Improved treatment services significantly reduce the prevalence of sexually transmitted diseases in rural Tanzania: results of a randomized controlled trial

Philippe Mayaud*†, Frank Mosha‡, James Todd*†, Rebecca Balira‡, Julius Mgara‡, Beryl West*, Mary Rusizoka§, Ezra Mwijarubi†, Reverianus Gabone‡, Awena Gavyole§, Heiner Grosskurth*†, Richard Hayes* and David Mabey*

Objective: To evaluate the impact of improved case management for sexually transmitted diseases (STD) at the primary health care level on the incidence and prevalence of STD.

Design: Community-randomized controlled trial.

Setting: Mwanza region, Tanzania.

Subjects: A random cohort of about 1000 adults aged 15–54 years from each of 12 communities, in six matched pairs. One member of each pair was assigned at random to receive the intervention, and the others served as a comparison community. This cohort was surveyed at baseline and at follow-up 2 years later. About 100 antenatal clinic attenders were also studied in each community on two occasions: the first shortly after the implementation of the intervention, and the second approximately 1 year later.

Intervention: Improved services were established for the management of STD, using the syndromic approach, in rural health units.

Results: A total of 12 534 individuals were enrolled in the cohort study, of whom 8844 (71%) were seen again 2 years later. The prevalence of serological syphilis (rapid plasma reagin titre ≥1:8, *Treponema pallidum* haemagglutinin assay positive) was 6.2% in both intervention and comparison communities at baseline. At follow-up it was 5.0% in the intervention community and 7.0% in the comparison community [adjusted relative risk (RR), 0.71; 95% confidence interval (CI), 0.54–0.93; $P < 0.02$]. The prevalence of urethritis in males did not differ significantly between intervention and comparison groups at follow-up, but the prevalence of symptomatic urethritis was reduced by about 50% (adjusted RR, 0.51; 95% CI, 0.24–1.10; $P = 0.08$). There was no significant difference between the groups in the incidence of self-reported STD symptoms over the last year of the follow-up period, or in the prevalence of any STD in antenatal clinic attenders.

Conclusion: The reduction in HIV incidence previously reported in this intervention study can be attributed to a reduction in the duration, and hence the prevalence of symptomatic STD.

AIDS 1997, **11**:1873–1880

Key words: Sexually transmitted diseases, syndromic management, Africa, impact evaluation

From the *London School of Hygiene and Tropical Medicine, London UK, the †African Medical and Research Foundation, the ‡National Institute for Medical Research and the §Office of the Regional Medical Officer, Mwanza, Tanzania.

Sponsorship: Supported by the European Communities (EC) Directorate General for Development (DG VIII), with additional funding from the EC Life Sciences and Technologies for Developing Countries Programme, the UK Overseas Development Administration, the Centre for International Migration and Development, Germany and the UK Medical Research Council.

Requests for reprints to: Professor David Mabey, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

Date of receipt: 7 April 1997; revised: 4 August 1997; accepted 7 August 1997.

Venous blood was taken at each visit for syphilis serology. After separation of serum, a rapid plasma reagin (RPR) test (VD-25; Murex, Dartford, Kent, UK) was performed in the field, and subjects with a positive test were treated for syphilis with a single dose of 2.4×10^6 U of benzathine penicillin. *Treponema pallidum* haemagglutination assay (TPHA; Fujirebio, Tokyo, Japan) was performed in the laboratory in Mwanza. A RPR test (as above) was performed in the laboratory on all sera positive for TPHA, and the results of laboratory (rather than field) tests were used to assess the impact of the intervention. Titres (1:2–1:32) were determined for RPR-positive sera.

