Heterogeneity in host HIV susceptibility as a potential contributor to recent HIV prevalence declines in Africa

Nico J.D. Nagelkerke, Sake J. de Vlas, Prabhat Jha, Ma Luo, Francis A. Plummer, and Rupert Kaul

1 Department of Community Medicine, United Arab Emirates University, Al Ain, United Arab Emirates
2 Department of Medical Microbiology, University of Manitoba, Winnipeg, Canada
3 Department of Public Health, Erasmus MC, University Medical Center, Rotterdam, the Netherlands
4 Center for Global Health Research, University of Toronto
5 National Microbiology Laboratory, Winnipeg, Canada
6 Department of Medicine, University Health Network and the University of Toronto, Toronto, Canada
7 Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya

Abstract

Background—HIV prevalence has recently declined in several African countries, and prior to this the risk of HIV acquisition per unprotected sex contact also declined in Kenyan sex workers. We hypothesized that heterogeneity in HIV host susceptibility might underpin both of these observations.

Methods—A compartmental mathematical model was used to explore the potential impact of heterogeneity in susceptibility to HIV infection on epidemic behavior, in the absence of other causative mechanisms.

Results—Studies indicated that a substantial heterogeneity in susceptibility to HIV infection, may lead to an epidemic that peaks and then declines due to a depletion of the most susceptible individuals, even without changes in sexual behavior. This effect was most notable in high-risk groups such as female sex workers, and was consistent with empirical data.

Discussion—Declines in HIV prevalence may have other causes in addition to behavior change, including heterogeneity in host HIV susceptibility. There is a need to further study this heterogeneity and its correlates, particularly as it confounds the ability to attribute HIV epidemic shifts to specific interventions, including behavior change.

Keywords

Modeling; epidemiology; heterogeneity in host susceptibility; HIV transmission
BACKGROUND

HIV prevalence has recently fallen in some severely affected countries, including Uganda and Kenya[1,2], but the cause(s) of these declines is unclear. In Uganda, a causal relationship has been inferred between prevalence declines and timely government-initiated programs with documented impacts on risk behavior[2-6]. However, such programs were less prominent in Kenya, leading some to attribute the decline in both countries to an increased, non-exponential AIDS mortality associated with “maturing” epidemics[6-8].

Recent data from a cohort of female sex workers in Nairobi, Kenya suggest that neither explanation is fully satisfactory[9]. Here, the risk of HIV acquisition risk per act of unprotected sex declined by more than four-fold, over a decade before prevalence declines were apparent in the general population, an observation that cannot be explained by behavior change or non-exponential mortality. We hypothesized that this decline might relate to heterogeneity in HIV host susceptibility, which would give rise to a high HIV incidence among the most susceptible individuals during early stages of an epidemic followed by a decrease in the susceptibility (and rate of HIV infection) in the remaining uninfected population. Such heterogeneity in HIV susceptibility has been demonstrated in several contexts, including the profound reduction in susceptibility associated with the CCR5Δ32 genetic polymorphism[10], as well as increased susceptibility associated with low copy numbers of the CCL3L1 gene duplication[11] and with persistent (life-long) infections such as herpes simplex type 2[12].

We explored this hypothesis using a simple compartmental mathematical model, and we also examined whether early depletion of susceptible individuals alone, in the absence of other proven causal factors, could partly account for the recent general population prevalence declines in Kenya and Uganda.

METHODS

COMPARTMENTAL MODEL

We modified an existing compartmental model[13,14] to explore the effect of heterogeneity in host susceptibility on the dynamic behavior of an HIV epidemic. Only heterosexual transmission was modeled. The model divided the population into groups of low-risk persons and high-risk persons (male clients and female sex workers) with movement between high and low risk categories; these groups were further subdivided into compartments by stage of infection: HIV negative; early stage HIV; and late stage HIV (Figure 1, Supplementary Table 1). To this model we added heterogeneity in biological susceptibility, by arbitrarily distinguishing four levels of susceptibility comprising 10%, 30%, 30%, and 30% of the population respectively, with the lowest (10% of the population) assumed to be completely resistant. Risk levels were life-long, with no transition between susceptibility levels. Disease progression after infection was modeled as a short (mean 6 months) initial phase, followed by a second phase of on average 8 years. This second phase was modeled as exponential, and infectiousness in the early phase of HIV infection was set equal to the level of infectiousness during the second phase. Although both these choices were in all likelihood counterfactual, they were intentionally made in order to explore whether heterogeneity in susceptibility alone, in the absence of other causative mechanisms, could cause epidemic overshoot (the situation where HIV incidence and prevalence during the early phase of the HIV epidemic exceed subsequent levels). In reality other factors, including differential infectiousness, epidemic phase, sexually transmitted infection rates, behavior and others, will have also played an important role in shaping the epidemic, and hence our empirical datasets. Fractions of high-risk groups (FSWs and their clients) were set at equilibrium levels in the absence of HIV. Two response variables were selected: (1) the per client contact risk of HIV infection in female sex workers, and (2) the sex-specific adult HIV prevalence. The fraction of each susceptibility
level, as well as the susceptibility levels themselves, were estimated by minimizing the sum of squared differences between the empirical risk of infection in the Nairobi sex worker cohort and the model predicted risk in this cohort [Supplementary Table 1]. ModelMaker® (version 3.0.3) was used to implement and run the model, with HIV introduced into the population in 1980. For the sex worker model, epidemic curves obtained with the modified compartmental model were compared to per-contact HIV incidence data that had been gathered empirically within a high risk cohort of Kenyan female sex workers, as previously described[9]. For the adult HIV prevalence model, the epidemic curves obtained were compared with longitudinal HIV prevalence previously reported from urban antenatal sentinel surveillance sites in Kenya [15,16].

