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The Role of Acute and Early HIV Infection in the Spread of HIV-1 in Lilongwe, Malawi: Implications for "Test and Treat" and Other Transmission Prevention Strategies

Kimberly A. Powers, **Azra C. Ghani**, **William C. Miller**, **Irving F. Hoffman**, **Audrey E. Pettifor**, **Gift Kamanga**, **Francis E.A. Martinson**, and **Myron S. Cohen**
Department of Medicine (KA Powers PhD; WC Miller MD, PhD, MPH; IF Hoffman, PA, MPH; MS Cohen, MD), Department of Epidemiology (KA Powers; WC Miller; AE Pettifor, PhD; MS Cohen), and Department of Microbiology and Immunology (MS Cohen), University of North Carolina, Chapel Hill, NC, USA; Department of Infectious Disease Epidemiology (AC Ghani, PhD), Imperial College, London, UK; and UNC Project Malawi, Lilongwe, Malawi (G Kamanga, CO; FEA Martinson, MD, PhD)

Abstract

Background—HIV transmission risk during acute and early HIV infection (EHI) is sharply elevated, but the contribution of EHI to ongoing HIV transmission is controversial. However, in settings where EHI contributes substantially to secondary transmissions, early diagnosis and intervention may be critical for HIV prevention. We estimated the contribution of EHI to HIV incidence in Lilongwe, Malawi and predicted the future impact of hypothetical prevention interventions affecting EHI only, chronic HIV infection (CHI) only, or both stages.

Methods—We developed a deterministic mathematical model describing heterosexual HIV transmission, informed by detailed behavioural and viral load data collected in Lilongwe. We included sexual contact within and outside steady pairs and divided the infectious period into multiple intervals to allow for changes in transmissibility by infection stage. We used a Bayesian melding approach to fit the model to HIV prevalence data collected over time at Lilongwe antenatal clinics. We evaluated interventions that reduced the per-contact transmission probability to 0·00003 in those receiving them and varied the proportion of individuals receiving the intervention in each stage.

Findings—We estimated that 38·4% (95% credible interval: 18·6%-52·3%) of ongoing HIV transmissions in Lilongwe are attributable to sexual contact with EHI index cases. Interventions acting only during EHI substantially reduced HIV prevalence, but did not lead to elimination, even with 100% coverage. Interventions acting only during CHI also reduced HIV prevalence, but coverage levels of 95%-99% were required to move the epidemic toward elimination. In scenarios

Correspondence to: Kimberly A. Powers, PhD, Center for Infectious Diseases, CB 7030, Bioinformatics 2nd Floor, Chapel Hill, NC 27599-7030, USA, powersk@email.unc.edu.

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with <95% CHI coverage, additional interventions reaching 25%-75% of EHI cases reduced HIV prevalence substantially.

Interpretation—Our results suggest that EHI plays an important role in HIV transmission in this sub-Saharan African setting. Without near-perfect coverage, interventions during CHI will likely have incomplete effectiveness unless complemented by strategies targeting the heightened transmission risk of EHI.

Introduction

Acute HIV infection (AHI) is the period between HIV acquisition and the development of detectable antibodies against the virus. Early HIV infection (EHI), including AHI, is characterized by rapid viral replication, intense immune response and immune destruction, and viral diversification.[1] Phenotypic factors unique to the founder virus(es) causing infection,[2] along with exceptionally high viral loads,[3, 4] result in greater transmission risk during EHI.[5-8]

The population-level effect of transmission prevention efforts during EHI will vary across settings, depending on the contribution of EHI cases to epidemic spread. Estimates of this contribution have varied widely,[6, 9-18] depending on site-specific factors such as risk behaviour patterns and the local epidemic stage. Recently, a strategy to use mass antiretroviral treatment to stop the spread of HIV-1 has gained considerable attention.[19] The "test and treat" strategy advocates regular, widespread HIV testing and immediate initiation of antiretroviral therapy (ART) for infected persons, based on the premise that ART-induced reductions in viral load will decrease infectiousness. However, the effectiveness of this approach will depend, in part, on the role of EHI in ongoing transmission. Where EHI has a major role, the effectiveness of test-and-treat strategies will likely be limited unless patients with EHI can be detected and included. A recent mathematical modelling exercise[19] that has sparked extensive controversy[20-29] concluded that an annual test-and-treat strategy could eliminate HIV, but EHI was not rigorously addressed in this model.[22, 24, 25]

In this study, we estimate the contribution of EHI to HIV spread in Lilongwe, Malawi, where HIV-1 is hyperendemic and transmission is almost entirely through heterosexual contact. We also examine the population-level impact of prevention interventions affecting only EHI, only chronic (post-"early") HIV infection (CHI), or both EHI and CHI, with a particular emphasis on estimating the impact of an annual test-and-treat strategy.[19] To address these aims, we used empirical data from our studies in Lilongwe[3, 30] to develop a mathematical model describing heterosexual HIV transmission. The results suggest that EHI plays an important role in the ongoing spread of HIV in Malawi, and that involvement of people with EHI will be required for maximal HIV prevention.

Methods

Modelling analyses proceeded in five steps (Figure 1): defining the model structure and equations (Step 1); conducting a Bayesian melding procedure to identify model parameter values most compatible with observed epidemic dynamics, given prior estimates for biological and behavioural parameters (Steps 2-4); and estimating the contribution of EHI and predicted intervention effects (Step 5). We describe our methods briefly below, with additional details in the Web Appendix.

Model structure

We constructed a compartmental, deterministic model explicitly describing heterosexual partnership formation and dissolution (Figure 2). Following previous modifications[15] on the

classic pair-formation model,[31] sexual contact was assumed to occur: 1) at a constant frequency within steady partnerships, 2) as casual, one-off contacts by paired individuals outside of steady partnerships, and 3) as casual, one-off contacts by unpaired individuals (singles). This structure captures phenomena that are important in the context of time-varying HIV infectivity: HIV is "trapped" within a pair while each infected member is monogamous, but HIV can "escape" upon partnership dissolution or sexual contact outside the pair. Additionally, pairs of uninfected individuals are "sheltered" from HIV while each partner is monogamous, but HIV can "enter" through outside contacts. Long-term concurrency is not captured, but the model allows consecutive partnerships and sporadic concurrency. Our data from Lilongwe suggest that long-term monogamy predominates in this population, with a minority engaging in narrowly spaced consecutive partnerships, sporadic concurrency, or long-term concurrency.[30] Individuals entered the model as singles, and exited after an average sexual lifespan of 35 years, with additional AIDS-related mortality in the final infection stage.

