilis (TPHA+) seroincidence from rounds 1 to 2 (not significant), 0% from rounds 2 to 3 |
| ● 29% reduction in active syphilis prevalence (TPHA+/RPR titre ⩾1:8) | ● 36% reduction in active syphilis prevalence at round 2 (TPHA+/TRUST titre ⩾1:4), 20% at round 3 |
| ● 49% reduction in symptomatic urethritis in men (borderline significance) | ● 42% reduction in trichomoniasis at round 2, 41% at round 3, 13% (borderline significance) reduction in bacterial vaginosis at round 3 |
| ● No significant reduction in gonorrhoea, chlamydia, overall urethritis, or reported symptoms | ● No significant reduction in gonorrhoea, chlamydia, urethritis, or reported symptoms between trial groups |
| **Impact on STDs in pregnant women** | |
| ● No significant reductions after 12–14 months of intervention for any STD (measured in antenatal clinic attenders, not in cohort) | ● 72% reduction in prevalence of trichomoniasis, 50% in gonorrhoea, 68% in chlamydia, 26% in bacterial vaginosis (measured in cohort) |

RCT=randomised controlled trial; RPR=rapid plasma reagin test; TPHA=*Treponema pallidum* haemagglutination assay; TRUST=toluidine red unheated serum test.

immunodeficiency in HIV-1-positive individuals and because of the increased exposure of HIV-1-negative individuals to HSV-2. Such changing epidemiology has been reported in Nairobi and South Africa.[28,29] This may explain a high frequency of herpes among patients with genital ulcers in Rakai. A high incidence of untreatable episodes of herpes in Rakai may partly account for the lack of impact of STD control on HIV-1.

### Role of bacterial vaginosis

The prevalence of bacterial vaginosis among women in Rakai was very high, at around 50%. Bacterial vaginosis is difficult to treat and commonly recurs after treatment, as was seen in the general Rakai population. However, mass treatment led to a temporary reduction in the prevalence of bacterial vaginosis among pregnant women. Associations have been seen between bacterial vaginosis and the prevalence and incidence of HIV-1;[30] the high prevalence of

bacterial vaginosis in Rakai, and the limited effect of treatment, may have contributed to the lack of effect on HIV-1. Bacterial vaginosis was not investigated in the Mwanza trial, but a prevalence of 44% was found among unselected women attending a rural general outpatient clinic, suggesting that bacterial vaginosis may also be highly prevalent in Mwanza (P Mayaud, personal communication).

### Importance of symptomatic and symptomless STDs

In Mwanza, services for the treatment of symptomatic STDs were made continuously available, but symptomless infections and those for which patients do not seek treatment were not covered, with the exception of symptom-free patients treated as partners of symptomatic patients through partner notification (34% of index cases).[31] In Rakai, by contrast, both symptomatic and symptomatic infections were covered periodically by mass treatment, but

only limited services were available to treat symptomatic STDs between these rounds of mass treatment. Untreated symptomatic STDs may have a greater cofactor effect on HIV-1 transmission than symptomless infections, since symptomatic STDs are likely to be associated with a greater degree of inflammation.[32] Although more research is needed, this hypothesis may help to explain the large effect on HIV-1 seen in Mwanza despite the low coverage of symptomless STDs. However, symptomless infections play an important part in maintaining transmission of STDs and contribute to the high burden of STD complications and sequelae.

### Reintroduction of STDs

In Rakai, despite intensive efforts to treat a high proportion of adults in the study communities, substantial STD prevalences were seen at the end of each 10-month follow-up period. These data suggest a high rate of infection and reinfection after mass treatment in this open cohort, which included newly enrolled persons and those who previously declined treatment. The overall coverage of mass treatment was about 70% of censused adult residents, representing more than 80% of adults present in the community. Individuals who missed the mass treatment may have included the more mobile members of the population, who possibly carry a higher than average STD risk. Also, each round of mass treatment took about 1 week to complete in each intervention community, so that some of those receiving mass treatment may have been reinfected by sexual partners not yet treated. Only limited treatment services were available for newly infected and reinfected cases. In Mwanza, new infections in previously uninfected people and reinfection in those who were successfully treated also occurred. However, because improved case-management services were continuously available, individuals with new symptomatic infections could obtain treatment. An estimated 50–75% of individuals with symptomatic STDs in rural Mwanza made use of the improved services.[31]