**Determination of HIV incidence in a high-risk cohort**

Empiric data regarding per-contact HIV incidence in a high risk cohort were obtained as previously described[9]. Briefly, female sex workers (FSWs) were enrolled through a dedicated clinic in Nairobi, Kenya from 1985-2005. All participants returned for a formal re-survey every 6 months. At enrolment and re-survey a standardized questionnaire was completed, and blood was drawn for HIV serology. Self-reported risk taking data included the number of casual clients per day, condom use with casual clients, the number of regular clients (“boyfriends”), condom use with regular clients, and sexual practices (anal sex, sex during menses). HIV-1 serology was performed at each visit using a synthetic peptide enzyme immunoassay [EIA; Detect HIV, Biochem ImmunoSystems Inc., Montreal, Canada], and positive tests were confirmed by recombinant antigen EIA [Recombigen HIV-1/2 EIA, Cambridge Biotech Corporation, Galway, Ireland]. Trends in the risk of HIV acquisition per unprotected sex act were analysed prospectively within initially HIV uninfected participants. The number of unprotected sex contacts per day was calculated as the product of the reported number of casual sex partners per day and the fraction sex acts unprotected by condoms[9].

**RESULTS**

The model that best fitted the observed empirical infection risk per 1000 client contacts within the Nairobi female sex worker cohort[9] estimated the susceptibilities in the second lowest susceptibility fractions at (near) 0. Thus a total fraction of 40% of the population was at a very low risk of HIV infection. In reality, it is likely that a much smaller fraction of the population is relatively resistant to HIV infection, but this may relate to our use of four discrete susceptibility levels in the model, as opposed to a continuous distribution. The two highest susceptibility levels were estimated at 0.0257 and 0.0347 (male-to-female) and half that value for female-to-male per-sexual-contact risk. Using these parameters, there was an approximately 4-fold decline in the modeled risk of per-contact HIV acquisition that followed peak infection rates. This closely mirrored empirical data collected in the Nairobi sex worker cohort (Figure 2a).

In the general population, an initial prevalence overshoot was followed by a decline in both men and women (Figure 2b). Again, this mirrored, although somewhat less so, empirical observations, in this case longitudinal antenatal adult HIV prevalence surveys from Kenya [15, 16]. It is possible that prevalence among (young) antenatal women more accurately reflects (changes in) incidence rather than (changes in) prevalence in the general population[17]. Infectiousness in the early epidemic phase of HIV infection was defined in the model as equal to the level of infectiousness during the second phase. Defining infectiousness during early HIV infection as substantially higher than during the second phase, which may be more realistic, yielded an overshoot pattern that was broadly similar, but that was more peaked and overly compressed in time. Defining late stage HIV as shorter and more infectious than early
stage infection widened the overshoot peak somewhat, and more closely approximated empirical observations.

DISCUSSION

Heterogeneity in susceptibility and/or transmissibility was recognized during the early phases of the HIV epidemic, when it was found that transmission in heterosexual partnerships was not solely dependent on the number of sex acts[18-20]. Strikingly, the risk of male-to-female HIV transmission in a discordant heterosexual partnership was as high as 10% for <10 unprotected contacts, but increased to only 23% after at least 2000 unprotected contacts[18]. While these studies could not differentiate between heterogeneity in infectiousness and in host susceptibility, it is plausible that the effect was at least partly due to the latter, given that several genetic, immune and infectious correlates of altered susceptibility have since been identified [10-12,21-23]. Further evidence for heterogeneity in host susceptibility is provided by the observation that some individuals appear to be relatively resistant[24]. However, it is difficult to measure this heterogeneity precisely: since individuals can only acquire HIV once, estimation of individual risks becomes extremely difficult. In theory, heterogeneity in host susceptibility could be estimated from the distribution of time to infection in cohorts of equally exposed HIV uninfected individuals, but such cohorts are not available. High-risk sex worker cohorts provide limited insights, albeit valuable ones[24], since most of these women had already been heavily exposed to HIV prior to enrollment in the cohort, presumably with infection of the most susceptible women. These difficulties in accurately measuring heterogeneity in host susceptibility may explain why the phenomenon has largely been overlooked.

