Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial

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Summary

Background The study tested the hypothesis that community-level control of sexually transmitted disease (STD) would result in lower incidence of HIV-1 infection in comparison with control communities.

Methods This randomised, controlled, single-masked, community-based trial of intensive STD control, via home-based mass antibiotic treatment, took place in Rakai District, Uganda. Ten community clusters were randomly assigned to intervention or control groups. All consenting residents aged 15–59 years were enrolled; visited in the home every 10 months; interviewed; asked to provide biological samples for assessment of HIV-1 infection and STDs; and were provided with mass treatment (azithromycin, ciprofloxacin, metronidazole in the intervention group, vitamins/anthelmintic drug in the control). Intention-to-treat analyses used multivariate, paired, cluster-adjusted rate ratios.

Findings The baseline prevalence of HIV-1 infection was 15·9%. 6602 HIV-1-negative individuals were enrolled in the intervention group and 6124 in the control group. 75·0% of intervention-group and 72·6% of control-group participants provided at least one follow-up sample for HIV-1 testing. At enrolment, the two treatment groups were similar in STD prevalence rates. At 20-month follow-up, the prevalences of syphilis (352/6238 [5·6%) *vs* 359/5284 [6·8%]; rate ratio 0·80 [95% CI 0·71–0·89]) and trichomoniasis (182/1968 [9·3%] *vs* 261/1815 [14·4%]; rate ratio 0·59 [0·38–0·91]) were significantly lower in the intervention group than in the control group. The incidence of HIV-1 infection was 1·5 per 100 person-years in both groups (rate ratio 0·97 [0·81–1·16]). In pregnant women, the follow-up prevalences of trichomoniasis, bacterial vaginosis, gonorrhoea, and chlamydia infection were significantly lower in the intervention group than in the control group. No effect of the intervention on incidence of HIV-1 infection was observed in pregnant women or in stratified analyses.

Interpretation We observed no effect of the STD intervention on the incidence of HIV-1 infection. In the Rakai population, a substantial proportion of HIV-1 acquisition appears to occur independently of treatable STD cofactors.

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Introduction

There is substantial evidence that sexually transmitted diseases (STDs) enhance transmission and acquisition of HIV infection,[1–3] and that genital-tract infections increase shedding of the virus.[4,5] Furthermore, treatment of disorders that lead to genital ulcer or discharge reduces, but does not eliminate, shedding.[4,5] Randomised clinical trials are needed to show whether STD control will result in a lower incidence of HIV infection and to estimate the magnitude of any such effects.[6] The only published trial so far, the Mwanza study in Tanzania, randomised 12 community clusters to improved, clinic-based, management of symptomatic STDs or to the existing standard of care.[7] In 1995, the Mwanza study reported a significantly lower incidence of HIV-1 infection in the intervention group than in the control (38% difference in the fully adjusted analysis), despite limited effects on STD prevalence and incidence.[7–9]

The Rakai STD Control for AIDS Prevention Study, initiated in 1994, was designed as an efficacy trial to test the hypothesis that population-level STD control would result in a lower incidence of HIV-1 infection. Because of the lack of a clinical infrastructure in Rakai District, and preliminary evidence of high STD prevalence,[10–12] we implemented community-level control of STDs through a home-based, mass-treatment strategy; all consenting adults were given directly observed STD therapy in the home every 10 months, irrespective of laboratory test results or the presence of symptoms. This approach was adopted so that all STDs (with or without symptoms) in HIV-infected and HIV-uninfected individuals would be treated, and official (marital/consensual) and other sexual networks would be covered. We report intention-to-treat analyses of STD prevalence and incidence and of incidence of HIV-1 infection in intervention and control populations for the baseline and first two follow-up surveys (20 months of follow-up), the period between trial initiation and unmasking by the Data Safety and Monitoring Board.

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Methods

Study design

The study was designed as a community-based, randomised, controlled, single-masked efficacy trial.

Study population

Rakai is rural district in southwestern Uganda, with a population in 1990 of 384 000. 56 communities were selected from among trading villages on secondary roads in the south and central regions of the district, because they met criteria of year-round road access, population stability, and projected incidence of HIV-1 infection of up to 2·0 per 100 person-years of observation.[12] Communities were aggregated into ten clusters of four to seven contiguous villages; clusters were designed to encompass social, and thus sexual networks, to keep to a minimum reintroduction of STDs.[12,13] Clusters were grouped into three blocks, based on model projections of prevalence of HIV-1 infection and were randomly assigned within blocks to intervention or control (five clusters per treatment group). Before analysis, the clusters were paired within randomisation blocks; pairing was based on observed prevalence of HIV-1 infection at baseline.

Clusters were randomly assigned either mass STD treatment or mass anthelmintic, vitamin, and iron-folate treatment. The study was single masked, and participants were told that their community would be assigned either regimen by chance. Although participants were not informed of their community's allocation, intervention and control regimens could not be concealed from project personnel. Intensive training and supervision were used to ensure the same activities and dissemination of information in both study groups; the numbers of contacts, treatment schedules, and all general heath and preventive measures (mobile clinics, health education, condom promotion and distribution, access to HIV-1 test results and to serological counselling) were the same in both groups, and drug formulations were selected to be similar in appearance.

All consenting permanent residents of study communities, aged 15–59 years, were eligible for enrolment, irrespective of HIV-1 status. In this open cohort, newly eligible individuals (including people who moved into the area, those previously absent, and those who had refused consent but subsequently consented to participate) were enrolled at each follow-up study round. The study was designed to provide sufficient person-years of observation to detect a difference in incidence of HIV-1 infection of at least 35% on the assumption of an incidence of HIV-1 infection of up to 2 per 100 person-years (α=0·05, 1-β=0·80). Sample-size estimates included adjustment for clustering and expected losses to follow-up.[12]

A follow-up study of pregnant women and their infants was incorporated within the main trials,[14] to assess the effect of STD control in these vulnerable populations. Pregnant women were identified by interview and by screening of urine: human chorionic gonadotropin was measured in women who were not visibly pregnant and who reported no menses within the previous month. Pregnant women were visited post partum for additional interview and collection of samples from mother and child for HIV-1 and STD testing. The mean interval between mass treatment and postpartum follow-up was about 4 months. Data are presented on pregnant women enrolled up to and including round 3 of the main study (the equivalent time reported for the overall STD-control trial).

Eligible individuals in the STD-control trial were read a consent form, which explained study goals, indicated that communities would be randomly assigned one of the two regimens, described study procedures (randomisation, masking of study assignment, enrolment procedures, data and samples to be collected, means of ensuring confidentiality of information), and explained potential risks and benefits of participation. Individuals were informed of the right to decline all or part of the study activities, without loss of benefits. Consenting individuals signed or fingerprinted the form. Participants were not paid, but all households, whether or not they participated, were offered a free bar of soap worth about US$0·50. Pregnant women were also provided with a second, detailed consent form outlining the mother and infant study, which they signed or fingerprinted if they agreed to enrolment. The trial was approved by the AIDS Research Subcommittee of the Uganda National Council for Science and Technology, the Columbia University Institutional Review Board, the Johns Hopkins University Committee on Human Research, and the National Institutes of Health Office for Protection from Research Risk. Safety was assessed by an independent Data Safety and Monitoring Board, composed of US-based and Ugandan participants, established by, but independent from, the National Institutes of Health.[12]

Methods

All households in both study groups were visited every 10 months (study rounds). Five rounds were planned originally. Data reported here are based in the first three rounds (initial and two follow-up rounds). About 10 days before each survey round in any given cluster, a complete household census was taken to list all residents whether present or absent from the community, to identify eligible individuals, and to record births and deaths and migrations in and out of the study clusters. At the time of the survey, census data were verified in each home, and field workers made two return visits within a week to attempt to contact absent eligible individuals. In the first follow-up round, a third return visit was made about a month after the main survey.