To capture variation in transmission probabilities over time, we divided HIV into EHI, asymptomatic HIV, early AIDS, and late AIDS. We defined EHI as the initial one- to six-month period of elevated infectivity, based on the best available estimates of transmission rates by infection stage,[6] calculated among HIV-serodiscordant couples in Rakai, Uganda.[5] We divided this period into five intervals to allow changes in transmission probabilities related to evolving viral loads. Intervals 1-4 were each one week in duration to capture the initial viral load changes.[3] We sampled interval 5 from a uniform distribution of 1·4 weeks to 5 months, corresponding to the total assumed EHI duration of ~1 to ~6 months.[6] We represented the asymptomatic period as three equal intervals (intervals 6-8) of 1·8 to 3·2 years each to approximate observed survival time distributions in untreated cases.[32] We based the durations of "early AIDS" (interval 9) and "late AIDS" (interval 10) on the Rakai analyses, specifying normal distributions with mean 0·75 year and 0·83 year, respectively.[6]

As an additional extension, we stratified the model population into two groups to accommodate sexual behaviour heterogeneity. The prior distributions that we specified corresponded to the "lower-risk group" having longer partnerships and lower rates of sexual contact by singles than the "higher-risk group." Individuals remained in one risk group and steady pairs were formed within groups. However, one-off contacts with casual partners were chosen without risk-group restrictions. The model allowed for increased HIV transmission probabilities for contacts with higher-risk partners, representing an assumed greater likelihood of transmission-amplifying cofactors, such as ulcerative sexually transmitted infections (STIs) or anal intercourse. Sexual behaviour parameters were held constant across infection status/stage categories. The model is readily adaptable to other settings with predominately heterosexual or homosexual transmission; adaptation to settings where parenteral transmission plays a large role is more complex.

Statistical analyses

We used a Bayesian melding approach[32, 33] to fit the model to empirical HIV prevalence data and to account for uncertainty in model inputs and outputs (Figure 1). This approach combines prior information about inputs (e.g., sexual behaviour, transmission probabilities) with data about a primary output (HIV prevalence). Sources of prior information on inputs are described below. For data on model output, we used HIV prevalence estimates from Lilongwe antenatal clinics (ANC) over the period 1987-2005.[34] We implemented a sample-importance-resample algorithm to identify the input parameter values producing epidemic curves most closely matching ANC data. Briefly, we ran 100,000 model simulations, sampling randomly from the prior distributions of all input parameters in each simulation. Next, we weighted each simulation according to its likelihood-based compatibility with ANC data, and then we resampled (with replacement) from the simulations, with probability

of selection proportional to the assigned weight. Under this approach, the simulation resampled most frequently (the *mode*) is the best-fitting simulation (i.e., the most compatible with empirical HIV prevalence data). The 2·5th and 97·5th percentiles were used to obtain 95% credible intervals (CrI) for model parameters and output.

We used the Runge-Kutta 4 algorithm in Berkeley Madonna 8·0·1 (Berkeley, California, USA) to solve the model numerically. We performed statistical and graphical analyses with SAS 9·1 (SAS Institute, Cary, North Carolina, USA), Stata 9 (StataCorp, College Station, Texas, USA), and R.

Parameter values

We based the initial size of the adult (ages 15-49) population on census data[35] (Table 1), and sampled uniformly in the range 1960-1985 for the year of the first HIV case in Lilongwe, reflecting the uncertainty around this time.

We based the per-contact transmission probability for asymptomatic HIV, along with transmission co-factor effects, on meta-analysis estimates.[7, 8] We allowed the transmission co-factor effect to range from 1 (no transmission amplification) to 6 (per-contact transmission probability 6 times as high in the higher-risk group than in the lower-risk group). The upper bound was based on estimates for the co-factor effect of concomitant STIs,[7, 8] but could also broadly represent other co-factors, such as the possibility of some contacts being anal rather than vaginal. To calculate per-contact transmission probabilities for EHI and *early* AIDS, we multiplied the asymptomatic-period estimate by the transmission rate ratios comparing EHI and early AIDS to asymptomatic infection in Rakai (Table 1).[6] We then used longitudinal viral load data from AHI cases in Lilongwe,[3] along with transmission rates according to viral load,[36] to estimate separate transmission probabilities within each EHI interval, subject to the constraint that the weighted average transmission probability across intervals equaled the overall EHI-period average. To match the lack of transmission events observed during *late* AIDS in the Rakai data (likely due to ceasing of sexual activity due to illness),[6] we set the per-contact transmission probability for this period to 0.

We estimated sexual behaviour parameters from data we collected at Kamuzu Central Hospital STI Clinic in Lilongwe.[3, 30] These data included detailed information about partnership durations and contact frequency by marital status and partner type.

Estimating proportion new infections from EHI

We calculated the annual proportion of new infections attributable to EHI transmitters from model equations tracking cumulative infections by calendar time and index infection period.

Predicting intervention effects by stage of initiation

We explored the potential effects of an HIV prevention intervention that was assumed to dramatically decrease the per-contact transmission probability in all contacts affected by the intervention. Such an intervention could be strictly behavioural (e.g., 100% condom use by the male partner), strictly biological (e.g., ART use by infected cases), or a combination of the two. The per-contact transmission probability in such contacts was reduced to 0·000033. This value is the midpoint of male-to-female and female-to-male transmission probabilities estimated under ART-induced viral suppression,[37] but can also approximate effective condom use or other highly effective interventions. The intervention was not assumed to affect pair formation or dissolution rates, nor the frequency of sexual contact within or outside of steady partnerships. We varied the intervention coverage in each period, i.e., the proportion of cases (0%, 25%, 50%, 75%, 85%, 90%, 95%, 100%) in whom transmission

probabilities were successfully reduced, to explore scenarios with intervention effects during EHI only (as a benchmark), CHI only, or both EHI and CHI.

To compare the maximum possible benefits of interventions in each period, we assumed that interventions began early in a given period. Interventions during EHI were assumed to start in week 3 and to end at the start of CHI. This assumption, which is based on our experience with AHI detection in Lilongwe,[3] allows for blood collection in the second week of infection and an additional week to report positive HIV RNA or p24 results. Interventions acting in CHI were assumed to start at the beginning of the earliest CHI interval (interval 6) and continue through AIDS. Although this assumption reflects HIV diagnosis earlier than most current diagnoses,[38] it approximates the time at which a highly effective test-and-treat program with annual HIV antibody tests would detect cases.[19] Under such a strategy, infected individuals would be detected (on average) ~6 months into infection, approximately the time at which CHI starts in our model.

Interventions were assumed to begin in 2010 (at a mature epidemic phase). Our main intervention effect measures were the predicted HIV prevalence and incidence over the years 2010-2040. We also calculated the levels of coverage required for "elimination" of HIV during this time frame, using two separate definitions: 1) the "Granich definition" (reduction in annual incidence to less than 1 case per 1000 persons);[19] and 2) the "Dahlem definition" (reduction in annual incidence to 0 cases), developed at the WHO-sponsored Dahlem Workshop on the Eradication of Infectious Diseases.[39] As a complementary analysis, we predicted the percentage of new infections averted between 2010 and 2015.

As intervention effects on index case life expectancy could range from minimal (with strictly behavioural interventions) to substantial (with ART), we modelled two extremes of CHI interventions: a) no effect on infection duration, and b) increased average infection duration by ~10 to ~15 years.[19, 40] The life expectancy increase in the latter scenario is based on survival-time estimates for individuals starting ART at the beginning of CHI.[19, 40] Therefore, the CHI-only intervention with increased life expectancy approximates an annual test-and-treat strategy.

