Can Population Differences Explain the Contrasting Results of the Mwanza, Rakai, and Masaka HIV/Sexually Transmitted Disease Intervention Trials?

A Modeling Study

Richard G. White, MSc, Kate K. Orroth, PhD,* Eline L. Korenromp, PhD,† Roel Bakker, PhD,† Mwita Wambura, MSc,*‡ Nelson K. Sewankambo, MBChB,§ Ron H. Gray, MD,‖ Anatoli Kamali, MSc,¶ James A. G. Whitworth, MD,*¶ Heiner Grosskurth, MD,* J. Dik F. Habbema, PhD,† and Richard J. Hayes, DSc**

Objective: To determine whether population differences can explain the contrasting impacts on HIV observed in the Mwanza trial of sexually transmitted disease (STD) syndromic treatment (ST), the Rakai trial of STD mass treatment (MT), and the Masaka trial of information, education, and communication (IEC) with and without ST as well as to predict the effectiveness of each intervention strategy in each population.

Methods: Stochastic modeling of the transmission of HIV and 6 STDs was used with parameters fitted to demographic, sexual behavior, and epidemiological data from the trials and general review of STD/HIV biology.

Results: The baseline trial populations could be simulated by assuming higher risk behavior in Uganda compared with Mwanza in the 1980s, followed by reductions in risk behavior in Uganda preceding the trials. In line with trial observations, the projected HIV impacts were larger for the ST intervention in Mwanza than for the MT intervention in Rakai or the IEC and IEC + ST interventions in Masaka. All 4 simulated intervention strategies were more effective in reducing incidence of HIV infection in Mwanza than in either Rakai or Masaka.

Conclusions: Population differences in sexual behavior, curable STD rates, and HIV epidemic stage can explain most of the contrast in HIV impact observed between the 3 trials. This study supports the hypothesis that STD management is an effective HIV prevention strategy in populations with a high prevalence of curable STDs, particularly in an early HIV epidemic.

Key Words: Africa, behavioral interventions, evaluation of program effectiveness, HIV/sexually transmitted disease (STD) prevention, mass treatment, mathematical models, syndromic treatment

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Around 5 million people became infected with HIV in 2003, and most were infected in Africa via heterosexual transmission.[1] In the absence of a vaccine, HIV prevention activities have focused primarily on sexual risk behavior reduction and sexually transmitted disease (STD) treatment.[2–4] Three randomized, controlled trials of STD treatment and behavior change interventions have been carried out in East Africa. In Mwanza, Tanzania, improved clinic based syndromic STD treatment (ST) reduced the incidence of HIV infection by 38% among the general population.[5,6] However, trials of STD mass treatment (MT) in Rakai, Uganda, and of an information, education, and communication (IEC) intervention with and without improved ST in Masaka, Uganda, showed no significant effect on the incidence of HIV infection[7–9] despite similar reductions in the prevalence of curable STDs in all 3 sites. The contrasting results of these trials have led to confusion regarding the effectiveness of these HIV prevention strategies.

Many hypotheses have been raised[10,11] and tested[12–17] to explain these results. Recently, we conducted a systematic comparison of trial data that suggested the results could relate to differences between the study populations at the start of the trials.[18] However, the data comparison alone did not allow us to determine whether these differences were sufficient to explain the magnitude of the differing impacts.

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From *London School of Hygiene and Tropical Medicine, London, UK; †Department of Public Health, Erasmus University Rotterdam, The Netherlands; ‡National Institute for Medical Research, Mwanza, Tanzania; §Makerere University School of Medicine, Kampala, Uganda; ‖Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA; and ¶Medical Research Council Programme on AIDS, Uganda Virus Research Institute, Entebbe, Uganda.

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Reprints: Richard G. White, Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK (e-mail: richard.white@lshtm.ac.uk).

The objectives of this modeling study were to explore whether differences between the study populations could explain the magnitude of the differences in observed trial impacts and to predict the effectiveness of each intervention strategy in each population.

METHODS

The Microsimulation Model STDSIM

STDSIM simulates the natural history and transmission of HIV and STDs in a population consisting of individuals with characteristics that can change over time. The formation and dissolution of heterosexual relationships and transmission of STDs during contacts between sexual partners are modeled as stochastic events.[19,20] The model has previously been used to explore the findings of the Mwanza and Rakai trials separately.[15,16,21–24]

Simulation Design

Three trial baseline model scenarios corresponding to the Mwanza, Rakai, and Masaka study populations were fitted iteratively using predetermined ranges of input and output parameters collated from trial data and literature review of STD/HIV biology. We constrained model assumptions by specifying that HIV/STD natural history, transmission probabilities, and STD cofactor effects should be the same across sites. To reduce the random fluctuations associated with stochastic simulations, results were based on means over 150 simulation runs for each scenario.

To project the impact of each intervention in the site in which it was investigated, we simulated 4 intervention scenarios: ST in Mwanza, MT in Rakai, and IEC and IEC + ST in Masaka. We compared the modeled and observed STD/HIV impact by calculating the projected incidence rate ratio (IRR) or prevalence ratio between intervention and comparison arms in the same age/sex group and over the same period as reported in the trials.

For comparison of the impacts of the 4 intervention strategies across all 3 populations, we calculated the impact on the incidence of HIV infection among adults aged 15–54 years over 2 years in all sites.

All interventions were modeled to start in 1992 in Mwanza, 1994 in Rakai, and 1995 in Masaka.

Simulated Study Populations

The baseline model representations were based on a systematic data comparison,[18] showing that although the prevalence of HIV infection was higher in the Ugandan sites than in Mwanza, markers of recent sexual risk behavior and curable STD rates were lower. Conversely, markers of past sexual behavior (low-titre serological syphilis, herpes simplex virus type 2 [HSV-2] seroprevalence, and lifetime partners) were as high in Uganda as in Mwanza.

