Model-based evaluation of single-round mass treatment of sexually transmitted diseases for HIV control in a rural African population

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Objectives: To compare the impact of single-round mass treatment of sexually transmitted diseases (STD), sustained syndromic treatment and their combination on the incidence of HIV in rural Africa.

Methods: We studied the effects of STD interventions by stochastic simulation using the model STDSIM. Parameters were fitted using data from a trial of improved STD treatment services in Mwanza, Tanzania. Effectiveness was assessed by comparing the prevalences of gonorrhoea, chlamydia, syphilis and chancroid, and the incidence of HIV, in the general adult population in simulations with and without intervention.

Results: Single-round mass treatment was projected to achieve an immediate, substantial reduction in STD prevalences, which would return to baseline levels over 5–10 years. The effect on syphilis was somewhat larger if participants cured of latent syphilis were not immediately susceptible to re-infection. At 80% coverage, the model projected a reduction in cumulative HIV incidence over 2 years of 36%. A similar impact was achieved if treatment of syphilis was excluded from the intervention or confined to those in the infectious stages. In comparison with sustained syndromic treatment, single-round mass treatment had a greater short-term impact on HIV (36 versus 30% over 2 years), but a smaller long-term impact (24 versus 62% over 10 years). Mass treatment combined with improved treatment services led to a rapid and sustained fall in HIV incidence (57% over 2 years; 70% over 10 years).

Conclusions: In populations in which STD control can reduce HIV incidence, mass treatment may, in the short run, have an impact comparable to sustained syndromic treatment. Mass treatment combined with sustained syndromic treatment may be particularly effective.
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Introduction

HIV/AIDS continues to spread rapidly in many developing countries. For example, HIV prevalence in the general adult population exceeds 30% in parts of southern Africa, and high incidence rates have been reported from parts of south-east Asia [1]. In most of these countries, neither vaccination nor affordable and effective treatments are likely to be available for many years, leaving preventive measures as the only realistic option for control.

The results of epidemiological studies strongly suggest that other sexually transmitted diseases (STDs) enhance the sexual transmission of HIV [2–4], by increasing both the susceptibility of HIV-uninfected and the infectiousness of HIV-infected individuals [5]. Increased shedding of HIV in the genital tract in STD-infected HIV patients seems to be one of the biological mechanisms underlying this cofactor effect [6,7]. Although STDs represent a major public health problem in their own right [8], it has been suggested that STD control should also reduce HIV transmission [9]. The World Health Organization has promoted syndromic case management of STDs in areas lacking reliable diagnostic services [10]. In a community-randomized trial in the rural population of Mwanza region, Tanzania (with an HIV prevalence of 4% in mid-1992), improved STD services using this approach reduced HIV incidence by 38% (95% confidence interval (CI), 15– 55) over 2 years [11,12].

Syndromic treatment of STDs relies critically on the occurrence and recognition of symptoms, and on appropriate treatment-seeking behaviour and therapy compliance [13–15]. Unfortunately, a considerable proportion of STDs are asymptomatic, and symptomatic patients often fail to recognize their condition or resort to ineffective sources of care. Furthermore, partner treatment rates are generally low in developing countries [16–18].

To overcome these limitations, STD mass treatment has been suggested as an alternative or complementary approach for the control of STDs and HIV [19,20]. Mass treatment has been applied successfully in eradication programmes for yaws and endemic syphilis [21,22]. As a test of concept, the effectiveness of repeated mass treatment of STDs has recently been investigated in a community-randomized trial in rural Rakai district, Uganda, with a high HIV prevalence (16%). After two rounds of mass treatment at 10-month intervals, the investigators observed significant reductions in the prevalence of syphilis and trichomoniasis and non-significant reductions in gonorrhea, chlamydia and bacterial vaginosis, but surprisingly no reduction in HIV incidence, the adjusted incidence rate ratio of HIV (intervention/control arm) over the first 20 months being 0.97 (95% CI, 0.81–1.16) [23].

Despite these disappointing results, STD mass treatment, possibly in combination with other interventions, may represent an effective strategy for STD and HIV control in some populations. It is therefore important to understand the mechanisms influencing the dynamics of STD and HIV transmission under conditions of mass treatment. Computer models that are sufficiently sophisticated to simulate the transmission dynamics of STD infections within human populations, are increasingly used to analyse complex problems of this kind [24–27].

Various models have been used to study the impact of alternative strategies to prevent the spread of HIV in Sub-Saharan Africa [28–32]. So far, simulations exploring the impact of STD control on HIV spread [27,32–35] distinguished at maximum two types of STDs (ulcerative and inflammatory) acting as cofactors for HIV transmission. However, the transmission dynamics, and hence the response to control measures, of STDs of different aetiologic origin within these types can be very different [36–38]. To predict the impact of STD control on HIV transmission, it is important, therefore, to distinguish between STDs. The stochastic microsimulation model STDSIM was specifically designed for this purpose.

This paper describes the application of the STDSIM model to predict the short- and long-term effects of a single round of STD mass treatment on STDs and HIV in a rural African population. We discuss a number of biomedical determinants of the effectiveness of this intervention, and examine the predicted impact of mass treatment in comparison with, or in combination with, the continuous provision of syndromic treatment services. The model was quantified using data from the Mwanza trial population, in order to assess the likely impact of mass treatment in a setting at a comparatively early stage of the HIV epidemic (as evidenced by a relatively low prevalence and a high incidence/prevalence ratio) compared with rural areas in Uganda [23,39]. We considered a single-round rather than a multi-round treatment strategy to better illustrate the short-term and long-term effects of mass treatment, and because a single-round approach is likely to be more feasible in resource-poor settings.

Methods

Microsimulation model STDSIM

The model has been described in detail elsewhere [40,41]. STDSIM simulates the natural history and transmission of HIV infection and four bacterial STDs

(gonorrhoea, chlamydia, syphilis and chancroid) in a population defined by a detailed set of parameters. The model population consists of individuals with assigned characteristics that change over time. The formation and dissolution of sexual partnerships between individuals, and transmission of STDs during contacts between sexual partners, are modelled as stochastic events.

The explicit representation of individuals, partnerships, instances of STD transmission and STD episodes is considered a valid approach to simulate STD transmission dynamics [27,33,35,38,42–46]. For example, it allows for concurrent partnerships, an important determinant of STD spread [45,47]. Moreover, the microsimulation approach makes STDSIM flexible in the specification of interactions between different STDs and HIV at the level of single sexual contacts between uninfected and infected partners. STDSIM allows us to simulate a variety of (combinations of) interventions, and to study their impact on various epidemiological outcome measures over time.

Model quantification

Demographic, behavioural and biomedical model parameters were quantified using data from the rural population of Mwanza region, Tanzania, documented through a series of studies conducted in the context of the trial of improved (syndromic) STD treatment services [11,12,48–53]. Baseline prevalences of HIV, syphilis, gonorrhoea and chlamydia were fitted to those measured at the start of the trial in 1992, whereas HIV incidence (in the absence of intervention) was fitted to that observed in the comparison arm of the trial during follow-up from 1992 to 1994. In the model, HIV was assumed to enter the population in 1983.

Demography

The model structure and the set of parameter values used in this study with respect to Demography and Sexual behaviour are described in detail in the Appendix. In brief, age-specific fertility rates per woman per year were specified using data from the 1996 Demographic Health Survey of rural Tanzania [54]. Mortality rates in HIV-uninfected individuals were quantified using data from the Mwanza trial cohort [53]. Migration was ignored. Simulated populations averaged 19 080 individuals in mid-1992. This population size, of which about half was in the age range of 15–54 years, was estimated to be roughly the average size of communities in the Mwanza trial [48]. The age/sex distribution and growth rate of the model population corresponded to that in rural Tanzania in 1996 [54].

Sexual behaviour

The model allows for three categories of (hetero-) sexual partnerships: steady relationships (e.g. marriages), short relationships, and 'one-off' sexual contacts between a small group of women, who may or may not define themselves as prostitutes, and a larger group of men. Formation of relationships is simulated using the concepts of availability for (supply) and selection of (demand) new partners [55]. Relationship formation follows age preference matrices guiding the search for new partners from the same or adjacent age groups.

Heterogeneity within the population in sexual behaviour, which has an important influence on STD transmission dynamics [26,44,56,57], is incorporated in three ways in STDSIM. First, the simulated population is heterogeneous in the number, type and overlap of sexual relations, which vary according to age, sex and an individual promiscuity level. Second, the frequency of having one-off contacts with female 'prostitutes' varies between males. This personal frequency can change with marital status, but is otherwise constant throughout a man's sexual life. Third, the age of sexual debut varies between individuals and between the sexes.

For this study, parameter values were based as far as possible on data on reported sexual behaviour collected from a random sub-sample of the Mwanza trial cohort [52]. Age of sexual debut in the model was assumed to average 15 years for males and 15.5 years for females, and was distributed between individuals uniformly over the age range 12–18 years for males and 12.5–18.5 years for females.

The values of parameters determining partnership formation and dissolution and the frequency of one-off contacts were determined by simultaneous fitting of the following types of data [52]: (i) the proportion currently married and the number of spouses, by age group and sex; (ii) the numbers of partners over the past year reported by males, by age group; (iii) the age pattern in the number of partners over the past year reported by females. In the absence of cross-sectional data on the occurrence of overlap in partnerships, we consider that fitting the model simultaneously to these static (i) and dynamic (ii, iii) measures of sexual activity should provide an adequate representation of partnership dynamics, including concurrency, in the Mwanza population.