We hypothesize that the decline in per-act acquisition of HIV observed over time in high-risk Kenyan sex workers[9], independent of behavior change, may have been partly related to heterogeneity in susceptibility within the cohort. This decline occurred during a period when HIV prevalence in high-risk men was stable, making it unlikely that it was related to changing HIV prevalence in male clients, and was prior to significant roll out of antiretroviral therapy in the region[9]. Altered patterns of sex worker client contact, particularly the establishment of “regular clients”, may impact STI and HIV prevalence[25], but this effect will be blunted by the fact that regular clients of sex workers in the cohort report high numbers of concurrent partners (Kaul R, unpublished data). Additional factors are likely to have contributed to this decline, including a reduction in the prevalence of bacterial (transient) sexually transmitted infections, phase of the HIV epidemic, and other factors not included our model. Indeed, such factors may partly explain why the reductions in population prevalence in our model were more gradual than the empirical data gathered from Kenya antenatal clinics (as demonstrated in Figure 2b).

Nonetheless, heterogeneity in susceptibility may have a significant impact on our ability to model future epidemic spread, as well as to interpret surveillance data. As an example, a high number of transmission events are attributed to individuals with very early HIV infection, so that this phase of infection may contribute disproportionately to HIV transmission[26-28]. This phenomenon may relate to high HIV levels in genital secretions during this stage of infection [29], but heterogeneity in the susceptibility of their uninfected partners may be another contributor, since many of these uninfected partners will be exposed to HIV for the first time by their acutely-infected partner. Available data cannot distinguish these two mechanisms. A study comparing the risk of seroconversion of steady partners of new seroconverters with that of new partners of people with established HIV infection should be able to clarify this.

Heterogeneity in host HIV susceptibility might also have more practical implications for prevention trials. HIV incidence within high-risk participants has been lower than expected in...
the context of trials testing STI prophylaxis/therapy[30], microbicides[31] and pre-exposure prophylaxis[32], often despite prior studies to determine “predicted” incidence, and this has been a significant setback in some cases. While it has been assumed that the reduced HIV incidence was a direct result of behavior modification and trial-associated prevention activities [30], it is also possible that early HIV acquisition by more susceptible hosts may have been followed by incidence declines within the remaining, less susceptible participants.

While there is good evidence that heterogeneity in susceptibility exists, we have little information on how it is distributed in the population. In our model we chose 4 discrete levels of susceptibility, although in reality a continuous distribution seems more realistic. In fact, 4 was the highest number of levels that we could fit in view of the dearth of data, although 3 levels yielded similar patterns (data not shown). This simple model demonstrates, at least qualitatively, that heterogeneity in HIV susceptibility may lead to epidemic overshoot. This overshoot is most pronounced in highly exposed populations, such as female sex workers.

In summary, we propose that the phenomenon of heterogeneity in HIV susceptibility may have contributed to the observed declines in HIV incidence and prevalence, both in highly-exposed “core transmitter” cohorts such as female sex workers, and in endemic countries. Heterogeneity in susceptibility is by no means the only contributor to these declines, and there is compelling evidence that at least part of the population HIV prevalence declines in many parts of Africa was caused by changes in risk behavior[2,3,33-36]. However, our model demonstrates that some of this decline may have occurred without behavioral change, confounding our ability to attribute HIV epidemic shifts to specific interventions.

Supplementary Material
Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Funding: Canadian Institutes of Health Research (R.K.; HOP-81735, HET-85518); the Bill and Melinda Gates Foundation (F.A.P.; BMG-77515) and CIHR Grand Challenges in Global Health (F.A.P.; #37873); National Institutes of Health (F.A.P.; R01 AI056980); Canada Research Chair Programme (salary support for RK, FAP).

REFERENCES

7. James JS. Uganda study found that death reduced HIV prevalence; did the public take home the wrong message? AIDS Treat News 2005:5–6.


Figure 1. Structure of the compartmental model
Boxes represent compartments defined by an individual's sex, risk behavior and HIV status. The model distinguishes low and high risk men and women defined by their involvement in trading sex for money. Individuals in each group can be either uninfected, be in early stage HIV, or late stage HIV. Transitions between low and high risk groups are permitted. The population is stratified by HIV susceptibility level. For each level of susceptibility different HIV transmission risks apply. An individual's level of susceptibility is treated as fixed.
Figure 2. Modeling the impact of heterogeneity in host HIV susceptibility on epidemic spread
(a) Modeled and empiric trends in the risk of HIV acquisition per 1000 acts of unprotected
vaginal sex within the Pumwani female sex worker cohort, Nairobi, Kenya. The figure displays
both empirically observed values (circles) and the results of the model (curve).
(b) Modeled trend in adult HIV prevalence in male clients of female sex workers, and general
population men and women, in the presence of heterogeneity in host HIV susceptibility
(curves), as well as empiric HIV prevalence data from surveillance of antenatal women in
Kenya (circles).