For base-case analyses, we used the *modal* input parameters. To explore intervention effects in situations with a greater or lesser importance of EHI, we used the input parameters producing the upper and lower 95% credible limits of the proportion of new cases attributable to EHI in 2010.

Additional sensitivity and influence analyses (described in more detail in Web Appendix)

To consider intervention effects under a variety of alternate conditions, we conducted analyses with greater assumed life expectancy increases among those receiving ART, as well as later intervention starts within EHI and/or CHI. We also explored the individual influence of each input parameter on results, examined epidemic dynamics within the high-risk and low-risk groups separately, and considered a model in which sexual behaviour parameters could change over the course of the epidemic.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Model Fit to HIV Prevalence Data

The Bayesian melding procedure yielded a posterior distribution of 380 unique epidemic curves in good agreement with the ANC data used to define HIV prevalence in Lilongwe (Figure 3). From the modal simulation, we estimated that HIV prevalence in Lilongwe's general adult population peaked at 24·7% in 1996, declined to 17·3% in 2005, and is currently 14·3%. ANC prevalence estimates peaked at 27·0% (95% confidence interval: 22·7%, 31·6%) in 1996 and declined to 18·6% (95% confidence interval: 16·0%, 21·3%) at the most recent survey in 2005.

The parameters producing the best fit to ANC data included an estimate that 40% of the population was in the initial "high-risk" group (Table 1); this proportion decreased to ~20% as the epidemic progressed. The best-fitting partnership durations were 2·5 years and 1·3 months in the low-risk and high-risk groups, respectively, with gaps of 1·5 years and 11 days between partners. Per-contact transmission probabilities were five times as great in the higher-risk versus lower-risk group (Table 1), representing transmission co-factor effects.

For most input parameters (e.g., viral load, transmission probabilities), the specified prior distributions were similar to the posterior distributions resulting from the fit to empirical data (see Web Appendix). The model fit was most informative for the size of the high-risk group, transmission co-factor effects, and high-risk pair formation and dissolution rates.

Estimated EHI contribution and related parameters

Based on the model results, 38·4% (95% CrI: 18·6%, 52·3%) of incident HIV infections resulted from contact with a partner with EHI in 2010 (Figure 4). The best-fitting EHI duration was 4·8 months (95% CrI: 1·6, 5·8) (Table 1). The best-fitting transmission rate ratio comparing EHI to asymptomatic chronic infection was 30 (95% CrI: 14, 47); that is, the weighted average per-contact transmission probability during EHI was 30 times as high as during asymptomatic infection (Table 1). The modal transmission rate ratio, in conjunction with other modal parameters, corresponds to per-contact transmission probabilities during EHI ranging from 3/1000 to 4/100 in the low-risk group (Table 1), and a cumulative transmission probability during EHI of ~26% within low-risk, HIV-discordant pairs (result not shown in Table 1).

Intervention effects

Biological or behavioural interventions assumed to sharply reduce HIV transmission probabilities during EHI (with no residual effect thereafter) were predicted to substantially reduce HIV prevalence in Lilongwe, but not to result in HIV elimination, even when 100% of EHI cases received the intervention (Figure 5A, solid green line). As the EHI-only intervention was not assumed to affect life expectancy, changes in HIV prevalence (Figure 5A) and incidence (Figure 5B) were similar.

In several scenarios, lifelong CHI-only interventions initiated ~6 months after infection were predicted to have greater effects on HIV prevalence and incidence than EHI-only interventions, but results were sensitive to assumptions about life expectancy (Figures 5C-5F). HIV elimination within 30 years under the "Dahlem definition" (reduction in annual incidence to 0 cases[39]) was not possible at any CHI-only coverage level, and elimination under the "Granich definition" (reduction in annual incidence to less than 1 case per 1000 persons[19]) was only possible with 95% or 99% CHI-only coverage, assuming no life expectancy increase or a 10-15-year increase, respectively (Figure 6). If the intervention was assumed to increase life expectancy (e.g., treatment as prevention[19, 41]), CHI-only coverage

levels of 75% or less were predicted to increase HIV prevalence above the level that would be expected with no intervention (Figure 5E).

The combination of EHI and CHI interventions reduced HIV prevalence and incidence substantially, even if CHI intervention coverage was only 75%-85% (Figures 5G-5N, dotted lines). Though the intervention coverage in each stage required for elimination depends on the definition of elimination and the intervention effects on life expectancy (Figure 6), the combination of results shown in Figures 5 and 6 suggests that if very high levels of coverage (i.e., ≥95%) cannot be attained with a CHI-only intervention, then the addition of EHI interventions will be necessary to sustainably reduce HIV prevalence and incidence in Lilongwe.

We observed these same patterns in sensitivity analyses where EHI was assumed to contribute 18·6% or 52·3% (our lower and upper 95% credible limits) of ongoing transmissions. Complementary analyses of infections averted showed similar trends. Sensitivity analyses in which CHI interventions increased life expectancy by 10-20 additional years provided further support for inclusion of EHI interventions, as did analyses where CHI interventions were assumed to start ~2 years – rather than ~6 months – into infection. (See Web Appendix for results of sensitivity analyses and other complementary analyses.)

Discussion

The magnitude of the HIV epidemic in sub-Saharan Africa has been difficult to explain. One explanation for the extensive spread of HIV emphasizes the importance of persons with acute and early HIV infection, who are highly infectious but rarely aware of their infection status.[42] Amplified transmission in this stage of infection has been ascribed to high viral loads[3, 4] and an apparent increase in viral infectivity.[43] In rhesus macaques, the ratio of infectious virions to total virions is up to 750 times as high during AHI as during CHI.[43] In Ugandan HIV-serodiscordant couples, transmission rates were approximately 25 times as high during early versus asymptomatic infection.[6] Phylogenetically-defined infection clusters[16-18, 44] and documented acute-to-acute transmission events[45, 46] further support the potential importance of early infection.

We undertook the current study to understand the contribution of EHI to the HIV epidemic in Lilongwe, Malawi, where we have conducted studies to identify patients with AHI,[47-49] characterize their sexual behaviours,[50] and measure viral load changes during EHI.[3] We estimated that EHI index cases are responsible for 19%-52% of HIV transmissions in Lilongwe, with a mode of 38%. Our results suggest that the initial period of elevated transmissibility may be fairly long (~5 months), and that transmissibility during EHI is 30 times as great as during CHI.