During the survey visit, consenting participants underwent a sociodemographic, behavioural, health, and treatment-seeking interview in the home. Names of marital/consensual partners were recorded. Questionnaires were administered in private by same-sex interviewers fluent in the local languages (predominantly Luganda).

Biological samples were collected in the home immediately after interview.[12] Venous blood was collected for testing for HIV-1, syphilis, and herpes simplex virus type 2 (HSV-2). All serum samples were assayed for HIV-1 by two different EIA tests (Vironostika HIV-1, Organon Teknika, Charlitte, NC, USA: and Cambridge Biotech, Worcester, MA, USA), with western-blot confirmation of EIA discordant tests and of all samples showing seroconversion (HIV-1 WB Bio-Merieux-Vitek, St Louis, MO, USA). Samples with indeterminate results on western blotting were further tested for HIV-1 RNA (Gen-Probe, San Diego, CA, USA) so that recent seroconverters could be identified.

Syphilis screening used the non-treponemal TRUST (Toluidine Red Unheated Serum Test, New Horizons, Columbia, MD, USA); positive samples were confirmed by *Treponema pallidum* haemagglutination (Sera-Tek, Fujirebio, Tokyo, Japan). Samples with high TRUST titres (reciprocal titres $\geqslant$8) but negative results on the latter test were further tested by fluorescent treponemal antibody absorption (IFA Test System, Zeus Scientific, Raritan, NJ, USA) for detection of early primary syphilis infections that might be missed by haemagglutination. HVS-2 serology was done at the Centers for Disease Control and Prevention (immunoblot assay for HSV-1 or HSV-2 glycoprotein).[15]

Participants provided 10 mL first-catch urine, which was assayed for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* by ligase chain reaction (Lcx Probe System, Abbott Laboratories, Abbott Park, IL, USA). The sensitivity and specifity of this test are higher than those of culture or gram strain.[16,17] Because of cost, ligase chain reaction testing was done on only a random sample of participants aged 15–29 years. Urine for HIV-1 test (Calypte HIV-1 urine EIA, Calypte Biomedical, Alameda, CA, USA) was done for individuals who declined to provide a blood sample or whose sample was insufficient; about 10% of HIV-1 results in both treatment groups were based on the urine assay. Samples positive on urine EIA underwent western-blot confirmation. The sensitivity of the urine EIA is 98·7%.[18] Leucocyte esterase dipstick testing (Boehring-Mannhein, France) was done on a random sample of 3879 urine samples from male participants at round 3, to assess male urethral

inflammation. Urine human chorionic gonadotropin was used to screen women for pregnancy, to guide treatment regimens in both study groups.

All women were asked to self-collect two vaginal swabs during the home visit.[12] One swab was inoculated into an *Trichomonas vaginalis* culture kit (InPouch TV, BioMed Diagnostics, San Jose, CA, USA). A second swab was rolled onto a microscope slide, which was gram-stained and read for bacterial vaginosis by a quantitative, morphologicak scoring system.[12,19] The presence of *Candida albicans* on the slides was also recorded.

Participants who reported genital ulcers were asked to permit study personnel to collect an ulcer swab for Multiplex PCR (Roche Molecular Systems, Alameda, CA, USA), for diagnosis of ulcers caused by HSV-2, *Treponema pallidum*, and *Haemophilus ducreyi*.[20] Ulcer swabs are the only samples for which collection depended on self-reporting of symptoms.

Most laboratory testing was done by staff unaware of treatment allocation. However, the TRUST syphilis test and trichomonas culture were done in the field laboratory on the day of sample collection, and allocation could not be concealed from the staff. Syphilis confirmatory testing was done in the main laboratory, with masking. Quality control, which included retesting of randomly chosen serum samples for syphilis and HIV-1, was carried out in both Uganda and the USA, by technicians unaware of treatment allocation.

STD mass treatment (intervention) and anthelmintic vitamin-iron-folate (control) were offered to all consenting individuals at each survey round, immediately after interview/sample collection, whether or not they had symptoms. Single-dose oral regimens were selected for all infections except syphilis. Drugs were taken in the presence of the project worker (directly observed treatment) so that compliance could be ensured and treatment coverage assessed.

The STD mass treatment consisted of azithromycin, ciprofloxacin, and metronidazole.[12] Azithromycin (1000 mg single dose) is active against *H ducreyi*, *Chlamydia trachomatis*, and many strains of *N gonorrhoeae*; data also suggest efficacy against incubating and early syphilis. Ciprofloxacin (250 mg single dose) is effective against *N gonorrhoeae* and *H ducreyi*. Ciprofloxacin (FDA category C) was not given to pregnant women, who instead received cefixime (400 mg; effective in a single dose against *N gonorrhoeae*). Metronidazole (2·0 g) is the recommended single-dose regimen for trichomoniasis and provides short-term remission in 70–85% of cases of bacterial vaginosis;[21] it is safe in pregnancy (FDA category B).[22] Benzathine benzylpenicillin (2·4 million IU intramuscular injection) was given in the home to TRUST-positive intervention-group participants within 24 h of serum collection; treatment was based on serological findings, since the administration of injections to uninfected individuals would be unacceptable. The drug regimen was given over 2 days (azithromycin and ciprofloxacin in day 1; metronidazole and intramuscular benzathine benzylpenicillin on day 2). To provide mass treatment in each community took about 4 days—a total of 1 month per cluster. Strategies to keep side-effects to a minimum, to avoid drug resistance, to screen for drug allergies, and to monitor adverse reactions, have been described previously.[12]

Participants in the control group were offered an anthelmintic drug (mebendazole 100 mg, two doses), an iron-folate tablet, and, as of the second survey round, a single low-dose multivitamin. Drugs were given over 2 days, as in the intervention group. Mebendazole (FDA category C) was withheld in pregnant women. For ethical reasons, control participants who reported current STD symptoms at interview were referred for free treatment to Rakai Project mobile clinics (present in the community only at the time of the survey); those with STD symptoms between survey rounds were advised to attend government health posts. STD management in Rakai Project and government clinics was in accordance with the Uganda Ministry of Health syndromic management regimens, based on Centers for Disease Control and Prevention guidelines.[23] Control participants positive for syphilis on serology were referred to government health posts for free treatment; the project stocked the government posts with penicillin to ensure adequate supplies, but undertook no additional activities in these facilities.

In both treatment groups, communities received identical education on prevention of HIV infection from project educators via community health meetings; confidential HIV-serological counselling services offered by trained project counsellors; free condoms made available by project health educators, counsellors, and survey teams; and free general health care at Rakai Project mobile clinics, provided to all community members, whether or not they consented to study enrolment. All participants were advised to seek care in government clinics if they experienced symptoms that suggested STDs between survey rounds and told where they could seek condoms between survey rounds (health posts, social marketing shops, Rakai project serological counsellors).

