The role of the natural epidemic dynamics and migration in explaining the course of the HIV epidemic in rural Uganda: a modelling study

Leigh A Shafer,1* Richard G White,2 Rebecca N Nsubuga,1 Ruth Chapman,2 Richard Hayes2 and Heiner Grosskurth1

1Medical Research Council Unit on AIDS/Uganda Virus Research Institute, Entebbe, Uganda and 2London School of Hygiene and Tropical Medicine, London, UK

*Corresponding author. Medical Research Council Unit on AIDS/Uganda Virus Research Institute, Entebbe, Uganda.
E-mail: shafer@umanitoba.ca

Accepted 29 September 2010

Background Human immunodeficiency virus (HIV) prevalence in Uganda fell during the 1990s and has risen since 2000. The changing trends since 2000 may be due to changing risky sexual behaviour, but other factors may also contribute. We explore the possible impact that two factors may have on cohort trends: natural epidemic dynamics and local migration. We simultaneously fit a mathematical model to the contrasting prevalence trends by age/gender in a southwest Ugandan cohort, which has never been done before.

Methods We fit a model to HIV trends, by age groups and gender, assuming: (i) neither migration nor intentional behaviour change, (ii) migration changes, (iii) intentional behaviour changes and (iv) both change. The model fits were assessed through sum of squares goodness of fits. We also explored the impact of the natural course of the epidemic on average partner acquisition rates, under the condition of no intentional behaviour change over time.

Results Without allowing intentional change in partner acquisition rates, an excellent fit was achievable to prevalence trends by gender. However, all of the contrasting trends by age/gender could not be replicated simultaneously. Adding intentional behaviour change improved the fit to some groups, but not all. Adding both intentional behaviour change and migration further improved the fit.

Conclusions While some of the increasing HIV prevalence in Uganda since 2000 may be due to increased risky behaviour, some of the observed epidemiologic trends would likely occur without any intentional change in behaviour. Average population-level behaviour can change due to preferential mortality among higher risk takers, without individuals changing their behaviour.

Keywords HIV, Uganda, epidemiological cycle, migration, mathematical modelling
Introduction

From the first cases of ‘slim disease’ reported in Uganda in 1982\textsuperscript{1} until the end of the 1980s, the human immunodeficiency virus (HIV) epidemic expanded rapidly. In the population cohort established by the Medical Research Council (MRC) in southwest Uganda, HIV prevalence by 1990/91 had reached 7.6 and 9.3\% among males and females respectively, aged \(\geq 13\) years. Around 1990, HIV prevalence started to fall, dropping to 6.2\% among males and 7.7\% among females by 2000.

Since approximately 2000, HIV prevalence has ceased falling, and may be rising.\textsuperscript{2} This phase of the epidemic evokes much concern. Most sources considered that reduced risky sexual behaviour played a role in the declining epidemic during the 1990s, and this was backed by some empirical evidence.\textsuperscript{3,4} However, these conclusions are considered controversial by some.\textsuperscript{5} It is possible that increases in risky sexual behaviour played a large role in the expanding epidemic in the early 2000s, before anti-retroviral therapy (ART) became available. Empirical evidence for increased risky sexual behaviour, however, is weak.\textsuperscript{6}

Weak evidence does not mean that sexual risk taking is not increasing. Social desirability bias\textsuperscript{7,8} may account for the lack of strong empirical evidence about the degree to which sexual risk taking is currently rising. It is also possible that factors other than changing sexual behaviour are influencing the HIV epidemic trends.

Because empirical evidence for increased sexual risk taking since the new millennium is weak, it is unclear what impact interventions aimed at reducing risk taking behaviour may have. How much of the epidemic trends can plausibly be attributed to natural rises and falls of the HIV epidemic? That is, how much may be explained by infections in one decade driving prevalence up, and deaths 10 years later, driving prevalence down? Finally, the upturn in HIV prevalence beginning in the early 2000s could result from youth aging into sexual activity, some of them being high-risk takers, and these new high-risk takers eventually being enough to replace those who died, causing prevalence to rise.