Mathematical modelling estimates of the importance of EHI have varied widely, [6, 9, 10, 12-15, 31, 51] due in part to differing assumptions and a paucity of data for parameter definitions. Endemic-phase estimates of the proportion of new infections due to EHI in sub-Saharan Africa have ranged from 7% to 31% in modelling studies.[6, 13] Phylogenetic studies conducted among MSM or mixed populations in western settings have estimated that 25%-49% of incident infections are due to EHI.[16-18, 44]

A strength of our model is the extensive use of local data for model parameterization. We used sexual behaviour data from Lilongwe[30] to define contact patterns specific to the setting of interest and viral load data from AHI patients in Lilongwe[3] to provide high resolution in the time-course of transmission probabilities during EHI. We fitted the model to local HIV prevalence data using a Bayesian melding approach. The close parameterization of the

model based on data from the setting of interest allows us to expect results with greater reliability and applicability – at least in Lilongwe and similar settings – than could be expected from a model using a combination of parameter values derived from disparate populations.

Our model was enhanced in several other ways in comparison to previous models addressing AHI/EHI. To model contact patterns relevant to HIV transmission, we explicitly incorporated both steady pairs and casual contacts, with consideration of both high-risk and low-risk groups. The Bayesian melding approach allowed us to account for input and result uncertainty. Finally, we conducted sensitivity analyses to assess intervention effects under a range of predicted EHI contributions.

The idea of using ART as a transmission prevention strategy has gained remarkable attention.[19, 41] This idea emerges from the reduction of HIV replication in the genital tracts of persons on ART,[52, 53] and apparent suppression of HIV transmission in serodiscordant couples when the index case receives ART.[54-56] A widely cited mathematical model has concluded that annual test-and-treat strategies could virtually eliminate the epidemic in South Africa,[19] but the importance of EHI appears to have been underestimated in that model,[22, 24, 25] and other modelling studies examining the potential benefits of ART have been less optimistic about the test-and-treat approach.[57, 58]

Accordingly, we examined the effects of behavioural and/or biomedical interventions that might drastically reduce sexual transmission at different stages of HIV. One such intervention was assumed to improve survival and reduce transmissibility from the onset of CHI, approximating an annual test-and-treat strategy.[19] Our results suggest that even highly effective behavioural and/or biological interventions – including “test-and-treat” – are unlikely to eliminate HIV in Lilongwe and similar settings unless people with EHI are included. Even if the contribution of EHI to ongoing transmission is as low as ~20% (the lower credible limit in our analysis), intervention only during CHI is unlikely to eliminate HIV unless nearly all CHI cases experience life-long transmission suppression. If CHI-only intervention coverage is imperfect, additional EHI interventions can lead to dramatic improvement. Our results suggest that strategies preventing transmission from both CHI *and* EHI cases provide the greatest chance for marked, durable reductions in HIV incidence and prevalence. Sensitivity analyses in which CHI interventions were assumed to provide even greater survival benefits, or to start at times more typical of current clinical practice, provided even greater support for inclusion of interventions during EHI.

Interventions directed toward patients with EHI have unique challenges. While antibody tests may detect some post-acute EHI cases, a “test-and-treat” approach for specifically identifying EHI cases would require a very brief interval for repeat testing (~3-6 months), and reliance on antibody tests would result in missed AHI cases. Large-scale programs of quarterly or semi-annual HIV testing would be difficult to implement and sustain. Both biological and behavioural interventions intended for EHI may require more targeted approaches, such as partner notification or campaigns aimed at encouraging HIV testing among individuals with recent risky behaviour and acute retroviral symptoms.[59] These case-finding strategies, in combination with pooling of blood samples,[47] targeted HIV RNA screening,[48, 60] and/or newer HIV detection tests[1, 61] could increase the numbers of EHI cases detected, even in resource-limited settings. Encouragingly, our best-fitting value of 4·8 months for the period of elevated transmissibility suggests that interventions provided during the first few months of infection, rather than the first few weeks, may have substantial public health benefit. In earlier work we demonstrated that the HIV concentration in seminal plasma remained elevated for more than two months after infection, consistent with this idea.[3]

Interventions initiated during EHI may also have unique benefits that are not explicitly captured in our model. Adherence to biological or behavioural interventions initiated during EHI may remain high at least through the most infectious period,[50] potentially maximizing cost-effectiveness and minimizing the detrimental effect of waning adherence observed with some interventions.[62, 63] Additionally, at least some studies suggest a clinical benefit from initiation of treatment during EHI.[64]

Mathematical models of HIV transmission depend heavily on assumptions about sexual behaviour. The input values for sexual behaviour parameters in our model were based on a cross-sectional study conducted among STD clinic patients in Lilongwe[30] that found long-term monogamy to be common, with only 14% reporting long-term concurrency, sporadic concurrency, or consecutive, monogamous partnerships in rapid succession. Although based on a relatively small sample (n=186) with generalizability likely limited to similar settings, these data represent some of the most detailed information available on partnership durations and gaps in sub-Saharan Africa. In our best-fitting model simulation, “steady” partnerships in the higher-risk group were 1.3 months in duration, with intervening gaps of 11 days; by contrast, steady partnership durations and gaps in the lower-risk group were 2.5 years and 1.5 years, respectively. Therefore, the difference between “steady” and “casual” partners appears to be considerably less distinct for higher-risk than lower-risk individuals, potentially explaining why some behavioural parameters resulting from the model fit vary in somewhat unexpected ways across groups. For example, despite the higher casual contact rate that we initially posited for higher-risk singles, the best-fitting parameter set suggests a lower rate, possibly because the shorter gap between “steady” partnerships translates to less time as a single in the high-risk group. We also note that the partner change rate in our higher-risk group was slower than in the highest-risk groups of several previous HIV epidemic models,[13, 65] and that none of our behavioural parameters was particularly extreme, despite being collected in an STI clinic population. The latter result may be due to the high prevalence of STIs in Malawi,[66, 67] which likely results in considerable overlap between STI clinic populations and the “general” population.

The importance of sexual partner concurrency in the HIV epidemic of sub-Saharan Africa has been emphasized and debated.[68-72] Intuitively, concurrency seems potentially important for transmission during EHI, because long-term monogamy would limit the high transmissibility of newly infected persons to a single partnership. Our model captured only a simple form of concurrency – one-off encounters outside of pairs; it did not include long-term concurrency. However, our best-fitting parameter set included short gaps between partners (11 days) in a relatively sizeable higher-risk group. These short gap lengths are consistent with (and based on) our data from Malawi,[30] and provide an alternate explanation for rapid HIV spread and the corresponding importance of EHI; however, the potential contribution of concurrency cannot be excluded.

All mathematical models have limitations. In our model, individuals and pairs were restricted to a given risk group, and only a very simple form of concurrency was captured, as noted above. Additionally, our model did not incorporate population age structure or male-female behavioural asymmetry. The inclusion of behavioural heterogeneity across two separate risk groups may capture some age-related behavioural variation, but the results give an average picture for the sexually active population overall. Nevertheless, our division of EHI into numerous intervals, our inclusion of more than one risk group, and our incorporation of both steady and casual contacts likely reflect transmission dynamics more accurately than previous models that have assumed only one-off contacts occurring at random within populations. Additional considerations, such as drug resistance, side effects, behavioural disinhibition, and cost, must also be carefully appraised before implementing specific treatment-based interventions.