Statistical analyses

An intention-to-treat analysis, based on the randomisation clusters, was used for the primary trial outcome (incidence of HIV-1 infection); this variable was calculated in a cohort of HIV-1-negative individuals (HIV-1 incidence cohort) enrolled at round 1 or 2 and followed up at round 2, 3, or both. Incidence rates per 100 person-years were calculated for the whole 20-month follow-up period (rounds 1–3), and for 10-month intervals. Incidence rates are also given for the women enrolled in the pregnancy study and for main study subgroups by sociodemographic characteristics at enrolment, behaviours, presence or absence of STD symptoms during the interval of seroconversion risk, and by STDs diagnosed at the visit before the interval of risk. Because treatment allocation was by cluster, all statistical assessments of variability used the cluster as the unit of analysis. Rate ratios of incidence of HIV-1 infection in intervention/control groups were calculated as geometric means of the cluster-pair ratios, with 95% CIs derived from *t* intervals of log-transformed incidence rates with equal weighting per cluster.[7,9,24,25] Adjusted rate ratios of seroconversion in the intervention group relative to the control group were based on a Poisson multiple regression model of incidence rates, by comparison of observed to expected seroconversions in each cluster.[24] Covariates in the model included community prevalence of HIV-1 infection at baseline, individual-level variables found to differ between study groups at enrolment, and variables thought to be related to risk of HIV-1 infection. These variables included sex, age (15–19, 20–29, 30–59), marital status (currently married or in union/not currently married), religion (Muslim/other, which also substantially adjusted for differentials in circumcisions and alcohol use), ever-use of condoms, numbers of reported sex partners in the past year, distance of sex partners' residence from respondent's home ($\leq$5 km, >5 km), and sex for payment or gifts.

For the secondary study outcomes (STD prevalence), we assessed all HIV-1-positive and HIV-1-negative participants (STD cohort), and report the prevalence of STDs in the whole population at each survey round, so that the population-level exposure to STDs can be estimated. The analysis represented a conservative estimate of the impact of the intervention on STDs: the observed population in this open cohort includes individuals who received STD treatment in preceding study rounds, as well as those newly enrolled at rounds 2 and 3 (including new migrants), who had not had the opportunity to receive the study treatment, and enrolled individuals who had previously refused treatment. Prevalence at round 1 was used to assess comparability of STD rates between the study groups before implementation of the trial. Analyses of differences in prevalence rates between the groups were based on cluster-paired observed and expected frequencies calculated by a multiple logistic regression model, incorporating individual covariates. Overall adjusted prevalence ratios were then estimated from the log-transformed cluster-pair observed/expected ratios with CIs based on the *t* distribution.[24,25] Covariates included in the models for

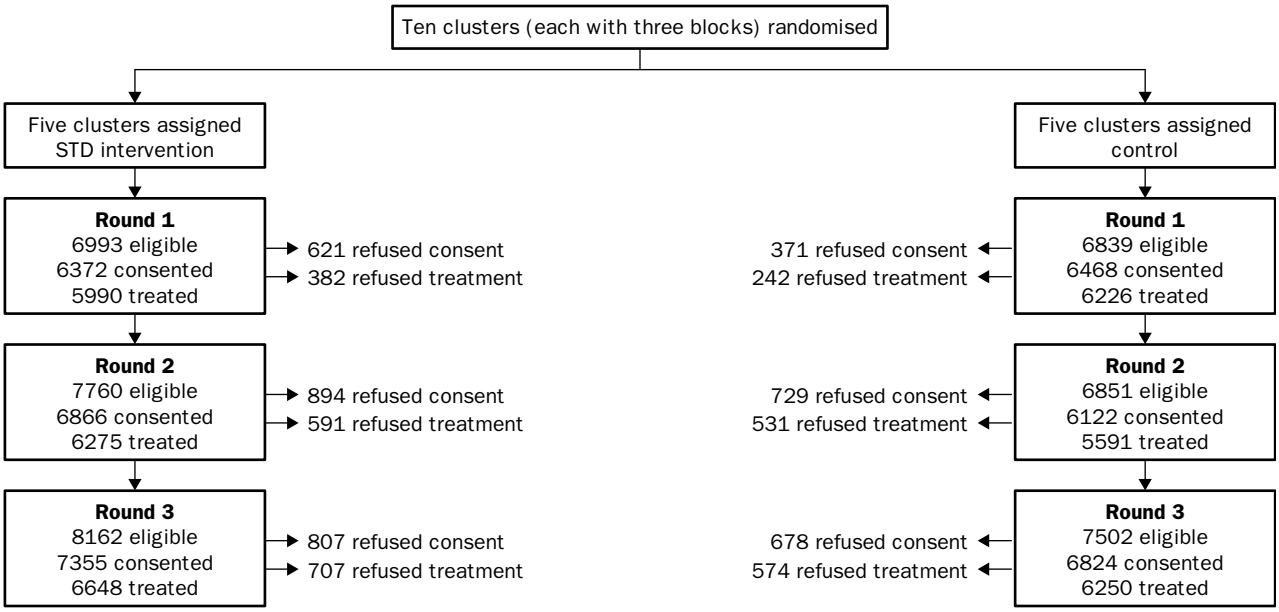

Figure 1: **Trial profile**

each STD endpoint consisted of the baseline prevalence of the relevant STD and the sociodemographic/behavioural covariates described above for Poisson analyses. When small numbers precluded estimates of CIs for cluster-adjusted risk ratios, a covariate adjustment was used and a Wilcoxon signed-rank test was used to assess the significance of differences between study groups. Rates of new syphilis and trichomonas infections per 100 person-years were estimated in previosly uninfected individuals, and statistical inference was based on the Poisson regression methods.

Incidence rates of HIV-1 infection among individuals with and without STDs or STD symptoms were used to estimate the risk of HIV-1 acquisition associated with these exposures, after adjustment for sex, age and number of sex partners, by Poisson regression. These adjusted risks and the prevalence of STD exposures among incident cases were then used to estimate the population attributable fraction of incident HIV-1 infection that might be attributed to STDs or symptoms in this population.[26]

The study Data Safety and Monitoring Board prospectively agreed to a stopping rule that the trial would be terminated if the primary HIV-1 infection endpoint was reached, as shown by a significant difference in the rate of this endpoint between the intervention and control groups, or by conditional power estimate indicating that no significant difference could be achieved. In January, 1998, the board judged that the study had met its primary objective. Analyses of HIV-1 infection were therefore initiated on the first three rounds for the main STD trial and for the maternal follow-up (ie, two 10-month follow-up intervals), for which laboratory STD testing was most complete. Further home visits were made after this decision, to provide participants with information on study findings, to collect supplementary data, and to offer STD mass treatment to all participants in both study groups, based on considerations of safety and STD health benefit data accrued in the first three rounds.

Results

Participants

Of all residents enumerated at baseline, 82·5% in the intervention group and 84·2% in the control group were present in the community at the time of the study visit to the community.[12] Of the people recorded in the census but absent at time of the survey visits, 58·7% were absent long term for reasons of employment or education, 5·9% had migrated away, and 0·4% had died. The remaining 35·0% of absentees (about 6% of the census population), were away short term for family visits, work-related travel, and other reasons. The proportions absent were similar in all three survey rounds, and were equivalent in both study groups. Two return visits over a period of a week were made to each household when a potential participant was not present.