We use a deterministic mathematical model, fitted to empirical data from the MRC cohort and literature, to explore the extent to which local migration, and the natural dynamics of an epidemic, may have influenced HIV epidemiologic trends in this rural Ugandan cohort in the 1990s and 2000s. Model fitting to empirical prevalence data was truncated at 2004, before ART influenced trends. A subsequent paper uses this model, but projects future HIV trends in the presence of ART.

Methods

Annual surveys are conducted among an open cohort in rural Masaka, southwest Uganda. The surveys comprise sexual behaviour reporting, as well as HIV seroesting. Details about the cohort have been reported previously.\textsuperscript{9–11} From 1990 to 1999, the population comprised approximately 6000 adults aged \(\geq 13\) years in 15 villages. Although 10 villages were added to the cohort in 1999/2000, trends for this article were restricted to HIV prevalence among the original villages.

Model fitting

A mathematical model was developed for this study. A description of the model and parameter value ranges for fitting can be found in the full model description, which is part of the online appendix (available at IJE online). The appendix also provides details of the model partial differential equations (online). Using Latin Hypercube Sampling,\textsuperscript{12} 150 000 data sets of parameter values were created from the plausible ranges of migration, sexual behaviour, demographic and biological values (Table S1 [available as supplementary data at IJE online] for parameter value ranges). In order to separately assess the impacts of changing partner turnover rate and migration on improving the model fit with empirical estimates of prevalence, we used these data sets to run 600 000 simulation scenarios:

(i) 150 000 scenarios in which neither migration nor intentional behaviour change over time were allowed (rather than use the parameter values related to changing partner turnover rate and migration, these parameters were not used, and there was no migration and no behaviour change);

(ii) 150 000 scenarios in which migration was allowed, but intentional behaviour change over time was not;

(iii) 150 000 scenarios in which migration was not allowed, but intentional behaviour change was; and

(iv) 150 000 scenarios in which both migration and intentional behaviour change were allowed.

With this strategy, we assessed the best possible fit to empirical HIV prevalence estimates in the absence of intentional sexual behaviour change, and compared this with the best fit in the presence of intentional behaviour change. We assessed this, assuming that local migration may have influenced HIV epidemiologic trends in the cohort, and compared that with the best fit possible under the extreme case of no migration.

HIV prevalence trends to which the model was fit have been reported previously.\textsuperscript{2,3,13,14} Fitting was conducted by comparing model results with annual empirical estimates of HIV prevalence from 1991 to 2004. The effect of ART is likely to influence prevalence trends from 2005 onwards. Although ART compartments exist in the model (A supplementary Appendix, available as supplementary data at IJE online), these compartments were not used in this article.

We first fit the model to prevalence trends by gender, as this is the level of detail that has frequently been
reported from this cohort,\textsuperscript{2,15} as well as the detail to which models are often fitted.\textsuperscript{16–18} We next fit to more complex patterns of prevalence over time, by age and gender. The age groups were: 15–19, 20–24, 25–34, 35–44, 45–54 years. The goodness of fit (GoF) was determined by summing the squared difference between the model predicted and the empirically estimated prevalence for each of the age/gender groups. We report results of best fits (lowest GoF) under four situations: allowing migration and intentional sexual behaviour change, no migration but some sexual behaviour change, migration but no sexual behaviour change, and neither migration nor sexual behaviour change. The amount of migration and behaviour change varied in each simulation and ranges are given in Table S1 in supplementary data available at \textit{IJE} online.

There were multiple sets of values with similar fits to empirical estimates of HIV prevalence. Which set of parameter values is ‘right’? Our objective was to find the best fits with empirical data, under plausible values of input parameters. It is unlikely that all 36 parameter values were right in the scenario with the best fit. However, by examining the best possible fit without allowing intentional behaviour change and comparing that with the best fit allowing intentional behaviour change, under plausible parameter values, we can assess the maximum role of the natural course of the epidemic and migration in explaining past HIV prevalence trends.