Two assumptions were used to fit STDSIM to these observed baseline population differences: (1) higher risk behavior in the Ugandan sites compared with Mwanza in the 1970s and 1980s that was followed by a behavioral risk reduction in Uganda from the late 1980s onward[25–29] after the cessation of the civil war in 1986[30,31] and the introduction of HIV/AIDS prevention programs from the early 1990s[27,32]; and (2) earlier introduction of HIV in the Rakai and Masaka populations. The differences in sexual risk behavior were represented as differing partner change rates, frequencies of one-off contacts (single random sexual contacts between a smaller group of women at high risk and a larger group of men), and condom use rates. This pattern of risk behaviors resulted in comparatively higher risk behavior in Rakai and Masaka than in Mwanza before 1986 (eg, 13.5%, 12.3%, and 7.2% of males with $\geq$5 partners per year, respectively) followed by less risky sexual behavior in Rakai and Masaka than in Mwanza by the start of the trials (eg, 4.2%, 4.0%, and 7.2% of males with $\geq$5 partners per year, respectively). HIV was introduced in the model in 1978 in Rakai and Masaka, before the first reported AIDS cases in 1982,[33,34] and in 1983 in Mwanza.[35] In line with baseline differences in condom use rates,[18] we assumed some condom use in one-off and casual contacts in Rakai and Masaka (10% from 1990) with a 10% failure rate but no condom use in Mwanza.

For Masaka, in line with trial observations of secular reductions in risk behavior during the trial,[7] we also simulated reducing partner change rates (eg, simulated proportion of males with $\geq$5 partners per year reduced from 4.0% to 3.5%) and a linear increase in condom use rates to 20% by year 2000.

STD Natural History, Transmission, Treatment, and Interaction

Table 1 shows the assumptions regarding HIV/STD natural history, transmission, treatment, and interaction.

HIV infection was represented by 4 stages: primary, asymptomatic, symptomatic, and AIDS with average durations of 10, 150, 200, and 40 weeks, respectively. Infectivity was higher during the primary and AIDS stages.[36–38] For simplicity, sexual activity and coital frequency were assumed not to change due to HIV infection.

Simulated STDs were infections due to *Treponema pallidum* (syphilis), *Haemophilus ducreyi* (chancroid), *Neisseria gonorrhoeae* (gonorrhea), *Chlamydia trachomatis*, *Trichomonas vaginalis* (trichomoniasis), and HSV-2. These STDs were included because they are thought to enhance HIV transmission and to be prevalent among the populations and were targeted by the interventions.

Syphilis was represented by 4 stages: infectious, early latent, latent, and late latent. The first stage, corresponding to primary and secondary syphilis, was highly infectious and associated with a cofactor effect on HIV.[39] Without treatment, syphilis progressed to early-latent syphilis with lower infectiv-

TABLE 1. STDSIM Parameter Values Concerning Natural History, Transmission, Treatment, and Interaction of STD/HIV Infections in the Simulated Rakai, Masaka, and Mwanza Trial Populations

Parameter			HIV						TV	
			Primary	Asymptomatic	Symptomatic	AIDS	NG	CT	Without Signs	With Signs
Transmission probability per contact (equal for recognized and unrecognized episodes)		M → F F → M	0.072 0.024	0.004 0.001	0.004 0.001	0.018 0.006	0.275 0.138	0.252* 0.126*	0.142 0.047	0.142 0.047
Relative increase in per-contact HIV transmission probability due to STD†			NA	NA	NA	NA	3	3	0[c]	2
Annual rate of infection by contact from outside the study population in those older than the age of sexual debut (/100 py)	Rakai Masaka Mwanza	M F M F M F	0.024 0.023 0.015 0.016 0.005 0.006	NA	NA	NA	0.142 0.073 0.121 0.053 0.154 0.166	0.128 0.163 0.098 0.120 0.796 0.125	0.782 0.409 0.704 0.368 0.957 0.368	NA
Mean duration of stage if untreated (wk)‖		M F	10 10	150 150	200 200	40 40	14 14	14 52	10 260	2.5 1.25
Probability that infection becomes symptomatic (curable STDs only)		M F	NA	NA	NA	NA	0.45 0.14	0.11 0.06	0‡ 0‡	0.25 0.15
Treatment seeking delay in symptomatic cases (wk, curable STDs only)		M F	NA	NA	NA	NA	3 6	3 6	NA	3 6
Fraction of symptomatic STD episodes for which treatment is sought (curable STDs only)	Non int[n] Masaka and Mwanza int[n]	M F M F	NA	NA	NA	NA	0.20 0.15 0.40 0.45	0.20 0.15 0.40 0.45	0‡	0.20 0.15 0.40 0.45
Fraction of STD clinic attendees cured by syndromic treatment services (curable STDs only)	Non int[n] Masaka int[n] Mwanza int[n]	 M F M F	NA	NA	NA	NA	0.30 0.60 0.60 0.60 0.60	0.30 0.60 0.60 0.60 0.60	0¶	0.30 0.40 0.60 0.40 0.60
Fraction of STD infections cured by mass treatment (curable STDs only)	Rakai	M and F	NA	NA	NA	NA	0.95	0.95	0.85	0.85

ity followed by the noninfectious latent and late-latent stages. A fixed proportion of individuals was assumed to seek treatment of ulcerative symptoms during the infectious stage. To enable fitting of the model to the available serological data, we categorized syphilis infection into high-titer serological syphilis as individuals testing TPHA positive with an RPR titer of ≥1:8 and low-titre serological syphilis as individuals testing TPHA positive with an RPR titer of ≥1:2. In the model, these 2 categories were assumed to comprise 92.5%/100%/100%/0 and 92.5%/100%/100%/40% of individuals in the 4 simulated syphilis stages, respectively.

Gonorrhea, chlamydial, and chancroid infections were each represented by a single stage characterized by constant infectivity, HIV cofactor effect, and proportion symp-

TABLE 1. *(continued)* STDSIM Parameter Values Concerning Natural History, Transmission, Treatment, and Interaction of STD/HIV Infections in the Simulated Rakai, Masaka, and Mwanza Trial Populations

	HSV-2						TP			
Parameter	**Primary**	**Early-Latent**	**Latent**	**Late-Latent**	**Recurrent Ulcers**	**HD**	**Infectious**	**Early-Latent**	**Latent**	**Late-Latent**
Transmission probability per contact (equal for recognized and unrecognized episodes)	0.400 0.200	0.010§ 0.005§	0.005§ 0.003§	0 0	0.300 0.150	0.25 0.15	0.350 0.175	0.035 0.018	0 0	0 0
Relative increase in per-contact HIV transmission probability due to STD†	25	0§	0§	0	10	25	7.5	0	0	0
Annual rate of infection by contact from outside the study population in those older than the age of sexual debut (/100 py)	0.089 0.039 0.083 0.028 0.089 0.022	NA	NA	NA	NA	0.081 0.060 0.073 0.054 0.073 0.054	0.020 0.029 0.009 0.014 0.080 0.064	NA	NA	NA
Mean duration of stage if untreated (wk)‖	3 3	104 104	520 520	∞ ∞	1 1	11 11	26 26	52 52	130 130	650 650
Probability that infection becomes symptomatic (curable STDs only)	NA	NA	NA	NA	NA	0.90 0.70	0.50 0.20	0 0	0 0	0 0
Treatment seeking delay in symptomatic cases (wk, curable STDs only)	NA	NA	NA	NA	NA	2.5 4	2.5 4	NA	NA	NA
Fraction of symptomatic STD episodes for which treatment is sought (curable STDs only)	NA	NA	NA	NA	NA	0.20 0.15 0.45 0.50	0.20 0.15 0.45 0.50	0	0	0
Fraction of STD clinic attendees cured by syndromic treatment services (curable STDs only)	0	0	0	0	0	0 0.60 0.60 0.60 0.60	0.50 0.60 0.60 0.60 0.60	0¶	0¶	0¶
Fraction of STD infections cured by mass treatment (curable STDs only)	0	0	0	0	0	0.95	0.95	0.95	0.95	0.95

