Understanding differences between contrasting HIV epidemics in East and West Africa: results from a simulation model of the Four Cities Study

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Abstract

Study Objective: To determine if the observed differences in risk behaviours, proportion of males circumcised and STI prevalences observed in two African cities with low HIV prevalence (Cotonou, Benin and Yaounde, Cameroon) and two cities with high prevalence (Kisumu, Kenya and Ndola, Zambia) could explain the contrasting HIV epidemics in the four cities.

Methods: An individual-based stochastic model, *STDSIM*, was fitted to the demographic, behavioural and epidemiological characteristics of the four urban study populations based on the data from the Four Cities Study and other relevant sources. Model parameters pertaining to STI and HIV natural history and transmission were held constant across the four populations. The probabilities of HIV, syphilis and chancroid acquisition were assumed to be doubled among uncircumcised males. *A priori* plausible ranges for model inputs and outputs were defined and sexual behaviour characteristics, including those pertaining to commercial sex workers (CSW) and their clients, that were allowed to vary across the sites were identified based on comparisons of the empirical data from the four sites. The proportions of males circumcised in the model, 100% in Cotonou and Yaoundé, 25% in Kisumu and 10% in Ndola, were similar to those observed. A sensitivity analysis was conducted to assess how changes in critical parameters may affect the model fit.

Results: Population characteristics observed from the study that were replicated in the model included younger ages at sexual debut and marriage in East Africa compared to West Africa and higher numbers of casual partners in the past 12 months in Yaoundé compared to the other three sites. The patterns in STI prevalences in females in the general population and CSWs were fitted well. HIV prevalence by age and sex and time-trends in prevalence in the model were consistent with study data with the highest simulated prevalences in Kisumu and Ndola, intermediate in Yaoundé and lowest in Cotonou. The sensitivity analysis suggested that the effect of circumcision on the development of the HIV epidemics may have been mediated indirectly by its effect on ulcerative STI.

Conclusions: The contrasting HIV epidemics in West and East Africa could be replicated in our model by assuming that male circumcision reduced susceptibility to HIV, syphilis and chancroid. Varying rates of male circumcision may have played a major role in explaining the strikingly different HIV epidemics observed in different parts of sub-Saharan Africa.

Introduction

The HIV epidemic shows considerable heterogeneity within sub-Saharan Africa. The Multicentre Study of Factors Determining the Different Prevalences of HIV in sub-Saharan Africa (known as the Four Cities Study) was designed to assess whether differences in sexual behaviour characteristics and/or factors affecting the probability of HIV transmission such as male circumcision or sexually transmitted infections (STIs) could explain the much more severe HIV epidemics observed in East Africa than in West Africa. This cross-sectional, population-based study sampled about one thousand men and one thousand women in each of two cities with relatively low HIV prevalence (Cotonou, Benin and Yaoundé, Cameroon) and two cities with high HIV prevalence (Kisumu, Kenya and Ndola, Zambia) (1).

The study found that some biological cofactors for HIV transmission differed between the high and low prevalence cities. In the low HIV prevalence cities, virtually all the males were circumcised whereas in the high prevalence cities the proportion was much lower, 28% in Kisumu and 10% in Ndola (2). In addition, the prevalence of *Herpes simplex virus* type-2 (HSV-2) was higher among young women and men in the East African cities than in the West African cities (3).

The study also identified some important differences in reported sexual behaviour between the four populations including younger age at first sexual intercourse and at marriage in East Africa compared to West Africa and larger age differences between spouses in East Africa (4, 5). However, other characteristics of sexual risk behaviour such as reported high partner change rates and having had sex with a sex worker were more prevalent in the low prevalence cities than in the high prevalence cities (5, 6). Hence, an important hypothesis raised by the study was that differences in risky sexual behaviour were outweighed by differences in biological cofactors which influence HIV transmission such as male circumcision and other STIs, especially HSV-2 (4).

The objective of the present study was to evaluate this hypothesis and determine if the observed differences in risk behaviours, proportion of males circumcised and STI prevalences observed in the four cities could explain the contrasting HIV epidemics. We tested this hypothesis by fitting an individual-based stochastic model to the demographic, behavioural and epidemiological characteristics of the four study populations based on the data from the Four Cities Study as well as other relevant sources (7-17). This is the first time a mathematical model portraying the urban populations from all four cities has been presented. In this paper, the results of the simulations and the corresponding model assumptions are presented. Our companion paper in this issue, based on the simulated populations in this paper, explores the changing role of other STIs on HIV transmission over the time course of the epidemics.

Methods

In order to test whether the observed differences in HIV epidemics could be explained by the observed population differences, the transmission model must replicate the demographic, sexual behaviour and epidemiological characteristics of the four urban populations. We first describe the *STDSIM* model, present a comparison of the empirical

data from the Four Cities Study and define *a priori* plausible ranges for model inputs and outputs. We then describe how the model was fitted to the study data and the sensitivity analysis that was undertaken to evaluate our parameter assumptions.

The STDSIM transmission model

STDSIM is a flexible individual-level stochastic model which allows simulation of the simultaneous spread of several STIs over time. Individual life histories of people and the sexual interactions between them are simulated. Sexual contacts and relationships form a network through which STIs can be transmitted. The formation and dissolution of partnerships as well as infection transmission are modelled as a sequence of stochastic processes (18). Some characteristics of simulated individuals such as sex and date of birth are held constant throughout their lives, while others such as sexual activity are allowed to vary over time. Characteristics of individuals are then aggregated to give population level characteristics such as STI prevalence and incidence (18).

In this study, HIV, chancroid (HD), syphilis (TP), HSV-2, gonorrhoea (NG) and chlamydia infection (CT) were modelled. The modelled natural history and transmission parameters of these infections were held constant across all four cities and were based on literature reviews and previous *STDSIM* modeling studies (19) (table 1). The natural history of each infection was compartmentalized into different stages. Infection transmission was simulated at the level of the individual sex act and interactions between STIs and HIV were modelled using stage-specific cofactor effects which can increase HIV acquisition, infectivity or both. These cofactor effects represent the relative increase in per-contact probability of HIV transmission during infections with other STIs.

For the per-contact transmission probabilities for HIV and the other STIs, ranges were defined based on literature reviews (19). While modelling the observed differences in sexual behaviour across the sites (see sexual behaviour section below, table 2), the transmission probabilities were then fitted within the predetermined ranges such that the model accurately reflected the prevalence of HIV and the other STIs across all four cities. For all modelled STIs, including HIV, the male-to-female transmission probability was set to be two times that of female-to-male.

In the model, HIV was represented by four stages, primary, asymptomatic, symptomatic and AIDS (table 1). The assumed average duration from infection until death from AIDS was ten years (20). The use of four stages for HIV infection allowed us to simulate changes in infectivity over the course of the infection (21) and changes in HIV effects on the natural history of HSV-2 which occur only in the later symptomatic and AIDS stages of infection (22, 23). Infectivity of HIV was simulated as high in the primary stage, lower during the asymptomatic stage and then increasing again during the symptomatic and AIDS stages (24). The *a priori* ranges for HIV transmission probabilities in each stage were based on a recent review of per contact transmission probabilities (25).

Chancroid was represented as a single infectious stage with an average duration of 11 weeks in males and females and was associated with a high HIV cofactor effect (26, 27) (table 1). Chancroidal ulcers are often described as painful, prompting patients to seek

treatment (28, 29). We therefore assumed 50% of symptomatic males would abstain from sexual activity during chancroid infection. Syphilis was represented by four stages: infectious, early latent, latent and late latent (table 1). Infectious syphilis was simulated to last on average six months and was associated with a high transmission probability and HIV cofactor effect (30). The proportion symptomatic was less than for chancroid (31). Without treatment, syphilis progresses to non-infectious stages that represent reductions in RPR titres over 10-15 years.

