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Behaviour change and competitive exclusion can explain the diverging HIV-1 and HIV-2 prevalence trends in Guinea–Bissau

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SUMMARY

The aim of this study was to determine whether a temporary rise in sexual risk behaviour during war in Guinea–Bissau could explain the observed trends in HIV-1 and HIV-2 prevalence, and to explore the possible contribution of competitive elimination of HIV-2 by HIV-1. A simulation model of the heterosexual transmission of sexually transmitted infections was parameterized using demographic, behavioural and epidemiological data from rural Guinea–Bissau, and fitted to the observed HIV-1 and HIV-2 trends with and without a historic rise in risk behaviour. The observed trends could only be simulated by assuming a temporary rise in risk behaviour. Around 30% of the projected decline in HIV-2 prevalence from a peak of 8.7% to 4.3% in 2010 was due to competitive elimination by HIV-1. Importantly for public health, HIV-1 prevalence was predicted to continue increasing and to become the dominant HIV type by 2010. Data collection is required to validate this prediction.

INTRODUCTION

In contrast to HIV-1, the spread of HIV-2 has been largely restricted to West Africa and countries with close historical links to Guinea–Bissau (e.g. Angola, Mozambique, Brazil) [1]. Guinea–Bissau has the highest HIV-2 prevalence worldwide (8%–10% in the general adult population) [2–4]. In recent years a decline in the prevalence of HIV-2 has been observed in most populations in West Africa including some communities in Guinea–Bissau [5–7]. HIV-2 prevalence decreased in men but not in women in a community study from urban Guinea–Bissau between 1987 and 1996 [8]. HIV-2 prevalence has also remained stable in a rural area in Guinea–Bissau (8.3% in 1990 vs. 7.9% in 1997; M. F. Schim van der Loeff, unpublished data).

At the same time, HIV-1 prevalence in Guinea–Bissau has risen from <0.5% in the late 1980s to around 2–3% 10 years later, suggesting an ongoing HIV-1 epidemic [5, 8, 9]. Differences in biology
and viral load may explain the conflicting trends of HIV-1 and HIV-2 prevalence [10–12]. Heterosexual transmission of HIV-2 seems to be less efficient compared to HIV-1 [13, 14]. Further, progression to AIDS is slower in HIV-2- than in HIV-1-infected individuals [15–19].

It has been suggested that the exceptionally high prevalence of HIV-2 in Guinea–Bissau, especially in older age groups, may be due to increased promiscuity and commercial sex work during the war of independence between 1963 and 1974 [1, 20]. We used the microsimulation model STDSIM fitted to data from a rural area in Guinea–Bissau to (1) determine whether such a temporary increase in sexual risk behaviour can help explain the observed trends in HIV-1 and HIV-2 prevalence, and (2) explore the potential role of HIV-1 in reducing the prevalence of HIV-2 (competitive elimination).

METHODS

The microsimulation model STDSIM

We used the stochastic microsimulation model STDSIM, that simulates the natural history and the dynamics of the heterosexual transmission of HIV and other sexually transmitted infections (STI) in a dynamic population of interacting individuals [21]. Transmission of STI and HIV are simulated at the level of the sexual contact which can occur within steady and short-term relationships and as one-off contacts between males and commercial sex workers (CSWs) [22].

The natural course of infection of the modelled STI and of HIV-1 was divided, where appropriate, into different stages allowing variation in transmission probability and cofactor effects. These were previously validated by simultaneously fitting to data from three rural sites in sub-Saharan Africa [23]. HIV-2 was newly parameterized in this study. Chancroid and primary HSV-2 ulcers were assumed to enhance HIV-1 and HIV-2 transmission 25-fold, recurrent HSV-2 ulcers 10-fold, primary syphilis including periods without ulcers 7.5-fold, gonorrhoea and chlamydial infection 3-fold and trichomoniasis 2-fold [23]. A priori model input and output constraints were determined using data from a rural population in Guinea–Bissau and literature review. The model was fitted iteratively to these constraints. Results of 150 runs were averaged to account for the stochastic nature of the simulations. The time-frame of the simulation was from 1910 to 2010.