In the resulting quantification, 55% of single and 25% of married sexually active males aged 15–49 years engaged in one-off sexual contacts, at an average frequency of once yearly. A further 5% of males in this age range had one-off contacts on average six times per year, irrespective of their marital status. This male demand for one-off contacts was fulfilled by a mean 0.5% of the female sexually active population, who each had on average one such contact per week. This

quantification provided a good fit to the proportion married and numbers of recent partners of males in different age groups (Fig. 1). For females, the model fitted the observed age pattern in numbers of partners, but the predicted number of partners was higher than reported. This is defensible because of likely under-reporting of non-marital partners by females and under-representation of high-risk females in the sub-cohort [52].

The frequency of intercourse was assumed to be 1.5 times per week in relationships where the male partner was younger than 35 years of age and once per week for older males, consistent with data on factory workers in Mwanza town [58]. These frequencies applied to both steady and short relationships, and were constant over the course of relationships. The prevalence of condom use during follow-up of the Mwanza trial was very low: only 2.4% of men and 2.3% of women reported ever using condoms with partners other than their spouse, and only three individuals (out of 1117) reported regular use [11]. Therefore, condom use was ignored in the model.

To model the effects of sexual contacts with individuals outside the study population (e.g. with visitors or during travel), additional risks of infection for HIV and each STD were assumed for each individual aged 15–44 years. These corresponded to an average of 0.40 and 0.15 extra sexual contact per person per year, for males and females respectively. Lacking corresponding data from Mwanza, these numbers were based on the proportion of study participants reporting outside partners during the last year in rural Rakai (12% for males, 7% for females [59]), multiplied by an assumed number of contacts per outside partner of three for males and two for females.

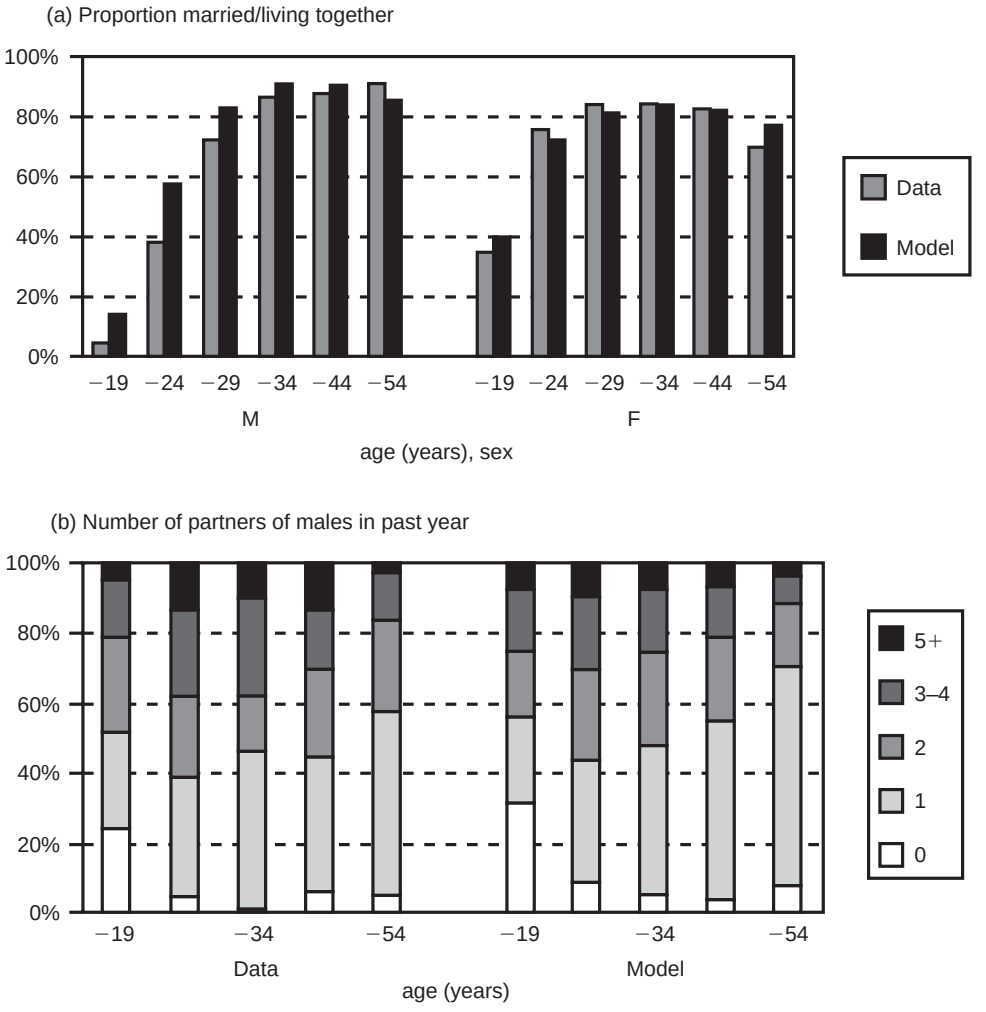

Fig. 1. Fit of the STDSIM quantification against data from a subcohort of the Mwanza trial population at start of the intervention in mid-1992 [52]. (a) proportion married and/or in a steady relationship, by sex and age group (youngest age group: 15–19 years); (b) number of sexual partners during the past year of males, by age group. Mean of 130 simulated populations.

Biomedical parameters

Assumptions regarding the natural history and transmission of HIV and other STDs (Table 1) were derived mostly from the literature. Since we focus on outcomes for adults, and since heterosexual transmission accounts for the great majority of adult infections in this region [72], other modes of transmission were not taken into account.

Durations of (stages of) STD infections were assumed exponentially distributed with means given in Table 1. As a convenient simplification, syphilis was assumed to consist of two consecutive stages. The 'infectious' stage corresponds roughly to primary and secondary syphilis, and this accounts for the relatively long duration assumed for this stage. In the absence of effective treatment, patients progress to a non-infectious 'latent' stage. HIV infection was represented as two consecutive stages, pre-AIDS (mean duration 7 years) and AIDS (mean duration 9 months), each following a Weibull distribution with shape parameter 2.

Of all biomedical parameters, per-contact transmission probabilities and STD cofactor effects are probably the most uncertain. Transmission probabilities were within plausible ranges adjusted to provide a good fit to HIV and STD prevalences in Mwanza. For chancroid, there is only one published empirical estimate of the per-contact transmission probability (43%, for male-to-female transmission) [60]. We adjusted this point estimate downwards to obtain a predicted chancroid prevalence consistent with the limited data from Mwanza. We estimated an approximate population prevalence of 1%, based on 1.3% of males reporting genital ulcers in rural Mwanza in 1990/1 [71], assuming some under-reporting of ulcers, and given (unpublished) data from an STD clinic in Mwanza town showing that 20–55% of ulcers were attributable to chancroid.

Transmission probabilities and cofactor effects of STDs were assumed identical for symptomatic and asymptomatic episodes. For syphilis, the cofactor effect applied only during the infectious stage. In the case of multiple cofactors (one partner in an HIV-discordant couple carrying multiple STDs simultaneously, or both partners carrying one or more STDs), the maximum cofactor for any single STD applied. We assessed the robustness of results to variations in these uncertain parameters by sensitivity analyses (see below).

Following cure of STD infections (either spontaneous or due to treatment), individuals were assumed immediately susceptible to re-infection, in line with clinical experience [70]. For syphilis, however, it is unclear whether this assumption is valid [74,75], and cure may be followed by a period of reduced susceptibility, particularly if treatment is given at a late stage of infection. Projections were therefore made not only for immediate susceptibility (default scenario), but also for alternative scenarios varying in the duration of non-susceptibility after mass treatment in the latent stage (means of 1 and 5 years).

Coverage and effectiveness of STD treatment

Assumptions regarding the coverage and effectiveness of (improved) syndromic services were based on observations from Mwanza. For each STD, a fixed proportion of symptomatic patients was assumed to be treated and cured clinically. The trial intervention was assumed to increase this proportion from 5 to 50%. STD episodes cured were assumed to have a shorter duration than untreated episodes (Table 1). Only the symptomatic STD for which the patient sought treatment was cured; concurrent asymptomatic infections were not. Partner referral in the intervention arm of the trial was represented as the simultaneous cure of the STD for which a patient sought treatment in 28% of steady partners infected with that STD. This level was based on estimates from Mwanza intervention clinics.

STD mass treatment was assumed to cover 80% of the population, in line with the coverage achieved in the Rakai trial [23]. Mass treatment was in the model delivered at a single point in time, and instantaneously cured 95% of infected individuals, irrespective of the STD and stage of infection. We also examined the effects of alternative mass treatment regimens, in which syphilis treatment either was excluded or covered the infectious stage only.

Simulation design

Projections of HIV and STD prevalence and incidence were made for four scenarios: (a) no intervention; (b) sustained syndromic STD treatment services commencing in mid-1992; (c) a single round of mass treatment in mid-1992; (d) a combination of single-round mass treatment in mid-1992 followed by sustained syndromic treatment. This timing corresponded to the Mwanza trial, in which the intervention was introduced between December 1991 and December 1992.

In order to reduce stochastic fluctuations in the projections, 500 simulation runs were conducted to generate 500 populations. This set of 500 simulated populations was used for fitting parameter values. Thereafter, populations with a HIV prevalence among adults (15–54 years) of < 2 or $> 6\%$ at start of the interventions were excluded, since they were inconsistent with the observed baseline prevalence in Mwanza of 4%. Applying these criteria, 130 out of the simulated populations were included. The full set of 500 populations and the selected 130 populations were very comparable in mean STD and HIV prevalences and incidences over time, age/sex patterns in numbers of partners, and age/

Table 1. STDSIM parameter values concerning transmission and natural history of STD infections, cofactor effects and performance of treatment, used to reflect the situation in rural Mwanza, Tanzania.