*Before first infection. After each episode, simulated individuals become 20% less susceptible to reinfection.

†For susceptibility and infectivity.

‡Except during signs.

§Except during recurrent ulcers.

‖Individual STD stage durations were sampled from Weibull distributions with shape parameter 2, except for the duration of primary HIV infection and early-latent HSV-2 infection, where we used exponential distributions and the duration of HSV-2 ulcers, which were modeled with a constant duration.

¶Except if treatment is sought for coinfection with another STD with the same syndrome, in which case the probability of cure is as for "with signs."

CT indicates chlamydial infection; F, female; HD, chancroid; HSV-2, herpes simplex virus type 2; int^n, intervention; M, male; NA, not applicable; NG, gonorrhea; TP, syphilis; TV, trichomoniasis.

tomatic. We assumed that the average duration of chlamydial infection was longer in females than in males and the average duration of gonorrhea in males and females was similar.[40] Chancroid was modeled with an average duration of 11 weeks in both sexes.[41,42] To achieve adequate model fit of the observed rapid decline in the prevalence of chlamydial infection with age, we assumed each episode of chlamydial infection induced a 20% reduction in susceptibility to reinfection. Such acquired immunity is analogous to observations on ocular infection due to *Chlamydia*.[43]

Trichomoniasis infection was represented by 1 stage characterized by constant infectivity, with a longer average duration in females than in males.[44–53] About 50% of females and 25% of males were assumed to have clinical signs,[48–50,54–61] which were associated with a probability of having symptoms and a cofactor effect. In common with other STDs, signs were modeled to be more frequently symptomatic in males than in females.[48,54,55,60–62] In line with empirical observations, the simulated HIV cofactor effect was restricted to those with signs.[63–66]

HSV-2 infection was represented by 4 stages: primary, early latent, latent, and late latent. A primary ulcer lasted on average 3 weeks.[67,68] After the primary ulcer, recurrent ulcers were modeled to occur with decreasing frequency,[69] on average every 2.5 months during the first 2 years and every 6 months for the subsequent 10 years. Recurrent ulcers persisted 1 week and were assumed to be less severe and less infectious than primary ulcers. In between recurrences, a low continuous level of infectivity was assumed, representing subclinical HSV-2 shedding.[70–73] In the late-latent stage, HSV-2 was no longer infectious, and ulcer recurrences ceased; however, individuals remained seropositive for life. The effects of HIV on the natural history of HSV-2 infection were ignored, because these have been shown not to have a substantial effect on HIV/STD interactions or the impact of the evaluated interventions.[21]

For all curable STDs, spontaneous cure or treatment resulted in immediate susceptibility to reinfection.

We assumed that STDs enhance HIV infectivity and susceptibility. For chancroid, we assumed a per contact HIV cofactor effect of 25, toward the low end of the range (3–300) estimated from studies of commercial sex workers and clients in Nairobi,[74] to account for possible residual confounding in these estimates.[75] This is larger than relative risks estimated from epidemiological studies because they reflect the cumulative result of numerous sexual exposures occurring over an extended follow-up period, during only some of which the STD will have been present.[76] The cofactor effects of the other STDs reflected their relative clinical severity, higher for primary HSV-2 infection than for recurrent HSV-2 infection and infectious syphilis, and lower for the nonulcerative STDs gonorrhea, chlamydial infection, and trichomoniasis (Table 1).

Simulated Interventions

The simulated MT intervention in Rakai[8,77] consisted of 2 rounds of STD MT at the beginning of 1994 and 1995, covering 70% of individuals aged 15 to 59 years. The cure rates of the single-dose regimens used in the Rakai trial approached 100% in clinical studies.[44,63,78–84] However, to account for likely lower efficacy of this regimen under field conditions, we assumed that MT cured 95% of gonorrhea, chlamydial, chancroid, and syphilis infections and 85% of trichomoniasis (Table 1).

The simulated ST intervention in Mwanza[5,85–87] increased treatment-seeking behavior and partner notification rates from 1992 onward. We simulated an increase in the average proportion of symptomatic STDs cured from 5% to 25%,[87,88] and 27% of steady partners of treated patients would be notified and cured on the basis of estimates of 34%[87]notified and 80% cured.[88] Treatment of 1 STD was modeled to result in treatment of all coinfections characterized to have the same syndrome (ulcer or discharge). No treatment of HSV-2 infection was modeled. The Mwanza trial cohort (comparison and intervention arm) had been surveyed for syphilis at baseline and, if RPR positive, treated for syphilis.[85] Therefore, we also simulated that 70% of the Mwanza study population was treated for syphilis in 1992.

The IEC and ST interventions tested in Masaka have been previously described.[7,89] From 1995, we assumed that the IEC intervention increased absolute condom use rates among one-off and casual contacts by 17.5%. The magnitude of this increase was consistent with findings of behavioral surveys[7] but was determined by fitting the model to the average reduction in the incidence of HSV-2 infection. For simplicity, we assumed that the Masaka ST intervention was identical to that in Mwanza, with the exception of partner notification rates, where data from Masaka supported simulating notification and cure of steady partners of 9% of males and 28% of female clinic attendees (unpublished data, Lawrence Muhangi). The Masaka trial did not include baseline mass treatment of syphilis.

Sensitivity Analysis

To assess the robustness of the results to uncertainties in model input parameters known to affect trial impact, the simulations were repeated using plausible "high" and "low" values for each parameter in turn. If there were insufficient data to inform the selection of a plausible range, then the default values were doubled and halved. Baseline prevalences of HIV infection were refitted if required, by varying the overall HIV transmission probability. HIV impacts in the 3 scenarios (default, high, and low) were then compared for each parameter in turn.