Figure 1 provides a trial profile summary; in this open cohort study census and enrolment of new participants occurred at each study round. Of residents aged 15–59 present at baseline, 91·1% (6372 of 6993) in the intervention group and 94·6% (6468 of 6839) in the control group consented to enrolment. The proportions consenting were similar in all three study rounds (figure 1). The proportion accepting treatment among those who agreed to enrolment was high (90% or more) in both groups at each round, and the study provided mass treatment coverage to over 80% of all eligible residents present in the community in each round. Over the three rounds, serum samples were provided by 92% of intervention-group participants and 89% of control-group participants, urine samples by 95% and 92%, and self-collected vaginal swabs by 94% and 96% of female participants.

Not all consenting participants provided samples for assessment of HIV-1 and STD status; the STD intention-to-treat cohort and the HIV-1 incidence cohort (figure 2) therefore represent a subset (over 90%) of all consenting individuals. The STD intention-to-treat cohort consisted of 15 127 individuals who provided serum or urine samples for assessment of HIV-1 status at enrolment in round 1 (n=11486) or round 2 (n=3641). Follow-up was achieved for 11 686 (77·3%) of these people—6143 were in the intervention group (follow-up rate 78·0%) and 5543 in the control group (follow-up 76·4%).

The HIV-1 incidence cohort consisted of the 12 726 HIV-1-negative eligible individuals among the STD intention-to-treat cohort. 9569 were enrolled during round 1 and 3157 during round 2. At least one sample for HIV-1 testing was provided during the 20-month follow-up period by 4927 (74·6%) of those in the intervention group and 4449 (72·6%) of those in the control group.

In the final study round, participants were asked whether they knew the study group to which they had been assigned. In preliminary data from 1237 interviews,

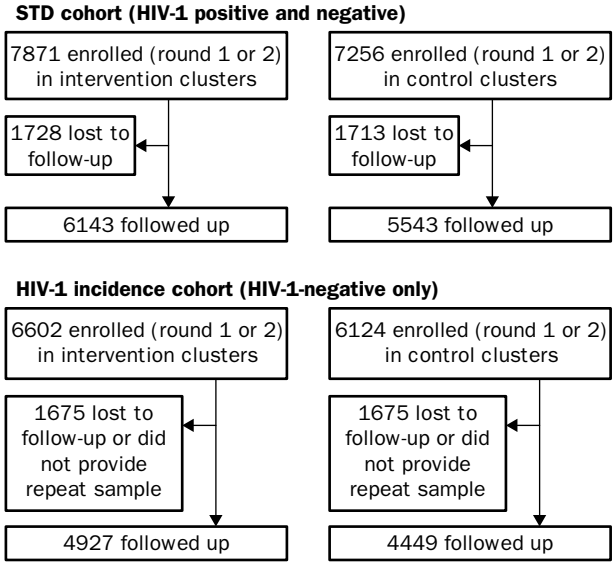

Figure 2: **Enrolment and follow-up of STD cohort and HIV-1 incidence cohorts**

748 respondents (60·5%) said they did not know their assigned regimen. 489 nominated a study assignment—204 (41·7%) were incorrect, and 285 (58·3%) correctly identified the allocation, only slightly more than the 50% expected by chance.

The randomisation produced study populations with similar distributions of age and sex (table 1). Absolute differences between the groups in sociodemographic and behavioural characteristics were small, and the estimates of STD prevalence/incidence and incidence of HIV-1 infection were adjusted for characteristics with differing distribution at baseline. The proportions of the two groups reporting ever having exchanged sex for money or gifts, and travel outside the district, were similar. High-risk occupations were reported by only 3% of men in either group (trucking, military, bar work) and 2% of women (mainly bar work).

Table 2 shows characteristics and behaviours at follow-up for members of the STD and HIV-1 incidence cohorts who provided repeat biological samples in round 2 or 3. The intervention and control populations were similar in sex and age distribution. Again, most differences in demographic and behavioural characteristics were small in absolute terms, and there was no evidence of differential change in characteristics or behaviours between baseline and follow-up. Consistent condom use with the primary partner increased in both groups, from 2·6% in round 1 to 5·5% in round 3 (p=0·001) in the intervention group and from 3·0% to 4·1% (p=0·001) in the control group. There was, however, no significant difference in consistent condom use between the groups.

At follow-up, a higher proportion of intervention-group than control-group respondents said that they had sought treatment for STD symptoms from Rakai project or government clinics. The difference was significant in the HIV-1 incidence cohort (p=0·05). Syphilis treatment was reported by 5·8% of control-group and 12·9% of intervention-group participants (p=0·004), consistent with the home-based syphilis treatment offered in the intervention group as opposed to referral in the control group (table 2).

In both groups, individuals lost to follow-up were younger than those who continued under observation. Individuals aged 15–29 years represented 72·3% and 73·5% of those lost to follow-up in the intervention and control groups. However, individuals lost to follow-up did not differ from those who continued in the study as regards other characteristics, sexual behaviours, or STD symptoms (results not shown).

STD prevalence at enrolment and treatment effects

At round 1, rates of syphilis, trichomoniasis, bacterial vaginosis, and gonorrhoea and of reported STD

	Proportion of group (%)*			
	STD cohort (HIV-positive and HIV-negative individuals)		HIV-1 incidence cohort (HIV-1-negative individuals only)	
	Intervention (n=7871)	Control (n=7256)	Intervention (n=6602)	Control (n=6124)
M/F	46·7/53·3	45·8/54·2	48·3/51·7	47·4/52·6
Age (years)				
15–19	24·4	24·2	28·3	27·6
20–29	36·4	36·7	34·3	34·9
30–39	20·5	20·6	18·1	18·1
40–59	18·7	18·5	19·3	19·5
Marital status				
Currently married/in union	56·9	60·9	55·4	60·3
Never married/in union	29·6	26·1	24·2	19·2
Sociodemographic data				
Occupation agriculture/housework	55·4	59·9	54·8	60·2
Any education	91·1	87·0	90·8	86·7
Religion Muslim	11·1	15·9	11·9	16·6
Circumcised (male participants)	13·5	18·4	14·4	19·0
Sexual and risk behaviours				
⩾2 sex partners previous year	18·3	16·6	18·0	16·3
Sex partner(s) >5 km away	14·4	11·6	14·3	11·3
Condom use, ever	25·2	20·6	24·8	19·3
Sex for money/gift, ever	18·8	21·3	12·2	11·9
Travel outside Rakai, previous year	50·7	50·0	50·8	50·2
Alcohol use, previous month	51·1	47·6	48·9	45·9
HIV-1 positive				
All participants	16·1	15·5	..	..
Male participants	13·3	13·0	..	..
Female participants	18·6	18·0	..	..

*Prevalence of variables reported at baseline; response rate exceeded 95% for all variables.