Model parameters

For the representation of HIV-1 we used fixed parameter values validated by previous modelling work on data from four populations in sub-Saharan Africa (Table 1) [24]. Parameters regarding HIV-2 infectivity and natural course of infection were estimated based on published data (Table 1). Based on estimates from a cohort study on CSWs in Dakar [13, 25], we assumed the ratio of HIV-2/HIV-1 infectivity was 1/4 (range 1/5 to 1/3). The HIV-2 transmission probability by stage was modelled to be proportional to HIV-1 transmissibility (Table 1). For both HIV-1 and HIV-2 the transmission probability from women to men was assumed to be half of the probability from men to women. Recent data showed no cross-immunity between HIV-1 and HIV-2. Therefore no interaction between HIV-1 and HIV-2 was modelled [5, 26–28].

Data on the duration of the different stages of HIV-2 infection (primary infection, asymptomatic/symptomatic non-AIDS stage, AIDS) are scarce, but progression to AIDS in HIV-2 seems very slow. Based on a CSW study from Dakar [29, 30], Anderson & May estimated an average incubation period of 30 years [31]. The risk of death attributable to HIV-2 found in cohort studies on seroprevalent cases with up to 9 years of follow-up was compatible with this estimate [17, 32]. We assumed that the average time from infection to death for HIV-2 was three times longer compared to HIV-1. Data also suggested that the HIV-2 AIDS stage may be up to three times longer than that of HIV-1 [19, 33]. For simplicity, we assumed each HIV-2 stage to be three times longer than the respective HIV-1 stage (Table 1). Therefore the ratio of the basic reproduction numbers in our model \( R_{0,HIV-2}/R_{0,HIV-1} = 0.75 \) was compatible with previous estimates (0.71) [31].

HIV-2 has been identified in a blood sample from Guinea–Bissau dating back to 1966 and may have been introduced as early as 1945 [34, 35]. We introduced HIV-2 into the model in 1950. In contrast, no HIV-1 infections were found in blood samples from several rural sites in Guinea–Bissau taken in 1980 and from Bissau in 1987 [17, 36]. In the study area, HIV-1 prevalence was 0.5% in 1990 [4]. Based on these data, the year of introduction of HIV-1 was assumed to be 1987.
Simulated population

The area for which HIV transmission was modelled consists of a set of 10 farming villages in the north-west of Guinea–Bissau. The characteristics of this population have been described [32]. The majority of the population belong to the Manjako ethnic group and is highly mobile. Many men outmigrate for work elsewhere in the region causing an adult male to female ratio of around 0.82 [37]. Women from the area form a significant proportion of prostitutes working in urban centres in Guinea–Bissau and neighbouring countries [32].

The demographic characteristics of the population were fitted to data from a survey carried out in 1997. The growth rate was 2.4% and the average life expectancy was 46 years as reported in census data from Guinea–Bissau (2000) [38].

The behavioural characteristics and HIV-1/HIV-2 prevalence were based on two cross-sectional studies carried out in the area in 1989–1991 and in 1997–1998 [27, 32]. To allow the comparison between the observed and simulated overall HIV-1 and HIV-2 prevalence, the simulated and the observed values were standardized using the age and sex distribution reported in the 1997 demographic survey.

Based on the field data, the average age of first sex was assumed to be 17.5 years for men and women. Studies across sub-Saharan Africa have shown that men and women may substantially misreport their sexual behaviour, with women potentially under-reporting and men over-reporting the number of recent partners [39, 40]. Thus, the proportion of men and women reporting more than one partner in the last 12 months was allowed to deviate downwards and upwards, respectively, relative to the observed data. In the area, men in polygamous unions may not have a sexual relationship with all of their spouses. Therefore we assumed the proportion of polygamous men was lower than the data suggest.

Data on which to base the quantification of commercial sex work in the area were limited. According to the 1997 study, up to 3% of women may have worked as a CSW at some point in their life, but there was no information on current CSW status. Based on the limited data we assumed that the majority of males did not visit CSWs (65%), or did so only once a year (31%). A smaller proportion of males (4%)...
visited CSWs nine times per year. CSWs were recruited from single and divorced females in the population according to male demand and serviced one partner per week to simulate low-level sex work assumed to be more prevalent in rural areas.

Modelling strategy

In the first scenario, the model was fitted to the increasing prevalence of HIV-1 between 1990 and 1997 using the *a priori* constraints on sexual behaviour. The simulated age and sex distribution of HIV-1 prevalence was fitted to the prevalence data from the cross-sectional study in 1997 by varying the age-specific rate of partner change within the predefined limits. Since HIV-1 was introduced in the late 1980s, this approach allowed us to simulate the conditions under which the HIV-1 epidemic occurred. We then used the model to estimate HIV-2 prevalence if these conditions had remained constant throughout the time-frame of the simulation.