RESULTS

Simulated Study Populations

The simulated population age and sex composition provided a good fit to the rural Rakai and Masaka district census data for 1990 and rural Mwanza region census data for 1987 and 1988 (data not shown).[90,91] As observed, we simulated a slightly higher annual growth rate in Rakai (model = 3.1%, data = 3.0%) than in Masaka (model = 2.9%, data = 2.7%) and Mwanza (model = 2.5%, data = 2.6%). The simulated all-age population size at the start of the trials was ~20,000 in all sites.

Simulated proportions of adults in steady relationships ("married") were lower in Rakai and Masaka than in Mwanza (model M,F: Rakai = 59%,65%; Masaka = 60%,66%; Mwanza = 65%,71%; data M,F: Rakai = 57%,61%; Masaka = 50%,57%; Mwanza = 64%,69%) in line with trial data.[18] This reflected the higher frequency of widowhood, due to higher HIV-related mortality rates in Uganda. Because of the assumed lower risk behavior in Rakai and Masaka than in Mwanza at the start of the trials, simulated proportions of adult males with ≥5 partners in the previous year were lower in Rakai and Masaka than in Mwanza (model = 4.2%, 4.0%, 7.2%; data = 1.4%, 2.2%, 9.6%; respectively).[18] In all sites, the simulated mean age of sexual debut was older in males (17.5 years) than in females (15 years). Males were modeled on average to be 4.7 years older than their steady partners, in good agreement with the reported average 5-year difference in marital relationships.[18]

Figure 1 shows a good model fit of the observed epidemiological differences between the trial populations at the start of the trials. The projected prevalences of longer duration STDs (low-titre serological syphilis and HSV-2 infection) were similar across all sites, whereas shorter duration STDs (high-titer serological syphilis, gonorrhea, chlamydial infection, and chancroid) were less prevalent in Rakai and Masaka than in Mwanza (women, Fig. 1a; men, data not shown for brevity). In addition, the simulated prevalence and incidence of HIV infection among adults were highest in Rakai, lowest in Mwanza, and higher for females than for males in all sites (Fig. 1b). Figure 1c shows that the modeled scenarios provided a good fit of the declining prevalence of HIV infection in Rakai and Masaka and of the increasing prevalence of HIV infection in Mwanza. Limited data, selection bias, and methodological differences precluded quantitatively fitting the incidence and/or etiology of genital ulcer disease in the 3 sites. However, the etiologic distribution of symptomatic ulcers was assessed qualitatively in our fitting where the model reproduced the observed rankings of a higher prevalence of chancroid in Mwanza (based on unpublished urban clinic data) than in Rakai and Masaka. In addition, most symptomatic ulcers in Mwanza were due to chancroid, while most in Rakai and Masaka were due to HSV-2.

Simulated Intervention Impact

Figure 2 shows the simulated and observed impact of the interventions on STD rates. In Rakai, the projected impacts of MT on all STDs were larger than measured during the trial, with the exception of the incidence of trichomoniasis. In Mwanza, the projected impact on prevalences of trichomoniasis, chlamydial infection, and gonorrhea was in reasonable agreement with the observed impact. However, the projected impact on the prevalence of high-titer serological syphilis was lower than observed but within the 95% confidence interval (CI). In Masaka, the projected IEC impact on prevalences of gonorrhea and chlamydial was in good agreement with the trial data. However, the impact on the prevalence of high-titer serological syphilis was larger than observed. In Masaka, the additional impact of the ST intervention in the IEC + ST arm was small, with the notable exception of a large increase in chancroid impact.

Figure 3a shows that the projected impacts on HIV were consistent with those observed during the trials. The projected impact of the ST intervention in Mwanza (model IRR = 0.72, data IRR = 0.62 [95% CI, 0.45–0.85]) was much larger than the projected impact of the MT intervention in Rakai (model IRR = 0.90, data IRR =0.97 [95% CI, 0.81–1.16]) or the projected impact of the IEC and IEC + ST interventions in Masaka (IEC: model IRR = 0.87, data IRR = 0.94 [95% CI, 0.60–1.45]; IEC + ST: model IRR = 0.84, data IRR = 1.00 [95% CI, 0.63–1.58]). All projected impacts were within the 95% CI around the empirical point estimates.

Simulated Intervention Impact in All Study Populations

Figure 3b shows the simulated impact of all 4 interventions in the 3 trial populations. The simulations show that at the time the trials were conducted, all of the simulated intervention strategies would have been much more effective in reducing the incidence of HIV infection among adults in Mwanza than in either Rakai or Masaka (projected IRR over 2 years: Rakai ST = 0.96, MT = 0.90, IEC = 0.85, IEC + ST = 0.83; Masaka ST = 0.98, MT = 0.91, IEC = 0.87, IEC + ST = 0.85; Mwanza ST = 0.72, MT = 0.71, IEC = 0.69, IEC + ST = 0.56).

Sensitivity Analysis

The sensitivity analysis (Table 2) showed that the projected impacts on HIV of MT in Rakai and ST in Mwanza were independent of the assumption that sexual contact continued during AIDS. The projected impact of IEC in Masaka was slightly larger if we simulated no sexual contact during AIDS. The projected impact of MT in Rakai and ST in Mwanza on the incidence of HIV infection was particularly sensitive to the assumed chancroid prevalence and STD cofactor effects, specifically in Rakai to the cofactor effects of nonulcerative STDs and in Mwanza to those of ulcera-