**Results**

**Fits by gender**

Fitting the model to empirical HIV prevalence trends by gender, we obtained a good fit, without allowing intentional change in partner turnover rates across time. This was true regardless of whether migration was allowed (Figure 1). Parameter values that led to these and other results presented in this article are in Tables S2–S5 in supplementary data available at \textit{IJE} online. Without migration, some sets of parameter values produced a rise and fall in prevalence as observed empirically, followed by a levelling off of prevalence. The best fitting set of parameter values had a GoF statistic of 4.12. This represents the sum of 28 squared differences between model estimates and empirically estimated prevalence by gender, two for each of 14 years (1991–2004). When migration was allowed, a second rise in prevalence was achievable. The best GoF was 3.44, an improvement over scenarios without migration. Without migration, the best fit showed prevalence peaks among women and men in 1988 and 1989, respectively (Figure 1). With migration, the best fit showed prevalence peaks among women and men in 1986 and 1988 (Figure 1). Table S2 in supplementary data available at \textit{IJE} online shows the amount of migration.

**Fits by age/gender**

HIV prevalence by age and gender in our cohort were complex. Over the same period, HIV prevalence among some age/gender groups declined, whereas prevalence among other groups rose (Figure S1 in supplementary data available at \textit{IJE} online).

Among scenarios with neither migration nor intentional behaviour change, the lowest GoF when fitting to age and gender was 1216. This represents the sum of 140 squared differences between model estimates and empirically estimated prevalence by age and gender, 10 for each of 14 years. Figure S2 in supplementary data available at \textit{IJE} online shows the result of this (fit 1), as well as two other fits. The GoF corresponding to fit 2 was 1528, whereas that corresponding to fit 3 was 1536. The

![Figure 1](image_url)
GoF for the worst fitting set of parameter values was 586.571.

Allowing migration, the lowest GoF was 967, an improvement over the best fit without migration. Under scenarios that allowed migration but no intentional behaviour change, the three that best fit empirical prevalence patterns by age and gender are presented in Figure 2. Parameter values are shown in Table S4 in supplementary data available at IJE online.

The results show rises and dips in prevalence over time, as observed empirically. The relative magnitude of prevalence among the age groups matches that observed empirically. We could reproduce some patterns of prevalence trends among the different groups. This is particularly seen with the pattern among 45- to 54-year-old women, alongside the high stable prevalence among 25- to 34-year-old women. Despite this, no set of parameter values produced an epidemic in which women aged 20–24 years and men aged 25–34 years experienced a rapid fall in prevalence, alongside an increase in prevalence among women aged 35–44 years.

In scenarios with intentional changes in partner turnover rates, we reproduced the rapid decline in prevalence among women aged 20–24 years and men aged 25–34 years, alongside an increase and decline in prevalence in both sexes aged 45–54 years.

Figure 2 Model fits—no intentional behaviour change, some migration (markers – empirical data, lines – model)
However, we no longer simultaneously reproduced the high, flat prevalence among 25- to 34-year-old women. Also, we were unable to simultaneously reproduce the rise in prevalence among 35- to 44-year-old women alongside the declining prevalence among younger women, even when allowing intentional behaviour change to differ by age (Table S5 in supplementary data available at IJE online has parameter values). The GoF for the best fit allowing intentional behaviour change but not migration was 1260. Comparing the top panel of Figure 3 with Figure S2 in the supplementary data available at IJE online, it appears that allowing intentional behaviour change produced an HIV epidemic that more closely matched empirical estimates among some age/gender groups, but not among others. The best-fitting GoF when allowing both intentional behaviour change and migration (Figure 3, bottom panel) was 903.

**Impact of migration**

Local migration patterns may help explain HIV prevalence trends within the cohort (Figures S3 and S5 in supplementary data available at IJE online). Among young HIV-negative men (aged 13–24 years), there are more out-migrants than in-migrants. However, among men aged 25–54 years, there are more in-migrants in most years. Young women migrate more, in and out, than older women, partly due to moving to their husbands’ households on marriage.

We assessed the impact of migration on the trends of prevalence displayed in the three scenarios of Figure 2. When we set migration to zero but left all other parameter values the same, the impact on trends displayed in the top panel was minor for women but prevalence among men was much lower in the absence of migration. In this scenario, when migration was not set to zero, net in- or out-migration was <2% per year for nearly all age and time periods for women, whereas it was as high as 5% per year among some groups for men (Table S4 in supplementary data available at IJE online). In the scenario displayed in the middle panel, migration reached 5–6% in some groups for both men and women (Table S4 in supplementary data available at IJE online). The impact of setting migration to zero in this scenario was more marked (Figure S4 in supplementary data available at IJE online).

