

Treating Curable Sexually Transmitted Infections to Prevent HIV in Africa

Still an Effective Control Strategy?

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Background: Evidence regarding the effectiveness of sexually transmitted infection (STI) treatment for HIV prevention in Africa is equivocal, leading some policy makers to question whether it should continue to be promoted for HIV control. We explore whether treating curable STIs remains a cost-effective HIV control strategy in Africa.

Methods: The model *STDSIM* was fitted to the characteristics of 4 populations in East and West Africa. Over the simulated HIV epidemics, the population-attributable fractions (PAFs) of incident HIV attributable to STIs, the impact of syndromic STI management on HIV incidence, and the cost per HIV infection averted were evaluated and compared with an estimate of lifetime HIV treatment costs (US \$3500).

Results: Throughout the HIV epidemics in all cities, the total PAF for all STIs remained high, with $\geq 50\%$ of HIV transmission attributed to STIs. The PAF for herpes simplex virus type 2 increased during the epidemics, whereas the PAF for curable STIs and the relative impact of syndromic management decreased. The models showed that the absolute impact of syndromic management remains high in generalized epidemics, and it remained cost-saving in 3 of the 4 populations in which the cost per HIV infection averted ranged between US \$321 and \$1665.

Conclusion: Curable STI interventions may remain cost-saving in populations with generalized HIV epidemics, particularly in populations with high-risk behaviors or low male circumcision rates.

Key Words: cost-effectiveness, epidemiology, mathematic model, primary prevention, sexually transmitted diseases

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HIV continues to spread throughout sub-Saharan Africa (referred to as Africa).¹ Interventions to reduce the transmission of HIV include behavior change interventions and interventions that reduce the per sex act transmission probability of HIV. Among the latter, prompt diagnosis and treatment of sexually transmitted infections (STIs) take a prominent place, although evidence regarding the population-level effectiveness of STI treatment for HIV prevention in Africa is equivocal. A randomized controlled trial (RCT) of improved clinic-based syndromic STI treatment in rural Tanzania was shown to reduce HIV incidence in the general population by 38% and to be highly cost-effective.^{2–4} Since then, however, 4 other RCTs of various STI treatment strategies, including mass and syndromic treatment in the general population, have failed to show an impact on HIV incidence.^{5–8} We have shown in previous studies that this may be because behavior change and the later stage of the HIV epidemic reduce the role of curable STIs in HIV transmission.^{9,10} This has led some policy makers to question whether curable STI treatment should continue to be promoted as an HIV control strategy in generalized epidemics in Africa.

We address this question here by extending previous work investigating the heterogeneity of the HIV epidemics across Africa. An empiric study of 2 East African cities with high HIV prevalence (Ndola, Zambia and Kisumu, Kenya) and 2 West African cities with relatively low HIV prevalence (Cotonou, Benin and Yaounde, Cameroon)¹¹ identified important differences between the populations.¹² The prevalence of male circumcision was lower and the prevalence of herpes simplex virus type 2 (HSV-2) infection was higher in the high HIV prevalence cities.^{13,14} Sexual risk behaviors were not found to be consistently more common in the high HIV prevalence cities,^{12,15,16} suggesting that the effects of any differences in sexual behaviors were outweighed by differences in biologic cofactors that influence HIV transmission

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such as male circumcision and HSV-2. This hypothesis was evaluated in a modeling study in which the characteristics of the 4 populations and the development of the HIV epidemics were simulated.¹⁷ This showed that the different HIV prevalences could be explained largely by the lower rates of male circumcision in the East African cities compared with the West African cities.

We use these simulations of the development of the HIV epidemics in the 4 cities¹⁷ to estimate the population-attributable fractions (PAFs) of STIs for HIV incidence (the proportion of new HIV infections in the population attributable to STI cofactor effects), the impact of treating curable STIs on HIV incidence, and how these effects vary over time.

We then explore the cost-effectiveness of improved syndromic STI case management in preventing HIV transmission. The study in Mwanza showing that this intervention is highly cost-effective⁴ took place in the 1990s in a population during an early HIV epidemic. To investigate how cost-effectiveness is likely to vary between different populations and at different phases of the HIV epidemic, we compare the empiric cost-effectiveness estimate for the early HIV epidemic in Mwanza with the predicted cost-effectiveness of the same simulated intervention during the HIV epidemics in the 4 cities in West Africa and East Africa.