To explore the hypothesis that a temporary rise in risk behaviour must have taken place to explain the observed high HIV-2 prevalence, a second scenario was modelled assuming an increase in risk behaviour from 1963 to 1974 contemporary with the war of independence. The sexual risk behaviour prior to 1963 and after 1974 was assumed to be similar. Since it has been suggested that HIV-1 may competitively replace HIV-2 [31], we repeated the second scenario without introducing HIV-1 to estimate the prevalence of HIV-2 if the HIV-1 epidemic had not occurred and therefore estimate the impact of the competitive elimination of HIV-2 by HIV-1.

Sensitivity analysis

To assess the robustness of the results to uncertainties in the HIV-2 transmission probability and the duration of infection, the scenario assuming no behaviour change and the scenario simulating behaviour change were repeated assuming the high and low values for each parameter shown in Table 1. Since there was also uncertainty regarding the simulated risk behaviour, we tested the sensitivity of the findings to changes in the number of male CSW visits per year in the high frequency group (6 or 12 visits per year resulting in a core group size of frequent CSW visitors of 8% or 2%, respectively). We explored whether a change in any of these parameters allowed fitting the model to the observed HIV-1 and HIV-2 prevalence without assuming a change in behaviour. The scenarios were refitted to the data by varying the overall risk behaviour within the predefined limits.

RESULTS

Simulated population characteristics

The simulated population provided a good fit to the age and sex distribution of the population in 1997 (not shown). In accordance with the data, the simulated adult male to female ratio was 0.85 resulting from substantial simulated outmigration of males older than 25 years. The simulated population consisted of around 22000 individuals of all ages in 1997.

As expected, to fit the observed HIV-1 prevalence by age and sex, we had to assume that the proportion of adults with more than one partner in the previous 12 months was higher than observed for females, but lower than observed for males (women: model 18%, data 3%; men: model 27%, data 41%). The proportion of women in steady relationships was slightly lower compared to the data (women: model 53%, data 66%), while in men it was somewhat higher (model 52%, data 42%). Also, we assumed a lower proportion of polygamous men compared to the data (model 8%, data 17%). In line with the data males were older than their female partners (4 years). The proportion of females recruited as CSW was 1.1%.

Simulated HIV-1 and HIV-2 prevalence

Figure 1(a) shows the simulated epidemic curve for HIV-1 fitted to the overall prevalence among ≥15-year-olds in 1990 and 1997 assuming no change in sexual behaviour over time. In this scenario, HIV-2 prevalence would have reached 1.4% in 1997, much lower than the 7.2% observed.

Figure 1(b) shows the second scenario assuming higher risk behaviour between 1963 and 1974 (proportion with more than one partner in preceding 12 months: men 31%, women 21%; proportion of frequent visitors to CSW 8%, 2-2% of females recruited as CSW). In this scenario the prevalence of HIV-1 and HIV-2 was fitted well. The peak of the HIV-2 epidemic (8.7%) occurred in 1979, 5 years after the end of the simulated period of high-risk behaviour. HIV-2 declines from its peak of 8.7% to 4.3% in 2010 (a 51% relative decline), while HIV-1 prevalence rises to 7.6%. Repeating Scenario 2
without introducing HIV-1 (the dashed line) showed that in the absence of HIV-1 the prevalence of HIV-2 would decline from 8.7% in 1979 to 5.5% in 2010 (a relative decline of 37%). Therefore, the model predicts that between 1979 and 2010, around 70% of the expected decline in HIV-2 prevalence could be due to the historic change of risk behaviour, and around 30% due to competitive elimination by HIV-1.

Figure 2 shows the observed and simulated HIV prevalence trends in Scenario 2 stratified by gender and by age (15–44 years and ≥45 years). The model fitted the gender-specific HIV-1 and HIV-2 prevalences well and predicted similar prevalence trends for males and females after 1997 (Fig. 2a). The increasing HIV-1 prevalence in younger and older adults and the declining HIV-2 prevalence in younger adults were also fitted well by the model, but the HIV-2 prevalence among older adults in 1990 was not fitted by the model (Fig. 2b).

Further stratifications by age and gender for the years 1990 and 1997 are shown in Figures 3 and 4 confirming a good fit of the overall HIV-1 and HIV-2 prevalence in women and men in Scenario 2. The model overestimates the HIV-1 prevalence in women in the 25–34 years age group and underestimates HIV-1 in the 55–64 years age group (Fig. 3). The observed age distribution of HIV-1 prevalence in men is represented well by the simulation.