HSV-2 was represented by four stages: primary, early latent, latent and late latent. A primary ulcer was assumed to last an average of 3 weeks, was highly infectious and was associated with a high HIV cofactor effect (32, 33). After the primary ulcer, ulcers were modeled to recur with decreasing frequency (34). Recurrent ulcers were assumed to persist for an average of one week and to be less severe than primary ulcers with lower infectivity and HIV cofactor effects (32). Primary ulcers were also assumed to be more often recognised than recurrent ulcers (35). In between recurrences, a low continuous level of infectivity was assumed, representing subclinical shedding in those infected with HSV-2 (36, 37), but no cofactor effect on HIV was assumed. In the final modelled stage, individuals did not have ulcers but remained seropositive for life. Study results suggest that the frequency and duration of ulcerative recurrences increase during the symptomatic and AIDS stages of HIV infection (22, 23). The magnitude of this effect is not known precisely and we assumed that frequency and duration were each doubled during these stages.

Both chlamydia and gonorrhoea were represented by one infectious stage with a low HIV cofactor effect. The average duration of infection was 14 weeks for gonorrhoea and chlamydia in males. Chlamydia in females lasted a year (38, 39). To achieve an adequate model fit of the observed rapid decline in chlamydia prevalence with age, each episode of chlamydia infection was assumed to induce a 20% reduction in susceptibility to reinfection, in line with observations on acquired immunity to ocular chlamydia (40). The proportion symptomatic was assumed to be less than for syphilis and chancroid (table 1).

STI cofactor effects on HIV acquisition and transmission per sexual contact are not known precisely (41, 42). Our assumed values were based on previous *STDSIM* studies (19) and are in line with the relative clinical severity of the various STIs (table 1). Chancroid and primary HSV-2 infection were assumed to have the highest per-contact cofactor effects for HIV transmission (increasing the transmission probability per contact by a factor of 25) and gonorrhoea and chlamydia infection the lowest (increasing by a factor of 3). The effects of male circumcision were modelled by assuming the probabilities of HIV, syphilis and chancroid acquisition were doubled in uncircumcised males in unprotected contacts with infected partners (43-45). Similar to rates measured in the Four Cities Study, the proportions of males circumcised were taken as 100% in Cotonou and Yaoundé, 25% in Kisumu and 10% in Ndola (2). For the STIs, the cofactor effects for HIV acquisition and transmission were assumed to be equal. If more than one cofactor (including for STIs and lack of circumcision) was present during a simulated sexual contact, only the highest cofactor effect was applied.

Three different types of sexual relationships are modelled including steady (marriages), short-term, and one-off contacts with CSWs. The rate of sex partner change in the model is determined by a supply and demand mechanism in which individuals search for an available sex partner (18). Demand and availability of partners depends on age, gender, and marital status. These parameters result in model outputs that can be compared with study data on the proportions married, the distribution of reported number of non-marital sex partners in the past year and the number of lifetime partners.

Data comparison and plausible ranges for model inputs and outputs

The initial step in fitting the model to the study data was to define *a priori* plausible ranges for certain model inputs and outputs based on the study data and other relevant data sources. We determined which demographic and sexual behaviour characteristics were allowed to vary across the sites by comparing relevant data from the original study, as well as other data sources including Demographic and Health Surveys and antenatal surveillance data.

We compared several demographic characteristics including the fertility rate, population composition by age and sex, population growth rates and sex ratios. The most critical demographic characteristic of the population to be fitted was the population composition at the time of the study in 1997 as this determines the number of available sex partners by age and sex. The demographic fit to the data was deemed acceptable if the simulated population composition was within 10% of the data for each age and sex group from recent censuses and analyses of demographic data (17, 46), (S. Kinyanjui, p.c.), and the population growth rates reflected similar patterns to those measured in recent censuses. The growth rate was highest in Yaoundé (6.8%), lowest in Kisumu (2.3%) and intermediate in Cotonou and Ndola (4%).

For sexual behaviour, the age of sexual debut, age patterns in marriage, partner change rates, changes in sexual behaviour over time, condom use and characteristics of commercial sex were compared across the four cities (table 2). The differences in behaviour between the sites include younger ages of sexual debut in the East African sites; higher proportions married in Kisumu and Ndola, lower rates in Cotonou and the lowest in Yaoundé; and highest partner change rates in Yaoundé, similar rates in Kisumu and Ndola and lowest rates in Cotonou (5). The proportion reporting condom use in their last casual contact was slightly higher in the East African than in the West African sites (47) (table 2) so our *a priori* assumption was that condom use should be slightly higher in East Africa compared to West Africa (table 3). Study data and other sources indicated characteristics of commercial sex also varied across the cities. In Cotonou, there was a relatively low number of sex workers with clients that visit them often compared to Yaoundé and the East African sites (6, 48-50) (table 2).

Based on the study data, and after considering reporting and selection biases, plausible ranges for model outputs were defined for proportions married, distributions of numbers of non-marital sex partners in the past year, and the size and characteristics of the core group, ie., commercial sex workers (CSW) and their clients (table 3). In all sites, the

number of reported non-marital sex partners in the past year was higher for males than for females. The reporting of sexual behaviour likely reflects biases due to sample selection (under inclusion of high risk individuals) and social desirability (leading to under-reporting of high risk behaviour among women)(51). Due to these biases we attempted to fit reported male behaviours as reporting bias was assumed to be less for males than females. To account for the likely under-representation of high risk individuals in the study sample, our *a priori* ranges for model outputs reflect higher than observed numbers of non-marital sex partners in the past year rather than lower than observed (table 3).

To assess whether a reduction in risky sexual behaviour had occurred prior to 1997 in the East African sites, we compared the reported numbers of recent and lifetime sex partners between sites. If behaviour change had taken place in Kisumu and Ndola, we would have expected to see higher numbers of lifetime partners but lower numbers of recent partners in these sites than in Cotonou and Yaoundé. In Yaoundé, about 50% of males reported two or more non-marital sex partners in the past year while similar numbers were reported for males in Cotonou (18%), Kisumu (18%) and Ndola (16%). Comparing lifetime numbers of partners, the most partners were again reported in Yaoundé and similar numbers were reported for the other three sites (table 2). These findings do not point to a significant shift towards safer sexual behaviour in Kisumu and Ndola. Hence, our *a priori* assumption is that the partner change rate has not varied over the time course of the epidemic in Kisumu and Ndola (table 3).

The level and timing of effective STI treatment based on available information from the four sites at the time of the study indicated treatment was slightly better in Yaoundé and Kisumu compared to the other cities (52).

The 95% confidence intervals for the age- and sex-specific HIV prevalences and STI prevalences as measured during the study (1) provided the plausible ranges for the fit of the model to the epidemiological data. The time trend in HIV prevalence was based on available data from antenatal clinic attenders (53, 54). The initial spread of HIV in a population depends upon the sexual behaviour of a few individuals a long time ago and is likely to have a large stochastic element. The date of HIV introduction was therefore allowed to vary slightly across the sites in order to better fit the time-trend in HIV prevalence.

Fitting the STDSIM model to study data and model assumptions

Fitting the model representations to the data from the Four Cities Study was an iterative process taking into account those model parameters which were allowed to vary across sites (fertility rates, mortality, age of sexual debut, probabilities of entering steady or short relationships by age, changes in relationship formation rates over time, condom use, aspects of commercial sex and STI treatment) and those that were restricted to be held constant (natural history, transmission probabilities and interactions of all the infections).