In summary, our analyses suggest that EHI remains a critical factor in the ongoing HIV epidemic in Lilongwe. This result suggests that acute and early HIV infection can be important not only in the earliest phases of HIV epidemics, but also in more mature epidemics. Consequently, prevention approaches directed at all stages of HIV will likely be necessary to ensure a durable effect on the epidemic in Lilongwe and similar settings. As plans for "treatment as prevention" are developed, our results suggest that strategies for detection and management of patients with acute and early HIV must be included.

Panel: Research in context

Systematic review

In a recent review of mathematical models estimating the contribution of AHI/EHI to ongoing HIV transmission,[73] we noted that estimates have varied widely, due to differences in epidemic stage, populations studied, model structure, parameter values, and assumptions in the absence of site-specific data. None of these modelling studies compared the potential impact of transmission prevention interventions initiated in acute/early HIV versus chronic infection. Previous modelling studies examining "treatment as prevention" strategies for established infection[19,57,58,65] have had mixed results related to the control of HIV.[74]

Interpretation

The events that transpire during acute HIV infection are critical to the health of the infected individual and the health of the public.[1] Our study suggests that transmission prevention interventions achieving intermediate levels of coverage during both early and chronic HIV will have a far greater impact on the spread of HIV in Malawi than interventions focused on chronic HIV alone. As such, the population-level impact of "test-and-treat" strategies is likely to be optimized only if individuals with acute/early HIV are included or if complementary interventions targeting the earliest phases of infection are incorporated into the overall prevention approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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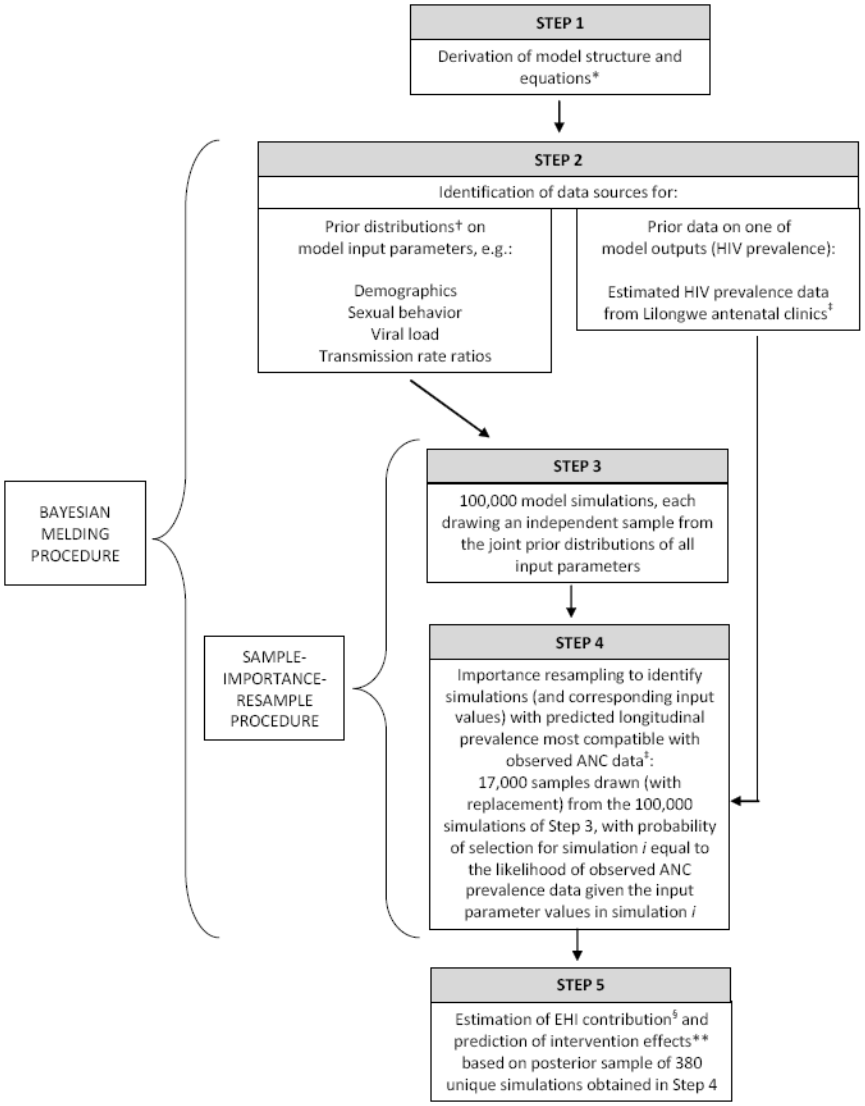

Figure 1. Flow diagram of modelling methods

Analyses began with model development (Step 1), followed first by a Bayesian melding procedure (Steps 2-4) to identify model parameter values most compatible with observed epidemic dynamics in Lilongwe, and next by estimation of the contribution of EHI and prediction of intervention effects (Step 5).

* See Figure 2 for schematic of basic model structure and Web Appendix for corresponding equations.

† See Table 1 for complete listing of model input parameters and corresponding prior distributions.

‡ See Figure 3 for plot of ANC data and posterior distribution of model simulations

§ See Figure 4 for estimated EHI contribution

** See Figure 5 for predicted intervention effects

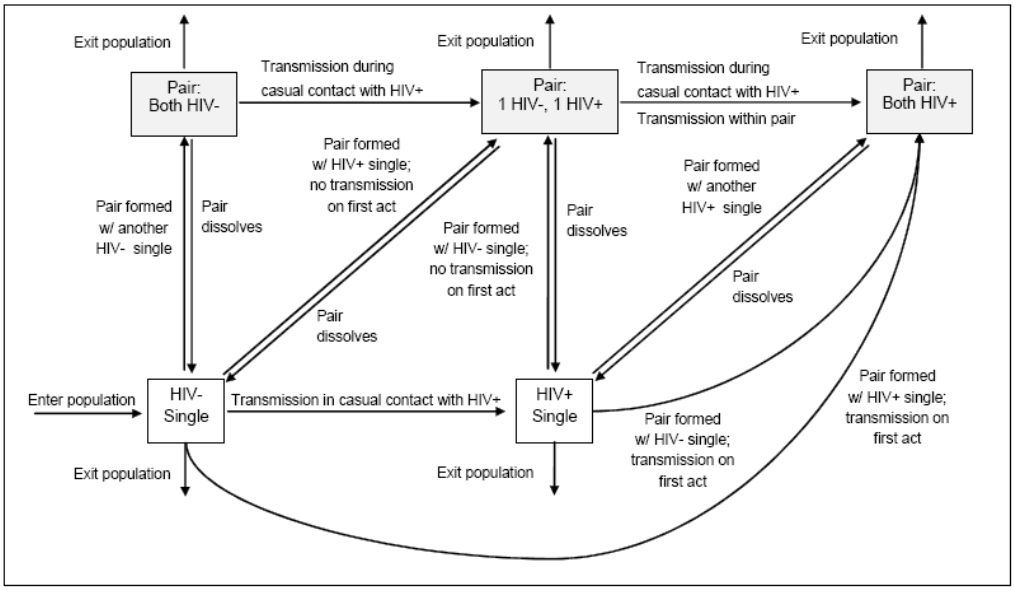

Figure 2. Simplified diagram of model structure

Unshaded boxes represent single (unpaired) individuals; shaded boxes represent steady partnerships. As detailed by the accompanying labels, arrows represent flows from one compartment to another via demographic processes (entering & exiting the population), partnership formation and dissolution, or HIV transmission. For ease of illustration, the diagram does not illustrate the two separate risk groups or the multiple stages of infection.