In the model, the peak age of HIV-2 prevalence shifts from the 45–54 years age group in 1990 to the 55–64 years age group in 1997, suggesting a cohort effect of past HIV-2 infection (Fig. 4). A similar effect can be seen in the data, but appears less obvious for men than for women. The model overestimates HIV-2 prevalence in older men and women in 1990, and men aged ≥65 years in 1997.

**Sensitivity analysis**

Assuming no change in behaviour (Scenario 1), the projected HIV-2 prevalence in 1997 was 1.6% if the ratio of HIV-2/HIV-1 infectivity was raised to 1/3. In all other simulations assuming no behaviour change, HIV-2 prevalence in 1997 was even lower (not shown).

The sensitivity analysis of Scenario 2 (increased risk behaviour 1963–1974) is shown in Table 2. Assuming a shorter duration of HIV-2 infection or a lower
transmission probability resulted in an earlier peak and a steeper decline of HIV-2. Similarly, concentrating visits to CSWs in fewer men (12 visits per year in the highest visiting frequency group) resulted in an earlier peak of HIV-2 (1976), but the rapid decline of HIV-2 between 1990 and 1997 was not consistent with the observed prevalence trend. In this scenario, HIV-1 prevalence reaches a plateau at 4.9% in 2010. Assuming a larger group of males who visited CSWs less often, resulted in a good fit to the HIV-2 prevalence data, but this resulted in a very steep rise of HIV-1 to 13% in 2010. In all counterfactual scenarios without introducing HIV-1, the absence of HIV-1 resulted in a higher HIV-2 prevalence in 2010 (by +0.8% to +1.4%).

**DISCUSSION**

The model supports the hypothesis that the high prevalence of HIV-2 found in Guinea–Bissau can be explained by a period of higher risk sexual behaviour during the war of independence between 1963 and 1974. It suggests that HIV-2 prevalence in rural
Guinea–Bissau is about to decline as observed in some urban settings in this country [5, 8], and that this decline may have been hastened by the ongoing HIV-1 epidemic.

Apart from Guinea–Bissau high levels of HIV-2 outside risk groups have only been observed in war-affected regions in northern Angola (11.3% in pregnant women [41]), suggesting that a substantial penetration of HIV-2 into the general population occurs only if an existing HIV-2 endemicity combines with prolonged periods of social disturbance.

Our model prediction for the HIV-1 prevalence trend in rural Guinea–Bissau was consistent with the available data on pregnant women in the capital city Bissau which shows prevalence rising from <1% prior to 1993 to 2.5% in 1997 and 4.8% in 2000 [42]. Our study predicts that HIV-1 prevalence has continued to rise since 2000 and will continue to do so over the next few years. This contrasts with the most recent model predictions by UNAIDS, in which HIV-1 prevalence in adults was modelled to have stabilized at 3.8% between 2003 and 2005 [43]. However, data on pregnant women in Bissau have been unavailable after 2000 and therefore we cannot determine which of these contrasting model forecasts is more likely to be correct.

The model findings are limited by uncertainty regarding the duration of HIV-2 stages, HIV-2 transmission probability and sexual behaviour in the area. However, the sensitivity analysis revealed that even large changes in any of these parameters still required a period of higher risk behaviour in the past to explain the observed HIV-2 prevalence. Moreover, in all scenarios HIV-2 is projected to decline in the future, while HIV-1 shows a further increase. However, the peak year of the HIV-2 epidemic, the slope of its subsequent decline and the magnitude of the HIV-1 epidemic strongly depended on the size of the simulated core group of male CSW visitors, as well as on the assumed parameters for the transmission probability of HIV-2 and the duration of infection until death. Therefore, predictions of the future prevalence of HIV-1 and HIV-2 remain somewhat uncertain.

Further, the modelled and observed HIV prevalences were not always consistent. The model overestimated the HIV-2 prevalence in older individuals in 1990 which could be due to an overestimation of sexual risk behaviour in these age groups relative to younger age groups, or because the two samples in 1990 and 1997 were drawn from slightly different populations. The latter possibility is compatible with the large age-specific changes in HIV-2 prevalence in women between 1990 and 1997 and the known high mobility of the people living in the area [37].