METHODS

Model

The individual-based stochastic model *STDSIM* simulates the natural history and transmission of HIV and STIs in a population consisting of individuals with characteristics that can change over time. The formation and dissolution of heterosexual relationships and transmission of STIs during contacts between sexual partners are modeled as stochastic events.¹⁸ *STDSIM* has previously been used to explore the findings of the Mwanza, Rakai, and Masaka STI treatment trials and the heterogeneity in the spread of HIV in Africa.^{9,17}

Default Scenarios

Descriptions of the simulated populations used in this study have been published.^{17,19} In summary, *STDSIM* was fitted to the demographic, behavioral, and epidemiologic characteristics of the 4 cities for the year 1997 and to available data on trends over time.¹⁷ HIV, HSV-2, chancroid, syphilis, gonorrhea, and chlamydia were simulated. It was assumed that STIs enhance susceptibility to HIV infection and the infectivity of HIV-infected individuals. For chancroid, a per-contact HIV cofactor effect of 25 was assumed, toward the low end of the range (3 to 300) estimated for genital ulcers from studies among commercial sex workers (CSWs) and clients in Nairobi,²⁰ to account for possible residual confounding in these estimates.²¹ The assumed per-contact cofactor effects of the other STIs reflected their relative clinical severity,²² which was higher for primary HSV-2 (25) than for recurrent HSV-2 ulcers (10) and infectious syphilis (7.5) and lower for the nonulcerative STIs, gonorrhea, and chlamydia (3). These per-contact cofactor magnitudes were larger than relative risks estimated from epidemiologic studies²² because the latter reflect cumulative incidence over numerous sexual exposures

over an extended follow-up period, during only some of which the STI would have been present. These cofactor magnitudes have been validated whenever possible by showing that models assuming these parameter values predict cumulative relative risks for HIV acquisition in line with those estimated from epidemiologic studies²³ and can simultaneously predict the large impact on HIV incidence measured in the syndromic STI treatment trial in Mwanza, Tanzania and the non-significant impacts of the syndromic STI treatment and mass STI treatment interventions tested in Masaka and Rakai, Uganda.^{9,10} Full details of the simulated STIs and HIV/STI prevalence trends are published elsewhere.^{17,19}

In line with the available data, previous simulations of the HIV epidemics in the 4 cities assumed improvements in STI treatment services and condom use over time.¹⁷ To avoid underestimating the contribution of curable STIs to HIV incidence, we removed all simulated STI treatment services from these model quantifications to create the default scenarios used in this study. The modeled increases in condom use over time were retained (condom use was simulated to increase gradually from 0% of sexual contacts before 1990 to 20% to 25% of casual contacts and 30% to 50% of sex worker contacts by 1995 [Table S1; available online via the Article Plus feature at www.jaids.com]). Simulated HIV prevalence trends in the default scenarios and observed HIV prevalence trends in the 4 cities are shown in Figure 1.

Simulated Population-Attributable Fractions and Intervention Impacts

To assess whether curable STIs play a decreasing role in HIV transmission in generalized epidemics, the simulated PAFs of incident HIV attributable to the curable STIs (syphilis, chancroid, chlamydia, and gonorrhea), HSV-2, and all STIs combined were calculated using the *STDSIM* model. The cofactor effects for HIV susceptibility and infectivity for each group of STIs were removed over a 2-year period, and the PAF was calculated according to the formula:²⁴

$$PAF = \left(1 - \frac{IR_{nocofactor}}{IR_{defaultcofactor}} \right) \times 100\%$$

where $IR_{nocofactor}$ is the HIV incidence among persons 15 to 49 years of age over 2 years in simulations with the cofactor removed and $IR_{defaultcofactor}$ is the corresponding incidence in simulations with default cofactor effects.

The simulated intervention was based on data from the syndromic treatment intervention tested in Mwanza, Tanzania,² as quantified in a previous modeling study.⁹ The simulated intervention was assumed to increase the average proportion of symptomatic STI episodes cured, and the proportion of steady partners of treated patients notified and cured, from 0% to 27%.⁹ Treatment of the incurable infection HSV-2 was not simulated in this study but has been explored elsewhere.²³ The ratio of HIV incidence among adults aged 15 to 49 years over 2 years in simulations with and without the intervention was used to compare the predicted impact of the intervention between cities.