**Natural epidemic dynamics**

Individuals with higher partner turnover rates become infected with HIV and die faster than those in lower risk groups. If others do not change behaviour to fill
During the void, the population proportion in higher risk categories therefore diminishes over time. Until HIV was introduced into the population, the proportion of people in the highest risk group in the scenario corresponding to Figure 2, top panel, was 4.4% (Figure S5 in supplementary data available at *IJE* online). This exceeds the 0.9% who entered that group on becoming sexually active because, in this scenario, people move from the high-activity group to the middle group at a rate of 5.6%/year and from the middle group to the high group at 0.9%/year. As the middle activity group is larger, more move from the middle group to high group than the reverse. After infection is introduced in 1979, people in the high-activity group become infected with HIV faster than others. This results in higher mortality and the proportion of the population in this group naturally declines, through no intentional behaviour change. By 2020, the proportion of the population in the highest activity group in this example had dropped from 4.4 to 2.3%.

The natural decline in the proportion of the population in the highest sexual activity group is steeper among older than among younger people (Figure 4). Even among the highest risk takers, some people escape HIV infection. As they age, however, more of them do eventually become infected. The mortality rate among the highest risk takers thus increases disproportionately with age, due to HIV-related mortality.

The natural course of the HIV epidemic also impacts realized partner turnover rates within activity groups. The number of all partnerships obtained by men of a particular age and activity group must equal the number of all partnerships provided by women to that age and activity group. If men of a particular age and activity group desire more partners than women desire to give to that age and activity group, then there must be compromise, until the partnerships balance.

In the scenario corresponding to Figure 2, top panel, before HIV infection is introduced in the population, men get almost their desired number of partners. In this scenario, the desired partner turnover rate among the highest activity group for men was 76 per year (Table S4 in supplementary data available at *IJE* online). When compromise occurred, in this particular scenario the compromise parameter leaned toward men receiving their desire and women having to compromise (Table S4 in supplementary data available at *IJE* online). In this scenario, women receive more partnerships per person than men because there are fewer women in the population at this point (Figure S6 in supplementary data available at *IJE* online); it is due primarily to a lower pre-1990 net in-migration among women than among men. When infection is introduced, the realized partner turnover rate among men declines, whereas that among women increases. This natural result of the epidemic occurs because, in this scenario, women generally became infected earlier in the epidemic than men, so they began to die earlier, resulting in a scarcity of women. Each woman needed more partnerships to satisfy the desire of the men. Around 2010, as the mortality rate among men approaches that among women, the realized partner turnover rate among women begins to decline, whereas that among men rises. We have no empirical estimates of prevalence during the early epidemic in this cohort. Men may have become infected earlier in the epidemic than women, as is believed the case in most sub-Saharan African countries. If so, the pattern of increasing partnerships among women and decreasing partnerships among men shown in Figure S6 (in supplementary data available at *IJE* online), as an illustrative example, would reverse. It is also possible that by the time the epidemic reached rural Masaka, women were already becoming infected faster than men.

**Discussion**

We first fit the model to prevalence by gender. Excellent fits with empirical data were obtained, despite no intentional sexual behaviour change over time. It could be argued that prevalence peaked too early in the fit obtained with migration (1986 for women and 1988 for men). However, these years are within a plausible range and fit well with data from our cohort.

Although Kamali and colleagues note the contrasting age-specific HIV prevalence trends using estimates through 1997, these contrasting trends have never been described in detail nor has any attempt been made to reproduce them through mathematical modelling. We were unable to reproduce all of the different trends by gender and age over time, but we could reproduce some of them more closely when we allowed intentional behaviour change (compare Figure 2 with Figure 3).
This indicates that some changes in sexual behaviour must be responsible for at least part of the epidemiologic trends. However, even without allowing for sexual behaviour to change over time, we were able to replicate some of the empirically estimated changes in HIV prevalence. This indicates that, in addition to changing sexual behaviour, the natural epidemiologic course of HIV infection can explain some of the epidemiologic trends in rural Uganda. We have shown that through the natural course of the epidemic, with higher risk takers dying at a faster rate than others, the average sexual behaviour in the population may change over time even without any purposeful change in individual behaviour.