Table 1: **Sociodemographic and behavioural characteristics of STD intention-to-treat cohort and HIV-1 incidence cohort at enrolment**

	Proportion of group (%)			
	STD cohort		HIV-1 incidence cohort	
	Intervention (n=6143)	Control (n=5543)	Intervention (n=4927)	Control (n=4449)
M/F	45·2/54·8	44·4/55·6	46·8/53·2	46·0/54·0
Age (years) at enrolment				
15–19	15·9	15·7	16·7	15·5
20–29	37·7	37·7	37·7	37·3
30–39	23·3	23·9	21·0	22·1
40–59	23·1	22·7	24·6	25·1
Sociodemographic data				
Currently married/in union*	61·0	65·6	59·4	64·9
Occupation agricultural/housework*	58·8	63·1	58·7	64·1
Religion Muslim†	11·2	16·3	12·0	16·8
Circumcised (male participants)†	13·5	18·3	15·4	19·7
Sexual and risk behaviours*				
⩾2 sex partners previous year	15·7	14·9	14·9	13·4
Sex partner(s) >5 km away	13·3	10·6	10·5	7·6
Any condom use in previous 6 months	13·8	10·7	14·2	10·5
Travel outside Rakai District	46·7	44·1	45·9	43·8
Alcohol use, previous month	52·5	48·9	51·2	45·9
STD treatment seeking*				
Received syphilis treatment	12·9	5·8	11·5	5·7
Reported STD symptom between rounds‡	13·9	13·2	11·8	11·4
% of those with symptoms receiving treatment between rounds	20·0	16·4	18·8	15·8
Current STD stmptom‡	3·8	3·7	3·4	2·8

*During follow-up. For participants followed up at rounds 2 and 3, status at round 3 is reported. †At enrolment. ‡Genital ulcer, discharge, and dysuria. Numbers with symptoms STD cohort: intervention=852, control=733; HIV cohort: intervention=580, control=507.

Table 2: **Sociodemographic and behavioural characteristics of STD intention-to-treat cohort and HIV-1 incidence cohort at follow-up (rounds 2 and 3)**

symptoms in the previous year were similar in the intervention and control groups (table 3). Among people aged 15–29 at enrolment in this rural population, the rates of gonorrhoea and chlamydia infection were fairly low. The rate of chlamydia infection was significantly higher in the intervention group than in the control group, but the absolute difference was small.

During follow-up, syphilis prevalence decreased in both treatment groups, but the reduction was greater in the intervention population and the differences between the groups were significant at rounds 2 and 3. We used a four-fold decrease in syphilis TRUST titre or seroreversion as a test of cure.[23] During the first-follow-up interval, among individuals with initial TRUST titres of 1 in 8 or higher, the proportion who met test-of-cure criteria was 64·7% in the intervention group and 25·5% in the control group (cluster-adjusted rate ratio 2·66 [95% CI 1·39–5·10]).

The prevalence of trichomoniasis fell in both groups, but the rate was significantly lower in the intervention group than in the control group at both follow-up rounds. There was a slight fall in the prevalence rate of bacterial vaginosis in intervention-group women and a rise among control-group women; the difference between the groups was of borderline significance at round 3.

In the random sample tested for chlamydia infection and gonorrhoea by ligase chain reaction, the rates of both diseases were higher in the intervention group than in the control group at round 1. During follow-up, however, the prevalence of both infections fell in the intervention group but not in the control group, and there were no significant differences between treatment groups at round 2 or 3. The cluster-adjusted mean rate of gonorrhoea fell by 0·8% in the intervention group and increased by 0·4% in the control group (p=0·003). The mean rate of chamydia infection fell by 1·8% in the intervention group but increased by 0·3% in the control group (p=0·001). Proportions of participants reporting symptoms that suggest genital-tract infection at the time of a follow-up visit or in the period between surveys did not differ between the intervention and control groups.

During the first 10-month follow-up interval (round 1 to 2), the incidence of new cases of syphilis (newly TRUST positive [titre 1 to 4 or higher], confirmed by *Treponema pallidum* haemagglutination or fluorescent treponemal anbibody absorption) was lower in the intervention group than in the control group (45/2645 [1·7 per 100 person-years] *vs* 45/2090 [2·2 per 100 person-years) but the difference was not significant (rate ratio adjusted for cluster and variables 0·65 [0·06–6·82]). Syphilis incidence decreased during the second follow-up interval, and for the whole 20-month interval, the incidence was 1·5 per 100 person-years in both groups. The cumulative incidence of newly diagnosed *Trichomonas vaginalis* infection was 4·8 per 100 person-years (116/2397 person-years) in the intervention group and 9·1 per 100 person-years (182/1993 person-years) in the control group (0·52 [0·35–0·79]).

The presence of vaginal candidosis was assessed on gran-stained slides at follow-up, and moderate or heavy infection was found in 89 (2·7%) of 3660 intervention-group women and 78 (2·3%) of 3393 control-group women at round 3. Vaginal pruritus was reported by 5·3% (302/5730) of women in the intervention group and 4·2% (228/5477) in the control group (rate ratio 1·23 [0·93–1·51]). Leucocyte esterase dipstick testing of urine, done for a sample of men in round 3, was positive in 3·2% (55/1705) of those in the intervention group and 5·2% (113/2174) of those in the control group (rate ratio adjusted for cluster and variable 0·64 [0·34–1·20]).

At enrolment, HSV-2 serological testing of a sample of participants aged 15–29 revealed a seroprevalence of 31·2% (79/253) in men and 60·9% (182/299) in women, with similar distributions in the treatment groups. To date, 207 genital-ulcer swabs have been tested by multiplex PCR: 89 (43·4%) were positive for HSV-2, eight (3·9%) *Treponema pallidum*, and six (2·9%) for *H ducreyi*. The remaining 103 (51·1%) samples were

	Round 1			Round 2			Round 3		
	Intervention	Control	Prevalence ratio (95% CI)*	Intervention	Control	Prevalence ratio (95% CI)*	Intervention	Control	Prevalence ratio (95% CI)*
STDs and genital-tract infections									
Syphilis	611/5780 (10·6%)	544/5773 (9·4%)	1·04 (0·61–1·75)	295/5932 (5·0%)	341/4807 (7·1%)	0·64 (0·42–0·99)	352/6238 (5·6%)	359/5284 (6·8%)	0·80 (0·71–0·89)
Trichomoniasis	797/3323 (24·0%)	785/3270 (24·0%)	0·93 (0·70–1·24)	361/3309 10·9%)	554/2970 (18·7%)	0·58 (0·38–0·87)	182/1968 (9·3%)	261/1815 (14·4%)	0·59 (0·38–0·91)
Bacterial vaginosis	1310/2598 (50·4%)	1311/2560 (51·2%)	1·00 (0·81–1·22)	1678/3307 (50·7%)	1522/2852 (53·4%)	0·92 (0·82–1·04)	1707/3660 (46·6%)	1827/3397 (53·8%)	0·87 (0·74–1·02)
Gonorrhoea	36/1701 (2·1%)	18/1580 (1·1%)	2·51 (0·52–12·2)	19/1062 (1·8%)	16/1008 (1·6%)	1·28 (0·22–7·47)	8/996 (0·8%)	14/1136 (1·2%)	0·66†
Chlamydia infection	68/1698 (4·0%)	35/1578 (2·2%)	1·50 (1·08–2·08)	35/1062 (3·3%)	31/1008 (3·1%)	0·96 (0·64–1·43)	24/997 (2·4%)	29/1136 (2·6%)	0·88 (0·50–1·53)
STD symptom‡									
Genital ulcer	566/6363 (8·9%)	532/6461 (8·2%)	1·03 (0·85–1·24)	400/6866 (5·8%)	337/6113 (5·5%)	1·02 (0·81–1·28)	419/7383 (5·7%)	364/6827 (5·3%)	1·02 (0·80–1·29)
Discharge	466/6362 (7·3%)	401/6461 (6·2%)	1·07 (0·50–2·29)	463/6865 (6·7%)	373/6113 (6·1%)	1·10 (0·96–1·27)	482/7384 (6·5%)	411/6827 (6·0%)	1·10 (0·93–1·31)
Dysuria	639/6363 (10·0%)	635/6461 (9·8%)	1·02 (0·82–1·27)	463/6866 (6·7%)	354/6113 (5·8%)	1·13 (0·83–1·54)	472/7388 (6·4%)	386/6831 (5·7%)	1·12 (0·89–1·41)

*Prevalence ratio=intervention/control; adjusted for cluster and covariates, STD rates at enrolment, sex, age, marital status, religion, number of sex partners in previous year, partners resident ⩾5 km distance from respondent's home, and condom use.
†Adjusted for covariates but not cluster; CI cannot be estimated owing to small numbers: Wilcoxon test p=0·44.
‡Symptoms in previous year for round 1 and in previous 10 months for rounds 2 and 3.

