Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial

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Summary

A randomised trial was done to evaluate the impact of improved sexually transmitted disease (STD) case management at primary health care level on the incidence of HIV infection in the rural Mwanza region of Tanzania. HIV incidence was compared in six intervention communities and six pair-matched comparison communities. A random cohort of about 1000 adults aged 15–54 years from each community was surveyed at baseline and at follow-up 2 years later. Intervention consisted of establishment of an STD reference clinic, staff training, regular supply of drugs, regular supervisory visits to health facilities, and health education about STDs.

12 537 individuals were recruited. Baseline HIV prevalences were 3·8% and 4·4% in the intervention and comparison communities, respectively. At follow-up, 8845 (71%) of the cohort were seen. Of those initially seronegative, the proportions seroconverting over 2 years were 48 of 4149 (1·2%) in the intervention communities and 82 of 4400 (1·9%) in the comparison communities. HIV incidence was consistently lower in the intervention communities in all six matched pairs. Allowing for the community-randomised design and the effects of confounding factors, the estimated risk ratio was 0·58 (95% CI 0·42–0·79, p=0·007). No change in reported sexual behaviour was observed in either group.

We conclude that improved STD treatment reduced HIV incidence by about 40% in this rural population. This is the first randomised trial to demonstrate an impact of a preventive intervention on HIV incidence in a general population.

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Introduction

The cumulative total of adult HIV infections rose to an estimated 18 million by late 1994, and is projected to reach 30 to 40 million by the year 2000.[1,2] Most new infections are acquired in the developing world and are heterosexually transmitted. Large numbers of infections continue to occur in sub-Saharan Africa, the region most severely affected during the first decade of the epidemic. Recently, the epidemic has begun to spread rapidly in some parts of southern Asia, and the number of new infections there may exceed that in Africa within the next 10 years.[2]

In the face of this severe and worsening epidemic, AIDS prevention programmes of varying intensity and efficiency have been set up in most affected countries. However, the impact of these programmes is unclear, due largely to lack of well-designed evaluation studies.[3]

In the absence of an effective cure or vaccine, the main preventive strategy has been health education aimed at achieving a reduction in risky sexual behaviour and, in some countries, the promotion of condom use. Other sexually transmitted diseases (STDs) are highly prevalent in many of the worst affected populations,[4] and observational studies suggest that the sexual transmission of HIV may be enhanced in the presence of such STDs.[5–8] For this reason, the WHO has recommended programmes to improve the managementof STDs as an additional HIV control tool, and it has been suggested that the treatment of bacterial STDs may be one of the most cost-effective health interventions available in some developing countries.[9,10] However, no empirical data have been available on the impact of such measures on the incidence of HIV infection, or on their cost-effectiveness as a public-health strategy.

It was against this background that we undertook a community-based randomised intervention trial in a rural area of north-western Tanzania. The objectives of the trial were to establish a programme for the improved diagnosis and treatment of STDs in the general population, and to measure the impact of this intervention on the incidence of HIV infection and on the prevalence and incidence of STDs. The improved STD services were designed to be feasible rather than optimal, were integrated with the Tanzanian primary-health-care system, and were based on syndromic treatment algorithms as recommended by WHO.[11] We report the impact of the programme on HIV incidence.

Methods

The trial was conducted between November, 1991, and December, 1994, in the Mwanza region of Tanzania, which is situated on the southern shores of Lake Victoria. The study population, and the rationale and design of the trial and of the intervention programme, have been described,[12] but the most important aspects are summarised below.