The sum of squares GoF was used to compare fits among different sets of parameter values. As expected, among scenarios without intentional behaviour change, allowing some migration resulted in a scenario with a better fit than allowing no migration (GoF 967 vs 1216). Unexpectedly, however, the GoF did not improve among scenarios without migration, once intentional behaviour was allowed. The best scenarios occurred when both intentional behaviour change and migration were allowed (GoF 903).

Comparing panels in Figure 3, migration appears to have little impact on prevalence. The scenario without migration looks similar to that with migration. However, the best fit for these two panels differed in other parameter values, such as sexual partnership mixing, proportion engaging in cross-generational sex, and partner turnover rates (Table S5 in supplementary data available at IJE online). When holding other parameter values constant, we saw that migration likely influences HIV prevalence trends (Figure S4 in supplementary data available at IJE online).

While the partner turnover rates among the highest risk group displayed in Tables S2–S5 (available as supplementary data at IJE online) appears huge at 48–80 partners/year among men and 38–75 among women, this group for the scenario depicted in the top panel of Figure 2 represents just 2.3% of the population. These could represent the very highly active men and perhaps sex workers. Even 2.3% may be higher than the real percentage of the population who have so many partnerships. In some well-fitting scenarios, however, this percentage was even lower. The scenario displayed in the bottom panel of Figure 2 results from just 0.51% of the females in the highest risk group before infection is introduced, and 0.38% of the males in this group. After infection is introduced, this drops to 0.18% of females and 0.16% of males. In short, while the core group of people with a very high partner change rate is required in order to sustain the epidemic, the percent of the population in this group can be extremely low, even <1%.

Limitations
This model has numerous compartments to account for varying sexual behaviour. It allows a proportion of women to form partnerships with men ≤30 years older than themselves (cross-generational), and for that proportion to diminish as women age. It allows desired partner turn-over rates to diminish as people age. It allows young and old people to differ in their change in partner turnover rates over time. However, there are only two age groups for differences in changing partner turnover rates, <25 years and ≥25 years. Also, although we tested 150,000 parameter sets, this may still have not adequately covered all ranges of parameters values. We may not have ‘tested’ a parameter set that would have provided a better fit to the contrasting prevalence trends by age/gender among the simulations that included intentional behaviour change.

Specific results in this article pertain to the cohort in rural Uganda under study. Some general results, however, such as the impact that the HIV epidemic can have on average sexual behaviour at the population level, may apply to other HIV epidemics.

Conclusion
Without intentional behaviour change, we could not fit to prevalence trends in all groups simultaneously. Allowing intentional behaviour change, without migration, improved the fit among some groups but not others. Combining the natural course of the epidemic with intentional behaviour change and some migration, we were able to replicate fairly well the HIV epidemic trends observed in the Masaka cohort. This indicates the multiple forces impacting HIV prevalence trends. The multiple forces driving the epidemic indicate that interventions aimed at reducing risky sexual behaviour are likely to help ameliorate the epidemic, but in themselves are unlikely to reverse it.

Funding
Funding for this work was provided by grants from the Wellcome Trust, U.K., and from the Medical Research Council, U.K.

Supplementary Data
Supplementary data are available at IJE online.

Conflict of interest: None declared.
KEY MESSAGES

- HIV prevalence trends in this rural Ugandan cohort are likely the result of three different factors: intentional behaviour change, migration, and the natural rise and fall of an HIV epidemic.
- While some of the increasing HIV prevalence in Uganda since 2000 may be due to increased risky behaviour, some of the observed epidemiologic trends would likely occur without any intentional change in behaviour.
- Average population-level behaviour can change due to preferential mortality among higher risk takers, without individuals changing their behaviour.
- Even limited local migration, <5% of the population in most years and most age/sex groups, noticeably impacts HIV prevalence trends within this cohort.

References