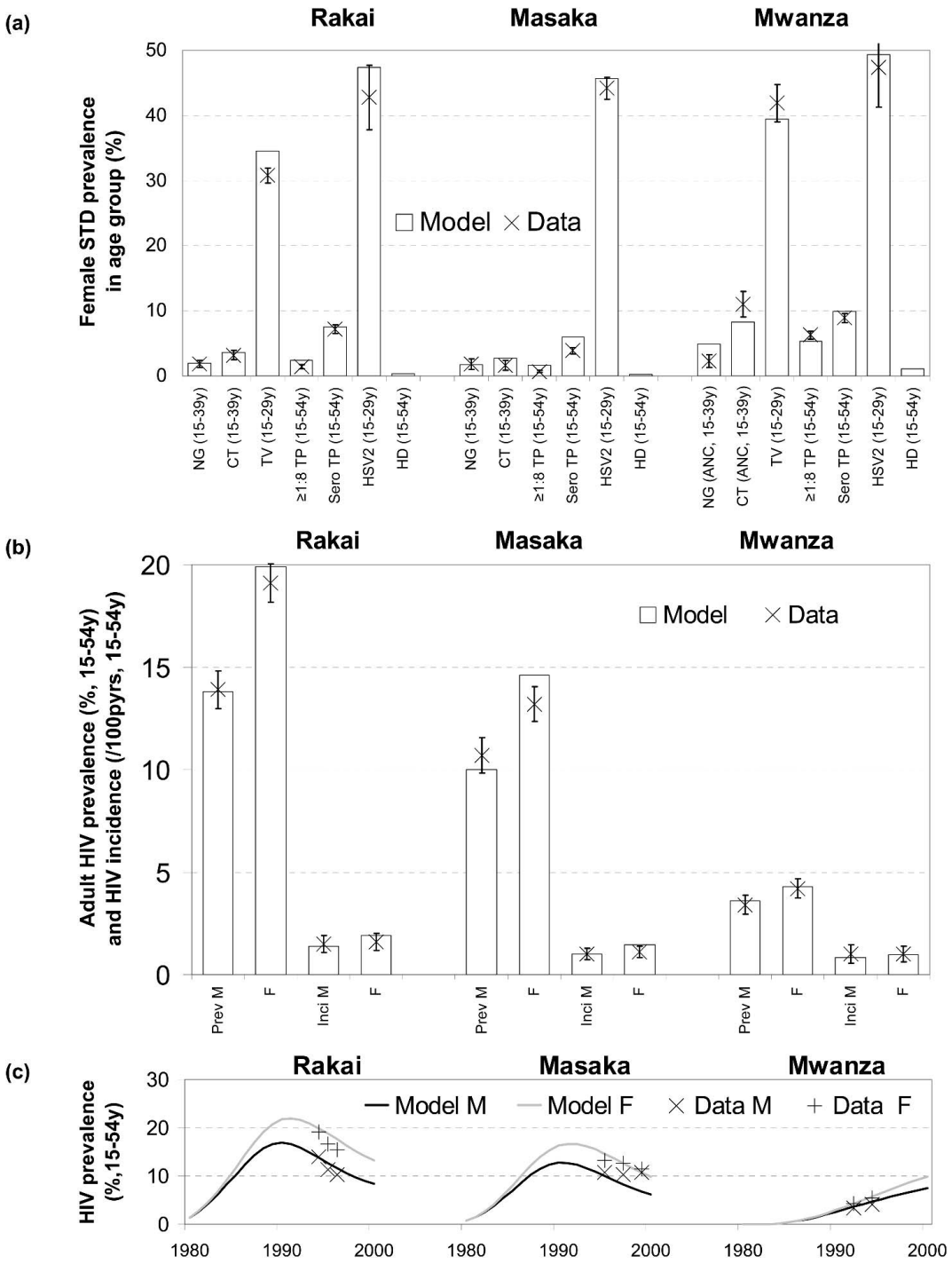

FIGURE 1. Simulated and observed prevalence of STDs among females at trial start (a), prevalence and incidence of HIV infection among adults by sex at trial start (b), and trend in prevalence of HIV infection among adults without intervention by sex during 1980–2000 (c). Observed prevalence data in A and B are from round 1 control and intervention(s) arms combined. Incidence data in B and prevalence data in C are from control arm only. ANC indicates antenatal clinic attendees; bars/lines, model prediction; crosses, observed data with 95% CI; CT, chlamydial infection; F, female; HD, chancroid; HSV2, herpes simplex virus type 2 infection; Inci, incidence; M, male; NG, gonorrhea; Prev, prevalence; pyrs, person-years; Sero TP, low-titre serological syphilis (TPHA positive/RPR titer, ≥1:2); ≥1:8 TP, high-titer serological syphilis (TPHA positive/RPR titer, ≥1:8); TV, trichomoniasis; y, year. The simulated prevalence and incidence were calculated for the same age and sex group and over the same period as the observed data. With the exception of the simulated HD prevalence, the simulated STD prevalence was omitted if observed data were not available. CIs around observed data were omitted from C to improve clarity.