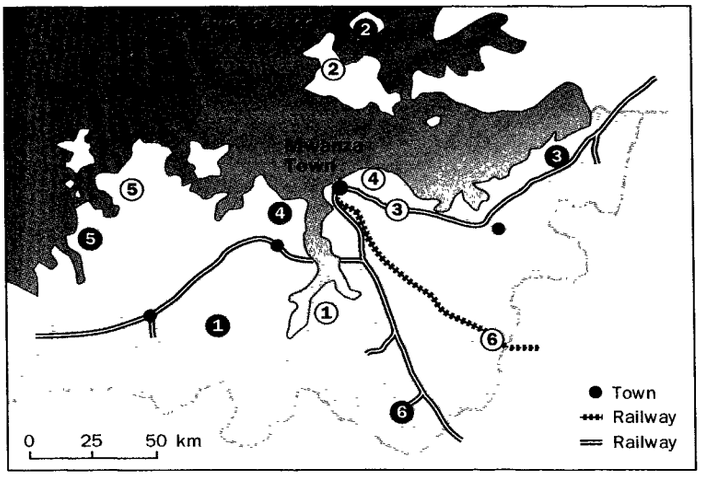

Figure 1: **Map of Mwanza region**
Numbered circles indicate location of six pairs of study communities; intervention communities are shown in black circles.

STD intervention programme

The programme had five components. First, establishment of an STD reference clinic and laboratory in Mwanza town to monitor the aetiology of STDs and the effectiveness of the treatment algorithms. Second, training of existing staff from health centres and dispensaries in the intervention areas in the diagnosis and treatment of STDs with syndromic treatment algorithms. The training comprised 1 week of classroom teaching followed by 2 weeks of practical training at the STD reference clinic in Mwanza town. The staff were also trained to provide patients with STDs with health education and to offer free condoms for use during the current STD episode. Third, regular supply of the drugs needed to treat STDs effectively. To ensure continuous availability of drugs, a special delivery system was set up to supplement the supplies provided through the national essential drugs programme. Fourth, regular supervisory visits by a programme officer to each health facility to provide in-service training, and to check drug supplies and patient records. Finally, periodic visits by a team of health educators to the villages served by each health facility to provide information on STDs, focusing on the availability of effective treatment and encouraging prompt attendance for treatment of symptomatic STDs.

Impact evaluation

12 large communities, each consisting of the catchment population of a health centre and its satellite dispensaries, were selected as the elements for randomisation. A previous survey in the region had demonstrated substantial geographical variations in HIV prevalence, with a higher prevalence in roadside settlements than in rural villages,[13] and a raised prevalence was also observed in villages close to the lake shore. To help ensure comparability of the intervention and comparison communities with respect to baseline HIV and STD prevalences and risk factors for infection, the communities were matched into six pairs according to the following criteria: roadside, lakeshore, island, or rural location; geographical area (paired communities were generally in the same district and less than 50 km apart); and prior STD attendance rates at the health centre, mainly to eliminate those health centres that were barely functioning.

In each matched pair, one community was randomly chosen to receive the STD intervention immediately following the baseline survey, whereas the comparison community received the intervention after the follow-up survey 2 years later. Locations of the study communities are shown in figure 1.

The impact of intervention on the incidence of HIV infection and on the prevalence and incidence of STDs was measured in a random cohort consisting of 1000 adults from each community. Clusters of households were sampled randomly from the population residing within 90 min walking distance of the health centre, by a sampling scheme described previously.[14] All adults aged 15–54 years in the selected households were eligible for inclusion.

Surveys of the study cohort were conducted at baseline and at follow-up 2 years later. Informed oral consent was obtained from each adult at enrolment, and personal characteristics, cirumcision status, and history of STDs were recorded through a confidential interview. A sample of venous blood was taken from all consenting subjects. Men were asked to provide a first-void urine sample, which was tested on the spot with a leucocyte esterase dipstick (LED, Nephur-Test+Leuco, Boehringer-Mannheim). Men with a positive LED test, and those reporting or found on examination to have urethral discharge, were asked to provide a urethral swab. All participants were seen by a clinician, who provided treatment for symptomatic STDs and other illnesses.