Table 3: **STD prevalence/symptoms at round 1 (before intervention) and rounds 2, 3 (follow-up) intention-to-treat cohort**

negative by PCR for all three pathogens. All 207 samples were positive for β-globin, which suggests that sample collection was satisfactory.

Prevalence and incidence of HIV-1 infection

At baseline, 1267 (16·1%) of 7871 participants in the intervention group and 1132 (15·6%) of 7256 in the control group were HIV-1 positive. The proportion positive was somewhat higher in female than in male participants, but sex-specific rates did not differ between the treatment groups (table 1).

The rate of incident HIV-1 infection was the same in both study groups for the whole follow-up period (round 1 to 3), in individual study rounds, and in each of the randomisation cluster pairs (table 4). The fully adjusted (covariate and cluster) rate ratio of incident HIV-1 infection in the intervention group compared with the control group was 0·97 (95% CI 0·81–1·16). Although STD rates decreased in both groups in the round 2–3 interval compared with the round 1–2 interval, the incidence of HIV-1 infection in both groups was somewhat higher during the second follow-up interval (1·8 per 100 person-years) than in the first period (1·3 per 100 person-years).

Incidence rates of HIV-1 infection did not differ between intervention and control subgroups based on sex, age, or marital status, among partners in HIV-1 discordant or HIV-1-concordant relationships, or among individuals reporting single or multiple partners, partners located nearby (5 km or less, most of whom lived within a given study cluster), or partners located more distantly (table 5). In both study groups, the incidence was somewhat higher among participants reporting ever-use of condoms at enrolment than in those reporting no such use, but the incidence rates were the same in both study groups. The incidence of HIV-1 infection was higher in the intervention group than in the control group among participants reporting condom use in the previous 6 months, but numbers were small and the difference was not significant (p=0·88). We did not observe any significant differences in incidence between the study groups among participants reporting STD symptoms (at follow-up or during the period between rounds), or among individuals with laboratory-diagnosed STDs at the beginning of the interval between rounds.

Mother and infant study

With the exception of syphilis, which was actively treated in pregnant women in both study groups, the prevalence rates of other STDs at the postpartum visit were significantly lower in the intervention group than the control group (table 6).

Data on incidence of HIV-1 infection are currently available for 705 initially seronegative mothers in the

	Intervention group			Control group			Rate ratio of incident HIV-1 infection	
	Incident cases/ HIV-1-negative individuals	Person-years	Incidence per 100 person-years	Incident cases/ HIV-1-negative individuals	Person-years	Incidence per 100 person-years	Cluster-adjusted rate ratio (95% CI)	Adjusted rate ratio (95% CI)*
Study rounds								
Rounds 1–3	101/4927	6611	1·5	89/4449	6056	1·5	0·99 (0·8–1·2)	0·97 (0·81–1·16)
Rounds 1–2†‡	33/3196	2531	1·3	27/2930	2125	1·3	1·09 (0·5–2·3)	1·08 (0·51–2·26)
Rounds 2–3†‡	55/3655	3126	1·8	47/2951	2690	1·8	0·96 (0·7–1·3)	0·94 (0·74–1·18)
Randomised blocks and clusters‡								
Block A, clusters A1	17/823	1071	1·6	9/353	475	1·9	0·84§	1·02
Block A, clusters A2	15/799	1144	1·3	28/1489	2082	1·3	0·97§	0·99
Block B, clusters B1	23/1178	1433	1·6	22/1082	1383	1·6	1·00§	0·99
Block B, clusters B2	17/1016	1389	1·2	13/716	981	1·3	0·92§	1·01
Block C	29/1111	1574	1·8	17/809	1135	1·5	1·23§	1·00

*For study rounds, multivariate Poisson regression including adjustment for baseline HIV-1 prevalence, cluster, sex, age, marital status, religion, number of sex partners, distance of partner, and condom use. For randomised blocks and clusters, multivariate Poisson regression for each cluster pair with same covariates as for study rounds. CIs are not applicable for pairwise comparisons. †Excludes individuals who provided samples only at rounds 1 and 3. ‡Cluster-specific incidence rates for all followed up between rounds 1 and 3. §Cluster-adjusted rate ratio for rounds 1–3.

Table 4: **Incidence rates of HIV-1 infection and rate ratios**

	Intervention group			Control group			Cluster-adjusted rate ratio (95% CI)
	Cases/HIV-1-negative individuals	Person-years	Incidence per 100 person-years	Cases/HIV-1-negative individuals	Person-years	Incidence per 100 person-years	
Sex							
Male	43/2307	3023	1·4	39/2044	2714	1·4	0·89 (0·59–1·34)
Female	58/2620	3588	1·6	50/2405	3342	1·5	1·10 (0·87–1·40)
Age at enrolment (years)							
15–19	12/1191	1464	0·8	11/1041	1294	0·8	1·22 (0·06–23·0)*
20–29	43/1731	2296	1·9	42/1552	2116	2·0	0·89 (0·46–1·73)
30–59	46/2005	2851	1·6	36/1856	2646	1·4	1·43 (0·68–3·04)
Marital status at enrolment							
Married/union	68/2921	4082	1·7	53/2882	4047	1·3	1·18 (0·68–2·06)
HIV-1 discordant	19/121	177	10·7	14/124	170	8·2	1·26 (0·73–2·16)
HIV-1-negative concordant	23/1471	2281	1·0	18/1543	2325	0·8	1·16 (0·67–2·01)
Any education	91/4463	5988	1·5	79/2829	5195	1·5	0·95 (0·77–1·19)
Muslim	5/589	795	0·6	10/748	1020	1·0	0·68 (0·43–1·09)
Sex partners†							
One in previous year	69/3169	4315	1·6	57/2958	4118	1·4	1·11 (0·90–1·36)
Two or more in previous year	30/1047	1394	2·2	28/871	1173	2·4	0·84 (0·51–1·40)
Partners ⩽5 km	88/4276	5817	1·5	80/4006	5486	1·4	1·00 (0·84–1·19)
Partners >5 km	13/651	795	1·6	9/443	57	1·6	0·87 (0·28–2·67)
Condom use at enrolment							
Ever	25/1038	1341	1·9	17/684	897	1·9	1·0 (0·08–12·4)*
Never	76/3889	5270	1·4	72/3759	5159	1·4	0·99 (0·53–1·87)
Condom use, previous 6 months†							
Any	19/701	918	2·1	8/468	623	1·3	..‡
None	82/4421	5687	1·4	81/3979	5431	1·5	0·98 (0·61–1·60)
Sex pay/gifts ever	20/915	1241	1·6	22/930	1326	1·9	0·92 (0·59–1·42)
Travel out of Rakai†	55/2441	3246	1·7	42/2167	2952	1·4	1·09 (0·48–2·50)
Alcohol previous month†	56/2486	3423	1·6	45/2125	2945	1·6	0·94 (0·51–1·46)
Circumcision (male)	3/339	434	0·7	7/379	498	1·4	..‡
STD symptoms							
Genital ulcer	10/375	523	1·9	8/321	447	1·8	1·02 (0·49–2·15)
Discharge	8/316	444	1·8	8/261	360	2·2	0·87 (0·04–18·7)*
Dysuria	8/459	626	1·3	11/429	616	1·8	0·63 (0·40–1·01)
STD genital-tract infection§							
Syphilis	10/400	588	1·7	11/401	568	1·9	0·87 (0·04–15·3)*
Trichomoniasis	15/529	723	2·0	16/521	752	2·1	1·12 (0·38–3·28)
Bacterial vaginosis	29/1274	1756	1·7	22/1255	1770	1·2	1·24 (0·69–2·21)
Gonorrhoea	1/25	35	2·9	1/9	11	9·1	. .‡
Chlamydia infection	1/57	79	1·3	0/36	48	0·0	. .‡