### Population-attributable fractions

The population-attributable fraction of HIV-1 infections due to STDs was estimated in both trial populations.[33,34] This fraction is the proportion of new HIV-1 infections that were attributable to STDs occurring during the study period, and is estimated from data on the relative risk of HIV-1 in those with and without STDs, combined with data on STD frequency. In Rakai, only 10% of new HIV-1 infections were attributable to STD symptoms or treatable STDs, and there was no significant difference between intervention and comparison groups.[33] In Mwanza, by contrast, 43% of new HIV-1 infections among men in the comparison group could be attributed to symptomatic STDs or new episodes of syphilis. In the intervention group, the population-attributable fraction among men was reduced to 11%. No significant effect was seen in women.[34] These findings suggest that symptomatic STDs may have played an important role in HIV-1 transmission in Mwanza, at least in men, and are consistent with the hypothesis that continuous syndromic treatment reduced HIV-1 incidence by reducing the duration of symptomatic STDs and hence their importance as cofactors. The higher population-attributable fraction, and larger difference in these fractions between intervention and comparison groups, in Mwanza compared with Rakai may reflect factors discussed previously, including the stage of the

epidemic and the prevalences of treatable and untreatable STDs. The calculations of population-attributable fraction are likely to be underestimates since they account for cofactor effects of STDs on susceptibility to HIV-1, but do not fully capture effects on enhancing the infectiousness of HIV-1-positive individuals. Although HIV-1 incidence among women was reduced by the intervention in Mwanza, the calculations showed no intervention effect on population-attributable fraction for women.[34] This is plausible, because women may still be protected through the protective effect of the intervention in their male partners.

### Chance

The potential role of sampling error should not be overlooked. Fully adjusted 95% CI for efficacy were 15–55% in Mwanza, and −16% to 19% in Rakai. Although the point estimates of efficacy differed significantly between the two trials, the data would clearly be consistent with a true efficacy in Mwanza less than 38%, and a true efficacy in Rakai greater than 3%.

## Implications for policy

What can we say based on current evidence about the role of STD control in HIV-1 prevention? First, there is overwhelming evidence that STDs do act as cofactors enhancing the transmission of HIV-1, and that this helps to explain the rapid spread of infection in populations with high STD rates. Mwanza and Rakai data are consistent with previous epidemiological findings. Thus, STD control needs to remain high on the agenda of AIDS control programmes as one of several strategies to reduce HIV-1 transmission. Second, data from the intervention trials are consistent with the hypothesis that improved STD treatment services can have a population-level effect on HIV-1 incidence in settings with low and moderate HIV-1 epidemics. The effect is likely to be greatest in areas where treatable STDs are highly prevalent, where current treatment provision is inadequate, and where HIV-1 prevalence has not reached very high levels in the general population. These conclusions are relevant to a large proportion of the world's population, including many countries in sub-Saharan Africa, south and central America, many parts of India, and other countries in Asia. But even in populations with high levels of HIV-1 prevalence, individuals with STDs are at increased risk of transmitting or acquiring HIV-1. The relative importance of STDs for HIV-1 spread may be lower in these areas, but the absolute number of HIV-1 cases due to STDs may be substantial. Furthermore, even if the HIV-1 epidemic has matured in the general adult population, adolescents and young people as they become sexually active constitute a subgroup that to some extent resembles a population at an early stage of the epidemic, and STDs may play a more important part in this group.

The question is not whether STDs should be controlled, but how this can best be achieved in any given context. In situations in which funds are limited, targeted STD control and condom promotion among sex workers and other high-risk groups should be the absolute minimum, particularly in the early stages of the HIV-1 epidemic and in situations in which commercial sex is thought to play an important part in HIV-1 transmission. STD control may include improved case-management services, screening, or periodic presumptive treatment of STDs. Improved case management of STDs in the general population is recommended, but

acquires greater importance once the epidemic has reached beyond the traditional high-risk core groups. In advanced epidemics, the relative effectiveness of STD management for HIV-1 prevention may decline, but should not be neglected.

The value of the syndromic approach to STD management depends on the symptoms and sex of the individual. Nevertheless, this strategy should be recommended in areas with inadequate diagnostic facilities. However, there are a number of unresolved problems with the syndromic approach. For example, a satisfactory strategy for the treatment of non-ulcerative infections among women has yet to be found. Vaginal discharge is often difficult to treat, and it is not an appropriate lead symptom for the diagnosis of cervical infections because these are mostly symptomless. Simple, accurate, and affordable screening tests for these infections are urgently needed. Hopefully, more single-dose oral treatments will soon become affordable so that they can be included in the syndromic treatment algorithms in less-developed countries. More research is needed on the cause of genital ulcers, since in areas where most ulcers are not due to syphilis or chancroid, current treatment regimens may need to be revised.

Whichever strategy is adopted, monitoring and evaluation are essential. Syndromic treatment should not be introduced without determining the key STDs in the population to be covered by the services. At least one regional STD reference clinic and laboratory is needed to study the aetiological pattern of STD syndromes, to monitor antibiotic resistance particularly of *Neisseria gonorrhoeae* and *Haemophilus ducreyi*, and to test treatment effectiveness.