Demographic outputs including the age and sex population composition and growth rates were fitted first, then behavioural outputs including the proportions married, distribution

of numbers of non-marital partners in the past year and the characteristics of commercial sex. Once the model representations reflected the sexual behaviour characteristics of the four populations, epidemiological model outcomes including HIV and STI prevalences by age and sex and time-trends in HIV prevalence were compared to the available data. If the fit did not reflect the correct epidemiological patterns as observed across the sites, the inputs were varied within the *a priori* ranges and sometimes outside these ranges if a good fit could not be found. The simulation period was 1910-2000 and the results are based on the average of 200 simulations. Model outputs from the year 1997 were compared to the study data.

The modelled differences in behaviour between the sites include younger ages of sexual debut in the East African sites; higher proportions married in Kisumu and Ndola, lower rates in Cotonou and the lowest in Yaoundé; highest partner change rates in Yaoundé, similar rates in Kisumu and Ndola and lowest rates in Cotonou (5); and higher number of CSW clients per week in Cotonou than in the other three sites (6) (table 4). Low rates of condom use were simulated for the general population in all four sites starting in 1990 and increased in 1995 such that condom use was slightly higher in East Africa compared to West Africa at the time of the study (table 4).

The modelled proportion cured for each STI is a product of the proportion symptomatic, the proportion seeking treatment and treatment efficacy. Prior to the early 1990's a low level of syndromic treatment was assumed (0-5% of NG, CT, syphilis and HD were cured). The effectiveness of STI treatment was increased slightly in the early 1990s to reflect recent improvements in these urban centres. The modelled proportion of symptomatic STI episodes cured increased to 30% in Yaoundé and Kisumu in 1992, to 18% in Ndola in 1992, and to 18% in Cotonou in 1995 (table 4).

Simulated STI screening and treatment among CSWs was most effective in Cotonou where it was assumed to be frequent (monthly) and with increasing coverage up to 40% in 1995 (55). Screening was assumed to be less frequent (every 3 months) and at lower coverage (25% in 1995) for CSWs in Yaoundé and Kisumu. In Ndola, screening was assumed to take place monthly at low coverage (table 3). These assumptions were made to help fit the differentials in curable STI prevalences between females in the general population and CSWs. In Yaoundé, we modelled an increase in partner change rates and male visiting of sex workers starting in 1993. This increase in risky sexual behaviour was simulated to help fit the increasing trend in HIV prevalence over time observed for Yaoundé (56). Condom use among sex workers was simulated to be highest in Cotonou and lower in the other three sites (table 4).

Sensitivity Analysis

A sensitivity analysis was undertaken to assess the influence of selected parameters such as STI and lack-of-circumcision cofactor effects, specific behavioural characteristics (e.g., condom use, STI screening among sex workers) and chancroid epidemiology on the prevalence of HIV, gonorrhoea and chancroid among women in the general population and among sex workers in 1997. The default scenarios for Cotonou and Ndola were used

as examples in the sensitivity analysis since these two quantifications represented extremes in sexual behaviour profiles and the proportion of males circumcised.

Results

Model Fit to Data

The model adequately replicates the age and sex composition of the four cities as measured by recent censuses (figure 1) as well as the sex ratios for the sexually active age-groups (not shown). Figure 2 shows the fit for proportions married by age and sex. Males and females in East Africa marry at younger ages than those in West Africa and the model fit accurately reflects this pattern. Simulated age differences between steady partners were slightly lower in Cotonou (5 years) compared to the other sites (about 6 years), consistent with the study data. Also, reported polygamy was highest in Cotonou and Kisumu. In the model, polygamy is higher in Ndola (7% model, 3% data) than Cotonou (3% model, 6.5% data) in order to fit the higher proportions married in Ndola compared to Cotonou. The model did not provide a good fit to the prevalence of polygamy in the four sites but this was not a major concern because this magnitude of difference in polygamy between the sites will not substantially affect epidemiological outcomes.

As reflected in the data, the highest partner change rate was simulated for Yaoundé (proportion of men with five or more non-marital partners in the past year, data = 6.3%, model = 8.0%), then Ndola (data = 2.4%, model = 6.1%) and the lowest rates are for Kisumu (data = 1%, model = 4.7%) and Cotonou (data = 1%, model = 1.3%). The simulated partner change rate for Cotonou was lower than our *a priori* range in order to fit the low HSV-2 prevalence observed in Cotonou.

The proportion of females who are sex workers was simulated to be lowest in Cotonou (table 4), as observed. The simulated proportion of males who visit sex workers often is higher in Yaoundé (11.3%) and Ndola (8.2%) than in Cotonou (5.4%) and Kisumu (6.2%), consistent with our *a priori* ranges (tables 3 and 4).

The model provided a reasonable fit to the age and sex patterns in HIV prevalence in all sites (Figure 3). The model replicated the observed patterns, including the much higher HIV prevalence among young females compared to young males. In Cotonou, HIV prevalence was very similar among males and females, as observed. For Yaoundé, the peak age in prevalence was slightly younger in females than males as observed in the data but prevalence among young males was slightly over-estimated. For Kisumu and Ndola the patterns in prevalence were similar to that for Yaoundé with peak prevalence in females slightly younger than in males.

As a further assessment of the fit, simulated STI prevalences among all females were compared to those for CSWs (figure 4). This contrast provides insight into how well the simulated sexual behaviour reflects the situation in the sites at the time of the study. The fit for Cotonou is good as the contrast in prevalences of short and long duration STI among females and CSWs is reflected by the model. In Yaoundé, the fit is also acceptable but the prevalence of ulcers (the sum of the point prevalence for those with

primary syphilis, chancroid and the ulcerative stages of HSV-2) among CSWs was lower in the data than in the model and the prevalence of gonorrhoea was overestimated among the CSW.

In East Africa, the fit is reasonable (figure 4). In Kisumu, the simulated prevalence of ulcers was higher among CSW than in the data. The prevalence of syphilis was overestimated slightly in the model. In Ndola, the contrasts for females and the sex workers were consistent with the data except that syphilis prevalence in CSW was underestimated in the model. The prevalence among sex workers was extremely high (42%) in the study and it would be difficult to fit this without making some specific assumptions regarding syphilis dynamics (for example that syphilis was epidemic and not endemic at the time of the study) in Ndola.

Figure 5 shows available data on time-trends in HIV prevalence among antenatal clinic attendees and the simulated prevalence over time from the model. In general, we would expect the simulated prevalences to be higher than those among ANC attendees since the latter have been shown to underestimate HIV prevalence among the general population (57). The model fits the observed trends across the four cities reasonably well. In order to accurately reflect the trend we introduced HIV earlier in Kisumu (1980) than in the other sites (1984).

Sensitivity Analysis

The sensitivity analysis illustrates which factors may be important for the development of the HIV epidemics over time in these cities. It shows that in both the Cotonou and Ndola scenarios the magnitude of the STI cofactor effects have a large impact on the development of the HIV epidemics (table 5). In Cotonou, however, non-ulcerative STI were more important for HIV spread whereas in Ndola ulcerative STI seem to have been the main determinant. This can be deduced by comparing HIV prevalence in the test scenarios where all cofactors were varied to that for the scenario when only the ulcerative cofactors were varied. This is primarily due to the marked difference in the contribution of chancroid to the spread of HIV in the first 15 years of the epidemics in Ndola and Cotonou; see Figure 2b in our companion paper in this issue (58).

