

Effects of Epidemiological Structure on the Transient Evolution of HIV Virulence

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Abstract

The evolutionary dynamics of parasite virulence change in important ways over the course of an emerging epidemic ~~have important implications both for our basic understanding of epidemiological dynamics and, potentially, for the outcomes of public health interventions~~. Changes in the fitness landscape ~~will~~ generally select for higher virulence ~~during the early phase of an epidemic, but quantitative outcomes can~~ early in an epidemic; however, quantitative outcomes may depend sensitively on ~~biological epidemiological~~ details and the structure of mathematical models used to ~~capture~~ portray them. Fraser ~~, Shirreff, and co-workers~~ et al. have proposed a ~~series of models for model for the~~ eco-evolutionary dynamics of HIV that ~~are relatively detailed in their portrayal of~~ captures the tradeoffs between transmission and virulence (mediated by set-point viral load, SPVL) and their heritability between hosts. However, these models use implicit representations of the transmission process that drastically simplify the partnership dynamics that previous research has found to be critical in driving epidemics of sexually transmitted diseases. ~~We explore models that~~ Our models combine HIV virulence tradeoffs with a range of epidemiological structures, modeling

partnership formation and dissolution and allowing for individuals to transmit disease outside of partnerships. We assess summary statistics such as the peak ~~value of~~ virulence (SPVL) and the time at which the peak occurs ~~virulence (corresponding to the minimum expected time of progression to AIDS)~~ across all models ~~and across a Latin hypercube sample that captures a realistic for a~~ range of partnership dynamic parameters ~~for applicable to the HIV epidemic in~~ sub-Saharan Africa. ~~In order to account for the different interpretations of parameters~~ Although virulence trajectories are broadly similar across model structures, ~~we scale all parameter sets to constrain the simulated epidemic growth rate to be identical, matching a realistic baseline value. For this particular model setting~~ the timing and magnitude of the minimum expected time to progression vary considerably. Models of intermediate complexity as used by Shirreff *et al.* predicted lower slower progression/lower virulence (a minimum of 15 years to progress to AIDS) compared to both more realistic models and simple random-mixing models with no partnership structure at all (both with a minimum of ≈ 7.25 years to progress to AIDS). In this range of models, the simplest random-mixing structure ~~is actually the best approximation to~~ best approximates the most realistic model; this surprising outcome occurs because the dominance of extra-pair contact in the realistic model tends to ~~mask~~ swamp the effects of partnership structure.

Author Summary

Pathogens such as HIV can evolve rapidly in response to changes in their environments; such changes include both increases in disease prevalence and disease virulence over the course of ~~the epidemic and an epidemic, or decreases in both after~~ treatment interventions. While researchers have successfully used computational models to explore these evolutionary dynamics, these models often neglect details such as the formation and dissolution of sexual partnerships; other research has shown that these processes can strongly affect epidemic outcomes. We built and compared models that used different methods to model both partnership dynamics and sexual contact outside of stable partnerships. Models of intermediate complexity predicted much lower ~~peak virulence (virulence over the course of the epidemic (a minimum of 15 years to progress to AIDS))~~ compared to both more realistic models and simple random-mixing

models with no partnership structure at all (both approx. 7.25 years to progress to AIDS); ~~extra-pair-contact~~ sexual contact outside of stable partnerships tended to wash out the effects of epidemiological structure. The large differences in evolutionary dynamics among different epidemiological models suggests that researchers trying to predict the evolution of pathogens should proceed with caution.

Introduction

The evolution of pathogen virulence ~~is a fundamental process in evolutionary biology, of~~ has both theoretical and ~~(potentially)-~~ potentially, practical importance. ~~The trade-off theory~~ [?] ~~In general, evolutionary theory suggests that disease strains that can reproduce more~~ — which postulates that parasite virulence can be explained as the long-term evolutionary outcome of a saturating relationship between parasite clearance rate and transmission rate ~~where reproduction is defined here as the amount of between-host transmission, or the number of new hosts infected~~ — has been criticized will increase in prevalence. Pathogens can increase their net reproduction rate either by increasing their transmission rate, the rate (per infected host) at which they infect new hosts, or by decreasing their clearance or disease-induced mortality rate, the rate at which hosts recover or die from disease. The trade-off theory [1] postulates that the transmission and disease-induced mortality rate are both linked to the rate at which the pathogen exploits host resources for within-host reproduction, and that pathogen evolution will thus strike a balance between the pathogen's rate of transmission to new hosts and its rate of killing its host (or of provoking the host's immune system to eliminate it). Some biologists have criticized the tradeoff theory [2,3], but ~~has also been successfully applied in~~ others have successfully applied it to a variety of host-pathogen systems [4–7]. ~~One particularly interesting application of these ideas is the work by~~ Fraser et al. have applied these ideas in a particularly interesting way by showing that HIV appears to satisfy the prerequisites of the tradeoff theory: in studies of discordant couples (i.e. long-term sexual partnerships with one infected and one uninfected partner), HIV virulence as measured by the rate of progression to AIDS was both heritable and covaried with the set-point viral load (SPVL: i.e., the characteristic virus load measured in blood during the intermediate stage of infection) ~~, which in turn~~

~~predicted~~ and the probability of transmission. Higher viral loads led to shorter progression times (higher virulence) and faster transmission, with a decelerating relationship between virulence and transmission as required by the tradeoff theory [8,9]. Subsequent studies ~~[10,11]~~ [10–12] used these data to parameterize mechanistic models of HIV virulence evolution, suggesting that HIV invading a novel population would initially evolve increased virulence, peaking after approximately 100–200 years and then declining slightly to a long-stable virulence level.