The results of the Rakai trial do not discredit the use of mass treatment as a strategy for HIV-1 or STD control in the general population. The Rakai trial failed to show an impact of mass treatment on HIV-1 incidence in a setting characterised by a mature HIV-1 epidemic and a high prevalence of incurable STDs, in particular genital herpes. However, computer simulations using data modelled on the Mwanza population suggest that mass treatment may have a substantial impact in areas with high prevalences of treatable STDs, and a low or moderate but rising HIV-1 prevalence.[35] For example, a combination of a single round of mass treatment with improved STD case-management services was predicted to lead to a rapid, steep, and sustained reduction in HIV-1 incidence, reaching 63% after 5 years. There is a place for empirical trials of this strategy in different epidemiological settings.

## Questions for research

Three main areas of research are required for future policy decisions: operational research, clinical and epidemiological research, and impact evaluation of intervention strategies.

### Operational research

Effective treatment services for STDs should form part of a basic package of health care. However, several limitations exist that require further operational research in different settings. First, how can treatment-seeking behaviour of STD patients be improved? Studies have shown that a substantial proportion of symptomatic STD patients do not seek services at health units that are able to provide effective treatment.[36] Second, how best can improved STD services be integrated into the private sector (including medical practitioners, pharmacies, and occupational health

services), which serves a large proportion of patients in many populations? Third, research is required in different populations to establish and validate effective treatment algorithms for each STD syndrome and the underlying causal agents, because antibiotic susceptibilities and aetiological patterns may differ from region to region. Better treatment approaches need to be developed for the management of vaginal discharge and herpetic lesions. Finally, STD control for HIV-1 prevention has been adopted in many countries, but has received limited resources. Policy research is needed to identify the reasons and solutions for this inadequate level of response.

### Clinical and epidemiological research

The Rakai findings suggest that incurable infections such as HSV-2, or those that are difficult to cure such as bacterial vaginosis, may have a major impact on HIV-1 transmission in some populations. The role, the relative importance, and the best strategy for effective control of HSV-2 need to be clarified. It is also important to ascertain whether the incidence of symptomatic and symptomless genital herpes in the general population increases as the HIV-1 epidemic matures. The role of bacterial vaginosis in HIV-1 transmission also needs to be clarified. Is prevalence influenced by sexual practices or menstrual hygiene? Why is bacterial vaginosis so highly prevalent in some populations?

Further studies are needed to explore the role of symptomless STDs in HIV-1 and STD transmission. Once simple, accurate, and affordable diagnostic tests have been developed, research will be needed to assess their performance in field settings and to develop cost-effective strategies for their operational use.

### Evaluation of intervention strategies

Randomised trials remain the gold standard for the evaluation of new health interventions. New strategies for the control of STDs and HIV-1 infection at the population level require rigorous community-based trials before they are introduced as a general policy that will require major resource provision. For example, targeted interventions in sex workers, including the provision of presumptive STD treatment, are being introduced in parts of South Africa, but their effect on HIV-1 incidence has not yet been assessed.[15] Potentially, single or multiple rounds of mass treatment combined with continuous provision of syndromic treatment may be an effective STD and HIV-1 control strategy for many countries.[35] In the face of the looming epidemics in Asia and elsewhere, too much is at stake for this option not to be carefully evaluated. We propose that the comparative advantage of such interventions should be assessed through randomised controlled trials, with improved case-management services for symptomatic patients as standard provision in the control group.

### Further trials of STD control for HIV-1 prevention

In the Masaka district of Uganda, a randomised trial is underway to compare the effect of a reproductive health education programme, with the combined impact of such an educational programme plus a Mwanza-style STD treatment intervention, and with general community development activities provided in the control group.[37] Results are expected later in 2000. A pilot study is currently being done in Zimbabwe to explore the feasibility of a targeted STD intervention among sex workers that comprises regular presumptive STD treatment and

condom promotion. If successful, this will be followed by a randomised trial to determine the effect on HIV-1 incidence among miners and plantation workers. A further randomised trial, already underway in Zimbabwe, aims to measure the effect of an intervention package comprising health education together with improved STD treatment services.

## Conclusions

STD control remains an urgent public-health priority for the prevention of HIV-1 and the prevention of the complications and sequelae of STDs. Effective STD treatment services remain an essential component of a basic package of health care, to which all people should have access. Improved STD treatment remains the only intervention that has been proven through a randomised trial to be effective in reducing HIV-1 incidence among adults in the general population in Africa. A renewed commitment is needed from governments and donors to ensure that this important and cost-effective opportunity for HIV-1 prevention is not missed.

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