In separate simulations, the PAFs, the intervention impacts, and the cost-effectiveness were calculated over 2

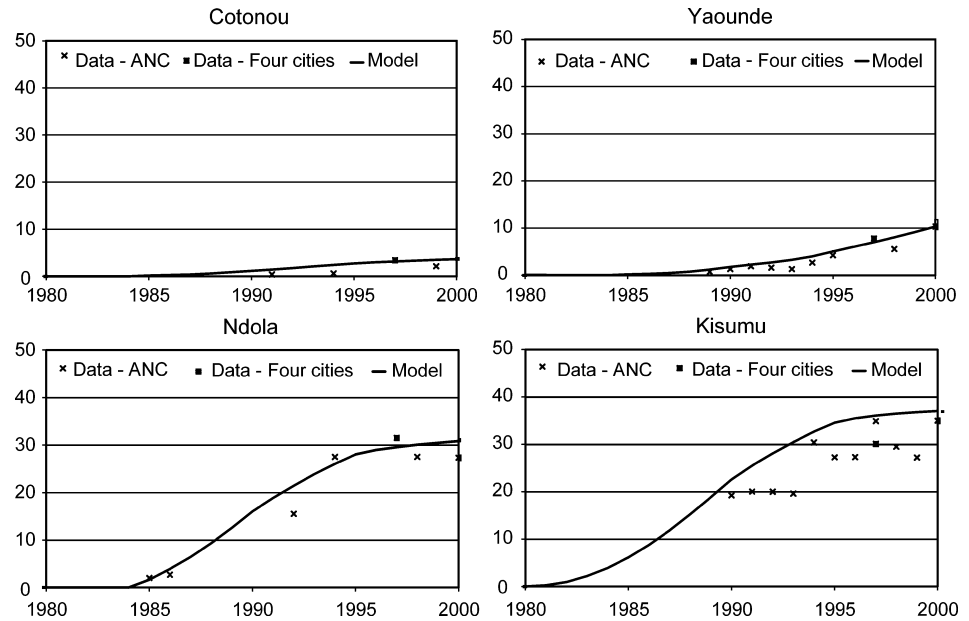


FIGURE 1. Simulated and observed female HIV prevalence (%; women 15 to 49 years of age). Panels show the simulated HIV prevalence in the default scenarios and the empiric data on women attending antenatal clinics (ANCs) and on women in the 4-city study in 1997. The data shown in the figure are restricted to women to allow comparison with HIV prevalence trend data, but both genders are modeled (see Methods section).

years starting 4, 8, 12, 14, and 16 years into the HIV epidemics in all 4 cities and also 18 and 20 years into the epidemic in Kisumu. Because we assumed HIV was introduced in 1980 in Kisumu and in 1984 in the other cities to fit the time trend in HIV prevalence better, the latest period (16 or 20 years into the epidemic) corresponded to the period 2000 to 2001 in all 4 cities. Results were based on means over 300 simulation runs for each scenario.

Cost-Effectiveness

The annual incremental cost of the improved syndromic STI treatment intervention in Mwanza was estimated by Gilson et al⁴ to be US \$54,839 in 1993 prices. By assuming that the at-risk population size was 72,000 (75,000 sexually active adults, of whom 4% were already HIV-infected) and that the absolute reduction in annual HIV incidence attributable to the intervention was 0.35 per 100 person-years, Gilson et al⁴ estimated that 252 HIV infections were averted by the intervention each year, at a cost of US \$218 per infection averted.

To compare this estimate for Mwanza in the early 1990s with that for the 4 cities over the HIV epidemic, the predicted impacts of the intervention were obtained from the simulations described previously for the 4 cities as well as from the results of a previous study that re-estimated the impact of this intervention in the early HIV epidemic in Mwanza and found that the true impact was likely to be slightly lower than the point estimate measured in the trial.⁹

The costs were based on those estimated by Gilson et al⁴ and were adjusted to reflect changes over time (including inflation and changes in treatment regimens) and between countries. Adjustment factors were obtained from a systematic review and regression analysis of studies containing unit STI cost data.²⁵ Per capita gross domestic product (GDP) data were obtained from the World Bank's World Development Indicators.²⁶ The adjustment factor for changes over time was 1.0258 per year, and the adjustment factor for differences in

per capita GDP was 0.9998 per US dollar. These adjustments were applied to the total fixed costs and unit variable costs of Gilson et al.⁴ The adjusted unit variable costs were then multiplied by the simulated annual number of STI episodes treated per 75,000 adults in each city in the year in which they were implemented to obtain total variable costs. This was added to their respective fixed costs to obtain the full costs. As in the report by Gilson et al,⁴ the control arm costs were subtracted from the full costs to obtain the incremental costs of the intervention. All costs were then adjusted for inflation to 2001 US dollars.^{27,28} Cost per HIV infection averted was calculated and compared with a recent estimate of the lifetime treatment costs of an HIV infection in Africa (US \$3500).²⁹