Laboratory methods

Serum was separated and tested for HIV antibodies by ELISA assay (Vironostika HIV MIXT Microelisa, Organon, Teknika, Boxtel, Netherlands). All positive samples underwent confirmatory testing with a methodologically independent ELISA (Wellcozyme HIV 1+2 GACELISA, Murex Diagnostics, Dartford, UK) and, in case of discrepant or indeterminate ELISA results, a western blot test (HIV-1 Westernblot, Epitope, Beaverton, Oregon, USA). Western blot results were considered positive if WHO criteria were fulfilled.[15] Indeterminate western blot results were considered negative in the analysis. HIV-2 has yet to be observed in this area, and data on HIV prevalence and incidence can be taken to refer to HIV-1 infection.

Serological tests for syphilis were carried out by the rapid plasma reagin (RPR) test (with VD 25 VDRL Carbon Antigen, Murex, Dartford, UK) and the *Treponema pallidum* haemagglutination test (TPHA, Fujirebio, Tokyo, Japan). TPHA seropositivity was considered to indicate past or current syphilis infection, while positivity on both TPHA and RPR tests was considered indicative of active syphilis. An initial RPR test was done in the field, and subjects with a positive RPR test were treated on the spot for syphilis.

Urethral swabs were tested for *Neisseria gonorrhoea* by gram stain, and for *Chlamydia trachomatis* by an antigen capture enzyme immunoassay (IDEIA Chlamydia, Novo Nordisk Diagnostika, Cambridge, UK). Gonorrhoea was diagnosed when intracellular gram negative diplococci were seen in urethral smears. For logistical reasons, it was not possible to attempt isolation of *N gonorrhoea* in this rural population-based study. Chlamydia infection was diagnosed after a confimatory blocking assay on all positive samples. Urethritis was defined as *N gonorrhoea/C trachomatis* infection and/or the presence of five or more polymorphs per high power field in urethral smears.

Sexual behaviour survey

To determine whether any differences in HIV incidence between intervention and comparison groups may have resulted from differences in sexual behaviour, separate random sampling of one in eight cohort members was done after the baseline and follow-up surveys. The selected individuals were revisited and interviewed concerning sexual attitudes and practices with a detailed questionnaire.

Statistical methods

Since randomisation was applied at the community level, statistical inference needed to take account of between-community variations in HIV incidence. Within each matched pair, the risk ratio (RR) of HIV incidence in the intervention community relative to the comparison community was computed. A point estimate of the overall RR was calculated as the geometric mean of the pair-specific RRs. Statistical significance was assessed with the paired t test on the logarithms of the RRs, and corresponding 95% CIs for the RR were obtained. Significance was further evaluated with the non-parametric sign test.

	Men		Women	
	Intervention (n=2881)	Comparison (n=2998)	Intervention (n=3261)	Comparison (n=3397)
HIV positive	3·4	4·1	4·1	4·7
Syphilis (TPHA+)	15	14	17	16
Active syphilis (TPHA+/RPR+)	7·9	7·8	9·5	8·8
NG/CT	2·4	3·2	..	..
Symptomatic NG/CT	0·3	0·5	..	..
Urethritis	10	11	..	..
Symptomatic urethritis	1·0	1·3	..	..
Reported GUS ever	14	16	5·1	6·1
Reported GDS ever	24	31	7·7	8·7

NG/CT=*N gonorrhoea/C trachomatis*, GUS=genital ulcer syndrome, GDS=genital discharge syndrome.

Table 1: **Baseline prevalence (%) of HIV infection and other STDs by sex, in intervention and comparison communities**

To adjust for differences between the intervention and comparison communities that might bias the estimate of impact, a logistic regression model was fitted using data on individuals and including terms for the matched pair, age-group (15–19, 20–24, 25–29, 30–34, 35–44, 45–54 years), sex, travel out of the village during the follow-up period, reported history of STD (ever) at the baseline survey, and male circumcision status. By computing observed and expected numbers of HIV seroconversions in the intervention (O_1, E_1) and comparison (O_0, E_0) communities, an adjusted RR was obtained for each pair as $(O_1/E_1)/(O_0/E_0)$. Adjusted significance tests and confidence intervals were calculated as before.