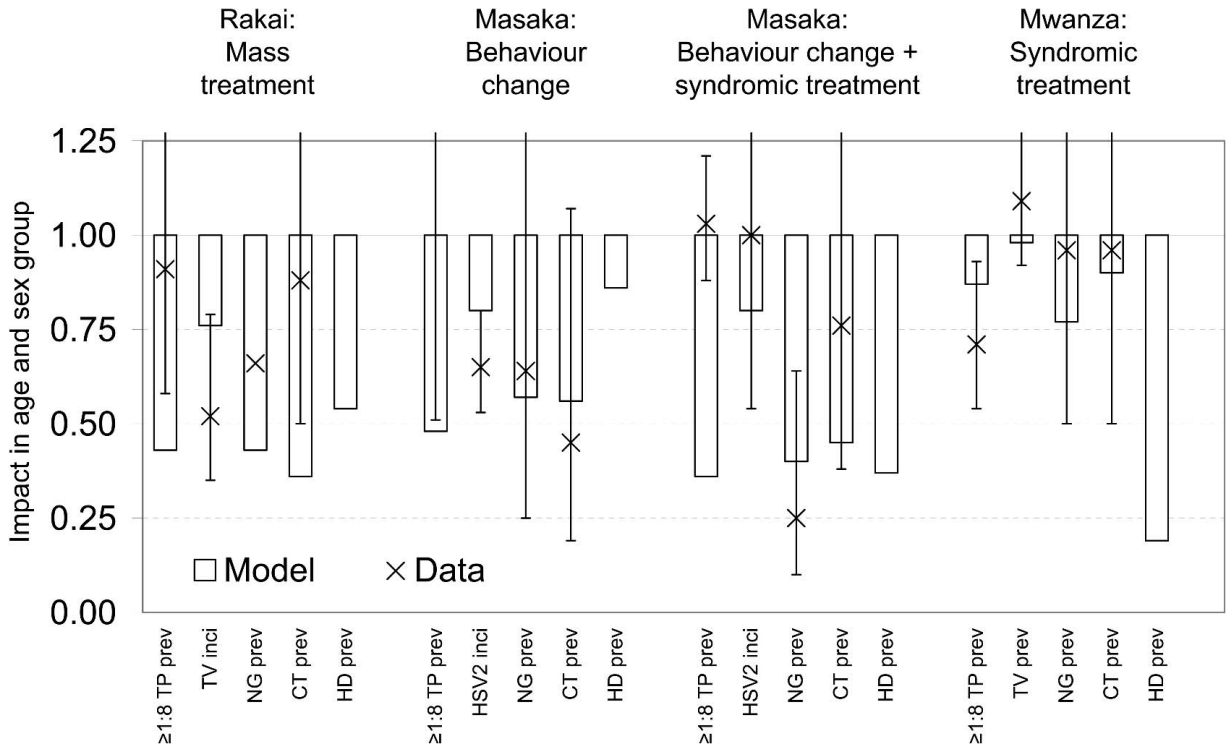

FIGURE 2. Simulated and observed STD impact rate ratios (mean, 95% CI) of the mass treatment intervention in Rakai, the behavior change and the behavior change with syndromic treatment interventions in Masaka, and the syndromic treatment intervention in Mwanza. Bars indicate model prediction; crosses, observed data with 95% CI; CT, chlamydial infection; HD, chancroid; HSV2, herpes simplex virus type 2 infection; inci, incidence; NG, gonorrhea; prev, prevalence; ≥1:8 TP, high-titer serological syphilis (TPHA positive/RPR titer, ≥1:8); TV, trichomoniasis. Observed data[5,7,8,98] and unpublished data on Masaka syphilis prevalence impact from Maria Quigley. Unless otherwise stated below, the observed STD impact refers to prevalence ratios (intervention arm prevalence/comparison arm prevalence) for males and females: Rakai, between 15 and 59 years after 2 years; Masaka, 13 years of age or older after 3 years; and Mwanza, 15- to 54-year-olds after 2 years. Note the following exceptions: Rakai: the ≥1:8 TP prevalence ratio was measured for pregnant women on average 4 months after the mass treatment, the TV impact was measured using an incidence rate ratio measured for females over 2 years, and the NG and CT prevalence ratio was measured for 15- to 29-year-olds; Masaka: the HSV2 impact was measured using an incidence rate ratio for 13- to 29-year-olds over 3 years, and the NG and CT prevalence ratio was measured for 13- to 39-year-olds; and Mwanza: the TV prevalence ratio was measured for antenatal clinic attendees 18 months after the start of the intervention, and the combined impact on NG and/or CT was calculated for males. The NG impact CIs were not reported for the Rakai intervention owing to small numbers. The simulated impacts were calculated using the same measure of effect (intervention scenario rate/comparison scenario rate) in the same age and sex group and over the same period as the observed data. With the exception of the simulated HD impact (the prevalence ratio for males and females aged 15 to 54 years), the simulated STD impact was omitted if observed data were not available. All interventions started in 1994 in Rakai, 1995 in Masaka, and 1992 in Mwanza.

tive STDs. In contrast, the projected impact of IEC and IEC + ST in Masaka was insensitive to these baseline assumptions, suggesting that the projected HIV impact of IEC was largely due to the direct effect of condoms in preventing HIV transmission and not to a reduction in the burden of cofactor STDs.

The projected HIV impact was also sensitive to some characteristics of the simulated interventions. The impact of MT in Rakai increased with assumed coverage, so that a lower assumed MT coverage would have provided a better fit to impact data. The projected impact of IEC and IEC + ST in Masaka was very sensitive to the assumed increase in condom use but insensitive to the proportion of STD episodes that were symptomatic and the proportion of these symptomatic episodes for which treatment was sought. The projected impact of ST in Mwanza increased with the proportion of STD episodes symptomatic and the proportion of STD patients seeking treatment. Increasing either would have provided a better fit of the projected and observed HIV impact but worsened the fit of STD impacts.

DISCUSSION

Of the hypotheses put forward for the contrasting results of the Mwanza and Rakai STD treatment intervention trials,[10–17]