Generalizability of Findings to Other Settings and Sensitivity Analysis

The simulated HIV and STI prevalences and the simulated impact of the intervention on HIV incidence are sensitive to trends in condom use. To explore the likely generalizability of our findings for settings with differing condom use trends and HIV prevalence, the effect on PAFs, intervention impacts, and costs per infection averted in 2000/2001 were recalculated for additional scenarios for each city in which simulated condom use rates were multiplied by 0, 0.5, and 1.5.

To assess the robustness of the results to uncertainties in model input parameters known to affect impact and cost-effectiveness, the Ndola simulations were repeated varying the values of each parameter in turn. For cofactor magnitudes, condom use rates and the proportion of symptomatic STI episodes cured by STI treatment, default parameter values were doubled and halved. For cost adjustments, the effect of each adjustment factor was removed in turn. Alternative scenarios were created that were refitted to the observed HIV prevalence data in Ndola employing the same procedure used to develop the default scenarios as described previously. The relative and absolute impacts of the intervention and the cost

per infection averted were then recalculated and compared for each parameter in turn. The parameter values used in the sensitivity analysis are shown in Table S3 (available online via the Article Plus feature at www.jaids.com).

RESULTS

Simulated Population-Attributable Fractions

The combined contribution of the simulated STIs to HIV transmission decreased over time but remained high throughout the HIV epidemics in all 4 cities (Fig. 2). The simulated PAFs for combined STIs ranged between 80% and 87% during years 4 to 5 of the HIV epidemics and between 50% and 70% in years 16 to 17.

The combined PAF masks different patterns for curable STIs and for HSV-2, however. In line with our previous findings,¹⁹ the simulated PAFs for curable STIs decreased markedly during the HIV epidemics, from 54% to 79% in years 4 to 5 to 13% to 33% in years 16 to 17. This was because of reductions in STI prevalences (see Fig. 1) attributable to simulated increases in condom use (Table S1, available online via the Article Plus feature at www.jaids.com) and to the spread of HIV from higher to lower risk groups with lower prevalences of curable STIs. Conversely, simulated PAFs for HSV-2 increased during the HIV epidemics, from 8% to 27% in years 4 to 5 to 25% to 37% in years 16 to 17. This was partly attributable to the fall in the PAF for curable STIs as HIV spread into lower risk groups in which HSV-2 was still common but also partly because of simulated increases in HSV-2 ulceration among HSV-2/HIV-coinfected individuals as a result of HIV-related immunosuppression.

Simulated Impact of Syndromic STI Case Management

The relative impact of improved syndromic STI case management on HIV incidence fell markedly during the HIV

epidemics (Fig. 3, left). The relative reduction in HIV incidence attributable to the intervention decreased in all 4 cities from between 39% and 2% in years 4 to 5 to between 9% and 1% in years 16 to 17. This was because of reductions in the PAF for curable STIs (see Fig. 2), particularly those that are most amenable to syndromic treatment such as the highly symptomatic STI chancroid.

Cost-Effectiveness

The estimated cost per HIV infection averted as a result of syndromic STI treatment in the early epidemic in Mwanza was US \$317 in 2001 prices. Table 1 shows this alongside the estimate made by Gilson et al⁴ in 1993 prices (US \$218). Our estimate is higher than that of Gilson et al⁴ because it was adjusted for inflation and other changes over time (eg, changes in treatment regimen) and was based on the smaller absolute reduction in HIV incidence and smaller number of STIs treated predicted by the model, compared with estimates from the trial data used by Gilson et al.⁴ Adjusting the estimate of Gilson et al⁴ for each of these factors in turn, the cost per HIV infection averted increased as follows: from US \$218 to \$252 after adjustment for inflation between 1993 and 2001, from US \$252 to \$307 after adjustment for other changes over time (eg, changes in treatment regimen), and from US \$307 to \$317 after adjustment for the differences between the modeled and observed impact on HIV incidence and the number of treated STIs.