Evaluation of the impact of the intervention on the prevalence of STDs at follow-up was based on the seroprevalence of active syphilis, and on the prevalence of confirmed urethritis and *N gonorrhoea/C trachomatis* infection in men. Since many urethral infections were symptomless,[16] additional analyses were done of the prevalence of symptomatic urethritis and *N gonorrhoea/C trachomatis* infections in men. Statistical methods were as for HIV incidence.

The number of communities and the size of the cohort were chosen to provide 80% power of detecting a 50% reduction in annual HIV incidence from 1% to 0·5%, taking account of the expected level of between-community variation in incidence rates.[12]

Results

Cohort enrolment and baseline comparability

12 537 adults were enrolled at the baseline survey, representing 85% of eligible individuals from the sampled households. Detailed results of the baseline survey have been presented previously.[14] The randomisation and matching procedures were shown to have provided intervention and comparison groups that were generally similar at baseline with respect to HIV prevalence, history and prevalence of STDs, and measured risk factors for HIV infection. However, there was some imbalance in reported history of STDs (ever), travel away from the village, and male circumcision, and so these variables were adjusted for in the impact analysis.

	Intervention	Comparison	Total
Men			
Recruited	2881	2998	5879
Seen at follow-up	2052	2187	4239
Coverage (%)	71	73	72
Women			
Recruited	3261	3397	6658
Seen at follow-up	2234	2372	4606
Coverage (%)	69	70	69
Total			
Recruited	6142	6395	12 537
Seen at follow-up	4286	4559	8845
Coverage (%)	70	71	71
Losses to follow-up	1856	1836	3692
Moved	814 (13%)	924 (14%)	1738 (14%)
Temporary absence	291 (5%)	459 (7%)	750 (6%)
Died	87 (1%)	109 (2%)	196 (2%)
Other	664 (11%)	344 (5%)	1008 (8%)

Table 2: **Numbers recruited to cohort, coverage at follow-up survey, and reasons for loss to follow-up in intervention and comparison communities**

Baseline prevalences of HIV and STDs are summarised in table 1. Overall HIV prevalences at baseline were 3·8% and 4·4% in the intervention and comparison groups, respectively, while prevalences of active syphilis were 8·7% and 8·3%, respectively. HIV prevalence was higher in the intervention community in three matched pairs, and in the comparison community in the other three pairs.

Implementation of intervention

The intervention programme was successfully established in all six intervention communities. Clinic records showed that 11 632 cases of STDs were treated in the intervention health units during the 2 years of follow-up. Previous data[17] (unpublished observations) have shown that the treatment regimens would be expected to achieve cure in over 90% of cases.

Coverage at follow-up survey

8845 (71%) cohort members were seen again at the follow-up survey 2 years later. 1738 (14%) had moved permanently away, 750 (6%) were temporarily away, 196 (2%) had died, and 1008 (8%) did not participate for other reasons (refusals, inaccessibility due to heavy rains, or reason not recorded). Coverage rates were very similar in the intervention (70%) and comparison (71%) groups (table 2). Reasons for non-participation were broadly similar in the two groups, although losses due to "other" reasons occurred somewhat more frequently in the intervention group.

Impact on HIV incidence

HIV prevalence at baseline, and HIV seroconversions over the 2 years of follow-up, are shown for each community in

	HIV baseline prevalence (%)		HIV seroconversions		Crude RR (95% CI)	Adjusted RR* (95% CI)
	Intervention	Comparison	Intervention	Comparison		
Matched pair/stratum						
1 Rural	3·9	3·0	5/568 (0·9%)	10/702 (1·4%)	0·62	0·59
2 Islands	2·0	1·6	4/766 (0·5%)	7/833 (0·8%)	0·62	0·65
3 Roadside	6·8	8·6	17/650 (2·6%)	20/630 (3·2%)	0·82	0·88
4 Lakeshore	5·4	4·3	13/734 (1·8%)	23/760 (3·0%)	0·59	0·62
5 Lakeshore	2·8	4·7	4/732 (0·5%)	12/782 (1·5%)	0·36	0·35
6 Rural	1·8	4·5	5/699 (0·7%)	10/693 (1·4%)	0·50	0·50
Overall	3·8	4·4	48/4149 (1·2%)	82/4400 (1·9%)	0·57† (0·42–0·76)	0·58† (0·42–0·79)

*Adjusted for age, sex, travel during follow-up period, history of STD (ever) at baseline, and male circumcision. †Geometric mean.