Male subjects were asked to provide a first-void urine sample, which was tested for the presence of leukocytes using the leukocyte esterase dipstick test (LED; Nephur-Test + Leuko; Boehringer-Mannheim, Lewes, Sussex, UK). Subjects reporting a urethral discharge, subjects with other complaints who were found to have a urethral discharge on examination and those with a positive LED test, were asked to permit the collection of an intra-urethral swab. The swab was smeared on a glass slide which was heat-fixed for subsequent Gram staining; the presence of intracellular Gram-negative diplococci was taken as evidence of *N. gonorrhoeae* infection. A second swab was inserted 2–3 cm inside the urethra, rotated and then placed in transport medium at +4°C for a maximum of 6 h before being frozen at −20°C and later tested for *Chlamydia trachomatis* using an antigen capture enzyme immunoassay (IDEIA Chlamydia; Novo Nordisk Diagnostika, Cambridge, Cambridgeshire, UK). Urethritis was defined as the presence of *N. gonorrhoeae* and/or *C. trachomatis* infection and/or five or more polymorphs per high power field of Gram-stained sample.

Antenatal study

In order to obtain further information on the impact of the intervention on STD in women, a sample of 100 consecutive women attending antenatal clinics in each of the 12 health centres was interviewed and examined with a speculum to collect vaginal and cervical swabs, as previously described [13]. A first survey was conducted 6 months after the beginning of the main cohort study, and a second survey 12 months later in the same communities (but with different antenatal clinic attenders), and the prevalence of STD compared in intervention and comparison communities.

Statistical methods

The intervention in this study was the provision of improved STD treatment services in health centres and dispensaries in the community. Thus the analysis of the impact of the intervention was carried out at the community level, within the matched pairs of the study. For each matched pair the relative risk (RR) of the outcome STD marker was calculated for the intervention community compared with the comparison community. The overall crude RR was calculated as the geometric mean of the RR from the six matched pairs. Statistical significance was assessed with the paired t test on the logarithms of the RR, and corresponding 95% confidence intervals (CI) for the RR were obtained.

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 about individuals and including terms for the matched pair, age group (15–19, 20–24, 25–29, 30–34, 35–44, 45–54 years), sex, circumcision in men, travel out of the village during the 2-year follow-up period, reported history of STD (ever) at the baseline survey, and the community prevalence of the STD outcome at the baseline survey. By computing observed and expected numbers for each outcome in the intervention (O_i, E_i) and comparison (O_c, E_c) communities, an adjusted RR was obtained for each pair as $(O_i/E_i)/(O_c/E_c)$. Adjusted significance tests and confidence intervals were calculated as before.

Results

Implementation of intervention

The intervention programme was successfully implemented in six communities immediately after the baseline survey. Sixty staff were trained in the use of syndromic algorithms in six health centres and 20 satellite dispensaries. The remaining six communities served as comparison areas for the study, and the intervention was implemented in them after the final follow-up survey. Clinic records showed that 11 632 STD syndromes were treated in the intervention health units during the 2-year follow-up period: 5466 in men, and 6166 in women. During the study period: 3722 sexual partners were treated in the intervention communities (0.32 per index case), but only 104 STD patients were recorded as having accepted condoms (0.9%).

Coverage of the evaluation cohort

A total of 12 534 subjects were enrolled at the baseline survey, representing 85% of eligible individuals. Detailed results of the baseline survey have been presented previously [12], and are summarized in Table 1. Prevalence of HIV infection, STD and risk factors for HIV infection did not differ significantly between intervention and comparison communities, but there were small imbalances in the reported history of STD (ever), travel away from the village, and male circumcision; these variables were adjusted for in the analysis.

Seventy-one per cent (8844) of the cohort members were seen again at the follow-up survey 2 years later. The reasons for non-attendance have been reported

Table 1. Baseline and follow-up prevalence of sexually transmitted disease (STD) markers and relative risk in intervention and compari groups in a cohort of 12 534 adults.