The sensitivity analysis suggests the direct protective effect of circumcision on HIV acquisition in males may not have had much impact on the development of the HIV epidemics in the four cities. If the lack-of-circumcision cofactor effect on HIV was doubled from 2 to 4 (in a scenario in which 10% of males were circumcised), the simulated prevalence of HIV among women in the Ndola scenario in 1997 increased from 29.7% to 31.5%. However, when the lack-of-circumcision cofactor effects for HIV, chancroid and syphilis were all increased there was a much larger impact on the subsequent development of the HIV epidemic so that the HIV prevalence in 1997 increased from 29.7% to 41% and chancroid prevalence increased from 0.1% to 0.8%. This occurred because in our simulations circumcision impacts the prevalence of chancroid which in turn has been shown to be a strong determinant of the rapid spread of HIV in early epidemics (59). If simulated chancroid prevalence among females in 1997 was increased in the Ndola scenario from 0.1% to 2% (by increasing the chancroid

transmission probability), HIV prevalence increased from 29.7% to 57.6% (table 5). Hence, our simulations suggest that the majority of the protective effect of circumcision on HIV transmission during the growth phase of the epidemics may have occurred indirectly through its effect on chancroid prevalence.

Condom use had a large impact on the prevalence of short duration STI as expected. Decreasing the screening frequency of CSW in Cotonou improved the fit for short duration STI in the general population but greatly increased gonorrhoea prevalence among CSW. Similarly, in Ndola, increasing treatment coverage of CSW improved the fit for gonorrhoea in the general population but worsened it for CSW. The probability that males will abstain from sex during chancroid infection also had a large impact on the results. The default scenario assumed 50% of males abstain during infection. If we assumed no change in coital frequency during chancroid infection, both chancroid and HIV prevalence increased significantly (table 5).

Discussion

The objective of this study was to determine if we could replicate the striking variations in the HIV epidemics as observed in Cotonou, Yaoundé, Kisumu and Ndola by simulating the observed patterns in demography, sexual behaviour, STI and circumcision from the Four Cities Study. By comparing the available data from the study and defining reasonable fit criteria we were able to fit the *STDSIM* model to the contrasting HIV epidemics in East and West Africa. Our model fit assumed the patterns of sexual behaviour were as observed during the study with the highest partner change rates in Yaoundé and younger ages of sexual debut and marriage in the East African sites, as observed during the study (5).

A reasonable fit of the model to the demographic, sexual behaviour and epidemiological characteristics of the populations was achieved holding the biological parameters for infection natural history and transmission constant across all four sites. The cofactor effects for STIs and male circumcision were also held constant across the sites. The cofactor effect for male circumcision was based on the available data which indicates that male susceptibility to HIV, chancroid and syphilis is doubled in uncircumcised males (43-45). The sensitivity analysis suggested that the primary impact of male circumcision during the growth phase of the HIV epidemics in these four cities may have been an indirect effect due to its impact on the prevalence of ulcerative STIs (table 4). A recent randomized controlled trial of male circumcision in South Africa showed male circumcision was strongly protective for HIV acquisition (60). Further analysis of the data from the South African trial and the results of the ongoing male circumcision trials in Kenya and Uganda may help distinguish between these direct and indirect effects. Although, in this study, the impact of male circumcision on the development of the contrasting epidemics in East and West Africa may have been mediated by the historical prevalence of chancroid in these populations, this study does not indicate the impact that male circumcision may have on new infections at the present stage of the epidemics in East Africa. This will be addressed during future work.

Although the model was successfully fitted to the data from all four cities, several limitations of our method and the model fits should be highlighted. Firstly, we were not able to fit every sexual behaviour output to the defined *a priori* ranges. This may have occurred because our *a priori* ranges were incorrect. Although extensive analyses were undertaken to define the *a priori* ranges including an assessment of time-trends in sexual risk behaviour and HIV/STI epidemiology and characteristics of CSWs and their clients, the resulting *a priori* ranges may have been incorrect. For example, in table 3 we indicated the proportion of males that visit CSW should be less in Kisumu compared to Cotonou. However, in the process of fitting the HIV/STI epidemiology for the general population and CSW, the best fit was achieved if these proportions were similar for Kisumu and Cotonou (table 4). In this instance, the epidemiological data were deemed to be more reliable than the behavioural data since the reference data (48-50, 55) used to help define the *a priori* ranges may not have been generalisable to The Four Cities study populations. This illustrates that in some cases, where the behavioural data were scanty, we preferentially fitted the epidemiological data instead of the sexual behaviour data since measures of infection prevalence are not subject to the same uncertainty and biases as reported sexual behaviour.

In addition, although the model seems to fit the data well, it is possible that there are unmeasured but important aspects of the underlying sexual networks that are not adequately represented by this simulation model. Due to the structure of the *STDSIM* model we do not have precise control over some of the behavioural outputs. For example, a supply and demand mechanism controls commercial sex in the model so the size of the core group cannot be specifically defined by the user even though these data could be estimated from the study. Further modeling studies, focused on the interaction between the sexual network structure, STI and circumcision cofactor effects on HIV spread, would be helpful. Other important structural constraints of the model include that cofactor effects did not combine in these simulations: if multiple cofactors were present (either multiple STI or an STI and lack of male circumcision), only the highest cofactor effect was applied. This assumption may overestimate the impact on HIV transmission of biological cofactors with the largest cofactor effects (chancroid and primary HSV-2). The combination of cofactor effects will be explored further to assess how this assumption may impact our findings.

The sensitivity analysis indicates our model fits depend heavily upon the model assumptions for chancroid. Firstly, chancroid was associated with a high HIV cofactor effect (25) in the model. However, our estimate is at the low end of the range (10-300) reported in the literature (61). Secondly, we assumed male susceptibility to chancroid was doubled in uncircumcised males. Although the magnitude of this effect is not precisely known, the assumption that uncircumcised males are more susceptible to chancroid is consistent with available data (28, 29, 43). In the simulations as reported here, the historic prevalence of chancroid was extremely low in West Africa (0% in Cotonou and 0.3% in Yaounde in 1980 prior to the introduction of HIV), because high rates of male circumcision controlled the spread of chancroid. On the other hand, the simulated prevalence of chancroid was 3.7% in 1980 in Kisumu and Ndola. This simulated prevalence subsequently drops rapidly due to the introduction of condom use

and STI treatment such that at the time of the study the simulated chancroid prevalence was 0% in Kisumu and 0.1% in Ndola. This dynamic is consistent with the principle that chancroid is easily controlled with even modest STI treatment as included in our simulations (29). Though there are no empirical data with which to compare our model estimates for chancroid prevalence, chancroid is known to have been more prevalent in southern Africa in the past (29). Hence, our simulations suggest the much less severe epidemics observed in West Africa may be due in part to the protective effect of male circumcision on ulcerative STI which may have inhibited the initial establishment of HIV in these circumcised populations.

The model scenarios included in the sensitivity analysis suggest the role circumcision may play in HIV prevention may be linked to the prevalence of other curable STI such as chancroid. If this is indeed the case, the effectiveness of male circumcision as an intervention to prevent HIV incidence may depend upon the stage of the HIV epidemic as has been found to be the case for STI treatment interventions (59). The protective effect of male circumcision early in an HIV epidemic may occur indirectly through the prevention of ulcerative STI but later in an epidemic, when HIV is more widespread and the prevalence of ulcerative STIs is less, the direct protective effect against HIV acquisition may be more important. In clinical trials of the effect of circumcision on HIV acquisition, it would therefore be important to determine the direct protection circumcision confers against HIV acquisition and that conferred through other STI such as chancroid.

The contrasting HIV epidemics of East and West Africa were replicated in our model primarily because of the differing prevalences of male circumcision in the four sites. Our preliminary conclusion is therefore that different rates of male circumcision in the four cities may have played a major role in these very different epidemics, and may also help to explain the striking variations in the HIV epidemics in different parts of sub-Saharan Africa. Our model fit will be used to gain further insight into the development and current state of the differing epidemics in East and West Africa as well as the projected impact of potential interventions. In the companion paper, we explore the role of different STIs in HIV spread over time across the sites and the results for HSV-2 prevalence are discussed in detail.