In 2000 to 2001, the simulated absolute reduction in HIV incidence attributable to the intervention in the 4 cities ranged widely between 0.01 per 100 person-years in Cotonou and 0.41 per 100 person-years in Ndola (see Table 1). Despite the smaller relative impact, the predicted absolute reduction in HIV incidence in Ndola was larger than in the early HIV epidemic in Mwanza during 1992 to 1993 (0.28 per 100 person-years) because of the much higher HIV incidence at this stage of the epidemic in Ndola.

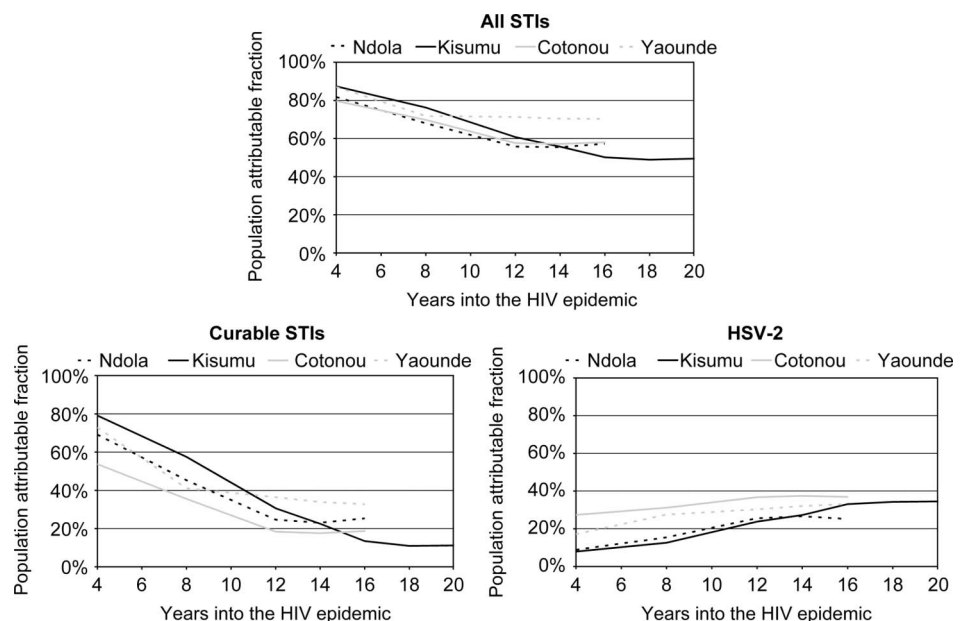


FIGURE 2. Population attributable fraction of STIs for HIV transmission (%; adults 15 to 49 years of age).

TABLE 1. Annual Cost Per HIV Infection Averted by Syndromic STI Case Management in an Early HIV Epidemic in Mwanza, 1992 to 1993, and in the HIV Epidemics in the 4 Cities, 2000 to 2001

	Mwanza		Ndola	Kisumu	Cotonou	Yaounde
	Data [†]	Model				
Annual HIV incidence, HIV-uninfected adults per 100 person-years						
Comparison arm or default scenario	0.93	1.02	4.63	5.27	0.52	2.01
Intervention arm or intervention scenario	0.58	0.74	4.22	5.21	0.51	1.93
Relative reduction, %	37.6	27.5	8.9	1.1	1.5	3.6
Absolute reduction	0.35	0.28	0.41	0.06	0.01	0.07
HIV prevalence, %	4.0	4.0	28.9	32.2	3.6	9.0
Size of at-risk population*	72,000	72,000	53,337	50,846	72,334	68,244
No. HIV infections averted annually	252.0	201.6	220.2	28.3	5.5	49.2
Annual incremental cost of the intervention, US\$ [†]	54,839	63,988	70,756	42,401	27,414	81,965
Cost per HIV infection averted, US\$	218	317	321	1499	4976	1665

*Assumes the same number (75,000) of sexually active adults in all populations, based on the estimate by Gilson et al⁴ for the Mwanza intervention communities. This is adjusted by the HIV prevalence in each population to calculate the number of HIV-uninfected sexually active adults in each population.

[†]Costs for the intervention in Mwanza (data column) were obtained from Gilson et al⁴ using 1993 prices. The costs for the simulated interventions (model columns) were based on the findings of Gilson et al;⁴ adjusted for differences in intervention timing, the per-capita GDP, and the simulated number of STI episodes treated; and updated for inflation to 2001 prices.