Parameter		HIV	Gonorrhoea	Chlamydia	Syphilis	Chancroid	Reference
Transmission probability per contact	M→F	0.003	0.22	0.20[a]	0.30[b]	0.15	60–67
	F→M	0.0008	0.121	0.20[a]	0.10[b]		
Relative increase in per-contact HIV-	susceptibility		10	10	100[b]	100	2,4,27,68,69
transmission probability due to STD	infectiousness		10	10	100[b]	100	
Annual risk of infection by contacts	M	0.043	2.1	2.4	0.72	0.48	59, E
from outside study population[c] ($\times 10^{-3}$)	F	0.061	1.2	1.5	0.41	0.27	
Probability that infection becomes	M	1.0	0.50	0.30	0.95	0.95	49,70, E
symptomatic	F	1.0	0.20	0.15	0.50	0.70	
Mean duration of infectious stage	M	400	9	12	26	16	53,70–73
if not treated (weeks)	F	400	13	16	26	16	
Mean duration of infectious stage	M	NA	2	3	2	2	70
if treated (weeks)	F	NA	8	10	2	2	
Mean duration of latent (non-infectious)	M				520		70, 74–76, E
stage (weeks)	F				520		
Fraction of symptomatic STD episodes	M		0.05	0.05	0.05	0.05	77
cured by unimproved services	F		0.05	0.05	0.05	0.05	
Fraction of symptomatic STD episodes	M		0.5	0.5	0.5	0.5	77, E based on unpublished data
cured by improved services	F		0.5	0.5	0.5	0.5	from intervention clinics in Mwanza
Fraction of steady partners of STD patients	M		0.28	0.28	0.28	0.28	E based on unpublished data
notified and cured under improved services[d]	F		0.28	0.28	0.28	0.28	from intervention clinics in Mwanza
Fraction of STDs cured by mass treatment	M		0.95	0.95	0.95	0.95	E
	F		0.95	0.95	0.95	0.95	

[a]In contrast to certain empirical observations [65], in the model the transmission probability of chlamydia was chosen not much lower than that of gonorrhea, to adjust for the low sensitivity of culture of chlamydia relative to gonorrhoea. [b]Refers to infectious stages only. [c]Product of transmission probability, prevalence in outside partners (assumed similar to that within the study population), proportion reporting outside partner(s) over the past year (12% for males and 7% for females in the age range 15–44 years [59], and an assumed number of contacts per outside partner of three for males and two for females. [d]Product of fraction of steady partners of patients treated (35%) and estimated efficacy of treatment (80%). M, male, F, female, NA, not applicable under conditions prevailing in rural Mwanza, E, authors' estimate.

sex patterns in HIV prevalence and incidence in mid-1992 (not shown). The selection reduced the variability around the mean for HIV prevalence and incidence, but not for STD prevalences. For instance, in mid-1992 HIV prevalence was 3.7 (2.2–5.6) [mean (10th and 90th percentiles)] for the 130 included populations, as compared with 3.7 (0.12–9.7) for all populations. In the remainder of the paper, we focus on average outcomes for the subset of simulated populations.

Simulations with and without interventions were run for each included population. The impact of an intervention on HIV was calculated as the cumulative reduction in the number of new HIV infections in adults (15–54 years) for each population separately (matched comparison), for different evaluation periods. Impact was expressed as the mean (the standard error of the mean (SE) over the 130 populations.

Sensitivity analyses

Simulations were repeated for alternative quantifications varying in the values of uncertain biomedical parameters. For each alternative scenario, the HIV transmission probability was re-adjusted to fit the prevalence measured at the start of the Mwanza trial (4%). Thereafter, populations fitting Mwanza with respect to HIV prevalence in mid-1992 were selected, interventions simulated and their impact calculated as described in the previous section.

Results

Simulations in the absence of intervention and fit against Mwanza baseline data

Model predictions for the prevalence of STDs and HIV and the incidence of HIV and syphilis in the absence of intervention are shown in Figures 2 and 3. Syphilis was the most prevalent STD (Fig. 2c), with a prevalence of around 7% in mid-1992. Most individuals with syphilis were in the latent stage, and the prevalence of infectious syphilis was about 0.5% (Fig. 4). Prevalences of chlamydia, gonorrhoea and chancroid in mid-1992 were around 5, 3 and 1% respectively; after the introduction of HIV, these showed a spontaneous decline over time (Fig. 2a,b,d), resulting from HIV-related mortality. Since having multiple sexual partners puts individuals at risk of both HIV and STDs, STDs are more prevalent among HIV-infected subjects, so that deaths of HIV-positive individuals also reduce the number of STD-infected individuals. In the absence of intervention, syphilis incidence remained almost constant (Fig. 3a). In contrast, HIV incidence increased from around 1% in 1992 to over 2% by 2005 (Fig. 3b), while HIV prevalence increased from 4% in 1992 to 15% in 2005 (Fig. 2e).

Where reliable population-based data were available, projections for 1992 were in good agreement with results from the comparison arm of the Mwanza trial (Fig. 2c, e) [11,48,51]. Furthermore, the projected prevalence of HIV in mid-1990 (2%) was in line with a point-estimate of 2.5% in mid-1990 in rural villages in Mwanza comparable to the trial communities (Fig. 2e) [78]. For outcomes measured in the trial by sex and age (HIV incidence, HIV prevalence and syphilis prevalence), age and sex patterns in model outcomes were consistent with the data.

Simulations of syndromic treatment and fit against Mwanza trial data

The improvement of syndromic treatment services was projected to increase the average number of STD episodes cured over 2 years (the duration of the trial) from 121 to 1074, for a model population of around 19 080 individuals. In comparison, during the Mwanza trial, an estimated 1551 STD episodes were treated per 19 080 individuals in the intervention arm [79]. Assuming that about 70% of these patients were cured (unpublished observations from the trial), this corresponds to 1036 STD episodes cured per 19 080 adults, with which the model predictions agree well.

After the onset of this intervention, HIV incidence was predicted to decrease markedly over time (Fig. 5; Table 2). The reduction was steepest during the first few years, but still continued 10 years later. Over 2 years of intervention, a cumulative reduction in HIV incidence of 30% was projected; over 10 years, the reduction amounted to over 60%. The predicted reduction in HIV incidence over 2 years was lower than that observed in the trial over 2 years of follow-up (30% versus 38%), but fell well within the limits of the 95% CI (15–55%) obtained from the empirical data [12].

For the STDs included, the model predicted that the introduction of improved syndromic management was followed by substantial reductions in prevalence. These predictions are difficult to compare with data from Mwanza. After 2 years, the prevalence of infectious syphilis in the model was reduced by 59% and that of all stages of syphilis by 13%. The empirical data showed a significant reduction in the prevalence of syphilis in the intervention compared with the comparison arm [51]. The reduction in active syphilis [Treponema pallidum haemagglutination assay (TPHA)+, rapid plasma reagin (RPR) $\geqslant 1:8$] was 29% (95% CI, 7–46), but this was observed after treatment of all RPR + cohort members for syphilis at baseline of the trial for ethical reasons. The observed reduction in new cases of active syphilis, which are more likely to represent cases of infectious syphilis [75], was 38% (95% CI, −2 to 62). These observations seem broadly consistent with the predicted prevalence reduction.