Author Contributions

The contributions of the authors were as follows. The study was designed by KO, JG, RH, RW, AB, and MCB. KO and EF designed and conducted the simulations and data analyses. RB and JDF designed and developed *STDSIM*. All authors contributed to the interpretation of the results and the writing of the manuscript.

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Table 1: Parameter values for representation of natural history and transmission of HIV and STI for the Four Cities Study. M=male, F=female, na=not applicable, w=weeks, y=years, m=months, durations are the same for males and females unless otherwise noted.

Infection and Stage	Duration	Transmission probability per act		Cofactor Effects			% Symptomatic[1]	
		M→ F	F→ M	STI on HIV	Lack of Circumcision on HIV/STI[2]	Effects of HIV	M	F
HIV								
Primary	10w	0.0275	0.01375		2	None		
Asymptomatic	5y	0.00183	0.00092		1	None		
Symptomatic	4y	0.0055	0.00275		1	HSV-2		
AIDS	40w	0.01375	0.00688		1	HSV-2		
Chancroid	11w	0.23	0.115	25	2		90%	70%
Gonorrhoea	14w M, 14w F	0.26	0.13	3	1		45%	14%
Chlamydia	14w M, 52w F	0.252	0.126	3	1		11%	6%
Syphilis								
Primary	6m	0.175	0.0875	7.5	2		50%	20%
Early latent	1y	0.0175	0.00875	1	1		0%	0%
Latent	2.5y	0	0	1	1		0%	0%
Late latent	12.5y	0	0	1	1		0%	0%
HSV-2								
Primary	3w	0.3	0.15	25	1			
Early latent with recurrent ulcer[3]	2y	0.01	0.005	1	1	4		
Latent with recurrent ulcer[3]	10y	0.005	0.0025	1	1	4		
Late latent	Lifelong	0	0	1	1	4		
Recurrent ulcer substage	7d	0.2	0.1	10	1	4	na	

[1]Proportion of symptomatic STI are defined for treatable STI including gonorrhoea, chlamydia, chancroid and syphilis.
[2] Pertains to increased acquisition uncircumcised compared to circumcised, males only.
[3] For HSV-2, recurrent ulcers occur at an average frequency of 2.5 months for males and 3 months for females in the early latent stage. For the latent stage, ulcers recur less frequently, every 6 months on average for males and every 8 months on average for females.

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Table 2: Sexual Behaviour Characteristics for the Four Cities. M=male, F=female, y=years

	Cotonou		Yaounde		Kisumu		Ndola	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Debut age (median, y)	18.2	18.3	17.1	17	16.1	15.8	17.4	16.7
Proportion married (%)	40.9	55.0	34.5	44.0	53.2	62.8	51.1	57.4
% Polygamous	6.5	17.4	2.5	6.0	6.8	14.8	3.0	3.1
Distribution of non-marital partners in past year (%)								
0-1	83.5	97.8	55.2	86.2	81.9	96.3	85.3	98.8
2-4	15.5	2.2	38.6	12.9	17.1	3.7	12.4	1.0
5+	1.0	0	6.3	0.9	1.0	0	2.4	0.2
Distribution of partners in lifetime (%)								
0-1	22.4	40.6	13.7	26.2	17.3	27.5	20.1	49.1
2-9	57.2	58.8	33.4	61.7	56.4	71.8	58.1	49.5
10+	20.4	0.5	53.0	12.1	25.8	0.7	21.8	1.4
Condom use in last casual Contact (%)	26.0	15.1	25.9	18.1	28.5	25.6	29.7	28.7
CSW Characteristics								
Ratio of CSW/100 men		1.0		1.5		2.0		1.9
# clients past week		7		2		1		3
Condom use in last contact (%)		69		28		50		28

Table 3: *A-priori* plausible bounds for sexual behaviour and STI treatment characteristics of simulated populations and plausible ranges for model outputs.
M=male, F=female, Cot=Cotonou, Ya=Yaoundé, Kis=Kisumu, Nd=Ndola.

Parameter	Cotonou	Yaounde	Kisumu	Ndola
CHARACTERISTICS				
Sexual Debut				
Age (y)	18 M, 18 F	17M, 17 F	17M, 15F	17M, 15F
Range	±3y M, ±4y F	±3y M, ±4y F	±3y M, ±4y F	±3y M, ±4y F
Vs other sites	> all	< Cot, >Kis, Nd	<Cot, Ya, =Nd	<Cot, Ya, =Nd
Partner change rate				
Factor[1]	1	>>1	>=1	>=1
Change in sexual behaviour over time	No	No	No	No
Condom use in non-marital partnerships	10-20% in early 1990's	10-20% in early 1990's	10-30% in early 1990's	10-30% in early 1990's
CSW Characteristics				
Start age minimum (y)	17	17	17	17
Start age maximum (y)	30	30	30	30
Min. duration career (y)	1	1	1	1
Clients/week	Highest	< Cotonou	Lowest	< Cotonou
# CSW visited/client	Highest	≤ Cotonou	< Cotonou	< Cotonou
Condom use	≥50% 1997	< Cotonou	≤ Cotonou	= Yaounde
STI treatment	Highest	<< Cotonou	< Cotonou	<< Cotonou
PLAUSIBLE RANGES FOR MODEL OUTPUTS				
Marriage (%)	41M, 55F	35M, 44F	53 M, 63 F	51 M, 57 F
Range	37-45 M 49-61 F	32-40 M 40-48 F	48-58 M 58 – 69 F	46-56 M 51-63 F
Distribution of non-marital partners in past year for males(%)				
0-1	65-75	45-55	65-75	65-75
2-4	20-30	40-50	20-30	20-30
5+	5-7	7-12	5-7	5-7
CSW				
% M that visit CSW	12-30%	≥ Cotonou	< Cotonou	≥ Cotonou
% CSW	~1%	> Cotonou	>> Cotonou	>> Cotonou
HIV%+ among CSW	40-60%	34-50%	70-80%	70-80%

[1]The partner change rate factor denotes how much higher or lower the partner change rate should be for each site compared to Cotonou

Table 4: Input parameters and fitted values for sexual behaviour, STI treatment and commercial sex in the Four Cities Study. M =male, F=female, Cot=Cotonou, Ya=Yaoundé, Kis=Kisumu, Nd=Ndola, ST = syndromic treatment

	Cotonou		Yaoundé		Kisumu		Ndola	
MODEL INPUTS								
General population								
Partner change	Lowest		Highest		>Cot, <Nd		<Ya, >Kis	
Change in partner change rate over time	No		Increase in 1993		No		No	
Age of debut (y)	M: 18y, F: 18y		M: 17y, F: 17y		M: 17y, F: 15y		M: 17y, F: 15y	
Condom use in non-marital partnerships	10% in 1990 20% in 1995		10% in 1990 20% in 1995		10% in 1990 25% in 1995		10% in 1990 25% in 1995	
Default ST								
% Cured[1]	M	F	M	F	M	F	M	F
NG	2.7	0.6	2.7	0.6	2.7	0.6	2.7	0.6
CT	0.7	0.3	0.7	0.3	0.7	0.3	0.7	0.3
Syphilis	5	1.5	5	1.5	5	1.5	5	1.5
HD	0	0	0	0	0	0	0	0
Improved ST (year)	1995		1992		1992		1992	
% Cured[1]	M	F	M	F	M	F	M	F
NG	8.1	1.7	13.5	3.4	13.5	3.4	8.1	1.7
CT	2.0	0.7	3.3	1.4	3.3	1.4	2.0	0.7
Syphilis	12.0	3.6	18	6	18	6	12.0	3.6
HD	21.6	12.6	32.4	21	32.4	21	21.6	12.6
Commercial sex								
Clients/week	4		2		1		2	
Client visiting frequency (visits/yr)[2]	0, 2, 24		0, 1, 12		0, 1, 12		0, 1, 12	
% clients/class[3]								
- single	0.51, 0.40, 0.09		0.29, 0.59, 0.12		0.27, 0.61, 0.12		0.15, 0.65, 0.20	
- married	0.79, 0.21, 0.004		0.65, 0.29, 0.06		0.64, 0.30, 0.06		0.6, 0.35, 0.05	
Change in CSW parameters over time	No		Increase in 1993		No		No	
Condom use	10% in ’90 25% in ’93 50% in ’95		10% in ’90 20% in ’93 30% in ’95		10% in ’90 20% in ’93 30% in ’95		10% in ’90 20% in ’93 30% in ’95	