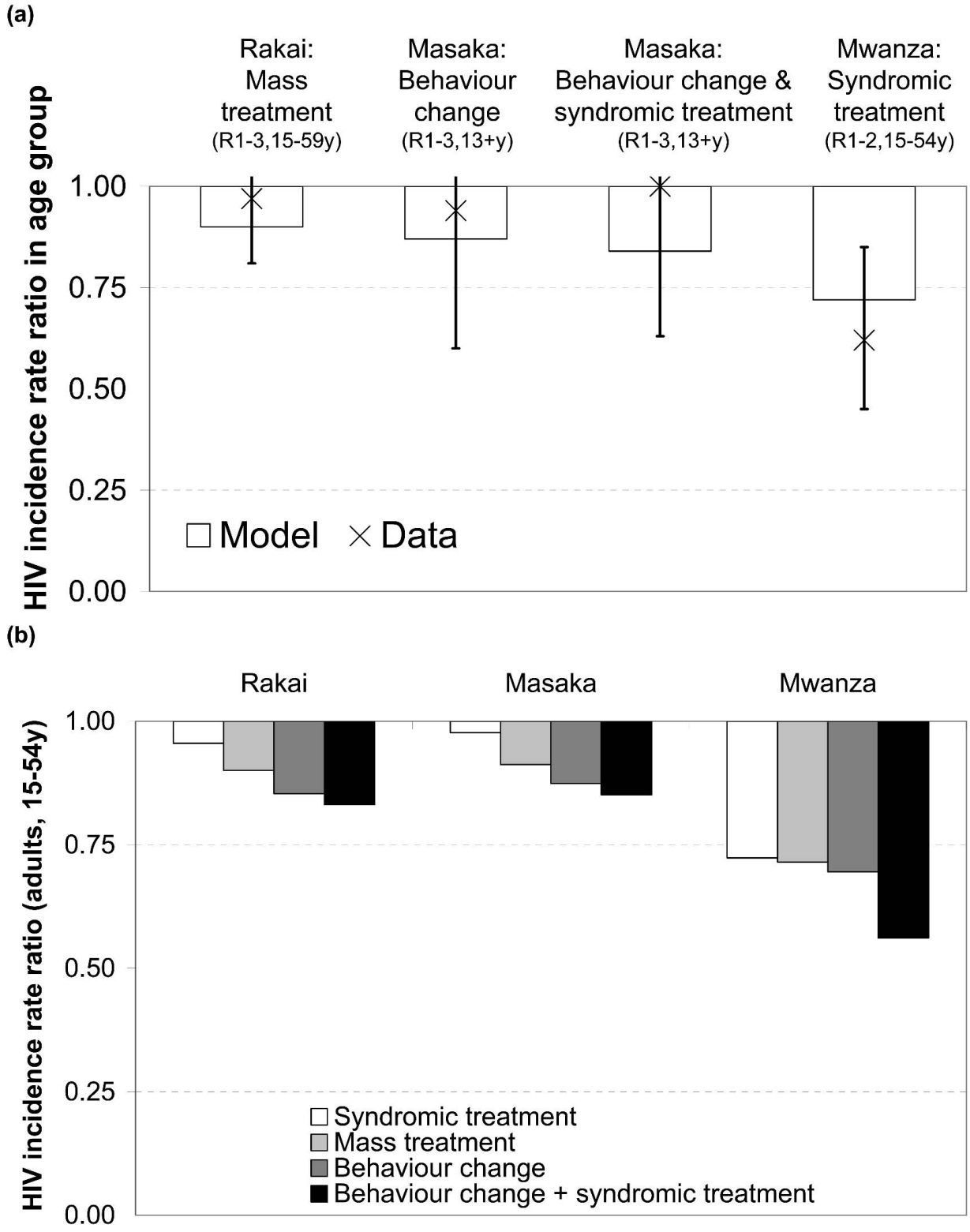

FIGURE 3. a, Simulated and observed (mean, 95% CI) HIV infection incidence rate ratios of the mass treatment intervention in Rakai, the behavior change and behavior change with syndromic treatment interventions in Masaka, and the syndromic treatment intervention in Mwanza. b, Simulated adult HIV infection incidence rate ratios of the 4 interventions in all 3 sites. Impact data for sample group and period are specified in category labels. Bars indicate model prediction; crosses, observed data with 95% CI; R, round; y, year. All interventions started in 1994 in Rakai, 1995 in Masaka, and 1992 in Mwanza.

TABLE 2. Sensitivity of Simulated Intervention Impact to Selected Model Assumptions

Scenario		(Adjusted) HIV Transmission Probability*		Projected Baseline Prevalence, %						Chancroid Prevalence Ratio and HIV Infection Incidence Rate Ratio							
				Chancroid			HIV Infection			Chancroid				HIV Infection			
										RK	Mk		Mw	Rk	Mk		Mw
		M → F	F → M	Rk	Mk	Mw	Rk	Mk	Mw	MT	IEC	IEC + ST	ST	MT	IEC	IEC + ST	ST
Data		NA	NA	NA	NA	NA	16.5	12.0	4.1	NA	NA	NA	NA	0.97	0.94	1.00	0.62
Model default (see Table 1 and Figures 1–3)		0.0036	0.0012	0.32	0.24	1.06	16.9	12.3	4.0	0.54	0.86	0.37	0.19	0.90	0.87	0.84	0.72
Model with changed baseline assumptions																	
No sexual contact during AIDS		0.0039	0.0013	0.27	0.21	1.01	14.9	10.8	3.9	0.61	0.70	0.32	0.20	0.89	0.82	0.81	0.73
STD cofactor effects																	
All	↑	0.0020	0.0007	0.31	0.23	0.89	17.0	12.4	3.9	0.54	0.73	0.34	0.17	0.86	0.84	0.81	0.71
	↓	0.0071	0.0024	0.32	0.23	0.93	20.1	15.8	4.0	0.59	0.77	0.34	0.19	0.94	0.86	0.84	0.80
Ulcerative only	↑	0.0022	0.0007	0.30	0.22	0.97	16.0	11.4	3.9	0.56	0.79	0.32	0.20	0.90	0.86	0.83	0.70
	↓	0.0059	0.0020	0.32	0.23	0.92	19.7	14.8	4.1	0.55	0.79	0.38	0.17	0.91	0.84	0.83	0.80
Chancroid prevalence	↑	0.0025	0.0008	0.63	0.44	2.10	14.8	11.7	4.1	0.46	0.65	0.27	0.21	0.88	0.86	0.84	0.68
	↓	0.0050	0.0017	0.19	0.14	0.50	18.5	15.6	4.0	0.60	0.80	0.47	0.20	0.93	0.84	0.83	0.82
Outside infection rate	↑	0.0032	0.0011	0.39	0.32	1.27	16.5	12.5	4.0	0.59	0.79	0.38	0.21	0.88	0.86	0.84	0.72
	↓	0.0044	0.0015	0.24	0.19	0.67	17.1	11.8	4.0	0.51	0.64	0.24	0.16	0.91	0.84	0.83	0.77
Model with changed intervention assumptions																	
MT coverage	↑ (90%)	0.0036	0.0012	0.32	—	—	16.9	—	—	0.34	—	—	—	0.86	—	—	—
	↓ (50%)	0.0036	0.0012	0.32	—	—	16.9	—	—	0.64	—	—	—	0.94	—	—	—
IEC (increase in condom use rate)	↑ (45%)	0.0036	0.0012	—	0.24	—	—	12.3	—	—	0.71	0.32	—	—	0.76	0.76	—
	↓ (18.75%)	0.0036	0.0012	—	0.24	—	—	12.3	—	—	1.03	0.40	—	—	0.93	0.90	—
ST																	
Proportion symptomatic	↑	0.0036	0.0012	—	0.23	1.02	—	12.8	4.0	—	—	0.28	0.11	—	—	0.84	0.68
	↓	0.0036	0.0012	—	0.24	0.97	—	12.9	3.9	—	—	0.51	0.49	—	—	0.85	0.85
Proportion treatment seeking	↑ (50% coverage)	0.0036	0.0012	—	0.24	1.06	—	12.3	4.0	—	—	0.18	0.03	—	—	0.83	0.61
	↓ (12.5% coverage)	0.0036	0.0012	—	0.24	1.06	—	12.3	4.0	—	—	0.61	0.45	—	—	0.86	0.83

*Per contact transmission probability for asymptomatic stage. Transmission probabilities for other stages adjusted to ensure consistent stage ratios.

Simulated baseline prevalence calculated in 1994 in Rakai, 1995 in Masaka, and 1992 in Mwanza. Model baseline HIV prevalence and incidence rate ratios were calculated for males and females aged 15–59 years in Rakai, 13 years or older in Masaka, and 15–54 years in Mwanza. Incidence rate ratios calculated over 2 years in Rakai, 3 years in Masaka, and 2 years in Mwanza. Chancroid prevalence and impact prevalence ratios calculated for males and females aged 15–54 years in all sites. Chancroid prevalence ratios calculated after 2 years in Rakai, 3 years in Masaka, and 2 years in Mwanza.