	Baseline		Follow-up		Relative risk		
STD marker	Intervention %	Comparison %	Intervention (%)	Comparison (%)	Crude	Adjusted*	95% confiden interval
TPHA†	15.8	15.1	108/3558 (3.0)	158/3864 (4.1)	0.70	0.69	0.35–1.38
Active syphilis‡							
RPR ≥ 1:2	8.7	8.3	452/4244 (10.7)	525/4528 (11.6)	0.90	0.90	0.79–0.99
RPR ≥ 1:4	7.3	7.1	316/4244 (7.4)	428/4528 (9.5)	0.77	0.77	0.67–0.88
RPR ≥ 1:8	6.2	6.2	214/4244 (5.0)	315/4528 (7.0)	0.69	0.71	0.54–0.93
RPR ≥ 1:16	4.8	4.7	136/4244 (3.2)	224/4528 (4.9)	0.62	0.63	0.43–0.91
RPR ≥ 1:32	3.3	3.4	91/4244 (2.1)	168/4528 (3.7)	0.56	0.58	0.38–0.90
New cases RPR ≥ 1:8			85/3893 (2.2)	141/4170 (3.4)	0.60	0.62	0.38–1.02
Urethritis	10.2	10.7	119/2052 (5.8)	152/2186 (7.0)	0.84	0.87	0.50–1.49
Symptoms in past year	1.4	1.8	37/2052 (1.8)	70/2186 (3.2)	0.48	0.51	0.25–1.03§
Symptoms now	1.0	1.3	32/2052 (1.6)	54/2186 (2.5)	0.48	0.51	0.24–1.10§
Neisseria gonorrhoeae and/or *Chlamydia trachomatis* infection	2.4	3.2	52/2052 (2.5)	66/2186 (3.0)	0.68	0.96	0.50–1.85
Symptoms in past year	0.4	0.7	21/2052 (1.0)	33/2186 (1.5)	0.47	1.14	0.46–2.83¶
Symptoms now	0.3	0.5	19/2052 (0.9)	26/2186 (1.2)	0.58	1.26	0.53–3.02¶

*Analysis adjusted for age, sex, community pair, circumcision in men, travel during the follow-up period, history of STD prior to baseline s vey and the community prevalence of STD marker at baseline. †*Treponema pallidum* haemagglutination assay (TPHA) prevalence is given baseline, and the 2-year incidence at follow-up. ‡Active syphilis defined as TPHA-positive and positive rapid plasma reagin (RPR) t §Adjusted for overall baseline prevalence of urethritis (symptomatic and asymptomatic). ¶Adjusted for overall baseline prevalence *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections (symptomatic and asymptomatic).

elsewhere; coverage and reasons for non-attendance were similar in intervention and comparison communities [8].

Syphilis

A definitive TPHA and RPR result was available at follow-up for 8772 individuals, as 20 refused to give blood and 52 TPHA results could not be resolved. Inconsistencies with the initial publication result from retesting of sera for which TPHA results at baseline and follow-up were discordant. A further 11 subjects had a missing TPHA result at baseline, and 1339 had been TPHA-positive, giving a denominator of 7422 for TPHA seroconversion. Seven hundred and nine subjects had a confirmed positive RPR test at the baseline survey; exclusion of these subjects gave a denominator for 'new cases' of syphilis of 8063.

Results of serological tests for syphilis at baseline and follow-up in intervention and comparison communities are shown in Table 1. The prevalence of TPHA positivity at baseline was similar in intervention and comparison communities (15.8% and 15.1% respectively). The incidence of TPHA seroconversion over the 2-year follow-up period was 108 out of 3558 in the intervention communities (3.0%), and 158 out of 3864 in the comparison communities (4.1%; adjusted RR, 0.69; 95% CI, 0.35–1.38). After adjustment, this represented a reduction in incidence of 30% in the intervention communities, although the difference was not statistically significant at the 5% level ($P = 0.25$).

The prevalence of serological syphilis (RPR-positive, TPHA-positive) at follow-up was significantly lower in intervention than in comparison communities. If an RPR titre of ≥ 1:8 was taken as positive, the adjust relative risk was 0.71 (95% CI, 0.54–0.93; $P < 0.0$ but whichever titre of RPR is considered, the prev lence was significantly lower in the intervention co munities. The adjusted relative risk decreased wi increasing titre, from 0.90 at a titre of ≥ 1:2 to 0.58 a titre of ≥ 1:32. After excluding subjects with positi RPR and TPHA at baseline (many of whom remain RPR-seropositive in spite of adequate treatment), t prevalence of new cases of serological syphilis (RP ≥ 1:8, TPHA-positive) was 85 out of 3893 in the int vention communities (2.2%), and 141 out of 4170 the comparison communities (3.4%; adjusted R 0.62; 95% CI, 0.38–1.02; $P = 0.06$).