*Based on randomisation blocks, since too few events within clusters. †During interval of risk of seroconversion. ‡Cluster-adjusted rate ratio cannot be estimated owing to small numbers. §At beginning of interval of risk of seroconversion.

Table 5: **Incidence of HIV-1 infection according to sociodemographic and behavioural characteristics, and STD symptoms and diagnoses**

intervention group and 600 in the control group. During pregnancy, incidence of HIV-1 infection was 3·6 per 100 person-years in the intervention group (ten in 278 person-years) and 2·7 per 100 person-years in the control group (seven in 256 person-years; covariate-adjusted rate ratio 1·3, p=0·81). The incidence between the post-partum visit and subsequent follow-up (average duration of postpartum follow-up 8 months) was 2·0 per 100 person-years (eight in 406 person-years) in the intervention group and 1·2 per 100 person-years in the control group (four in 340 person-years; covariate-adjusted rate ratio 1·55, p=0·81). These findings suggest that the mass-treatment strategy significantly decreased the rate of maternal cervical and vaginal infections during pregnancy, with no concomitant reduction in incidence of HIV-1 infection either during pregnancy or after delivery.

	Prevalence of infection post partum		Rate ratio (95% CI)*
	Intervention group	Control group	
Syphilis	80/1323 (6·0%)	75/1056 (7·1%)	0·91 (0·58–1·45)
Trichomoniasis	72/1350 (5·3%)	198/1137 (17·4%)	0·28 (0·14–0·58)
Bacterial vaginosis	533/1364 (39·1%)	609/1154 (52·8%)	0·74 (0·67–0·81)
Gonorrhoea	8/770 (1·0%)	15/714 (2·1%)	0·50 (0·27–0·91)
Chlamydia infection	9/770 (1·2%)	25/714 (3·5%)	0·32 (0·14–0·71)

*Adjusted for cluster and covariates.

Table 6: **STD prevalence at delivery in mother and infant study**

Discussion

This study took place in a rural area with high rates of HIV-1 infection and STDs. The study implemented an intensive STD control strategy in this underserviced setting. The intervention resulted in significant differences from the control group in prevalence and incidence of some STDs (table 3), particularly in pregnant women, and declines in STDs over time. These data represent a conservative assessment of intervention STD effects; so that we could assess community-level exposure to STDs in both groups, we report STD data for all consenting individuals at baseline and follow-up rounds, whether or not they had an opportunity to receive treatment in previous rounds.

We found no differences in incidence of HIV-1 infection between the study groups, either in the whole HIV-1-negative cohort or in pregnant women. The rate ratio was close to unity overall and in all clusters and subgroups.

We believe that the lack of an effect on HIV-1 incidence was unlikely to be due to problems in design or

follow-up. Blocked randomisation achieved reasonable similarity between the treatment groups at baseline (table1) and during follow-up (table 2), and follow-up rates were similar and over 72% in both groups (figure 1). The distribution of individuals lost to follow-up (disproportionately younger individuals), was similar in both groups. Stratified and multivariate analyses adjusted for suspected confounding variables and factors for which there was any imbalance by treatment group at enrolment or follow-up. Treatment coverage was high; over 80% of all eligible adults present in the communities (and over 90% of those enrolled) accepted treatment. The study was single masked, and participants may have discerned their randomised assignment. Preliminary data collected in the final survey round suggest that a minority of participants knew their treatment assignment, and unmasking is unlikely to be a substantial cause of bias. Laboratory technicians were also masked to treatment for key outcomes. Unmasking tends to result in overly large estimates of treatment effect,[27] which has not occurred in this study. Moreover, unmasking of participants would presumably operate through differential behavioural change or differential loss to follow-up, for which we observed no evidence (tables 1 and 2).

An important issue is whether the ethically mandated STD services offered to participants in the control group might have resulted in convergence of treatment intensity between groups and possibly diluted an effect on incidence of HIV-1 infection. Although we cannot dismiss the possibility that the services offered to the controls could have diluted impact, we believe this factor alone cannot explain the absence of an effect on HIV-1 infection. The prevalence of symptomatic illness (genital ulcer, discharge, or dysuria) at the time of the survey visits was less than 4% in either group, and fewer than 14% of participants reported these symptoms between rounds (table 2). Of those with symptoms between survey visits, 20% or less reported they had used adequate treatment services (Rakai Project or government clinics), and the proportion reporting such use was higher in the intervention group than the control group (table 2). Although prevalences of STDs were lower in both groups at the end of the second follow-up visit (round 3) than at the first follow-up (round 2), there was no commensurate decline in incidence of HIV-1 infection, which was higher in the second follow-up period than in the first (table 4). Historical comparisons are difficult to interpret, but incidence of HIV-1 infection among members of HIV-1-discordant couples and HIV-1-negative concordant couples in this trial was almost identical to that observed in 1990 to 1991.[28] In pregnant women, differences in STD rates between treatment groups were significant for all infections except syphilis, which shows a substantial effect of the intervention on STDs. There was, however, no observed effect on incidence of HIV-1 infection. Thus our data do not suggest a reduction in incidence of HIV-1 infection over time associated with either intervention or control STD regimens.

There is no evidence that the mass treatment intervention had adverse effects on vaginal ecology. Vaginal candidosis was found in only 2·7% of intervention-group and 2·3% of control-group women. The prevalence of bacterial vaginosis fell in the intervention group, and the difference from the control group was highly significant in pregnant women. The proportions of women reporting vaginal symptoms (discharge or pruritus) were low and similar in the two groups.

Reinfection with STDs or introduction of HIV-1 infection via sexual contact with partners outside the study communities may have diluted treatment effects. However, few HIV-1-negative participants (10·5% intervention, 7·6% control) reported sexual contacts with outside partners (table 2), and the incidence of HIV-1 infection was similar among people reporting or not reporting such contacts (table 5). *Trichomonas vaginalis*, which is prevalent and highly transmissible, provides a possible surrogate marker for potential contamination. In the intervention group, the prevalence of trichomoniasis infection fell from 24·0% in round 1 to 9·3% in round 3. The persistence of this infection could reflect the contribution of individuals who previously refused treatment (about 10% of participants), of newly enrolled women who had no previous opportunity for treatment, and of treated women who had become reinfected by internal or external partners. Overall, however, the reduction in trichomoniasis over time, and the significant difference in prevalence between the treatment groups, suggest that the intervention achieved a reasonable measure of STD control, and that the absence of an effect on incidence of HIV-1 infection cannot be ascribed to contamination in the intervention group. Nevertheless, the persistence of STDs over the 20-month follow-up illustrates the difficulty of eliminating these infections from a population in the short term.