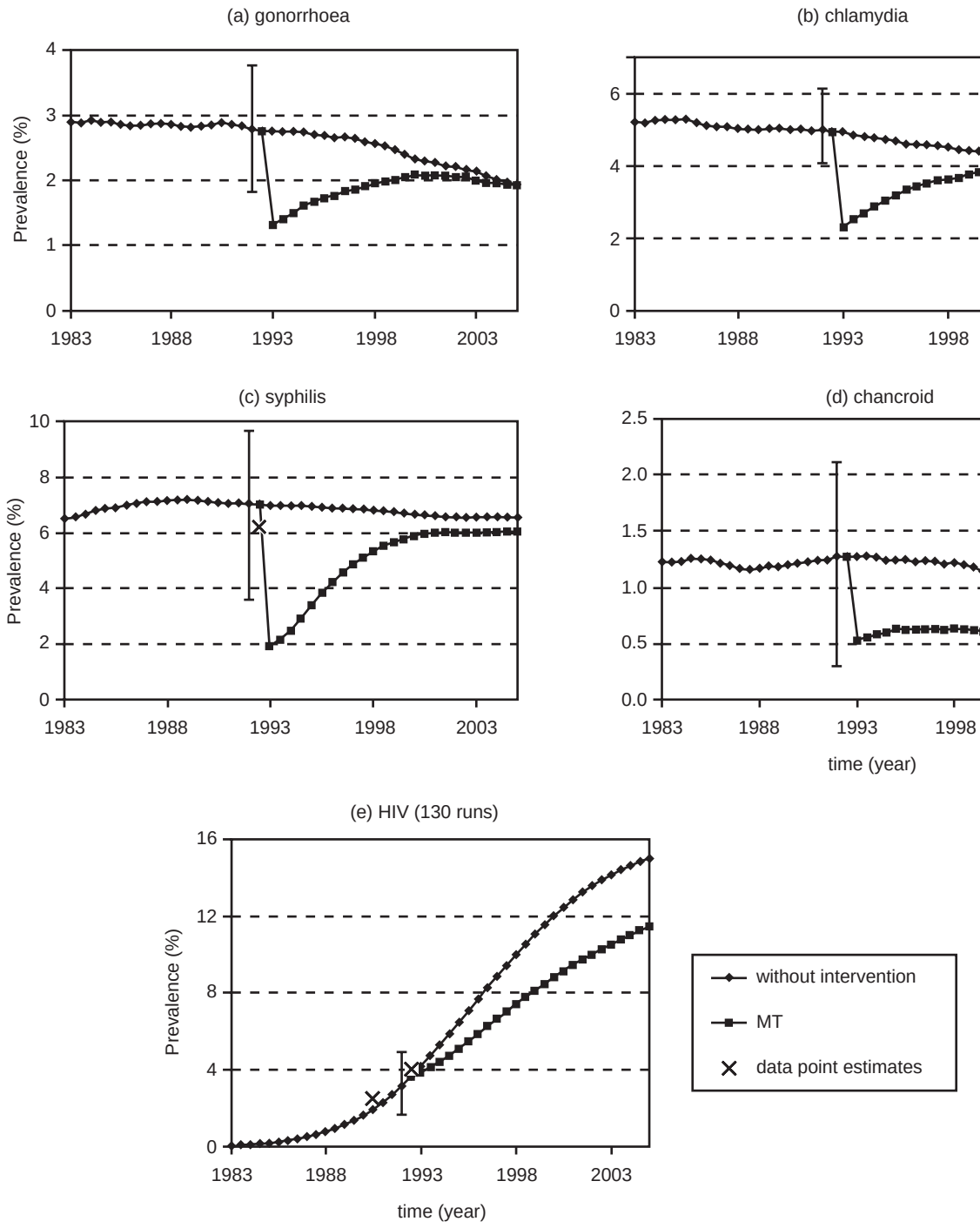

Fig. 2. Dynamic effect of single-round mass STD treatment with 80% coverage (default scenario) in mid-1992, in comparison with the scenario without intervention, on the prevalences of (a) gonorrhoea; (b) chlamydia; (c) syphilis; (d) chancroid and (e) HIV in the general adult population (15–54 years). Mean of 130 simulated populations. Tenth and 90th percentiles for mid-1992 are plotted, but for clarity slightly shifted to the left. Empirical point estimates of prevalences of syphilis and HIV from the trial baseline survey and of HIV in mid-1990 [78] are indicated as ×. This default scenario of mass treatment assumed immediate susceptibility to syphilis re-infection after treatment of all forms of syphilis. Numbers on the x-axis reflect the beginning of each calendar year.

The prevalences of chlamydia and gonorrhoea were in the model reduced by 20 and 43% after 2 years. In comparison, among a subset of men in the trial, the prevalence of gonorrhoea and/or chlamydia was reduced by only 4% (95% CI, −85 to 50), but the prevalence of symptomatic urethritis was reduced by 49% (95% CI, −3 to 75) [51]. Among female antenatal clinic attenders, the reduction in the prevalence of

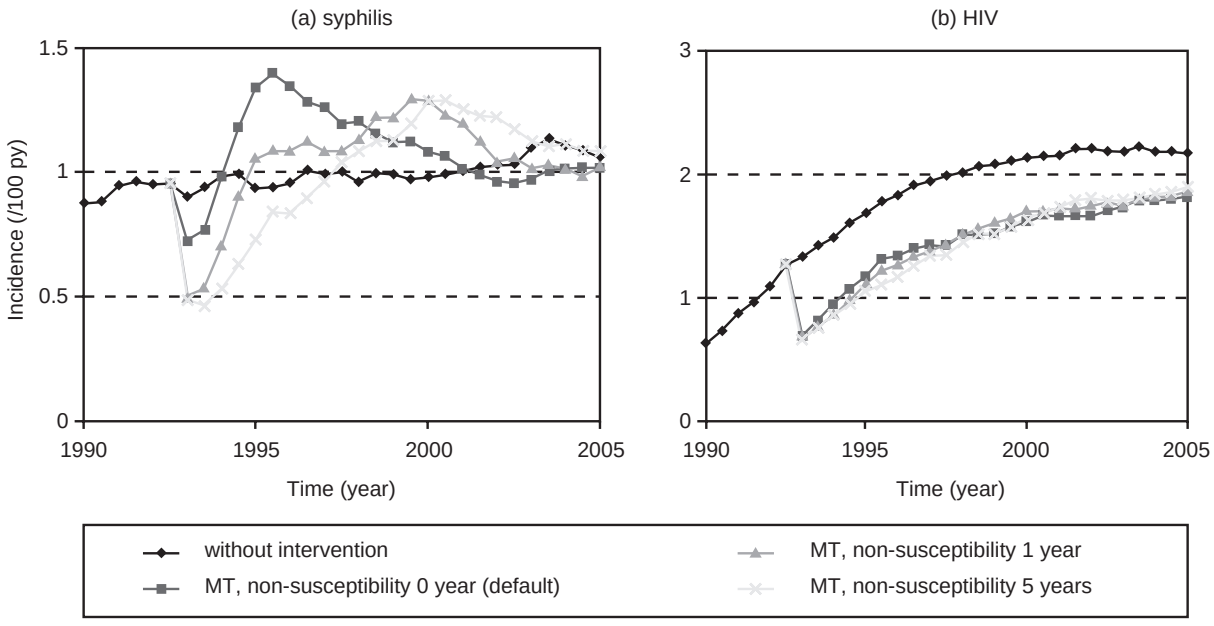

Fig. 3. Impact of single-round mass treatment on (a) syphilis incidence and (b) HIV incidence in the general adult population (15–54 years), for varying durations of non-susceptibility to re-infection after cure of latent syphilis. The curves with 0 years of non-susceptibility constitute the default scenario, corresponding to the results shown in Figures 2 and 4. Mean of 130 simulated populations.

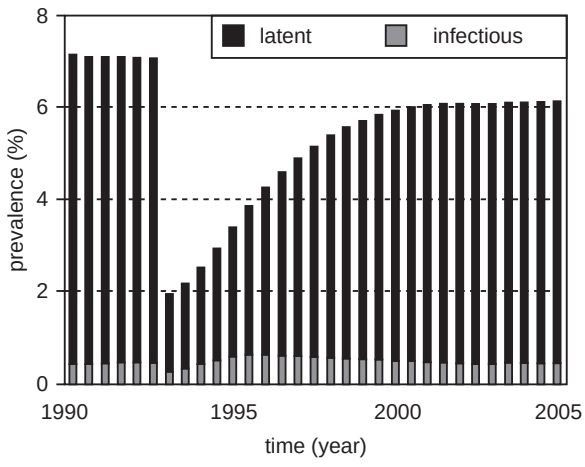

Fig. 4. Dynamic effects of single-round mass treatment (default scenario) on the prevalence of syphilis in the general adult population (15–54 years), differentiated by disease stage. Mean of 130 simulated populations.

gonorrhea and/or chlamydia was 7% (95% CI, −75 to 51). These data were, however, based on small numbers, available for only subsets of the trial population, and there were limitations in the sensitivity and specificity of the diagnostic tests. The model predicted an 81% reduction in the prevalence of chancroid; in the trial it was not possible to determine the prevalence of chancroid.

Simulations of single-round mass treatment

The projected single-round mass treatment cured 1119 STD episodes in the total population of 19 080. By reducing STD incidence, the intervention reduced the number of symptomatic episodes cured by clinical treatment in the years thereafter, for example, over the first 2 years from 121 to 67.

Mass treatment resulted in an immediate and steep reduction in all STDs, and prevalences 1 year later were 50–80% lower than without intervention (Fig. 2). Thereafter, without further intervention, prevalences increased over time and approached the levels observed in the absence of intervention within 5 to 10 years. The recurrence was comparatively slow for chancroid.

The reduction in the prevalence of syphilis was due mainly to a marked decrease in latent syphilis (Fig. 4). The prevalence of infectious syphilis showed a much smaller reduction, and returned to and exceeded its previous level within a short time. The incidence of syphilis also showed an initial reduction, but thereafter increased rapidly, exceeding initial levels by around 50% within 3 years (Fig. 3a). The size of these effects depended critically on the assumed period of non-susceptibility to re-infection following cure. The longer the period of non-susceptibility, the greater was the initial fall in incidence, and the slower and less marked the subsequent increase above baseline levels. How-

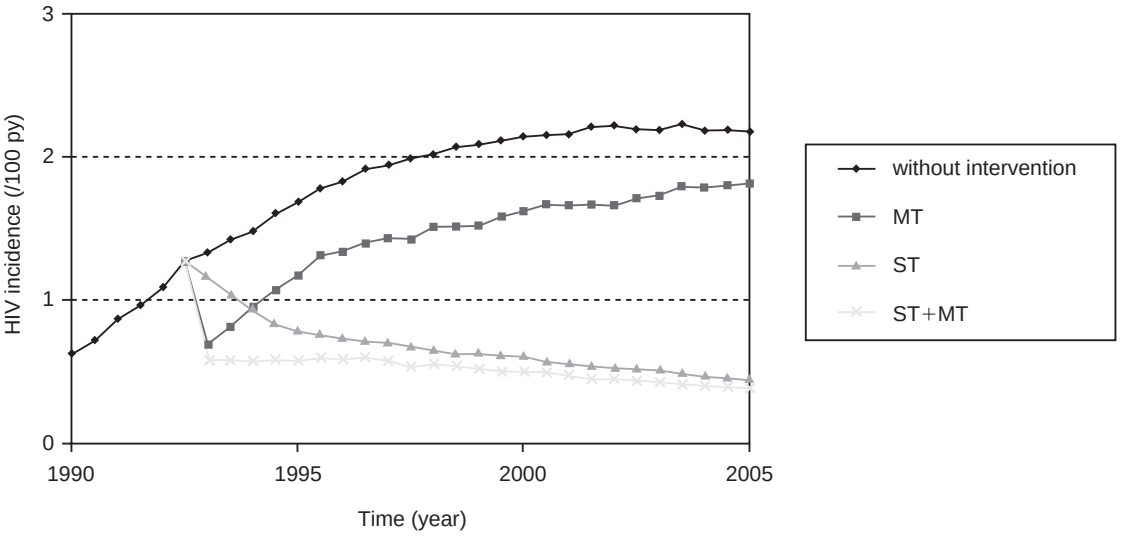

Fig. 5. Impact of different STD treatment strategies on HIV incidence in the general adult population (15–54 years). MT, single-round mass treatment (default); ST, sustained syndromic treatment; ST + MT, combination of single-round mass treatment (default) with sustained syndromic treatment. Interventions were implemented in mid-1992. Mean of 130 simulated populations.