Urethritis

Urethral swabs were taken from 1144 men (96% those eligible). Of the 51 eligible men from whc swabs were not obtained, 29 were in the interventi communities and 22 in the comparison communiti Six men refused to give a urine sample, none of whc reported symptoms. All men from whom swabs we not taken were considered negative in the subsequc analysis.

The prevalence of urethritis and of *N. gonorrhoe* and/or *C. trachomatis* infection in men at follow-up shown in Table 1. The prevalence of urethritis and *N. gonorrhoeae*/*C. trachomatis* infection was lower in t intervention communities, but not significantly so. T prevalence of confirmed urethritis in men wl reported having had a urethral discharge in the p year was lower in the intervention communiti (adjusted RR, 0.51; 95% CI, 0.25–1.03; $P = 0.0$ The prevalence of confirmed urethritis in men repo

ing urethral discharge at the time of examination was also reduced by approximately 50% (adjusted RR, 0.51; 95% CI, 0.24–1.10; $P = 0.08$). The reduction in the overall prevalence of urethritis in the intervention group was entirely accounted for by the reduction in symptomatic cases.

Self-reported STD symptoms

Of 2052 men in the intervention communities, 236 reported a genital discharge or ulcer in the past year at follow-up (11.5%), compared with 269 out of 2186 men in comparison communities [12.3%; crude RR, 0.90 (95% CI, 0.51–1.59); adjusted RR, 0.94 (95% CI, 0.57–1.56); difference not significant]. Among women, 137 out of 2234 complained of one of these symptoms in the past year at follow-up in intervention communities (6.1%), and 155 out of 2372 in comparison communities [6.5%; crude RR, 0.96 (95% CI, 0.54–1.72); adjusted RR, 1.00 (95% CI, 0.58–1.72); difference not significant].

Antenatal clinic attenders

A total of 1149 women were enrolled in the first survey. Of these, eight (0.7%) declined examination and were excluded from the analysis, leaving 575 women in the intervention and 566 in the comparison communities. Mean age was 25.0 years in both groups. At the second survey, 1239 women were enrolled, all of whom agreed to be examined and provided samples; 614 were from intervention, and 625 from comparison communities. Mean age was 25.0 and 24.9 years respectively.

The prevalence of STD in sampled antenatal clinic attenders at the first and second surveys are shown in Table 2. Approximately 40% had an STD, and there was no significant difference in the prevalence of any STD between intervention and comparison communities on either occasion. Analysis using different titres to define RPR positivity (from 1:2 to 1:32) failed to reveal any differences between the two groups (data not shown).

Discussion

We have previously reported that improved syndromic management of STD reduced the incidence of HIV infection in this population by 42% over a 2-year period [8], and postulated that this was achieved through a reduction in the duration of symptomatic bacterial STD, which can facilitate heterosexual HIV transmission. The initial publication failed to provide conclusive evidence in support of this hypothesis [8]. Since that time, the results of syphilis serology by RPR titre have become available, and we have performed an analysis of the impact on STD prevalence which was appropriately adjusted for the community prevalence of STD at baseline. By removing an important source of variation, the latter adjustment resulted in an appreciable increase in precision for certain outcome measures. We have demonstrated that after adjustment, there was a significant reduction in the prevalence of serological syphilis in the intervention communities, and that the prevalence of symptomatic urethritis in men was reduced by approximately 50%. We have also documented a reduction in TPHA seroconversion of approximately 30% in the intervention communities, although this did not achieve statistical significance.