We considered the possibility that recurrent disorders, such as bacterial vaginosis (which is refractory to long-term cure with currently available single-dose or multidose regimens[21]), or untreated disorders such as herpetic ulcers, might overwhelm any effects associated with treatment of classic STDs. Bacterial vaginosis was very common in this population (50·4% at enrolment), and although the rate was somewhat lower in the intervention group than in the control group, prevalence remained high despite metronidazole treatment. We and others have shown that bacterial vaginosis is associated with both prevalent and incident HIV-1 infections,[29,30] and its persistence in the study population may have contributed to the lack of an intervention effect on incidence of HIV-1 infection. 43·5% of reported genital ulcers were positive for HSV-2. Moreover, only 6·8% of ulcers were positive for *Treponema pallidum*, *H ducreyi*, or both, which suggests that the majority of self-reported genital ulcers in this population may not be amenable to STD treatment regimens. Future research should address the causes and importance of such lesions.

The Rakai setting represents a mature HIV-1 epidemic, with a prevalence of the infection of 15·9%. The high level of HIV-1 exposure, particularly in discordant couples (table 5), could compromise the ability of the study to show STD treatment effects. Simulations by Robinson and colleagues[31] estimated a lower contribution of STDs to HIV-1 acquisition in such established epidemics.

To assess further the contribution of STDs to acquisition of HIV-1 in the Rakai setting, we estimated the population attributable fraction[26] of HIV-1 acquisition associated with STDs.[32,33] We estimate that if syphilis, trichomoniasis, gonorrhoea, chlamydia infection, and chancroid could be completely controlled in this setting, the rate of HIV-1 acquisition might be reduced by about 17%.[32] Although the intervention decreased the rates of

treatable infections in the general population (table 3) and in pregnant women, even the intensive mass treatment could not eradicate these endemic disorders. We further estimate that the population attributable fraction of HIV-1 acquisition associated with STDs that are difficult to control (bacterial vaginosis and genital ulcers due to HSV-2) is about 20%.

We undertook analyses to assess whether the periodic mass treatment may have been less effective than other STD control strategies, such as continuous availability of syndromic STD management. Thus, we estimated the population attributable fraction of incident HIV-1 infection associated with STD symptoms reported at time of interview or during the interval between surveys. We concluded that about 10% of HIV-1 acquisition could be attributed to such symptoms.[33] Furthermore, our data suggest that a substantial proportion of reported symptoms are not associated with a treatable STD. Previous data from our own and other studies indicate that STD symptoms have low sensitivity and specificity for the identification of laboratory-proven treatable STDs.[34–36]

Our findings contrast with those of the community-based trial in Mwanza, Tanzania, which implemented a symptom-based, syndromic strategy for STD control.[7,8] The Mwanza study reported a significantly lower incidence rate of HIV-1 infection in the intervention group than in the control group (0·6 *vs* 0·9 per 100 person-years), while observing limited STD effects[9] (we have calculated incidence estimates per person-year for purpose of comparison, with permission from R Hayes). In the Mwanza trial, the prevalence of active syphilis was significantly lower in the intervention group than in the control group at follow-up (adjusted rate ratio 0·90 [95% CI 0·79–0·99]). The rates of newly diagnosed syphilis and of reported male urethritis were also lower in the intervention group than in the control group, and these findings were of borderline significance, but there were no differences in STD rates among pregnant women, and gonorrhoea and chlamydia infection rates remained essentially unchanged among men in both groups.[9]

The difference between the Mwanza and Rakai studies with respect to the effects of STD control on incidence of HIV-1 infection is unlikely to be due to random error. The fully adjusted rate ratio of incident HIV-1 infection associated with the intervention was 0·97 (95% CI 0·81–1·16) in Rakai and the adjusted risk ratio in Mwanza was 0·62 (0·45–0·85). The difference between these estimates is significant ($p<0·01$). The contrasting results of these two studies are unlikely to be explained by differences in the background epidemiology of target STDs. Despite differences in diagnostic methods, the baseline prevalences of syphilis and trichomoniasis were similar in the two studies.[9] The combined prevalence of gonorrhoea and chlamydia infection in pregnant women of the control group (the group in which assessment was most comparable in the two studies) was 5·6% in Rakai, and 6·6% in Mwanza.[9] Bacterial vaginosis was common in Rakai,[29] as has been observed elsewhere in east Africa,[30] but was not reported in the Mwanza study. The prevalence of positive leucocyte dipstick esterase tests in men was about 27% in Mwanza,[55] compared with 4·3% in Rakai. The high proportion of Mwanza men with a positive result for this test probably reflects the prevalence of endemic schistosomiasis in the lakeside communities,[35] whereas schistosomiasis was not prevalent in the Rakai study communities. HSV-2 was a common genitourinary pathogen in the Rakai population: swab data are not available from the Mwanza trial population, but HSV-2 seroprevalence was similar in both the Mwanza and Rakai populations (R Hayes, personal communication, 1998). The most important difference between the two study populations seems to be the degree of HIV-1 exposure. In Rakai, prevalence of HIV-1 infection at baseline was 15·9%, and the observed incidence was 1·5 per 100 person-years, whereas in Mwanza, the corresponding values were 4·1% and 0·6–0·9 per 100 person-years. In Rakai, with high background rates of HIV-1 infection, a substantial proportion of acquisition seems to occur independently of treatable STD cofactors. The Mwanza and Rakai investigators are collaborating on joint analyses of empirical data and on modelling, to assess the contribution of STDs to incidence of HIV-1 infection in these different epidemic settings.

STD control remains an important public-health priority in its own right. Previously reported findings in Rakai[40] are consistent with other reports on the benefits of STD control for maternal and infant health. Also, our unpublished data show increased individual-level risks of HIV-1 acquisition and transmission in the presence of STDs. However, although both our mass treatment strategy and the Mwanza syndromic approach resulted in reductions in STD prevalence, both studies indicate that intensive population-level control or eradication of these endemic disorders is difficult, particularly in the short term. There is therefore a need for research to find out whether modifications of existing STD control strategies, including integration of mass treatment with syndromic approaches, could be effectively applied for STD control in underserviced communities.

Contributors

All investigators contributed to the interpretation of results and the preparation of the paper. Maria J Wawer assisted with study design, implementation, execution, and data analysis. Ronald Gray contributed to study design, implementation, and data analysis. Nelson Sewankambo was responsible for study design, implementation, and execution. David Serwadda contributed to study design, implementation, and monitoring in Uganda. Lynn Paxton oversaw project execution, and assisted with study design and analysis. Noah Kiwanuka assisted in project implementation, fieldwork, and data collection. Fred Wabwire-Mangen oversaw the maternal-infant substudy. Chuanjun Li coordinated data collection and oversaw the analyses. Thomas Lutalo oversaw data collection and all analyses. Fred Nalugoda developed and oversaw data-collection and quality-control procedures. Thomas Quinn and Charlotte Gaydos were responsible for laboratory testing for chlamydia and gonorrhoea and quality control for other laboratory testing, and contributed to data interpretation. Lawrence Moulton was the primary statistician in the preparation of the paper. Mary Meehan was responsible for field laboratory testing and quality control. Saifuddin Ahmed contributed to statistical analysis. The Rakai Project Team conducted field activities, sample and data collection, treatment, data management, and laboratory testing.

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