We also predicted a slightly faster decline of HIV-2 prevalence between 1990 and 1997 than was observed, probably due to our simplified assumption of an abrupt reduction of risk behaviour in 1974. Assuming a more gradual decline in risk behaviour after 1974 would have resulted in a slower HIV-2 decline. The high prevalence of HIV-1 in the 55–64 years age group in women was also not well represented by the model. This observation from the data may be due to...
<table>
<thead>
<tr>
<th>Data</th>
<th>Prevalence (%) in 1990, age ≥15 yr (95% CI)</th>
<th>Prevalence (%) in 1997, age ≥15 yr (95% CI)</th>
<th>Prevalence (%) in 2010, age ≥15 yr</th>
<th>HIV-2 without HIV-1*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HIV-1</td>
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<td></td>
<td>0·5 (0·2–0·8)</td>
<td>7·5 (6·5–8·5)</td>
<td>2·7 (2·1–3·3)</td>
<td>7·2 (6·3–8·1)</td>
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<td>Default (Fig. 1, Scenario 2)</td>
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<td>(time from HIV-2 infection to death = 30 years &amp; HIV-2 TP per contact = 1/4 × HIV-1)</td>
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<td></td>
<td>1979</td>
<td>0·3</td>
<td>7·9</td>
<td>2·5</td>
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<td></td>
<td>Time from HIV-2 infection to death</td>
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<td>20 years</td>
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<td>40 years</td>
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<td>HIV-2 per contact transmission probability</td>
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<td>1/3 × HIV-1 TP</td>
<td>0·4</td>
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<td>1/5 × HIV-1 TP</td>
<td>0·3</td>
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<td>Number of visits in frequent CSW visitors</td>
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<td>6 visits per year</td>
<td>0·3</td>
<td>7·3</td>
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<tr>
<td></td>
<td>12 visits per year</td>
<td>0·6</td>
<td>8·2</td>
<td>2·6</td>
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TP, Transmission probability; CSW, commercial sex workers.

* Projected HIV-2 prevalence in 2010 without introduction of HIV-1.
to the high average age of active CSWs in the area [44] or to an increased susceptibility of post-menopausal women to HIV infection [8, 45, 46]. However, the current STDSIM model does not allow age-specific variations in susceptibility.

Finally, the model does not take into account non-sexual transmission routes that may explain the high HIV-2 prevalence in Guinea–Bissau. A recent study on elderly people in Bissau, the capital of Guinea–Bissau, found a moderate association between female circumcision, medical injections and HIV-2 infection [47], although an earlier study in Bissau failed to find an association between medical injections and HIV-2 infection [20]. Lifetime blood transfusions were a risk factor for HIV-2 infection in the 1990 survey conducted in the rural area on which our model was based (odds ratio 2.1) [4]. Therefore, the screening of blood supplies since 1987 may contribute to the decline of HIV-2 [8]. However, since blood transfusions were reported by only 2% of the study population [4], the population attributable fraction of HIV-2 infections preventable by blood screening is likely to be <4%. Our study cannot exclude the possibility that other routes of transmission may have contributed to the high HIV-2 prevalence in Guinea–Bissau, but it does show that a moderate rise in risk behaviour compatible with existing data is sufficient to explain the observed trends in HIV-1 and HIV-2 prevalence.

To our knowledge there is only one previous modelling study of HIV-1 and HIV-2 transmission. In 1996, Anderson & May used a deterministic model of HIV-1 and HIV-2 transmission in a randomly mixing population [31]. Assuming homogenous risk behaviour they predicted that HIV-1 may competitively replace HIV-2 within 200 years of the introduction of HIV-1, and that no significant impact on HIV-2 prevalence in Guinea–Bissau, but it does show that a moderate rise in risk behaviour compatible with existing data is sufficient to explain the observed trends in HIV-1 and HIV-2 prevalence.

In conclusion, our model confirms that the diverging trends of HIV-1 and HIV-2 prevalence in Guinea–Bissau can be explained by the combination of behaviour change after the war of independence and competitive elimination by HIV-1. While the exact future HIV prevalences remain uncertain, the public health burden of HIV-1 is likely to continue to increase relative to HIV-2 and it may become the dominant HIV type in Guinea–Bissau by 2010. Indeed, this may have already happened in younger age groups. Our analysis raises the possibility that HIV-1 prevalence in Guinea–Bissau may exceed that in neighbouring West African countries, where, with some exceptions, HIV-1 prevalence has remained <5%. Further data collection is required to validate this model prediction.

DECLARATION OF INTEREST
None.

REFERENCES