Over the same period, the predicted cost-effectiveness of the intervention varied markedly between the 4 cities. The cost per infection averted was US \$321, \$1499, \$1665, and \$4976 in Ndola, Kisumu, Yaounde, and Cotonou, respectively (see Table 1), suggesting, by comparison with the US \$3500 estimate of the lifetime treatment costs of an HIV infection in Africa,²⁹ that the intervention would be cost-saving in 3 of the 4 sites. The highest cost per infection averted was predicted for Cotonou because of the small absolute impact of the intervention. This small impact was attributable to the combination of the low STI prevalences (Fig. S1, available online via the Article Plus feature at www.jaids.com) and the lower HIV incidence in this city. The intervention was more cost-effective in Kisumu and Yaounde because of the large relative impact of the intervention (Yaounde) and the higher HIV incidence (Kisumu). The intervention was most cost-effective in Ndola, where a larger relative impact of the intervention combined with a high HIV incidence.

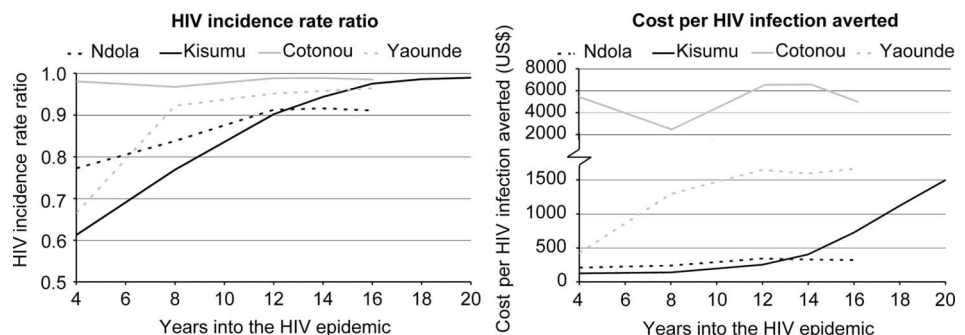
The trends in the cost-effectiveness of the syndromic treatment intervention over the simulated HIV epidemics are shown in Figure 3 (right). Estimated cost per infection averted was low 4 years into the HIV epidemics (<US \$500) and then increased over time in all cities except Cotonou, where it remained high throughout the epidemic.

The increase in the cost per infection averted was predicted to occur earlier in Yaounde than in Ndola/Kisumu because of the earlier fall in the relative impact of the intervention on HIV incidence in Yaounde (see Fig. 3, left). This earlier fall was primarily attributable to the larger impact of the simulated increase in condom use in 1990 on chancroid prevalence, because the predicted basic reproduction number of chancroid was closer to 1 in Yaounde than in Kisumu/Ndola; therefore, it was more sensitive to small changes in condom use. As reported previously,¹⁷ chancroid prevalence was predicted to be lower in Yaounde than in Kisumu and Ndola because of the much higher prevalence of male circumcision in Yaounde. Male circumcision has been shown to be associated with a lower risk of chancroid infection.³⁰ Similarly, the cost per infection averted by the intervention increased rapidly in Kisumu 14 years into the HIV epidemic, as increasing rates of condom use resulted in adequate control of chancroid.

Generalizability of Findings to Other Settings and Sensitivity Analysis

As expected, the cost-effectiveness of the intervention was sensitive to the simulated trends in condom use (Fig. 4A). As condom use rates increased, HIV and STI rates fell and the cost per HIV infection averted tended to increase. Our results

FIGURE 3. Relative impact of syndromic STI case management on HIV incidence and estimated cost-effectiveness. Left panel, Simulated rate ratio for the effect of syndromic STI case management on HIV incidence (adults aged 15 to 49 years). Right panel, Cost per HIV infection averted by syndromic STI case management (note change of scale in y axis).