Table 2. Model projections of proportions (%) of new HIV infections prevented by STD interventions, for different evaluation periods. Evaluation periods are specified in years since the onset of the interventions in mid-1992. Cumulative number of new infections among those aged 15–54 years for the scenario without intervention were averaged over 130 simulated populations (each including approx. 10 000 persons aged 15–54 years), and rounded to whole numbers. Impact of interventions, based on a matched comparison of 130 simulated populations, is expressed as the mean ± standard error (SE) of the mean.

	% reduction in cumulative HIV incidence (mean ± SE)				
Intervention	0.5 year	1 year	2 years	5 years	10 years
Cumulative number of new HIV infections without intervention	n = 62	n = 128	n = 276	n = 838	n = 2012
Single-round mass treatment[a]	46 ± 1.7	43 ± 1.9	36 ± 2.1	28 ± 2.5	24 ± 2.3
Sustained syndromic treatment	11 ± 1.7	19 ± 1.4	30 ± 1.2	49 ± 1.2	62 ± 1.0
Single-round mass treatment[a] + sustained syndromic treatment	53 ± 1.3	55 ± 1.3	57 ± 1.3	63 ± 1.5	70 ± 1.2
Mass treatment excluding syphilis	37 ± 1.9	35 ± 1.9	33 ± 1.7	29 ± 1.9	24 ± 2.1
Mass treatment including only infectious syphilis[a]	47 ± 1.6	44 ± 1.6	41 ± 1.7	35 ± 1.7	26 ± 2.0
Mass treatment, syphilis non-susceptibility 1 year	49 ± 1.4	46 ± 1.6	41 ± 1.7	31 ± 2.2	22 ± 2.3
Mass treatment, syphilis non-susceptibility 5 years	48 ± 1.6	46 ± 1.6	42 ± 1.6	36 ± 1.9	26 ± 2.1

[a]Projections assuming immediate susceptibility to syphilis reinfection after treatment of all forms of syphilis (default scenario).

ever, a 'rebound' effect was observed even assuming a 5-year period of non-susceptibility, albeit delayed.

Mass treatment reduced HIV incidence by up to 50% for the first 6 months after the intervention (Fig. 3b; Table 2). Thereafter incidence increased over time, but 10 years later it was still lower than without intervention. The short-term effect of mass treatment on HIV incidence was slightly greater assuming a period of non-susceptibility following cure of latent syphilis (Fig. 3b). When alternative regimens of mass treatment were considered, the reduction in HIV incidence was in the longer term comparable if treatment for syphilis was excluded or if infectious syphilis cases were treated while latent cases were not (Table 2).

Simulations of mass treatment combined with improved STD treatment services

The projected combined intervention achieved cure of 1119 STD infections by mass treatment in mid-1992; the sustained improvement of syndromic treatment resulted in a further 513 episodes cured over the first 2 years, compared with 121 effective clinical treatments for the scenario without intervention.

Under this combined intervention, HIV incidence was reduced steeply within the first year and continued to decrease thereafter (Fig. 5; Table 2). The reduction in cumulative HIV incidence over 2 years (57%) was much larger than the impact of either mass treatment (36%) or syndromic treatment (30%) in isolation. In the

long run, incidence levels achieved under either the combined intervention or syndromic treatment alone converged. However, the cumulative reduction in HIV incidence over 10 years achieved with the combined intervention (70%) was larger than that of syndromic treatment alone (62%), because of a greater number of infections prevented over the first few years.

Sensitivity analyses for STD parameter assumptions

As an indication of the robustness of the results, we assessed the sensitivity of the predicted impact of treatment strategies to variations in STD parameter assumptions (Table 1), some of which were based on limited data. Table 3 shows prevalences of HIV and STDs by mid-1992 and the impact of the treatment strategies on HIV incidence over the first 2 years, for several alternative scenarios.

Decreasing all cofactor magnitudes in the same direction markedly decreased the projected impact on HIV of all interventions in comparison with the default scenario. At cofactor values above the default, however, impact hardly increased, indicating a saturation effect. These variations did not affect the ranking of impact between the three treatment strategies.

The impact of mass treatment was insensitive to the relative cofactor strengths of gonorrhoea and chlamydia (inflammatory STDs) as compared to syphilis and chancroid (ulcerative STDs). The impact of syndromic treatment, in contrast, would be larger (40% reduction over 2 years) if the cofactor effect of inflammatory STDs was decreased (from 10 to 2.5 times) and the cofactor effect of ulcerative STDs was, at the same time, increased (from 100 to 250 times). If inflammatory and ulcerative STDs had equal cofactor effects (25 times), the impact of syndromic treatment was much less (14% over 2 years) than in the default scenario.

Increasing or decreasing STD transmission probabilities caused an increase or decrease in the prevalence of the respective STD of a much larger magnitude, reflecting the non-linearity in STD transmission dynamics [29,80]. The resulting prevalence levels of gonorrhoea, chlamydia and syphilis, differed markedly from those observed in Mwanza. For chlamydia, the higher the transmission probability and, consequently, its prevalence, the more favourable the impact on HIV incidence of mass treatment would be compared with syndromic treatment. In contrast, for chancroid, the higher the transmission probability and prevalence, the less favourable the impact of mass treatment would be relative to syndromic treatment. These opposite effects reflect the low proportion of chlamydia episodes that are symptomatic (Table 1) and, hence susceptible to syndromic treatment, and the high proportion symptomatic for chancroid. For gonorrhea, the relative impact on HIV incidence of the different STD interventions was insensitive to variations in the transmission probability and prevalence. Assuming a higher transmission probability for syphilis, the impact of mass treatment was markedly less than in the default scenario, and less than that of syndromic treatment even in the first year of intervention. This reflects the critical influence of the rate of re-infection with syphilis on the impact of STD mass treatment.

The relative impact over time of the different treatment strategies on HIV was independent of whether HIV infectivity was assumed to be constant (the default scenario) or to vary over the course of infection, with peaks during primary infection and AIDS (Table 3).

In all scenarios except those varying the transmission probability of syphilis and the relative cofactor effects of inflammatory and ulcerative STD, single-round mass treatment reduced cumulative HIV incidence over the first 2 years as much as or slightly more than sustained syndromic treatment. In all scenarios, the combined intervention had about twice the impact of syndromic treatment alone over this period. Time patterns in HIV incidence under the respective interventions were comparable between all scenarios. In all scenarios except that equalling the cofactor effects of inflammatory and ulcerative STD, the instantaneous HIV incidence rate under conditions of syndromic treatment fell below that for mass treatment within 2 years (results not shown).

Discussion

The projections indicate that single-round mass treatment may substantially reduce the prevalence of gonorrhoea, chlamydia and chancroid. Lacking regular repetition, however, the impact of mass treatment on the transmission dynamics of STDs is only temporary, so that prevalences will finally return to their equilibrium levels. The rate at which this occurs depends on the case reproduction rate of each STD, the coverage achieved, and the rate of re-introduction of STDs due to sexual contact with infected individuals from outside the study population. In these projections, chancroid, the STD with the lowest assumed transmission probability, re-emerged slowest.

The model showed that effects on syphilis are complex. In a population with poor treatment services, most prevalent cases have a latent infection and are therefore immune to new episodes of syphilitic ulceration [75,81]. Relatively few have ulcers or are in the infectious secondary stage, but mass treatment reaches both the infectious and the latent cases. As cured patients become susceptible again and are re-infected,

Table 3. Sensitivity analyses for STD assumptions. Results refer to the subset of simulated populations with an HIV prevalence among adults (15–54 years) in mid-1992 between 2 and 6% (varying between 105 and 263 out of 500 populations). Impact of interventions is expressed as the proportion reduction in cumulative HIV incidence over 2 years (mean ± SE, in %).

		(adjusted) HIV transmission probability		Projected STD prevalences in mid-1992 (%)					Proportional reduction in HIV incidence over 2 years (%)		
Scenario/parameter change		M → F	F → M	HIV	gonorrhoea	chlamydia	syphilis	chancroid	ST	MT	ST + MT
Default	(see Table 1)	0.003	0.0008	3.7	2.8	5.0	7.0	1.3	30 ± 1.2	36 ± 2.1	57 ± 1.3
STD cofactors	cofactor values:										
	gonorrhoea/chlamydia 2.5 × syphilis/chancroid 25 ×	0.01	0.003	3.6	2.8	5.0	7.3	1.3	24 ± 1.6	28 ± 1.7	44 ± 1.3
	gonorrhoea/chlamydia 25 × syphilis/chancroid 250 ×	0.0012	0.00035	3.8	2.8	5.0	7.0	1.2	29 ± 1.5	38 ± 1.8	61 ± 1.2
	gonorrhoea/chlamydia 2.5 × syphilis/chancroid 250 ×	0.0017	0.00045	4.0	2.8	4.9	6.5	1.1	40 ± 1.9	36 ± 2.7	62 ± 2.2
	gonorrhoea/chlamydia 25 × syphilis/chancroid 25 ×	0.0041	0.0011	3.7	3.0	5.0	6.9	1.1	14 ± 0.9	37 ± 0.8	48 ± 0.7
STD transmission probabilities:											
	gonorrhoea ↑	0.0028	0.00075	3.9	***12***	4.9	6.8	1.1	23 ± 1.1	30 ± 1.5	49 ± 1.1
	↓	0.0032	0.00085	3.7	***0.2***	5.0	7.1	1.2	30 ± 1.6	37 ± 1.9	57 ± 1.5
	chlamydia ↑	0.0028	0.00075	3.8	2.8	***15***	6.8	1.2	21 ± 1.3	32 ± 1.4	48 ± 1.2
	↓	0.0034	0.0009	3.9	2.8	***0.4***	7.0	1.2	34 ± 1.3	34 ± 2.4	59 ± 1.2
	syphilis ↑	0.0029	0.008	3.8	2.9	5.0	***13***	1.0	25 ± 1.5	11 ± 2.4	41 ± 1.9
	↓	0.0032	0.00085	3.9	2.9	5.1	***2.5***	1.6	32 ± 1.2	43 ± 1.4	61 ± 0.9
	chancroid ↑	0.0009	0.00025	3.8	2.9	5.1	6.7	***12***	35 ± 0.6	34 ± 0.7	65 ± 0.4
	↓	0.0056	0.0015	3.9	2.8	5.0	7.2	***0.1***	16 ± 1.3	26 ± 1.9	41 ± 1.6
	stage of infection:										
HIV infectivity over the course of infection ('bathtub' pattern)	first 10 weeks	0.026	0.007	4.0	2.8	4.9	7.0	1.1	33 ± 1.9	40 ± 2.6	61 ± 1.5
	asymptomatic (350 weeks)	0.0013	0.00035								
	AIDS (40 weeks)	0.0065	0.00175								