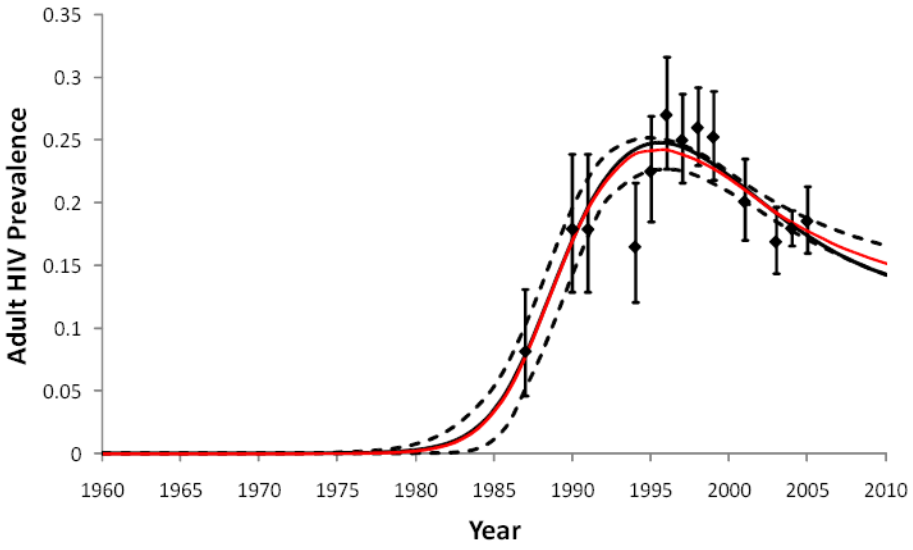

Figure 3. HIV ANC prevalence data and posterior distribution of output prevalence curves

HIV prevalence data from the sentinel surveillance site in a Lilongwe antenatal clinic are shown as points, with the corresponding 95% confidence intervals as bracketed vertical lines. HIV prevalence output generated from the mode (i.e., best-fitting) set of input parameters is shown as the solid black curve. The dashed curves were generated from the $2{\cdot}5^{th}$ and $97{\cdot}5^{th}$ percentile values from the entire posterior set of model-produced prevalence predictions at each time point. The red curve represents the median value at each time point.

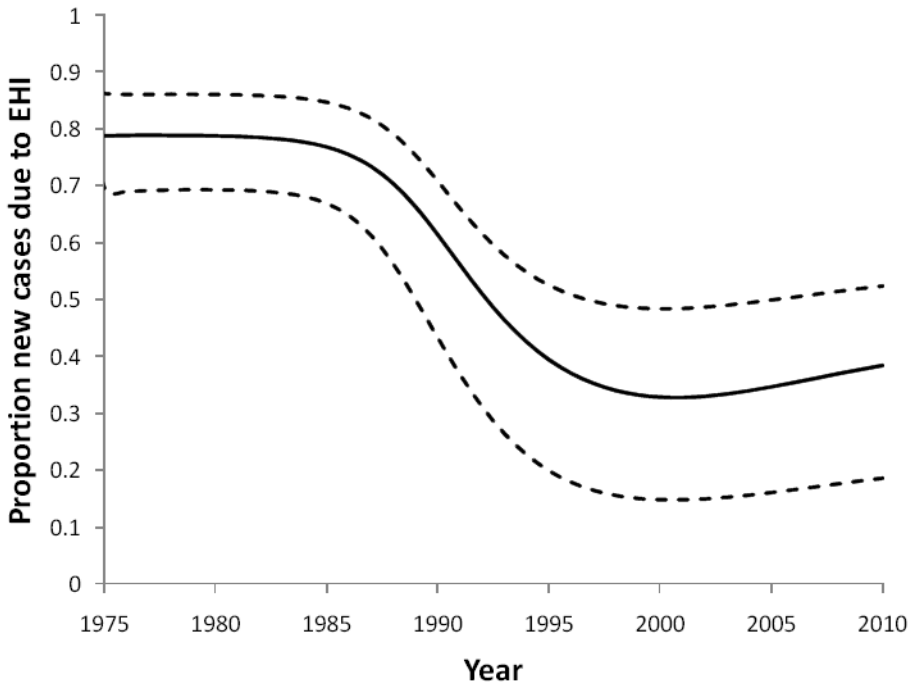

Figure 4. Estimated proportion of incident HIV infections attributable to contact with EHI index case

The solid curve represents the annual proportion of incident HIV infections attributable to contact with an EHI index case predicted by the mode set of input parameters. The dashed curves correspond to the simulations producing the 2·5th and 97·5th percentile values in the year 2010.