F, female; M, male; Mk, Masaka; Mw, Mwanza; NA, not available; Rk, Rakai; ↑, double, unless otherwise stated; ↓, half, unless otherwise stated; —, not applicable.

findings from the Masaka trial, in which a "Mwanza-like" ST intervention was evaluated, helped refute the hypothesis that differences in intervention strategy contributed substantially to the differing outcomes.[7] The present study supports this finding. We have shown that baseline population differences (sexual risk behavior, STD rates, and HIV epidemic stage) at the time the trials were conducted were able to account for most of the observed differences in HIV impact. The simulations show that all the interventions would have been more effective in reducing HIV transmission in Mwanza than in either of the Ugandan sites (Fig. 3b). This was primarily because of the greater importance of cofactor STDs in HIV transmission in Mwanza. In the Mwanza trial, HIV infection was still clustered in individuals with higher risk sexual behavior, who were also more likely to be infected with STDs. In contrast, in the Ugandan trials, curable STDs played a relatively minor role in HIV transmission due to lower STD rates and the more generalized HIV epidemic, in which HIV transmission occurs predomi-

nately between regular partners and transmission may be primarily determined by HIV load.[92]

The ranking of the effectiveness of the simulated interventions was consistent across all sites. This study suggests that IEC + ST would have been the most effective intervention in all sites, followed by IEC alone, MT, and ST (Fig. 3b). However, this finding is primarily dependent on the assumed effectiveness of IEC, which may vary between populations. The relative HIV impact of ST and MT differed between the Ugandan and Mwanza scenarios. In Mwanza, the projected impact on the incidence of HIV infection was similar for MT and ST, but in both Ugandan scenarios, MT had a markedly higher impact than ST. The latter is because ST, unlike MT, depends on the symptomaticity of the STDs that contribute to HIV transmission. In Uganda, the simulated behavior risk reduction preceding the trials had resulted in large reductions in especially the highly symptomatic STD chancroid, so that the proportion of the incidence of HIV infection due to the less symptomatic STDs chlamydial infection and trichomoniasis increased. These STDs were more effectively controlled with MT, which also included treatment of asymptomatic episodes.

The projections could not fully explain the contrast in HIV impact between the trials. This may be due to the uncertainty in observed data or in assumed model parameters. Both the projected HIV and STD impacts of MT in the Rakai scenario were larger than observed. This may have been because the projected impact of 70% coverage may have been too large because (1) we did not simulate lower coverage of higher risk individuals,[12] (2) we underestimated rates of reinfection due to contact with individuals from outside the study population, or (3) we overestimated the STD cure rates of MT. Alternatively, the 70% assumed coverage may have been too high, although this was based on direct estimates.

The projected impact of ST in Mwanza was slightly larger than observed for most STDs and yet slightly smaller than observed for HIV. The comparatively low projected impact on HIV may be explained by incorrect model assumptions. Intervention coverage was not known accurately because direct data were not available. Coverage was calculated using estimates of the percentage of STD cases cured based on data collected up to 3 years after the trial ended.[88] If ST services deteriorated after the trial, coverage and therefore projected HIV/STD impact would have been underestimated. However, although increased coverage would have provided an improved fit of HIV and syphilis impact, it would have provided a poorer fit of impact on other STDs. Alternatively, the comparatively low projected impact on HIV may be due to random error in the data or random imbalances in the prevalence of HIV infection between study arms at baseline.[16,93]

Two alternative model scenarios would have provided a larger (ie, better fitting) HIV impact of ST in Mwanza without resulting in a larger (ie, worse fitting) STD impact: first, if the assumed cofactor effects would be higher for symptomatic STDs than for asymptomatic STDs (equality was assumed); second, if chancroid was more prevalent. The projected 1% population prevalence of chancroid in Mwanza was consistent with data on the incidence of ulcers and was projected by fitting sexual risk behavior to the observed prevalence of other STDs. However, because data were unavailable, we cannot exclude the possibility that the baseline prevalence of chancroid was higher or lower than simulated. Thus, the exact magnitude of the projected impact on HIV of the ST intervention in Mwanza must be treated with caution, because it is strongly dependent on this assumption (Table 2). A higher prevalence of chancroid would have led to a larger projected impact on HIV of ST in Mwanza and vice versa. This is because chancroid is highly symptomatic, and therefore amenable to ST; in addition, chancroid was also assumed to have the largest cofactor effect, and it has the lowest reproduction number.[94] This results in chancroid clustering in high risk individuals, the same individuals who are likely to be infected with HIV or at risk for HIV infection early in an HIV epidemic.

The projected STD impact of IEC and IEC + ST in the Masaka scenario was in line with trial observations. However, the projected HIV impact was larger than observed. The projected impact was largely due to the IEC component, assumed to increase condom use by 17.5%. Lower rates of condom use would have provided a better fit of HIV impact but would also leave the observed HSV-2 impact unexplained.

Recent empirical estimates of the population fraction of HIV infection attributable to HSV-2 infection in Mwanza[95] are higher than those simulated in this modeling study.[96] It is therefore possible that our modeling underestimates the contribution of HSV-2 to HIV spread in these populations. An alternate explanation for this difference is that the empirical PAF of HSV-2 suffered from residual confounding by shared underlying risk factors for HIV and HSV-2.[75] Importantly, empirically measured PAFs (as presented by del Mar Pujades Rodriguez et al[95]) and our simulated proportion of infections attributable to STDs are not equivalent and cannot be directly compared. Further work is being carried out to address this apparent inconsistency.

Finally, recent data suggest that HIV transmission probabilities by stage of infection may be somewhat lower than what we assumed,[97] and considerable uncertainty remains in the magnitude of STD cofactor effects. Assuming lower HIV transmission probabilities would necessitate refitting the model to the observed baseline prevalence of HIV infection in all sites, by assuming higher risk sexual behavior or higher STD cofactor effects. Increasing sexual risk behavior in all sites would be expected to have little effect on projected HIV impacts. Similarly, we showed in the sensitivity analysis that modeling higher cofactor magnitudes has little effect on the HIV impact projected in the 3 sites. Therefore, neither of these uncertainties alters our primary study finding that the contrast-

ing trial impacts were primarily due to differences in the study populations.

CONCLUSION

Our findings support the hypothesis that differences between study populations (sexual risk behavior, STD rates, and HIV epidemic stage) and not intervention strategy were the main determinants of the contrasting HIV impacts in Rakai, Masaka, and Mwanza. STD control for HIV prevention is likely to be most effective in populations with early and concentrated sexually transmitted HIV epidemics (eg, some parts of Asia) and in populations with a high prevalence of STDs and high risk sexual behavior (eg, in some parts of southern Africa). There is an urgent need to develop more effective prevention strategies for use in more generalized HIV epidemics.

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