	Cotonou	Yaoundé	Kisumu	Ndola
STI Screening				
Frequency	1m	3m	3m	1m
Coverage (%)	10% in '93 40% in '95	10% in '93 25% in '95	10% in '93 25% in '95	10% in '93 25% in '95
MODEL OUTPUTS				
Numbers of non-marital partners in past year for males (%)				
0-1	76.5	57.3	64.5	60
2-4	22.2	34.7	30.7	33.9
5+	1.3	8.0	4.8	6.1
% CSWs	0.7	1.8	2.3	1.3
% Clients by # Visits				
1	7.4	19.8	12.9	14.6
2-4	13.7	13.6	9.1	10.3
5+	5.4	11.3	6.2	8.2
HIV prevalence among CSW	50.3	34.8	70.7	65.4

[1]% cured = % symptomatic*% seeking treatment*treatment efficacy
[2]The frequency at which males visit CSWs is divided into three classes.
[3]The proportion of clients in each visiting class for married and single males, respectively.

Table 5: Sensitivity analysis model scenarios of simulated HIV and STI prevalence in Cotonou and Ndola in 1997 for selected model parameters. ↑ represents doubling default value and ↓ represents halving default value unless otherwise noted. HIVp = HIV prevalence, NGp = gonorrhoea prevalence, HDp = chancroid prevalence, F = female, CSW = commercial sex worker.

Parameter		Cotonou						Ndola					
		HIVp F	HIVp CSW	NGp F	NGp CSW	HDp F	HDp CSW	HIVp F	HIVp CSW	NGp F	NGp CSW	HDp F	HDp CSW
Data		***3.4***	***55***	***0.9***	***12***	***na***	***na***	***31.9***	***69***	***2.3***	***15***	***na***	***na***
Default Model Projection		***3.1***	***51.5***	***0.4***	***14.0***	***0.0***	***0.0***	***29.7***	***65.4***	***3.8***	***17.9***	***0.1***	***0.3***
STI cofactors	↑	10.6	84.3	0.3	12.1	0.0	0.0	50.9	92.4	3.6	18.3	0.0	0.3
	↓	0.6	14.6	0.4	13.4	0.0	0.0	9.5	39.0	4.4	19.5	0.1	0.5
Ulcerative cofactors	↑	5.3	71.0	0.4	11.4	0.0	0.0	44.6	83.4	3.6	18.0	0.0	0.3
	↓	1.8	37.0	0.4	13.7	0.0	0.0	11.9	45.5	4.3	19.5	0.1	0.3
Lack of circ cofactor		--	--	--	--	--	--						
HIV (default = 2)	↑ = 4							31.5	68.4	3.9	18.2	0.1	0.3
	↓=1.5	--	--	--	--	--	--	29.5	66.4	3.9	18.5	0.0	0.2
Lack of circ cofactor		--	--	--	--	--	--						
all (default = 2)	↑ = 4							41.0	81.7	2.9	15.5	0.8	5.7
	↓=1.5	--	--	--	--	--	--	26.9	61.9	4.2	19.9	0.0	0.1
Condom use general population.[1]	↑	2.5	44.5	0.1	4.3	0.0	0.0	25.0	58.3	1.4	5.9	0.0	0.0
	↓	3.4	57.1	0.6	18.7	0.0	0.0	32.2	69.2	7.0	28.2	0.1	0.8
Condom use CSWs[2]	↑	2.7	41.9	0.1	1.1	0.0	0.0	28.1	58.9	2.4	6.6	0.0	0.0
	↓	3.3	60.6	1.0	37.9	0.0	0.0	30.0	67.1	4.6	24.7	0.1	0.7
CSW screening freq	↓=6m	3.1	54.3	0.9	36.5	0.0	0.0	29.9	67.9	5.0	41.8	0.1	1.2
CSW treatment coverage[3]	↑	3.0	51.2	0.2	5.2	0.0	0.0	29.3	64.8	3.1	6.5	0.0	0.1
	↓	3.1	52.5	0.6	23.2	0.0	0.0	29.7	66.1	4.6	30.8	0.1	0.6
Prob no sex HD[4]	0	2.9	50.2	0.5	16.1	0.0	0.0	46.2	82.1	3.7	19.7	0.7	3.9
HDp	↑	4.1	55.2	0.4	13.5	0.0	0.0	57.6	92.2	3.5	18.7	2.1	12.8

[1] High Cotonou = 20% ('90), 40% ('95); Low Cotonou and Ndola = 5% ('90), 10% ('95), High Ndola = 20% ('90), 50% ('95).
[2] High Cotonou = 20% ('90), 40% ('93), 80% ('95); Low Cotonou = 5% ('90), 10% ('93), 20% ('95); High Ndola = 20% ('90), 50% ('93), 70% ('95); Low Ndola = 5% ('90), 10% ('93), 15% ('95).

[3] High Cotonou = 20% (’93), 60% (’95); Low Cotonou = 5% (’93), 20% (’95); Low Ndola = 20% (’93), 50% (’95); Low Ndola = 5% (’93), 10% (’95).
[4]Probability of abstaining from sex for males with chancroid, default = 50%.

Figure 1: Observed and simulated population structure by age and sex for the four cities. Grey bars represent data, white bars are the model projections. Data for males on left, females on right. Error bars reflect +/-10% for each age and sex group and acceptable range for model fit.