As reported previously [8], we believe the impact of this intervention on HIV infection and other STD reflects improved access to effective STD treatment; this would be expected to reduce the duration, and hence the prevalence of symptomatic STD in the population; a reduced prevalence should, in turn, lead to a reduction in incidence, although this may not be immediately apparent if the main reservoir of infected individuals are not symptomatic. It seems unlikely that this intervention had a great impact on sexual behaviour (e.g., a reduction in the number of sexual partners, or increased use of condoms), as this was not its primary intention. At follow-up of the main cohort, the reported total number of sexual partners, and of casual partners, did not differ from baseline or between intervention and comparison communities [8]. Less than 1%

Table 2. Prevalence of sexually transmitted disease (STD) markers and relative risk in intervention and comparison groups in two random surveys of antenatal clinic attenders.

STD marker	First round		Second round		Relative risk, second round (95% confidence interval)	
	Intervention n = 575 (%)	Comparison n = 566 (%)	Intervention n = 614 (%)	Comparison n = 625 (%)	Crude	Adjusted*
Neisseria gonorrhoeae/ Chlamydia trachomatis prevalence†	7.0	9.9	6.7	6.6	0.91 (0.48–1.73)	0.93 (0.49–1.75)
Trichomonas vaginalis	28.5	28.6	25.4	23.2	1.08 (0.92–1.28)	1.09 (0.92–1.28)
Active syphilis prevalence‡	7.6	8.3	6.8	6.4	1.08 (0.68–1.73)	1.08 (0.66–1.79)
Any STD§	37.3	41.3	34.4	32.3	1.11 (0.88–1.39)	1.07 (0.79–1.43)

*Analysis adjusted for age only. †For baseline prevalence of *N. gonorrhoeae* and *C. trachomatis* n = 964; missing data are due to contaminated *N. gonorrhoeae* cultures. ‡Active syphilis defined as *Treponema pallidum* haemagglutination assay positive and rapid plasma reagin titre of ≥ 1:8. §Any STD is defined as *N. gonorrhoeae, C. trachomatis, T. vaginalis* or active syphilis.

to long-standing infections; unfortunately antenatal screening for syphilis is not routinely performed in these rural health centres.

We have shown that it is possible to reduce the incidence of HIV infection by approximately 40% in a rural African population by improving the management of symptomatic STD at health centres and dispensaries. The intervention also reduced the prevalence of serological syphilis and of symptomatic urethritis in men. Our data suggest that a high proportion of HIV infections in sub-Saharan Africa may be attributed to the increased risk of heterosexual HIV transmission in the presence of a 'classical' STD. They also suggest that this cofactor effect is more pronounced for symptomatic than for asymptomatic STD. Recent data showing that symptomatic STD increase shedding of HIV in the genital tract provide a plausible biological mechanism for this interaction [23–25]. The implementation of improved services for the treatment of STD at the primary health care level should be given the highest priority.

If it were possible to reduce STD rates in developing countries to those prevailing in Northern Europe, this could have a dramatic impact on the heterosexual HIV/AIDS epidemic in Africa and Asia. At present, given the lack of appropriate screening tests and the high prevalence of asymptomatic infection in both men and women, mass treatment of STD may be the only feasible way to do this. Since HIV infection is now the leading cause of death among young adults in many African countries [26,27], and is spreading rapidly in some parts of Asia, there is an urgent need to measure the impact and cost-effectiveness of this approach: if it is shown to be effective, the international community must be mobilized to provide the resources needed to apply it on a wide scale.

Acknowledgements

We thank the Principal Secretary, Ministry of Health, the manager of the National AIDS Control Programme, and the Director General of the National Institute for Medical Research, Tanzania, for permission to carry out and publish the results of this study; the Municipal Officer of Health, Mwanza, the Director General of the African Medical and Research Foundation, and regional, district, ward and community leaders for their support; and we thank the populations of the study communities for their support and hospitality.