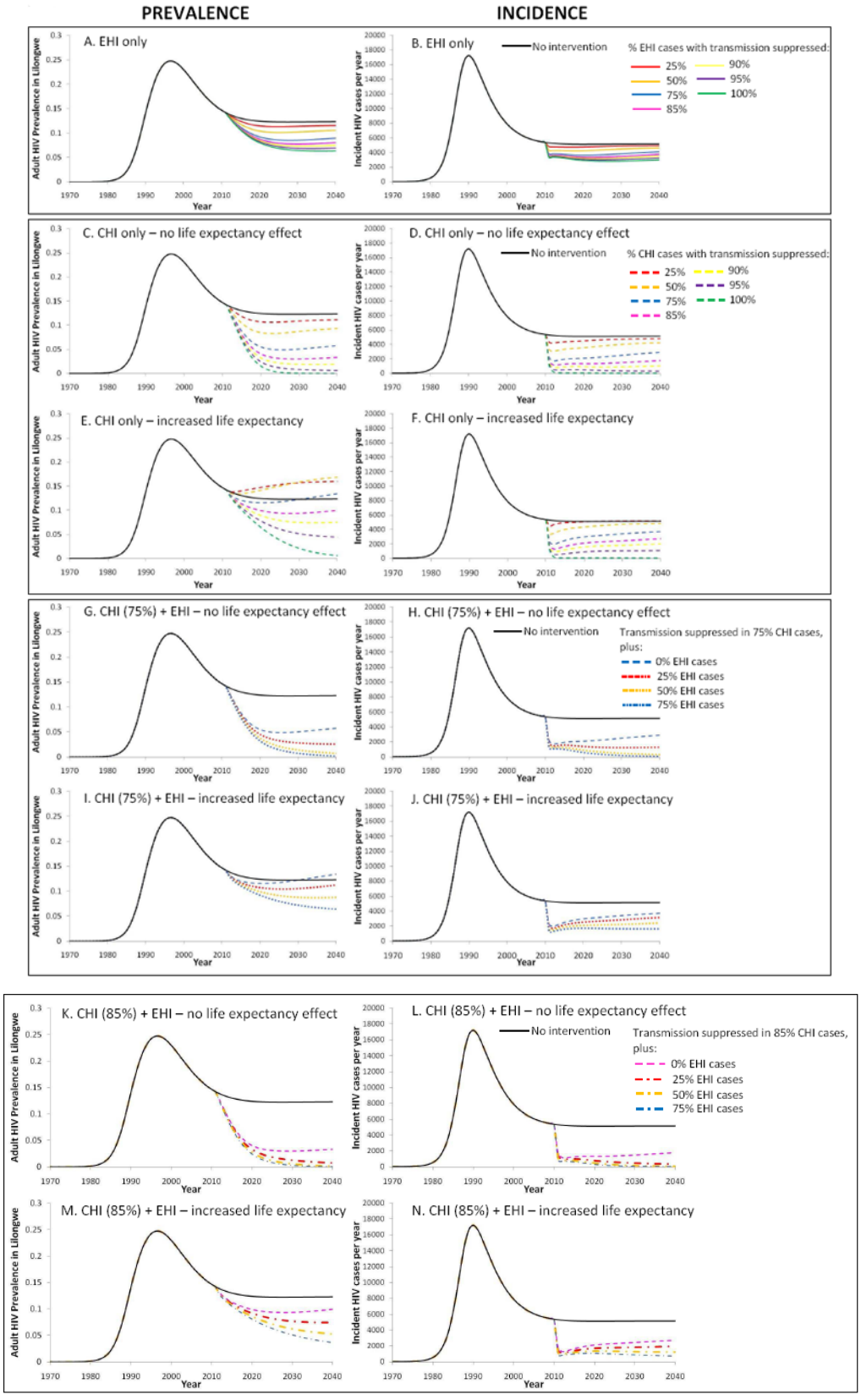

Figure 5. Predicted effects of interventions during EHI only, CHI only, or both periods on HIV prevalence and incidence

HIV prevalence (left panel) and incidence (right panel) in Lilongwe is shown for scenarios with no intervention (solid black curve) and for interventions initiated in 2010 with various levels of coverage in early HIV infection (EHI) and/or chronic HIV infection (CHI). The figures in the top row (5A, 5B) compare the “no-intervention” scenario with “EHI-only” interventions suppressing transmission in 25%, 50%, 75%, 85%, 90%, 95%, and 100% of those with EHI. Figures 5C-5F compare the “no-intervention” scenario with “CHI-only” interventions suppressing transmission in 25%, 50%, 75%, 85%, 90%, 95%, and 100% of those with CHI; 5C and 5D assume no increase in life expectancy associated with the intervention, while 5E and 5F assume increased life expectancy associated with the intervention (see Methods). Figures 5G-5J and 5K-5N compare the “no-intervention” scenario with four different strategies in which 75% of CHI cases (5G-5J) or 85% of CHI cases (5K-5N) are reached: one that suppresses transmission only in CHI cases, and three that also suppress transmission in 25%, 50%, and 75% of EHI cases, respectively. In these last two sets of figures, 5G, 5H, 5K, and 5L assume no increase in life expectancy associated with the CHI intervention; 5I, 5J, 5M, and 5N assume increased life expectancy associated with the CHI intervention (see Methods). All figures are based on input parameters from the modal simulation.

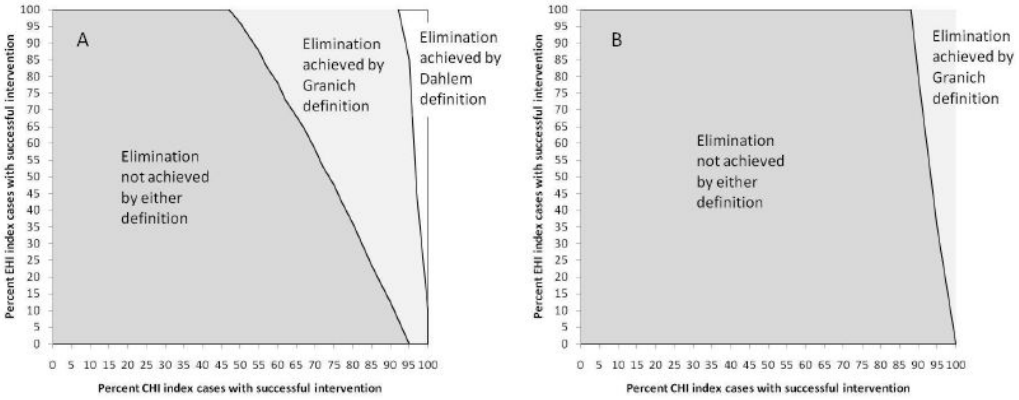

Figure 6. Intervention Coverage Levels Required for HIV Elimination in Lilongwe

Predicted levels of coverage required in EHI and/or CHI to result in HIV elimination within 30 years of intervention implementation, assuming (A) no increase in life expectancy associated with CHI interventions or (B) increased life expectancy associated with CHI interventions (see Methods). The “Granich definition” requires a reduction in annual HIV incidence to 1 case per 1000 persons. The “Dahlem definition” requires a reduction in annual incident cases to 0.

Table 1

Input parameter definitions, prior distributions, and posterior distributions

Parameter	Definition	Input value / Prior distribution*	Posterior distribution Mode (95% CrI)
Demographic parameters			
μ	Rate of leaving sexually active population	0·029/year	N/A
n	Initial size of entire Lilongwe population	976,625	N/A
θ	Proportion of initial population in 15-49-year age group	Uniform (0·43,0·48)	0.44 (0·43, 0·48)
τ	Year of first HIV infection in Lilongwe	Uniform (1960,1985)	1969 (1964, 1978)
Sexual behaviour parameters†			
π_0	Proportion of initial population in low-risk group	Uniform (0·1,0·9)	0·60 (0·54, 0·71)
Parameters specific to lower-risk group			
Q_0	Proportion of low-risk individuals in a steady partnership	Uniform (0·6,0·9)	0·60 (0·60, 0.89)
ρ_0	Rate of steady pair formation by singles in low-risk group (steady pairs formed per year)	N/A‡	0·66 (0·35, 4·01)§
σ_0	Rate of steady pair separation in low-risk group (separations per year)	Uniform (0·05, 0·47)	0·38 (0·06, 0·45)§
ϕ_0	Unprotected contact frequency in low-risk pairs (contacts/year)	Normal (65·1, 18·6)	33·1 (26·1, 88·6)
s_0	Rate of low-risk singles having one-off, casual contacts (casual partners/year)	Uniform (0,6)	3·0 (0·2, 5·2)
χ_0	Rate of low-risk paired individuals having one-off, casual contacts (casual partners/year)	Normal (2·1, 0·97)	2·4 (0·3, 3·0)
Parameters specific to higher-risk group			
Q_1	Proportion of high-risk individuals in a steady partnership	Uniform (0·1, 0·9)	0·79 (0·41, 0·88)
ρ_1	Rate of steady pair formation by singles in high-risk group (steady pairs formed per year)	N/A‡	33·7 (9·9, 176·1)¶
σ_1	Rate of steady pair separation in high-risk group (separations per year)	Uniform (0·2, 26·1)	9·0 (6·5, 25·2) ¶
ϕ_1	Unprotected contact frequency in high-risk pairs (contacts/year)	Uniform (16,45)	33·5 (20·8, 44·6)
s_1	Rate of high-risk singles having one-off, casual contacts (casual partners/year)	Uniform (0,24)	0·8 (0·6, 23·1)
χ_1	Rate of high-risk paired individuals having one-off, casual contacts (casual partners/year)	Uniform (0,24)	2·1 (0·3, 23·2)
Parameters related to per-contact HIV transmission probabilities†			
Viral loads over course of early HIV infection			