Table 3: **HIV incidence over 2 years in intervention and comparison communities, and crude and adjusted risk ratios**

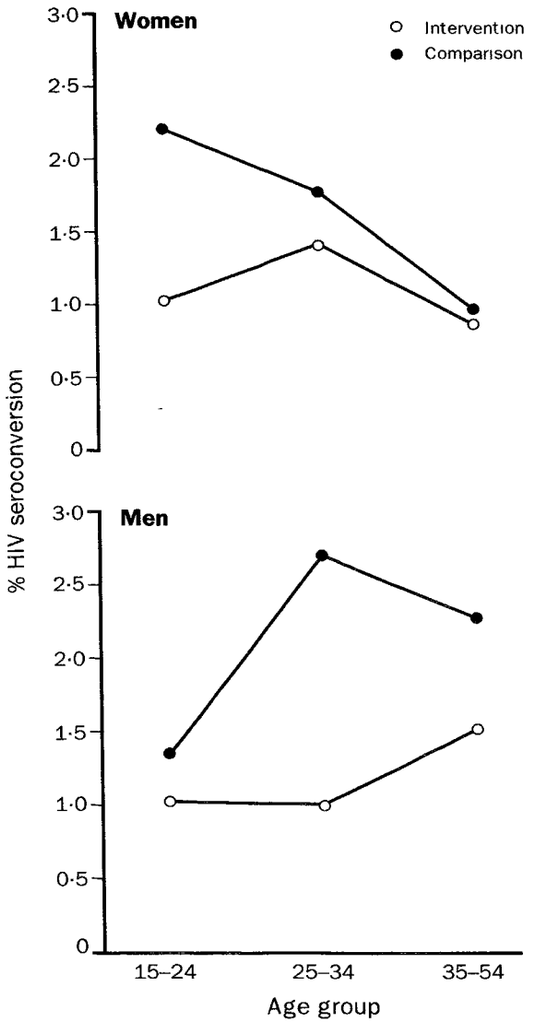

Figure 2: **Incidence of HIV infection over 2 years by age and sex in intervention and comparison communities**

table 3. HIV results were available at both baseline and follow-up for 8825 (99·8%) of those seen at follow-up. Of these, 276 (3·1%) were HIV positive at baseline, so that HIV incidence calculations were based on 8549 initially seronegative individuals—4149 in the intervention group and 4400 in the comparison group.

Over the 2 years of follow-up there were 48 seroconversions (1·2%) in the intervention group and 82 (1·9%) in the comparison group. HIV incidence varied substantially between matched pairs, but was consistently lower in the intervention community than the comparison community in all six matched pairs (table 3). When the data were analysed to take account of between-community variation, the RR for seroconversion in intervention compared with comparison communities was 0·57 (95% CI 0·42–0·76, p=0·004). When the analysis was adjusted for variables showing an imbalance beteeen the two treatment groups at baseline, the RR was virtually unchanged (0·58, 0·42–0·79, p=0·007). A non-parametric test gave similar results (two-sided p=0·03 for both unadjusted and adjusted analyses).

Seroconversion rates are shown by age and sex in figure 2. HIV incidence in the comparison group was highest in women aged 15–24 years and men aged 25–34 years. In the intervention group, the greatest proportionate reductions in incidence occurred in the same two age/sex groups. However, numbers of seroconversions at each age were small, and the differences in effect between age/sex groups were not statistically significant (test for interaction obtained by logistic regression, ignoring between-community variation, gives χ^2=2·69, 5 df, p=0·75).