↑, transmission probability × 1.5; ↓, transmission probability × 0.67. Bold italic text indicates the projected prevalence of the STD for which parameters were changed in that scenario. ST, syndromic treatment; MT, mass treatment; ST + MT, combined intervention; M, male; F, female.

syphilis incidence increases steeply, resulting in rates higher than before intervention. This effect is enhanced by heterogeneity in sexual behaviour. For example, in the simulation, the baseline syphilis prevalence in women engaging in one-off contacts was 38% compared with 7% in all women. Thus, although the overall pool of susceptible individuals increased only marginally as a result of mass treatment (from 93 to 98%), the number of those susceptible, among persons at high risk, and consequently of potential new source infections, increased substantially.

The extent and timing of any increase in syphilis incidence depends on the duration of non-susceptibility to re-infection following cure (Fig. 3a). Unfortunately empirical data on the duration and extent of non-susceptibility are sparse [74,76], and both may depend on the stage of infection when treatment is given. Epidemiological evidence for or against resurgence of syphilis at a population level following mass treatment is also scarce. Mass treatment campaigns against endemic syphilis and yaws were generally successful, although in some cases resurgence was noted [22,82–84]. However, the majority of these campaigns were uncontrolled, accompanied by general improvements of health services and living conditions, which may themselves have led to reductions in endemicity, and followed by regular re-treatment rounds. Furthermore, comparability with STD mass treatment is limited by differences between the endemic treponematoses and venereal syphilis in their mode of transmission (and consequently in the role of population heterogeneity in sexual behaviour), and in baseline prevalences. Prospective studies involving long-term follow-up of patients treated for venereal syphilis at different stages are needed to address this question.

Model simulations were based on cofactor effects by which STDs enhance the transmission of HIV. The results of cohort studies and intervention trials strongly argue for the existence of these effects [2–4,11,85], and biological studies have provided evidence for underlying mechanisms [6,7,68]. However, the magnitudes of these cofactor effects are not yet known. Odds ratios from observational studies are likely to considerably underestimate them, since they usually refer to extended periods of exposure during only some of which an STD would have been present [46]. Data from cohort studies in Nairobi [2,3] have been estimated to be consistent with a 10- to 50-fold increase in the probability of male-to-female HIV transmission per single sexual exposure, and a 50- to 300-fold increase for female-to-male transmission, in the presence of genital ulcers [69]. In simulations of a rural population cohort in Uganda, the assumption most consistent with empirical data was that the probability of HIV transmission per sexual contact was enhanced 100-fold during episodes of ulcerative STDs, and five-fold during episodes of non-ulcerative STDs [27]. Assuming similar cofactor effects in our study, we obtained a satisfactory fit to HIV prevalence and incidence rates observed in the comparison arm of the Mwanza trial cohort, and to the impact of syndromic treatment. Assuming weaker or stronger cofactor effects, the predicted impact of both mass treatment and syndromic treatment would be smaller or larger, respectively (Table 3). Some conditions with potentially sizeable cofactor effects, such as Herpes simplex virus type-2 (HSV-2) infection and bacterial vaginosis [86,87], cannot be effectively treated. At present such infections are not included in STDSIM. If incurable STDs are prevalent and their cofactor effects are substantial, we may have overestimated the cofactor magnitudes for curable STDs and, consequently, the impact on HIV incidence of any STD treatment strategy.

The projected impact of mass treatment on HIV incidence was determined by the beneficial effect of comparatively long-lasting decreases in the prevalence of gonorrhoea, chlamydia and chancroid, and the adverse effect on the incidence and prevalence of infectious syphilis occurring soon after mass treatment. In these simulations, including the scenario assuming immediate susceptibility to re-infection after treatment in the latent phase (Fig. 3b; Table 2), the net effect was positive. Yet this may differ according to epidemiological conditions, depending for example on the relative prevalences of syphilis and other curable STDs in a population.

In the investigation of alternative regimens of mass treatment of syphilis the model predicted a similar long-term impact on HIV incidence if syphilis treatment was excluded from the mass treatment regimen altogether, or if infectious stages of syphilis were covered but latent syphilis remained untreated (Table 2). The first of these scenarios might be achieved if mass treatment consisted of a combination of single-dose oral antibiotics including azithromycin and ciprofloxacin, which would cover all four target STDs except syphilis. Azithromycin may have some effect on active infections with *Treponema pallidum*, but is unlikely to be curative unless given over a longer period [88]. The second scenario would be achieved if single-dose benzathine penicillin injections were given only to individuals presenting with the symptoms or signs of a genital ulcer or condylomata lata (a common and highly infectious form of secondary syphilis). This regimen would combine features of mass treatment and syndromic treatment. Its disadvantages would be that genital examination would be required to detect unrecognized ulcers, which is unlikely to be feasible in mass treatment campaigns, and that patients with non-syphilitic ulcers would be treated unnecessarily, including some with latent syphilis. It is of note that the

treatment strategy most effective in reducing HIV incidence may not be the best strategy for reducing the disease burden of syphilis at the individual level. Untreated latent syphilis may lead to serious late complications, and in women to perinatal infection and adverse birth outcomes. The design of STD interventions clearly needs to take such ethical considerations into account.

In our projections for the Mwanza population, the impact of a single round of mass treatment on HIV incidence was in the long run much smaller than that of sustained syndromic treatment (Fig. 5, Table 2). However, mass treatment achieved a much steeper initial decline in HIV incidence. From an epidemiological perspective, the effectiveness of mass treatment relative to syndromic treatment depends on the relative contribution to HIV transmission of commonly asymptomatic curable STD, like gonorrhoea and chlamydia, in compared with commonly symptomatic curable STD, like chancroid. This in turn depends on the relative prevalences of these infections and on their cofactor effects (Table 3). Other influential factors are the frequency of occurrence and the relative cofactor effects of a symptomatic relative to an asymptomatic course of an episode with a certain STD. Cofactor effects may be stronger for symptomatic than for asymptomatic STD, as suggested by a study of HIV-infected men with urethritis in which viral shedding correlated with the degree of inflammation [7]. In our model, identical cofactor effects were assumed for symptomatic and asymptomatic episodes. Thus our projections may underestimate the impact of syndromic treatment, provided that a significant proportion of symptomatic patients would recognize their symptoms and act upon them. This latter effect could however not be explored with the present STDSIM, in which the cofactor effect of each STD is assumed to be the same regardless of symptomatology. If both treatment strategies were combined, the short-term decrease in HIV incidence resulting from mass treatment was sustained over time, because individuals experiencing new STD infections could thereafter access syndromic treatment services. This advantage would be particularly strong if syphilis incidence were to increase following mass treatment, as our projections suggest.

A number of comparisons were made between model projections and trial outcomes. The reduction in HIV incidence observed in Mwanza over the 2 years of follow-up was 38% (95% CI, 15–55) after adjustment for potential confounding variables [12]. In the simulations, a reduction of 30% was achieved over the first 2 years (Table 2), which is well within the confidence interval of the trial.

In addition to random error, several factors may have contributed to the simulated impact being slightly lower than the point estimate from the trial:

(i) Some reproductive tract infections treated in the Mwanza intervention such as trichomoniasis, candidiasis, bacterial vaginosis and non-specific urethritis were not incorporated in the model;
(ii) Syndromic management in Mwanza covered not only the symptomatic infection presented by the patient but also concurrent, possibly asymptomatic, STDs, but this was not the case in the model;
(iii) The time between infection and cure may in reality have been shorter than assumed, reflecting an improvement in treatment-seeking behaviour in the intervention arm;
(iv) In the simulations, patients were assumed immediately susceptible to re-infection for all STDs considered, and re-infection may therefore have occurred earlier than in reality in some cases;
(v) The model assumed identical cofactor effects for asymptomatic and symptomatic STDs.

On the other hand, omission from the model of untreated STD such as HSV-2, and of immigration and mobility, which re-introduce STD from outside the study population, may have worked in the opposite direction, leading to overestimation of impact on HIV in Mwanza.

In the Rakai trial, periodic mass treatment resulted in only a small and non-significant reduction in HIV incidence (relative risk, 0.97; 95% CI, 0.81–1.16) over the first two rounds [23], which is much smaller than the reduction in our simulation (36% over 2 years). A number of factors may explain this apparent discrepancy:

(i) Our model fitted the demographic and epidemiological situation in Mwanza rather than Rakai, and the two situations are different. In particular, the HIV epidemic in Rakai has reached maturity, with an HIV prevalence and incidence of 16% and 1.5/100 person–years, compared with 4% and 1/100 person–years in Mwanza. In the later stages of an HIV epidemic, transmission may depend to a lesser extent on the enhancing effect of STDs [27];
(ii) Incurable STDs, such as HSV-2, and genital tract infections only temporarily cured by single-dose mass treatment, such as bacterial vaginosis, may have played a substantial role in ongoing HIV transmission in Rakai. More than 40% of genital ulcers in Rakai were due to HSV-2 [23], and bacterial vaginosis is highly prevalent [86]. Neither of these infections was incorporated in STDSIM;
(iii) In the model, mass treatment was given through-

out the population at a single point in time. In Rakai, mass treatment of a cluster of villages took several weeks, as it was delivered at household level in order to achieve high coverage [20]. In a situation of extended sexual networks, the time taken to deliver mass treatment may influence the re-infection rate;

(iv) The model ignored inward migration and may have underestimated the rate of re-introduction of infection from outside the study population. Mobility may reduce the long-term impact of STD mass treatment on HIV incidence by increasing STD re-infection rates [89]. In a mass treatment trial for the control of trachoma in The Gambia, ocular chlamydial infection was re-introduced rapidly by returning residents, visitors and migrants, in spite of high coverage and the use of effective antimicrobials [90].