Parameter	Definition	Input value / Prior distribution*	Posterior distribution Mode (95% CrI)
VL_1	Log_{10} viral load in early HIV, interval 1 (week 1)	Normal (1·709, 0·5)	1·7 (0·9, 2·6)
VL_2	Log_{10} viral load in early HIV, interval 2 (week 2)	Normal (5·273, 0·5)	5·5 (4·5, 6·3)
VL_3	Log_{10} viral load in early HIV, interval 3 (week 3)	Normal (6·769, 0·5)	6·7 (6·2, 7·5)
VL_4	Log_{10} viral load in early HIV, interval 4 (week 4)	Normal (6·157, 0·5)	6·2 (5·5, 7·0)
VL_5	Log_{10} viral load in early HIV, interval 5	Normal (5·219, 0·3)	4·5 (4·5, 5·7)
Per-contact transmission probabilities over course of infection			
$h_{1,0}$	Per-contact transmission probability in week 1 of EHI (low-risk group)	N/A‡	0·003 (0·001, 0·004)
$h_{2,0}$	Per-contact transmission probability in week 2 of EHI (low-risk group)	N/A‡	0·03 (0·007, 0·04)
$h_{3,0}$	Per-contact transmission probability in week 3 of EHI (low-risk group)	N/A‡	0·04 (0·01, 0·05)
$h_{4,0}$	Per-contact transmission probability in week 4 of EHI (low-risk group)	N/A‡	0·03 (0·01, 0·05)
$h_{5,0}$	Per-contact transmission probability in final interval of EHI (low-risk group)	N/A‡	0·02 (0·01, 0·03)
$h_{6,0}$, $h_{7,0}$, $h_{8,0}$	Per-contact transmission probability in Asymptomatic HIV (intervals 6-8) (low-risk group)	Normal (0·0007, 0·00007)	0·0007 (0·0006, 0·0008)
$h_{9,0}$	Per-contact transmission probability in early AIDS (interval 9) (low-risk group)	N/A‡	0.006 (0.003, 0.015)
$h_{10,0}$	Per-contact transmission probability in late AIDS (interval 10) (low-risk group)	0	N/A
Relative transmission rates/probabilities			
$\ln(r_E)$	Natural log of relative transmission rate: EHI vs. asymptomatic HIV	Normal (3·26, 0·37)	3·4 (2·6, 3·9)
$\ln(r_L)$	Natural log of relative transmission rate: early AIDS vs. asymptomatic HIV	Normal (1·97, 0·32)	2·0 (1·1, 2·9)
$\ln(r_v)$	Natural log of relative transmission rate per log_{10} increase in viral load	Normal (0·896, 0·145)	0·9 (0·7, 1·1)
r_E	Relative transmission rate: EHI vs. asymptomatic HIV	N/A‡	30·3 (13·6, 47·1)
r_L	Relative transmission rate: early AIDS vs. asymptomatic HIV	N/A‡	7·1 (3·1, 18·8)
r_v	Relative transmission rate per log_{10} increase in viral load	N/A‡	2·5 (2·0, 3·1)
c	Relative change in transmission probabilities in high-risk group	Uniform (1,6)	5·4 (3·1, 6·0)
HIV infection interval durations (without treatment)†			
Duration of early HIV infection, overall and by interval			
$1/\gamma_1$, $1/\gamma_2$, $1/\gamma_3$, $1/\gamma_4$	Duration of each of first 4 intervals of early HIV (intervals 1-4)	1 week each	N/A
$1/\gamma_5$	Duration of early HIV, interval 5 (weeks)	Uniform (1·4, 21·8)	16·6 (3·1, 21·3)
$1/\gamma_1 + 1/\gamma_2 + 1/\gamma_3 + 1/\gamma_4 + 1/\gamma_5$	Total duration of EHI (intervals 1 – 5) (months)	N/A‡	4·8 (1·6, 5·8)

Parameter	Definition	Input value / Prior distribution*	Posterior distribution Mode (95% CrI)
Duration of chronic HIV infection, overall and by interval			
$1/\gamma_6$, $1/\gamma_7$, $1/\gamma_8$	Duration of each interval of asymptomatic HIV (intervals 6-8) (years)	Uniform (1·83, 3·17)	1·9 (1·8, 2·8)
$1/\gamma_9$	Duration of early AIDS (interval 9) (years)	Normal (0·75, 0·2)	0·9 (0·3, 1·0)
$1/\gamma_{10}$	Duration of late AIDS (interval 10) (years)	Normal (0·83, 0·12)	1·1 (0·7, 1·1)
Duration of entire infectious period			
$1/\gamma_1 + \ldots + 1/\gamma_{10}$	Time from HIV infection to death from AIDS (years)	N/A‡	8·0 (7·2, 10·5)

*For parameter values that varied across model runs, distributions are given as: Uniform(lower limit, upper limit), Normal(mean, standard deviation). Parameters not specified in this format were held constant at the listed value across runs.

†Derivation of input values for these parameters are described in detail in the Web Appendix.

‡Parameter was not specified directly in this form as an input parameter, but as a function of other parameters.

§In the low-risk group, the posterior mode for the pair separation rate (σ_0 = 0·38 per year) corresponds to an approximate average pair duration of 1/0·38 ≈ 2.5 years. The posterior mode for the pair formation rate (ρ_0 = 0·66 per year) corresponds to an approximate average gap between partners of 1/0·66 ≈1.5 years.

¶In the high-risk group, the posterior mode for the pair separation rate (σ_1 = 9·0 per year) corresponds to an approximate average pair duration of 1/9·0 ≈ 0·11 year ≈ 1.3 months. The posterior mode for the pair formation rate (ρ_1 = 33·7 per year) corresponds to an approximate average gap between partners of 1/33·7 ≈0.03 year ≈ 11 days. Together, these durations correspond to an approximate average of 7 “steady” partners per year for individuals in the high-risk group.