Marker	Prevalence		Crude RR* (95% CI)	Adjusted RR*† (95% CI)
	Intervention	Comparison		
Active syphilis	445/4260 (10·4%)	516/4539 (11·4%)	0·90 (0·76–1·06)	0·92 (0·78–1·07)
NG/CT‡	52/2052 (2·5%)	66/2187 (3·0%)	0·68 (0·27–1·68)	0·65 (0·26–1·62)
Symptomatic NG/CT‡	19/2052 (0·9%)	26/2187 (1·2%)	0·58 (0·14–2·51)	0·72 (0·25–2·07)
Urethritis‡	119/2052 (5·8%)	152/2187 (7·0%)	0·84 (0·31–2·26)	0·84 (0·32–2·20)
Symptomatic urethritis‡	32/2052 (1·6%)	54/2187 (2·5%)	0·48 (0·09–2·70)	0·49 (0·09–2·55)

NG/CT=*N gonorrhoea/C trachomatis*.
*Geometric mean of pair-specific risk ratios. †Adjusted for age, sex, travel during follow-up period, history of STD (ever) at baseline, and male circumcision.
‡Men only.

Table 4: **Markers of STD prevalence at follow-up in intervention and comparison communities, and crude and adjusted risk ratios**

Impact on STD prevalence

Markers of STD prevalence at follow-up in the intervention and comparison communities are shown in table 4. Prevalence was consistently lower in the intervention group for all markers. However there was substantial between-community variation, and none of the differences were statistically significant when this variability was taken into account. The greatest effect observed was on symptomatic urethritis in men, with prevalences at follow-up of 1·6% in that intervention group and 2·5% in the comparison group, giving an adjusted RR of 0·49 (CI 0·09–2·55, p=0·32).

Sexual behaviour

Results from the sexual behaviour surveys at baseline and follow-up are summarised in table 5. At baseline,

	Men		Women	
	Intervention	Comparison	Intervention	Comparison
Baseline				
n	237	281	298	301
Lifetime partners (%)				
0	1	3	3	4
1	7	5	28	26
2–4	18	22	47	53
5–19	44	44	19	16
20+	31	26	3	1
Partners past year (%)				
0	7	10	9	10
1	44	36	78	83
2	22	25	9	6
3–4	18	22	3	1
5+	10	8	1	0
Follow-up				
n	216	268	248	255
Partners past year				
0	5	4	10	10
1	42	46	81	75
2	27	26	7	12
3–4	18	19	2	2
5+	8	6	0	0
Casual partners past 2 years				
0	62	55	89	87
1	14	17	6	7
2	10	11	3	3
3+	14	17	2	3

Table 5: **Numbers of sexual partners reported in intervention and comparison communities at baseline and follow-up**

reported numbers of lifetime sex partners and of sex partners during the past year were similar in the intervention and comparison groups in both sexes. At follow-up, reported partners during the past year showed no change from baseline, and there was still no material difference between the intervention and comparison groups. Data were also collected at follow-up on reported "casual" partners during the past 2 years, defined as all sex partners other than those described as "regular" or living with the respondent. Similar results were again obtained in the intervention and comparison groups.

At baseline only 2% of men reported sexual contact with bar girls or prostitutes during the past year, and this question was not repeated at follow-up. Information was collected at follow-up on condom use during the follow-up period. Condom use with sex partners other than their spouse was reported by only 2·4% of men (intervention 1·6%, comparison 3·0%) and 2·3% of women (intervention 2·7%, comparison 1·8%). Only three individuals reported regular use of condoms.

Discussion

Rational health policy decisions depend on reliable data on the cost-effectiveness of different health interventions. Because of the urgency of the AIDS epidemic, interventions have had to be made without the benefit of such data. Although a few evaluation studies have been published,[18-20] these have been observational in design, and this is the first report of a randomised controlled trial of a preventive intervention against HIV in the general population anywhere in the world.