Finally, considering the many uncertainties in its determinants, no firm conclusions can yet be drawn on the effectiveness of STD mass treatment for HIV prevention. Our simulations predicted that in a rural African setting in which syndromic STD treatment can reduce HIV incidence, single-round mass treatment may also be effective in the short term. Mass treatment followed by sustained syndromic treatment would be particularly effective, both in the short and long term. The impact of mass treatment on syphilis is complex and requires further investigation.

As we have shown, the impact of mass treatment relative to syndromic treatment depends on the relative prevalence and cofactor effects of symptomatic and asymptomatic curable STD. However, the effectiveness and cost-effectiveness of different STD treatment strategies are also affected by many other epidemiological and non-epidemiological determinants which were beyond the scope of this study. Simulation modelling of alternative STD control strategies in different settings may help to identify those determinants, estimate their relative importance, and identify needs for further empirical research. We will use the STDSIM model to address these issues using the population-based longitudinal data of the trials of STD control for HIV prevention in Mwanza, Rakai and Masaka. The results may have major implications for the design of effective STD and HIV control strategies in populations in Africa, Asia and Latin America exposed to high STD prevalences.

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Appendix

Demography and sexual behaviour in STDSIM: model structure and parameter values used in the simulation of rural Mwanza

The microsimulation model STDSIM simulates the spread and control of HIV and four bacterial STDs (gonorrhoea, chlamydia, syphilis and chancroid) over time in a population consisting of hypothetical individuals in a computer program [40,41]. Each individual is represented by a number of characteristics, of which some remain constant during simulated life (e.g. sex and date of birth), whereas others change (e.g. number of sexual partners and infection status). Changes in personal characteristics result from events such as the start and end of sexual relationships, or the acquisition of infection. These events are stochastic: if and when an event occurs is determined by Monte-Carlo sampling from probability distributions. Model outcomes for a simulated population are generated by aggregating the characteristics of the simulated individuals.

STDSIM is event-driven: all events are listed and performed in chronological order. At the occurrence of an event, the characteristics of the individual and/or relationship to which the event pertains are updated. In addition, events can generate new events, which occur either immediately, for example, the death of an individual terminates all relationships of this individual; or later in the simulation, for example, acquisition of HIV infection advances a person's earlier scheduled moment of death.

Aspects affecting the transmission and control of STDs are grouped into six modules. The modules: Transmission, Natural history, Health care and Interventions are described in Methods, subsections 'Biomedical parameters' and 'Coverage and effectiveness of STD treatment'. Below, we describe the structure and parameter quantification for the modules Demography and Sexual behaviour. For all parameter specifications, the distribution functions, numbers and borders of age groups and values listed are those used to represent rural Mwanza in this study. The modeller can however change these in an input file, for example to base assumptions on differently structured data-sets, or to do projections for populations with other endemic conditions.

Demography

Fertility is simulated by attributing pregnancies to sexually active females on the basis of user-specified fertility rates. The duration till each subsequent pregnancy in a certain age group a is sampled from an exponential distribution with mean $b_a \times F_a(t)$, where: b_a is the user-specified birth rate for age group a and $F_a(t)$ is the number of females in age group a at time t.

Each new pregnancy is attributed randomly to a female in the age group concerned who is engaged in a sexual relationship and not already pregnant. All pregnancies result in live births 9 months after their start. The period of pregnancy can be used to simulate the effects of STD on pregnancy outcomes, for example, stillbirth due to syphilis, but this option was not used in the current study. The fertility rates used to simulate rural Mwanza in this study were based on the 1996 Demographic Health Survey of rural Tanzania [54] and are listed in Table A1. We assumed half of all births to be males.

At the birth of a simulated person, the moment of his or her death is sampled from a stepwise linear life table specifying the proportion still alive at certain ages. For

the simulation of rural Mwanza, the lifetable was specified according to mortality estimates for HIV-uninfected individuals in the trial cohort (Table A1) [53]. If a simulated person contracts HIV, a moment of HIV-attributable death is sampled from the survival distribution of HIV patients (see Methods, subsection 'Biomedical parameters' and Table 1). If the moment of HIV-attributable death is earlier than that of non-HIV-attributable death, the actual moment of death is advanced to the former, and this event is recorded as an HIV-attributable death.

Although STDSIM can simulate migration into and out of the population, this option was not used in this study.

Table A1. Specification of fertility and mortality among HIV-negatives in STDSIM, and parameter values used to represent rural Mwanza.

Age group (years, upper limits)	Birth rate per woman per year	Survival probability	
		Males	Females
−1	0	0.90	0.90
−5	0	0.85	0.85
−15	0	0.80	0.80
−20	0.143	0.784	0.787
−25	0.288	0.771	0.772
−30	0.270	0.752	0.756
−35	0.239	0.722	0.733
−40	0.192	0.683	0.722
−45	0.097	0.644	0.711
−50	0.040	0.602	0.667
−55	0	0.560	0.622
−60	0	0.506	0.620
−70	0	0.33	0.46
−80	0	0.1	0.2
−90	0	0	0

Sexual behaviour

Sexual contacts and relationships between men and women in STDSIM constitute a dynamic network through which STDs can be transmitted. We consider three types of (exclusively hetero-)sexual contact: steady relationships ('marriages'); short relationships; and one-off contacts between a small group of females, who may or may not define themselves as prostitutes, and a larger group of males. In the remainder of this Appendix, we will refer to these individuals as prostitutes and clients, respectively.

Formation of relationships is simulated using the concepts of availability for (supply) and search (demand) of new partners [55]. Figure A1 illustrates this process. New relationships are formed between available men and available women. People become available for relationships for the first time at sexual debut (t_1 in Fig. A1). At each subsequent change in the number of current partners, a new duration till availability is determined. This duration (e.g. the interval between t_5 to t_7) may be shorter than the duration of an ongoing relationship (t_5 to the end of the horizon in Fig. A1), thus allowing for concurrent relationships (t_8 to t_9). Availability temporarily ends when a new relationship is formed. This happens either when someone is selected by a new partner (t_5 in Fig. A1), or when a full 'period of availability' (t_1 to t_2) has elapsed and the person selects a partner from the pool of available people of the opposite sex in a preferred age group (e.g. at t_2). The mechanisms of availability and partner selection do not reflect actual (psychological, behavioural or social) processes, but allow us to steer the representation of behaviour from both the male and the female population.

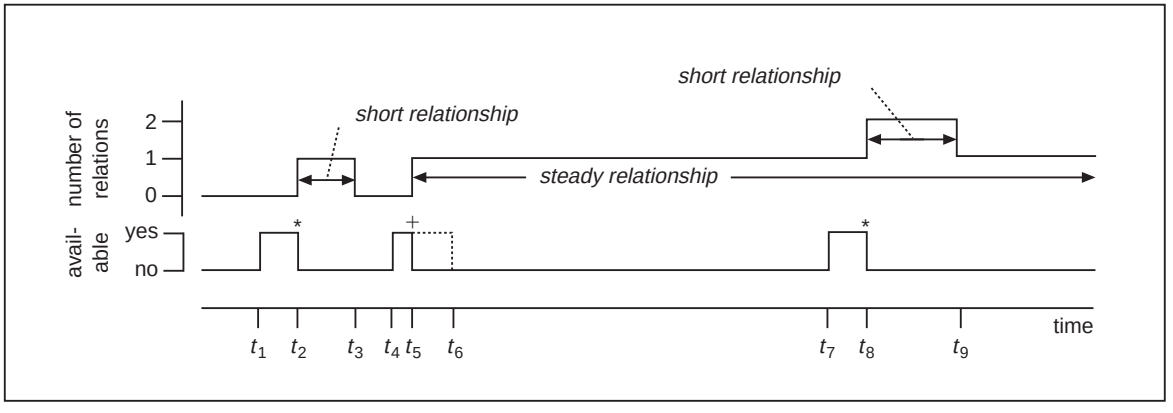

Fig. A1. Example of the relationship history of a young male in STDSIM. The man becomes first available at t_1 (sexual debut). Because he is not selected during his 'period of availability' between t_1 and t_2, he selects a partner himself (*) and starts a short relationship at t_2. This relationship ends at t_3. After a delay, he becomes available again at t_4 for a period which might have lasted until t_6. During availability, the man is selected (+, at t_5) by a female for a steady relationship, which terminates this period of availability (the no longer applicable remainder is indicated with a dashed line). During this relationship, he becomes available again at t_7. After this period of availability, at t_8, he selects (*) a partner for a concurrent short relationship which ends at t_9. On top of the relationships depicted in this figure, one-off contacts with female prostitutes can occur (see text).

Sexual debut

Sexual debut is defined as the start of a first 'period of availability' for sexual relationships. In the representation of Mwanza, the timepoint of first availability was drawn from a uniform probability distribution with a range of 12–18 years for males, and 12.5–18.5 years for females.