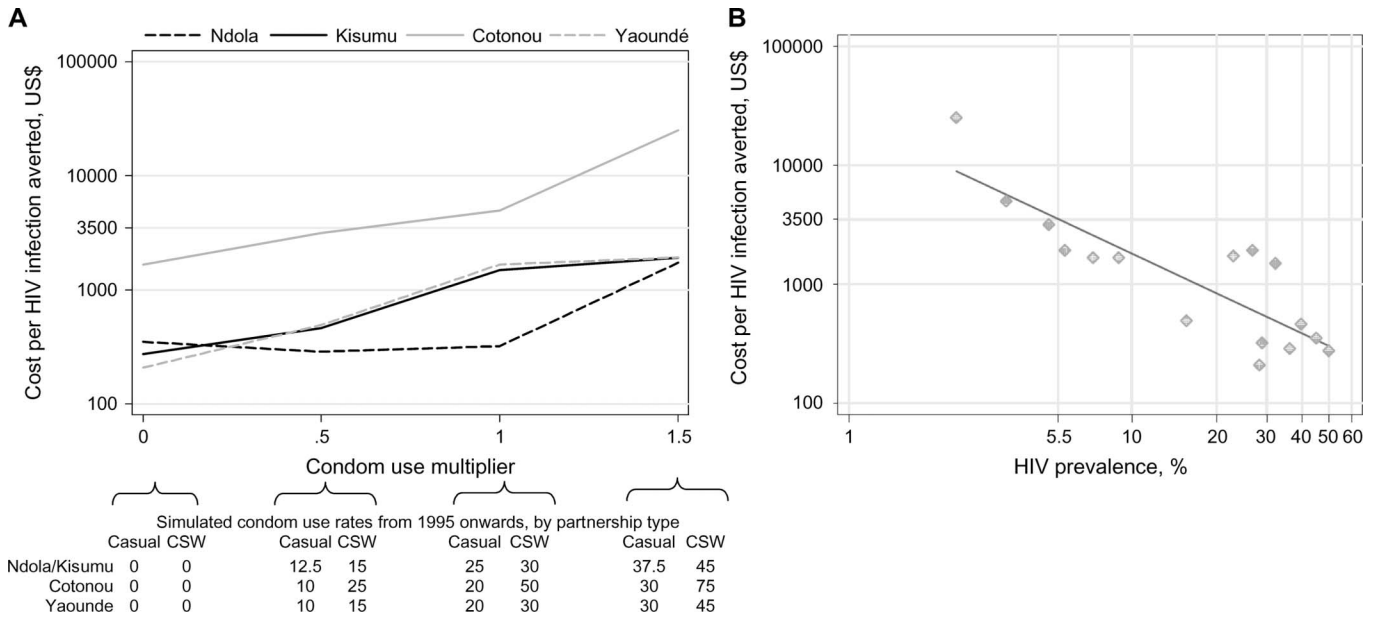


FIGURE 4. Cost per HIV infection averted by trend in condom use rates (A) and cost per HIV infection averted by projected HIV prevalence in the year 2000 for the 16 model scenarios shown in A (B) (2000 to 2001, adults aged 15 to 49 years). Simulated condom use rates from 1995 onward in casual and sex worker CSW contacts in these scenarios are shown below A (for full details, see Table S1; available online via the Article Plus feature at www.jaids.com). For STI/HIV rates in these scenarios, see Table S2 (available online via the Article Plus feature at www.jaids.com). For comparison, a recent estimate of the lifetime treatment costs of an HIV infection in sub-Saharan Africa (US \$3500)²⁹ is highlighted on the y axis. Note that the cost per HIV infection averted and HIV prevalence are plotted on a log₁₀ scale. The equation of the regression line shown in B is $Cost (US\$) = 23,572 \times 10^{-1.11 \times \log_{10}(HIV\ prevalence, \%)}$, $R^2 = 0.73$.

suggest that in populations like Cotonou with relatively low-risk sexual behavior, near-universal male circumcision, and, consequently, relatively low HIV prevalence, syndromic treatment in the general population may cease to be cost-saving when condom use rates rise to >10% to 20% of casual contacts and to >25% to 50% of sex worker contacts. In populations with relatively high risk behavior or low rates of male circumcision (eg, Ndola, Kisumu, Yaounde), however, our findings suggest that syndromic treatment in the general population may remain cost-saving even with condom use rates as high as 30% to 37.5% of casual contacts and 45% of sex worker contacts or higher. In these mature African HIV epidemics, syndromic treatment was always found to be cost-saving if HIV prevalence was above ~5.5% (see Fig. 4B).

In line with these findings, the impact and cost-effectiveness predictions for Ndola were shown to be most sensitive to the assumed trend in condom use (see Table S3, available online via the Article Plus feature at www.jaids.com). If condom use was doubled, STI treatment was predicted to be less cost-effective because of the lower STI rates (cost per HIV infection averted in 2000 to 2001 = US \$2321 and \$276, respectively), and vice versa. By comparison, the cost-effectiveness predictions were shown to be relatively robust to doubling and halving of the magnitude of the STI cofactor effects (US \$406 and \$287, respectively) and to the assumptions used to calculate the costs of the intervention (range: US \$277 to \$327). Interestingly, the cost-effectiveness of the intervention was also shown to be relatively robust to doubling or halving of the proportion of symptomatic STI episodes cured by the intervention (US \$326 and \$372,

respectively). This was because, over this relatively short 2-year follow-up period, increases or decreases in the number of HIV infections averted were roughly balanced by increases or decreases in variable costs attributable to treating more or fewer STI episodes. Results for the other 3 cities were similar (not shown).