References

1. Arya OP, Lawson JB: Sexually transmitted diseases in the tropics. Epidemiological, diagnostic, therapeutic and control aspects. *Trop Doctor* 1977, 7:51–56.
2. De Schryver A, Meheus A: Epidemiology of sexually transmitted diseases: the global picture. *Bull WHO* 1990, 68:639–654.
3. Schulz KF, Cates W, O'Masra PR: Pregnancy loss, infant death, and suffering: legacy of syphilis and gonorrhoea in Africa. *Genitourin Med* 1987, 62:320–325.
4. Wasserheit JN: The significance and scope of reproductive tract infections among third world women. *Int J Gynecol Obstet* 1989, 3 (suppl):S145–S168.
5. Cameron DW, Simonsen JN, D'Costa LJ, *et al.*: Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989, ii:403–407.
6. Pepin J, Plummer FA, Brunham RC, Piot P, Cameron DW, Ronald AR: The interaction of HIV and other sexually transmitted diseases: an opportunity for intervention. *AIDS* 1989, 3:3–9.
7. Laga M, Alary M, Nzila N, *et al.*: Condom promotion, sexually transmitted disease treatment, and declining incidence of HIV-1 infection in female Zairian sex workers. *Lancet* 1994, 344:246–248.
8. Grosskurth H, Mosha F, Todd J, *et al.*: Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995, 346:530–536.
9. World Health Organization: Recommendations for the management of sexually transmitted diseases. *WHO Advisory Group Meeting on Sexually Transmitted Diseases Treatments. WHO/GPA/STD/93.1.* Geneva: WHO; 1993.
10. Hayes R, Mosha F, Nicoll A, *et al.*: A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 1. Design. *AIDS* 1995, 9:919–926.
11. West B, Changalucha J, Grosskurth H, *et al.*: Antimicrobial susceptibility, auxotype and plasmid content of *Neisseria gonorrhoeae* in Northern Tanzania: emergence of high level plasmid mediated tetracycline resistance. *Genitourin Med* 1995, 71:9–12.
12. Grosskurth H, Mosha F, Todd J, *et al.*: A community trial of the impact of improved sexually transmitted disease treatment on the HIV epidemic in rural Tanzania: 2. Baseline survey results. *AIDS* 1995, 9:927–934.
13. Mayaud P, Grosskurth H, Changalucha J, *et al.*: Risk assessment and other screening options for the identification of gonorrhoea and chlamydial infection in rural Tanzanian antenatal clinic attenders. *Bull WHO* 1995, 73:621–630.
14. Grosskurth H, Mayaud P, Mosha F, *et al.*: Asymptomatic gonorrhoea and chlamydial infection in rural Tanzanian men. *BMJ* 1996, 312:277–280.
15. Buvé A, Mosha F, Watson-Jones D, *et al.*: Is asymptomatic urethritis in men an obstacle to effective STD control? A community study in Mwanza, Tanzania. *XI International Conference on AIDS*. Vancouver, July 1996 [abstract Mo.C. 341].
16. Newell J, Senkoro K, Mosha F, *et al.*: A population-based study of syphilis and sexually transmitted disease syndromes in North-Western Tanzania. 2. Risk factors and health seeking behaviour. *Genitourin Med* 1993, 69:421–426.
17. Hira SK, Bhat GJ, Chikamata DM, *et al.*: Syphilis intervention in pregnancy: Zambian demonstration project. *Genitourin Med* 1990, 66:159–164.
18. Temmerman M, Mohamed Ali F, Fransen L: Syphilis prevention in pregnancy: an opportunity to improve reproductive and child health in Kenya. *Health Policy Planning* 1993, 8:122–127.
19. Vuylsteke B, Laga M, Alary M, *et al.*: Clinical algorithms for the screening of women for gonococcal and chlamydial infection: evaluation of pregnant women and prostitutes in Zaire. *Clin Infect Dis* 1993, 17:82–88.
20. Larsen SA, Steiner BM, Rudolph AH: Laboratory diagnosis and interpretation of tests for syphilis. *Clin Microbiol Rev* 1995, 8:1–21.
21. Goeman J, Kivuvu M, Nzila N, *et al.*: Similar serological response to conventional therapy for syphilis among HIV positive and HIV negative women. *Genitourin Med* 1995, 71:275–279.