Sexual relationships: availability and partner selection

At each change in an individual's number of current partners, a new duration τ till availability for a new relationship is drawn from an exponential distribution with mean $\delta_{s,r} / r_{s,a} \times p_i)$, where: $\delta_{s,r}$ is the mean duration till availability, which depends on the person's sex (s) and relationship status (r) (currently engaged in a steady, short or no relationship); $r_{s,a}$ is the sex (s) and age (a) group specific promiscuity factor; and p_i is the personal promiscuity level.

In this study, the values of $\delta_{s,r}$ were set at 10 and 25 years for males and females, respectively, at the start of a steady relationship; at 2 and 4 years for unmarried males and females, respectively, at the start of a short relationship; and at 0.5 years for both sexes at the end of a last relationship, i.e. if becoming single again. The values of $r_{s,a}$ are listed in Table A2. Every time an individual passes an age border at which an age-specific parameter that affects a waiting time (e.g. $r_{s,a}$) changes value, a new duration is drawn according to the parameter value of the new age group. This applies also to the duration of availability (see below).

The personal promiscuity level p_i of individual i, which reflects the heterogeneity in promiscuity within age groups, is determined by a gamma distribution with mean 1.0 and shape parameter α:

$$f(p_i) = [\alpha/\Gamma(\alpha)](\alpha p_i)^{(\alpha-1)} \exp(-\alpha p_i) \qquad (1)$$

Variation in promiscuity within age groups decreases with increasing values of α. In this study, α equalled 1.5.

While being available for new relationships, an individual can be selected by someone of the opposite sex who has just ended his/her period of availability. If a person has not been selected by the end of his/her period of availability, he/she him-/herself then selects a partner from the pool of available people of the opposite sex. This period of availability is drawn from by an exponential probability distribution with a mean of $\varepsilon/(r_{s,a} \times p_i)$, with $\varepsilon = 0.25$ years in this study. See Table A2 for quantification of $r_{s,a}$ and Eq. (1) for p_i.

Sexual relationships: partner preferences

Partnership formation is guided by age preference matrices (one for each sex, Table A3) specifying the probability to select a partner from a certain age class. In case no potential partner is available in the preferred age class, a partner is selected in another age class by immediately renewed sampling among the remaining age classes for which the preference is larger than zero (e.g. in Table A3a, for males aged 15–19 years: the three female classes < 24 years, but not the older female age classes). If no partner is available in any of the preferred age classes, the person remains available for another period sampled as described above. This cycle repeats until the person has found a new partner.

As the age preference matrices determine age differences at the start of simulated relationships, the realized age differences in partnerships existing at a single point in time, in which long relationships are relatively over-represented, do not necessarily match the user-specified preferences. In the present simulations, the matrices specified males to prefer on average females that were 5 years younger and for females on average to prefer 5-year-older males (Table A3), in line with reported age difference between spouses in Mwanza [52]; realized age differences in the model population on cross-section averaged only 2 years. Apart from assortativeness by age, no other preferences apply. Thus,

Table A2. Values of parameters describing partnership formation in the STDSIM representation of rural Mwanza.

	Age- and sex-dependent promiscuity levels (rs,a)		Probability that a new relationship is steady, depending on the age of the male partner	
Age group (years)	Males	Females	Neither partner already in a steady relationship	One or both partners already in a steady relationship
< 15	3.5	4.0	0	0
15–19	3.5	4.0	0.1	0
20–24	4.0	2.5	0.3	0.1
34–39	3.0	1.5	0.6	0.15
30–34	2.0	1.0	0.8	0.2
35–44	1.0	0.6	0.8	0.15
45–54	0.4	0.4	0.8	0.1
55+	0.2	0.2	0.8	0.1

Table A3. Age preferences in partner selection in the STDSIM representation of rural Mwanza, (a) males and (b) females.

(a) Age of male (years)	Age of female (years)							
	< 15	15–19	20–24	25–29	30–34	35–44	44–54	55+
<15	0.8	0.2	0	0	0	0	0	0
15–19	0.6	0.3	0.1	0	0	0	0	0
20–24	0.3	0.4	0.2	0.1	0	0	0	0
25–29	0.1	0.25	0.4	0.2	0.05	0	0	0
30–34	0	0.1	0.25	0.4	0.2	0.05	0	0
35–44	0	0	0.1	0.25	0.4	0.2	0.05	0
45–54	0	0	0	0.1	0.25	0.4	0.2	0.05
55+	0	0	0	0	0.1	0.25	0.4	0.25
(b) Age of female (years)	**Age of male (years)**							
	< 15	15–19	20–24	25–29	30–34	35–44	44–54	55+
< 15	0.4	0.3	0.2	0.1	0	0	0	0
15–19	0.15	0.25	0.3	0.2	0.1	0	0	0
20–24	0	0.1	0.2	0.35	0.25	0.1	0	0
25–29	0	0	0.1	0.2	0.35	0.25	0.1	0
30–34	0	0	0	0.1	0.2	0.35	0.25	0.1
35–44	0	0	0	0	0.1	0.2	0.35	0.35
45–54	0	0	0	0	0	0.1	0.3	0.6
55+	0	0	0	0	0	0	0.2	0.8

promiscuous individuals have no explicit preference for promiscuous partners.

Types and durations of relationships

The probability that a new relationship is steady depends on whether or not at least one of the partners is already engaged in a steady relationship, and on the age of the male partner (Table A2). At the start of a new relationship its duration is drawn, in this study from an exponential distribution with a mean of 25 years for steady relationships, and from a gamma distribution with a mean of 0.5 years and shape parameter 0.5 for short relationships. These distribution functions and parameter values were chosen to obtain fit against the data of Mwanza [52] for the proportions of males and females married in different age groups (Fig. 1a), simultaneously with the total number of partners during the past year of males in different age groups (Fig. 1b).

In the current version of STDSIM, the frequency of intercourse in relationships varies with the age of the male partner, but does not depend on the number and type of ongoing relationships. For this study, we assumed frequencies of once a week for relationships in which the male was < 15 or between 35 and 54 years of age, 1.5 weekly for males aged 15–34 years, and 0.5 weekly for males aged 55 and over, consistent with data from factory workers in Mwanza town [58].

One-off contacts/prostitution

The occurrence of one-off contacts between male 'clients' and female 'prostitutes' is specified by defining a number of frequency classes of prostitute visiting, and subsequently specifying the proportions of married and unmarried males (up to a maximum age, in this study 50 years) in each class. A personal inclination to visiting prostitutes, assigned to each male at birth, determines to which classes a male belongs for the married and unmarried parts of life. As the inclination remains the same throughout life and does not depend on relationship situation, frequency of prostitute visiting is always the same before marriage and after divorce or widowhood. For the distribution of males in this study (Table A4), this means that 5% of males visits prostitutes six times per year irrespective of marital status. Of the 55% visiting prostitutes once yearly while unmarried, 30% quits this practice upon marriage, but would take up prostitute visiting again in case of divorce or widowhood. The other 25% visiting prostitutes once yearly does so irrespective of marital status.

At each prostitute contact as well as at sexual debut, the time interval until the client's next contact is determined according to the exponential distribution with mean φ, where $1/\varphi$ is the personal frequency of prostitute visits.

Table A4. Frequency of prostitute visits of males assumed in the STDSIM representation of rural Mwanza.

Frequency (contacts per year)	Fraction of unmarried males	Fraction of married males
0	40%	70%
1	55%	25%
6	5%	5%

Prostitutes are recruited according to the male demand from all sexually active females within a user-specified age range, in this study 15–30 years. A prostitute's 'career' lasts at least 1 year and ends somewhere before a user-specified maximum age (in this study 35 years), according to a uniform distribution. In this study, the frequency of client contacts per prostitute averaged 1 per week. In the absence of adequate data, we believe this is not unreasonable for rural Mwanza, and it allowed us to achieve adequate fit of numbers of partners of males, which includes each one-off contact as a separate partner, (Fig. 1b) and STD epidemiology (Figs 2 and 3). In this study, client contacts were divided over the pool of prostitutes in time order.

Each year, the model checks, and, if necessary, adapts the number of prostitutes to match the user-specified frequency number of client contacts per prostitute as closely as possible, given the number of visits by clients and the frequency of client contacts of prostitutes. If the number of prostitutes is too small, additional females are recruited. If the number of prostitutes is too large, a randomly selected prostitute terminates her career before the scheduled date. In addition, every time a woman in the starting age range (15–30 years) becomes widowed (i.e. loses her steady partner), a similar check for the number of prostitutes is performed; and if there is a shortage, the widow is recruited as a prostitute.

Start of the simulation

At start of a simulation, an initial population is created; the population used in this study is given in Table A5. All individuals start as singles; formation of sexual relationships and one-off contacts then occurs as described above. STD infections are attributed to the initial population at user-specified prevalences, in this study 3.5% for gonorrhea, 5% for chlamydia, 9% for syphilis and 1.2% for chancroid. Initial STD infections are randomly distributed only among individuals with a high individual promiscuity level ($p_i > 1$) who have had their sexual debut.

Table A5. Specification of the initial population (in absolute numbers) in STDSIM, and values used to represent rural Mwanza, for starting year 1930.

Age group (years)	Males	Females
0–9	500	500
10–19	375	375
20–29	223	223
30–39	150	150
40–49	100	100
50–59	80	80
60–69	40	40
70–79	20	20
80–89	10	10

Simulations are started in a user-specified year (here 1930) well in advance of the introduction of HIV. This allows the model population to reach dynamic equilibria with respect to demography, partnership formation and STD epidemiology, before the simulated start of HIV spread. Neither the chosen composition of the initial population nor the user-specified STD rates in the initial population are critical to the situation of equilibrium.

HIV is introduced into the model population by randomly infecting one prostitute, in a user-specified year (here 1983). In applications of the model in which one-off contacts are not assumed, HIV introduction occurs by simultaneous infection of 10 sexually active males and 10 sexually active females in the general population.