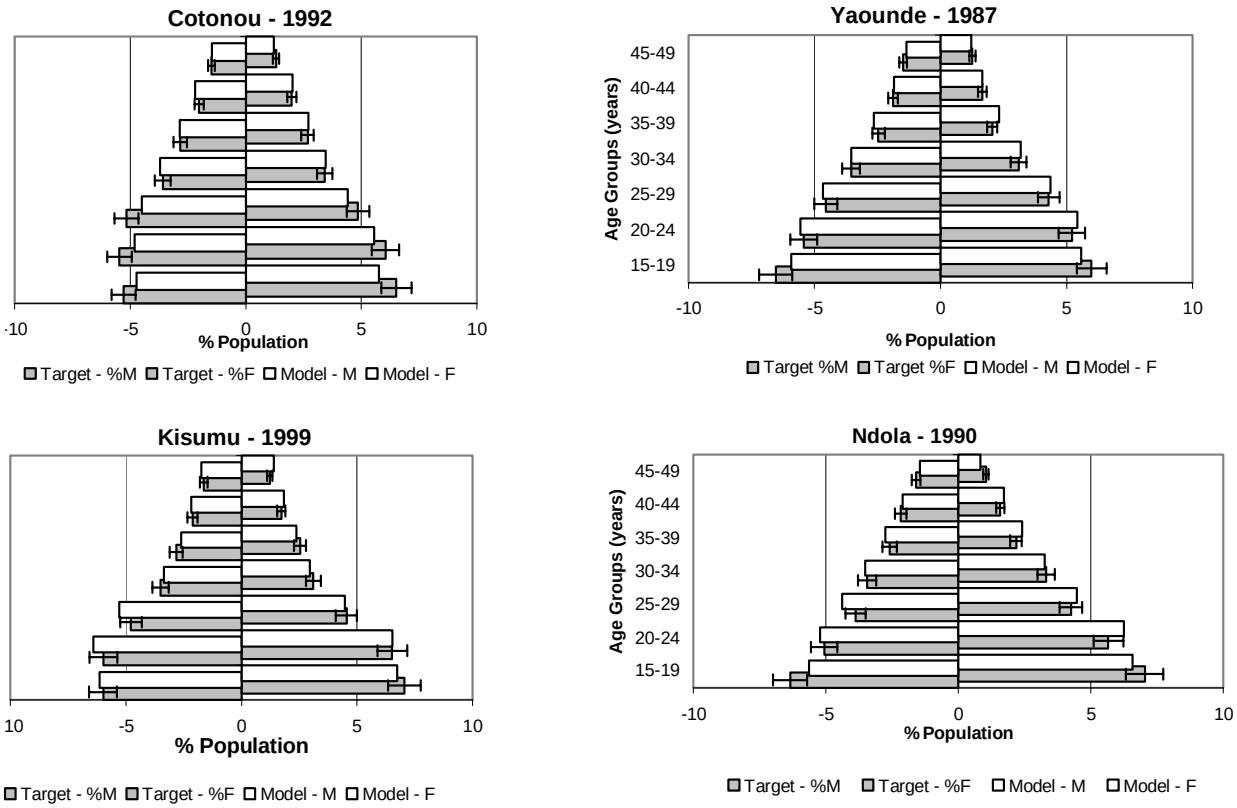


Figure 2: Simulated and actual proportions married by age and sex for the Four Cities Study in 1997. Points reflect data, lines reflect model fit in 1997.

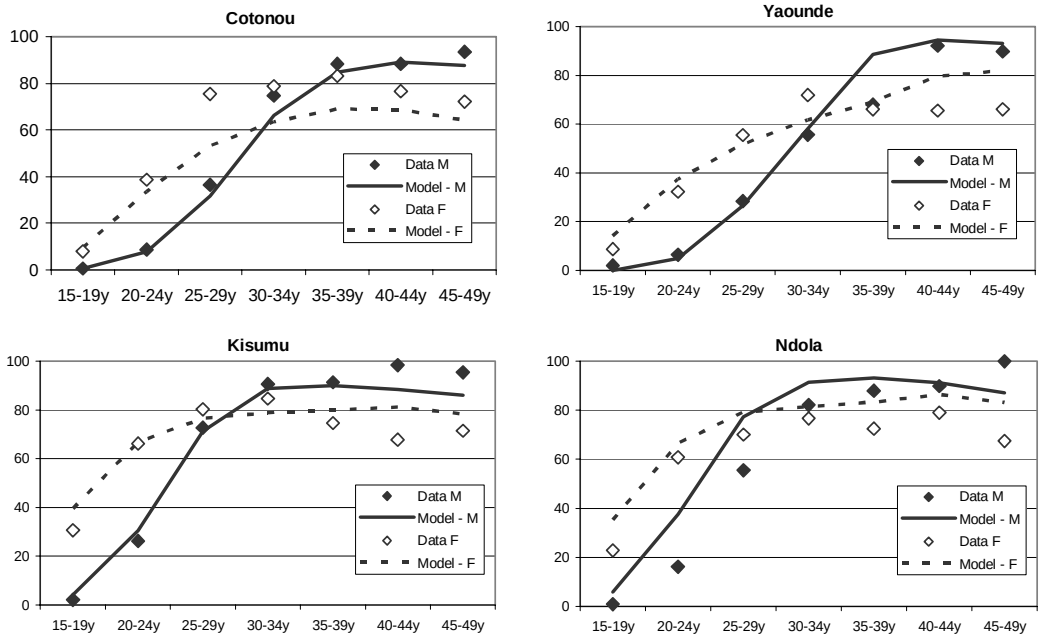
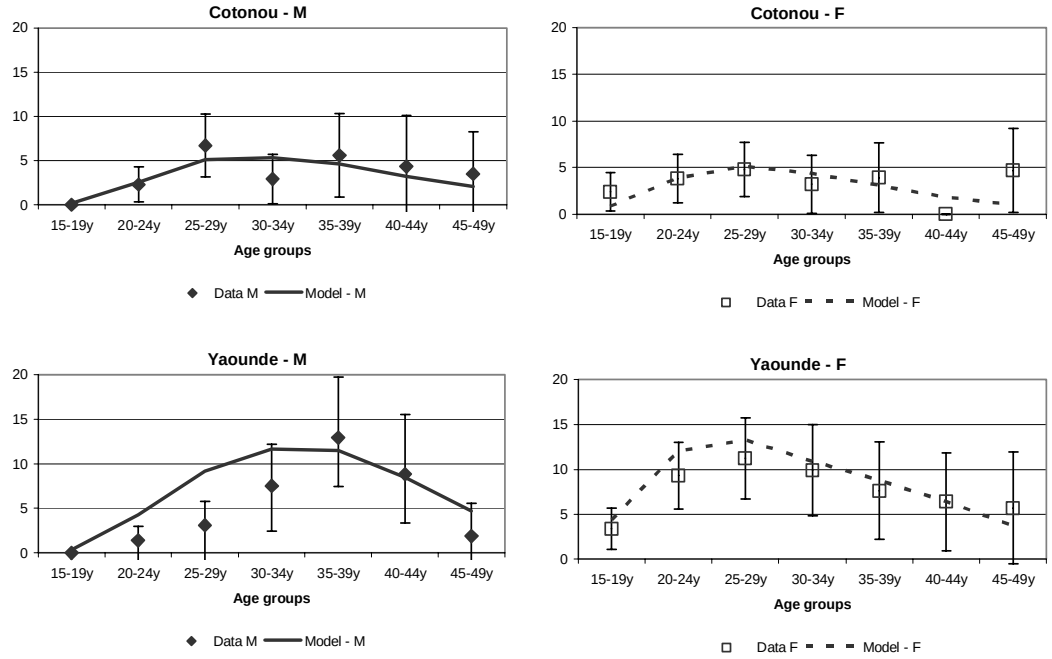


Figure 3: Observed (mean, 95% CI) and simulated HIV prevalence by age and sex for the Four Cities Study in 1997. Males on left, females on right. Note differing y-axis scales.

3a West Africa



3b East Africa

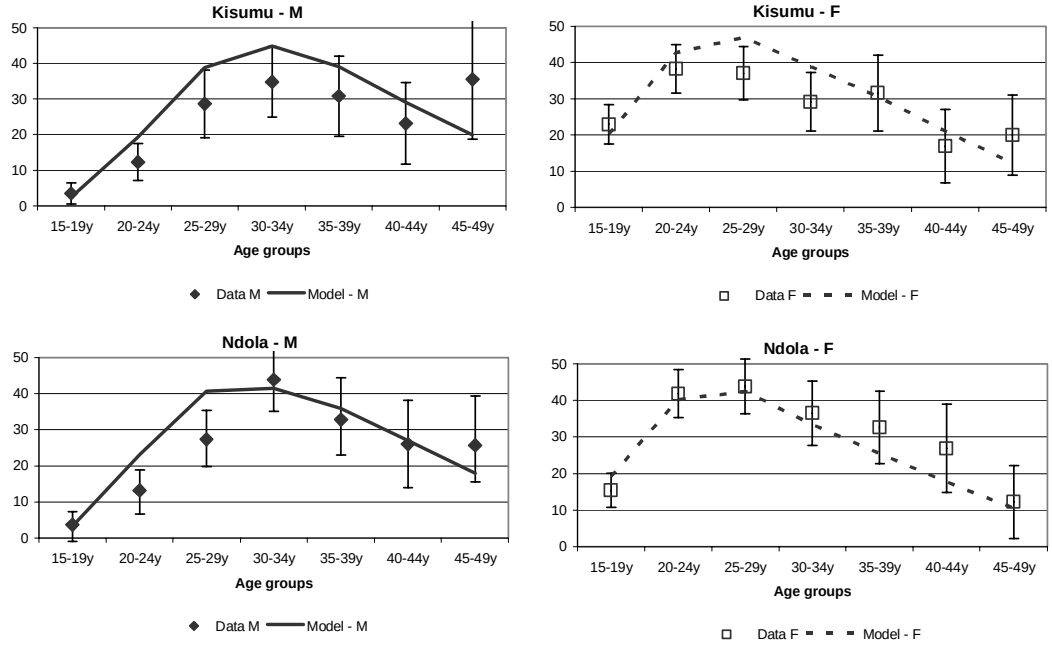


Figure 4: Observed (mean, 95% CI where available) and simulated STI prevalence among females in general population and among CSWs in four African cities in 1997. NG: gonorrhoea, CT: Chlamydia, TP: syphilis