Although WHO has advocated improved STD treatment as an additional HIV control strategy for some years, the empirical basis for this policy has been slender. While evidence from observational studies is consistent with the hypothesis that STDs act as a biological cofactor for HIV transmission,[5-8] there are substantial difficultes in interpreting such data, and the magnitude of any such effect is unknown.[21-23] The impact of improved STD treatment depends on the proportion of HIV infections in the general population that are attributable to the cofactor effect of STDs, and on the reduction in STD prevalence that might be achieved by an intervention programme, and neither is easy to predict. By incorporating randomisation within the phased introduction of an STD intervention programme in the Mwanza region of Tanzania, we have been able to obtain reliable data on the impact of this programme on HIV incidence.

We have demonstrated an overall reduction in HIV incidence of about 42% over 2 years of follow-up. The reduction occurred in both sexes, and was observed consistently in all matched pairs of study communities. The observed annual incidence of 0·9% in the comparison group was close to the 1% assumed in the study design, and similar to the incidence observed in the rural population of neighbouring Kagera region.[24] Since the intervention was randomised at the community level, it was essential to use statistical methods that took account of between-community variation in incidence. Such analysis demonstrated a highly significant impact, and it is therefore very unlikely that chance accounted for the observed differences. Are there any sources of bias which might account for the findings?

These results might be explained by a lack of comparability between the treatment and comparison communities, such that HIV incidence would have differed in the absence of intervention. Although matching and randomisation should have minimised this problem, with 12 study communities some differences cannot be ruled out. However, data collected at baseline support the comparability of the two groups and, in particular, baseline prevalences of HIV and syphilis were similar.[14] Where imbalances in risk factors were identified, these were adjusted for in the analysis, with little effect on the impact estimates.

Losses to follow-up are an important source of bias in prospective studies, since those lost may differ in risk from those continuing under follow-up. Of our cohort, 71% were seen at follow-up, or 83% after excluding those who had died or moved away permanently. These coverage rates are within the range generally considered acceptable in population-based studies. Coverage rates were almost identical in the intervention and comparison groups, and reasons for loss to follow-up were broadly similar, although losses due to "other reasons" were somewhat higher in the intervention group. This discrepancy was due mostly to a low coverage rate in one intervention community, which became inaccessible due to onset of the rains, and to field worker error in another intervention community resulting in failure to record reasons for some losses. It seems unlikely that the comparison of the two groups has been influenced substantially by losses to follow-up.

The HIV testing algorithms employed were highly sensitive and specific, but a small number of false positives or negatives cannot be ruled out. Since the HIV testing laboratory was kept blind to the origin of the serum specimens, any such misclassification should not be different between the two study groups, and the effect of misclassification would be modest dilution of the intervention effect.

Further bias may have resulted from "contamination" effects—for example, if individuals from comparison communities travelled to intervention villages to take advantage of the improved services. In our trial, the study communities were carefully chosen with respect to the geography of the region, so that distances between communities were large, and travel between them difficult and time-consuming. To check for this possibilty, however, data were collected at the intervention health units on the place of residence of patients treated for STDs. During the 2 years of follow-up, only 59 patients from the comparison communities were recorded at these units, representing only 0·5% of those treated for STDs. The effect of any contamination bias would again be to dilute the effect of the intervention. The estimate of impact may therefore be an underestimate.