DISCUSSION

We have explored the changing role of STI cofactors in HIV transmission during the HIV epidemics in 4 cities in West Africa and East Africa. Throughout the HIV epidemics, the contribution of STIs to HIV transmission remained high, with 50% or more of HIV transmission attributed to STIs in all 4 cities. This relative stability in the overall PAFs concealed opposing trends in the contribution of curable and incurable STIs. The attributable fraction for curable STIs was predicted to fall during the HIV epidemic, whereas the attributable fraction for HSV-2 was predicted to rise.

This has important implications for the (cost-)effectiveness of interventions seeking to target curable STIs. Over time in all 4 cities, the relative impact of STI treatment on HIV incidence fell, tending to increase the cost per HIV infection averted. In populations with a rapidly expanding HIV epidemic, however, this increase in cost was offset by the rapidly rising HIV incidence that increased the absolute impact of the intervention. Our findings suggest that in African populations with mature HIV epidemics, STI treatment interventions are likely to remain highly cost-effective and may even be cost-saving, particularly in populations in which

safer sexual behaviors have not adequately controlled STIs and HIV incidence remains high.

These results should be interpreted with some caution. The simulated HIV epidemics in the 4 cities were largely parameterized using data from a cross-sectional study carried out in 1997,¹¹ with limited data on STI trends over time. Although the observed sexual behaviors and STI rates in 1997 and HIV prevalence trends over time were fitted well, actual trends in STI rates may have differed from those simulated. This may affect the quantitative findings of this study but is less likely to affect the qualitative conclusions.

The magnitudes of STI cofactor effects on HIV transmission remain poorly quantified.^{20,21} Our sensitivity analysis showed that the cost-effectiveness of the intervention was relatively insensitive to their variation, however.

Although the simulated STI treatment intervention was based on extensive review of data from the randomized controlled trial (RCT) in Mwanza and adequately explained the observed impacts of this empiric trial and the observed impacts of the STI treatment trials in Masaka and Rakai,⁹ the coverage achieved by this intervention may vary between populations. As our sensitivity analysis showed, however, in the short term, this may not affect the cost-effectiveness of the intervention. Over the longer term, increased cure rates would be expected to increase the cost-effectiveness of the intervention.

The adjustments to the cost data were based on the results of an analysis of data from developing countries. Although these adjustments enabled us to estimate the true costs of the intervention more accurately, they are approximations and cannot fully control for differences in implementation and changes over time.

Our findings may help to explain why the STI treatment strategies tested since the trial in Mwanza have failed to show a significant impact on HIV incidence. Our results suggest that even if the STI treatment interventions in Rakai, Masaka, and Zimbabwe^{5,6,8} had led to large reductions in STI rates, in these generalized HIV epidemics, the relative impact on HIV incidence would have been relatively small, and therefore undetectable.

This study suggests that despite the small relative impact on HIV incidence, STI treatment in the general population is likely to remain highly cost-effective and even cost-saving in contemporary African populations with HIV prevalences >~5.5% because of the substantial absolute impact on HIV incidence. In African populations with lower HIV prevalences, syndromic STI treatment may not be as cost-effective for HIV prevention but is recommended for STI control and to reduce HIV transmission among patients with STIs and their sexual partners.

Rational health policy requires that scarce resources be allocated to interventions with the best cost-effectiveness even if relative impact at the population level is modest. Effective STI management may prevent a decreasing fraction of new HIV infections as the epidemic expands but is an inexpensive intervention with important collateral public health benefits, which effectively protects patients with STIs from the enhanced risk of HIV acquisition and transmission.

In conclusion, our study has shown that throughout HIV epidemics in sub-Saharan Africa, a large proportion of HIV

transmission may remain attributable to other STIs but that the proportion attributable to curable STIs is likely to fall. Despite this, we have shown that in populations with generalized HIV epidemics, interventions that target curable STIs may remain highly cost-effective and even cost-saving if changes in risk behaviors have not adequately controlled STIs.

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