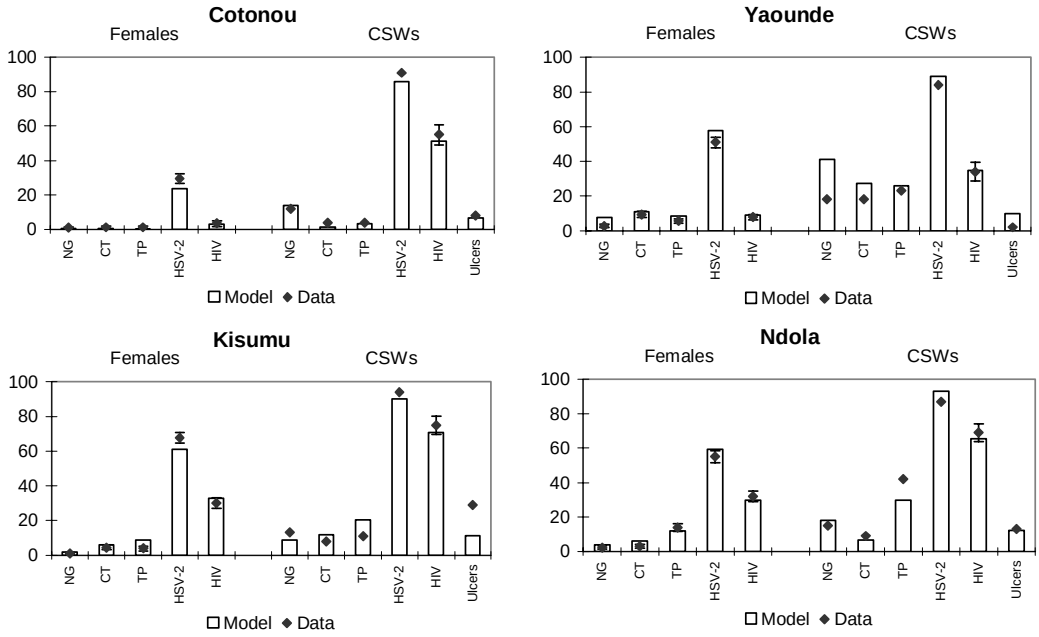
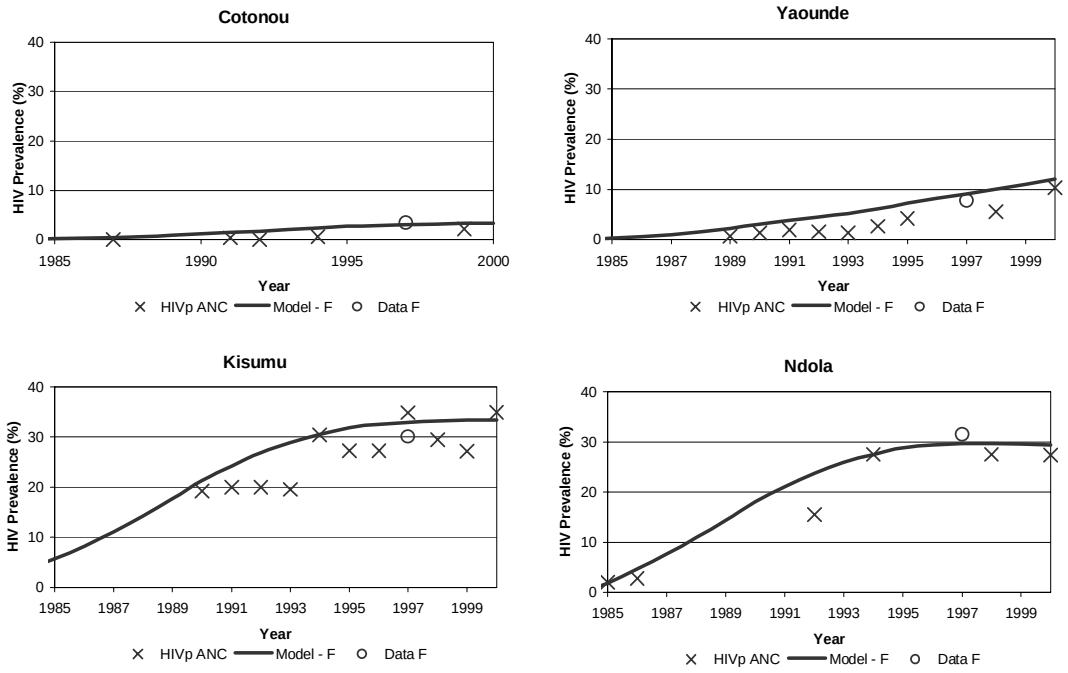


Figure 5: Observed and simulated female HIV prevalence over time for the four cities. ANC = antenatal surveillance data, circle = observed female HIV prevalence from the Four Cities Study.



conflict with UK guidelines. Their preferred regimen for the treatment of pelvic inflammatory disease is in particular surprising (doxycycline and metronidazole) since it conforms with neither UK nor US guidelines and three studies have now shown it to be inferior to alternative regimens.

Overall *Fast facts: sexually transmitted infections* is to be recommended with just a few caveats.

Jonathan Ross

CORRECTIONS

doi: 10.1136/sti.2006.021782.corr1

There was an error in the August issue of the journal (Dodds JP, Johnson AM, Parry JV, *et al*. A tale of three cities: persisting high HIV prevalence, risk behaviour and undiagnosed infection in community samples of men who have sex with men. *Sex Transm Infect* 2007;**83**:392–6.) The last sentence on page 2 should read as follows: ''All were screened by GACELISA HIV 1 and 2, whose sensitivity and specificity had been determined as 99.5% (95% CI 97.1% to 99.9%) and 99.7% (95% CI 98.9% to 99.9%), respectively.[13 14]

doi: 10.1136/sti.2006.023283.corr1

Several errors occurred in an article published in the July issue of the journal (Evans AR, Wiggins RD, Mercer CH, *et al*. Men who have sex with men in Great Britain: comparison of a self-selected internet sample with a national probability sample. *Sex Transm Infect* 2007;**83**:200–5.) A corrected version of the article is available on our website at http://sti.bmj.com/supplemental.

doi: 10.1136/sti.2006.023531.corr1

Two articles from the August 2007 supplement were unlocked online but not in print. The articles are: Orroth KK, Freeman EE, Bakker R, *et al*. Understanding the differences between contrasting HIV epidemics in east and west Africa: results from a simulation model of the Four Cities Study. *Sex Transm Infect* 2007;**83**(Suppl 1):i5–i6 and Freeman EE, Orroth KK, White RG, *et al*. Proportion of new HIV infections attributable to herpes simplex 2 increases over time: simulations of the changing role of sexually transmitted infections in sub-Saharan African HIV epidemics. *Sex Transm Infect* 2007;**83**(Suppl 1):i17–i124. Both articles are freely available.