We conclude that there is strong evidence that our STD intervention programme has a substantial effect on HIV incidence in this rural population. Might this be explained by changes in risk behaviour in the intervention communities? The main focus of the intervention was on the provision of improved STD treatment services. Periodic visits were made by the project team to the intervention villages to inform the population about STDs, the main emphasis being on the importance of seeking treatment promptly and on publicising the improved treatment services available. These visits were not expected to have a substantial impact on patterns of sexual behaviour. Health education activities of the National AIDS Control Programme continued equally in the intervention and comparison communities during the

follow-up period. Although health workers in intervention units were trained to offer condoms to patients attending with STDs, patient registers indicate that only 0·9% of patients took condoms. To provide empirical data on behavioural change, special surveys of sexual behaviour were conducted at both baseline and follow-up in random samples selected from the study cohort. These data indicated no change in sexual behaviour over the 2-year follow-up period, and no material difference between the intervention and comparison communities. Furthermore, condom use remained at a very low level in both groups. Whereas condoms now seem to be relatively well-accepted in Mwanza town, due partly to the intensive condom promotion activities there, acceptability and use of condoms remain low in rural areas and more intensive interventions will be needed to change this pattern.

In the absence of sexual behaviour change, the most plausible explanation for our results is that the STD treatment programme reduced HIV incidence by shortening the average duration of STDs, thus effectively reducing the probability of HIV transmission. The data on STD prevalences were consistent with this hypothesis, all measured indicators showing a lower prevalence in the intervention group than in the comparison group at follow-up, but none of these effects was statistically significant. Moreover, some indicators showed some imbalance at baseline.

An intervention based on syndromic treatment of self-reporting cases would not be expected to have a substantial effect on the prevalence of symptomless infections. The high frequency of symptomless infections in men in this population was not recognised when the trial was designed,[16] and the sample size was too small to detect a significant effect on symptomatic infections. The most reliable measure of symptomatic infections in our study cohort was the prevalence of confirmed urethritis in men reporting symptoms at the time of our survey, and it is of interest that this indicator showed the greatest reduction in the intervention group compared with the comparison group.

Our data on STDs were limited by logistical constraints on the diagnostic methods that could be employed in a rural field survey, and by the subjective nature of responses on symptomatic infections. Future trials will need to pay careful attention to these difficulties.

The magnitude of the effect on HIV incidence is the clearest evidence to date that a large proportion of HIV infections in this population are attributable to the cofactor effect of STDs, and this may help to explain the rapid heterosexual spread of HIV in many parts of sub-Saharan Africa. The largest impact of intervention was seen in women aged 15–24 and men aged 25–34; these are the age/sex groups in which the highest incidences of HIV were observed in the comparison communities, and STDs might play a particularly important part in facilitating HIV transmission in these groups. If an STD intervention strategy that relied on effective treatment of self-presenting symptomatic cases is able to reduce HIV incidence by almost half, more intensive STD control measures might have a greater effect.

How generalisable are our results to other rural populations in Africa? With an adult HIV prevalence of around 4% and an annual incidence of around 1%, the rural population of Mwanza region is fairly typical of many other parts of eastern and southern Africa. Although information on the prevalence of STDs in African population is sparse, our data are similar to other published results.[4,25] Furthermore, the intervention strategy we adopted was chosen for its potential replicability in low-income countries, and was designed to be implemented through routine primary-health-care services. However, ease of implementation will clearly vary according to the structure and funtioning of the health services. To ensure a constant supply of the drugs needed for STD treatment, the intervention in Mwanza region incorporated a special delivery system to supplement the supplies provided through the national essential drugs programme. The cost analysis will need to examine likely variations in cost and effectiveness if a less intensive intervention were established—for example, if the programme were to rely on the routine drug supply system, or if supervisions were carried out less frequently.

Many other parts of the developing world, including southern Asia where the HIV epidemic is now spreading rapidly, have high rates of STDs and poor STD treatment services, so our intervention strategy is potentially of much wider applicability. Educational interventions, aimed at modifying risk behaviour, were not evaluated in this trial, but should in our view 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 wherever STDs are highly prevalent. Commentators have emphasised the inadequacy of the resources being directed globally to HIV prevention, in particular in the developing countries most affected by the epidemic. This failure may partly reflect "donor fatigue" and doubts about the impact of control activities. The demonstration that HIV incidence can be almost halved by a modest intervention in one of the world's most disadvantaged countries should provide a message of hope, and help stimulate renewed efforts to control this epidemic throughout the developing world.

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