The work of Shirreff *et al.* [10], and particularly the predicted transient peak in HIV virulence midway through the epidemic, highlights the importance of interactions between epidemiological and evolutionary factors [13,14]. However, despite these studies' attention to detail at the individual or physiological level, the epidemiological structures used in these models are relatively simple.

As we discuss in detail below, ~~the~~ existing models of HIV eco-evolutionary dynamics either use implicit models that incorporate the average effects of within-couple sexual contact — without representing the explicit dynamics of pair formation and dissolution or accounting for extra-partnership contact — or use an agent-based formulation with parameters that effectively lead to random mixing among infected and uninfected individuals. Here we explore the effects of incorporating *explicit* epidemiological structure in eco-evolutionary models.

We add complexity to the epidemiological model following the general approach of Champredon *et al.* [15], which is in turn based on work of Dietz and Haderl [16]; individuals join and leave partnerships at a specified rate, and can have sexual contact both within and outside of established partnerships. In order to explore how virulence evolution depends on epidemiological structure, we consider a series of models with increasing levels of complexity. In order to avoid dependence of the results on a particular set of parameters — as we explain below, finding matching sets of parameters across models with widely differing epidemiological structures is challenging — we evaluate our models across a wide range of parameters, again following Champredon *et al.* [15] in using a Latin hypercube design. For each model run, we compute a set of metrics (minimum progression time/peak virulence, timing of ~~virulence peak~~maximum virulence, equilibrium virulence) that summarize the evolutionary trajectory of a simulated HIV epidemic.

As our primary goal is to explore how different epidemiological structures (i.e. partnership dynamics and contact structures) affect our conclusions about the evolution of virulence, our models use a simplified description of within-host dynamics and heritability derived from Shirreff *et al.*'s multi-strain evolutionary model [10]. Like Shirreff *et al.*, we use a simple susceptible-infected-susceptible demographic formulation; rather than modeling birth and death (or more specifically, recruitment into the sexually active population and death), we assume that whenever an individual dies from infection, another enters the susceptible compartment.

Materials and Methods

Infection dynamics

~~Like As in~~ Shirreff *et al.* [10], ~~we focus on our models explicitly track~~ the evolution of mean \log_{10} ~~set-point viral load~~, SPVL (which we denote as α), rather than the rate of progression to AIDS itself (~~we refer to SPVL as hereafter~~ “virulence” ~~hereafter will refer~~ either to the SPVL, or to the rate of progression to AIDS; these two quantities are deterministically linked in the model). In contrast to Shirreff *et al.*, we use a single-stage disease model instead of accounting explicitly for progression through the three main stages of HIV infection (primary, asymptomatic, and disease), and we use a simple exponentially distributed infectious period instead of a more realistic Weibull-distributed infectious period; we show below that our results are not overly sensitive to this simplification. We account for varying transmission rates and durations of each disease stage by summing the durations of three stages (again based on Shirreff *et al.*'s model) and taking the duration-weighted average of transmission rates of three stages. Thus the within-couple transmission rate, β , for our models is given by:

$$\beta(\alpha) = \frac{D_P\beta_P + D_A(\alpha)\beta_A(\alpha) + D_D\beta_D}{D_P + D_A(\alpha) + D_D}, \quad (1)$$

where the duration of infection (D_P and D_D) and rate of transmission (β_P and β_D) of the Primary and Disease stages of infection are independent of the host's SPVL. Following Shirreff *et al.*, the duration of infection (D_A) and rate of transmission (β_A) for the Asymptomatic stage are Hill functions of the SPVL:

$$D_A(\alpha) = \frac{D_{\max} D_{50}^{D_k}}{V_{\alpha}^{D_k} + D_{50}^{D_k}},$$

$$\beta_A(\alpha) = \frac{\beta_{\max} V_{\alpha}^{\beta_k}}{V_{\alpha}^{\beta_k} + \beta_{50}^{\beta_k}},$$
(2)

where $V_{\alpha} = 10^{\alpha}$.

The uncoupled and extra-couple transmission rates (i.e., the rates of transmission among people outside of a stable partnership, or between people inside of a stable partnership and people other than their partner) are scaled by multiplying the within-couple transmission rate β by the contact ratios c_u/c_w and c_e/c_w (see Appendix S1). Simplifying the model of HIV pathogenesis from three stages to a single stage could affect our conclusions about the evolution of virulence (e.g. Kretzschmar and Dietz [17] show that pair formation dynamics and multiple stages of infectivity have interactive effects on \mathcal{R}_0). However, our simplified model produces results that are qualitatively similar to those of Shirreff *et al.*'s [10] model; when our model is calibrated to have a similar initial epidemic growth rate r , the peak \log_{10} SPVL occurs at the same time (≈ 200 years) but slightly higher ($4.6 \log_{10}$ SPVL vs. $4.3 \log_{10}$ SPVL, or 7% higher; Fig 1).

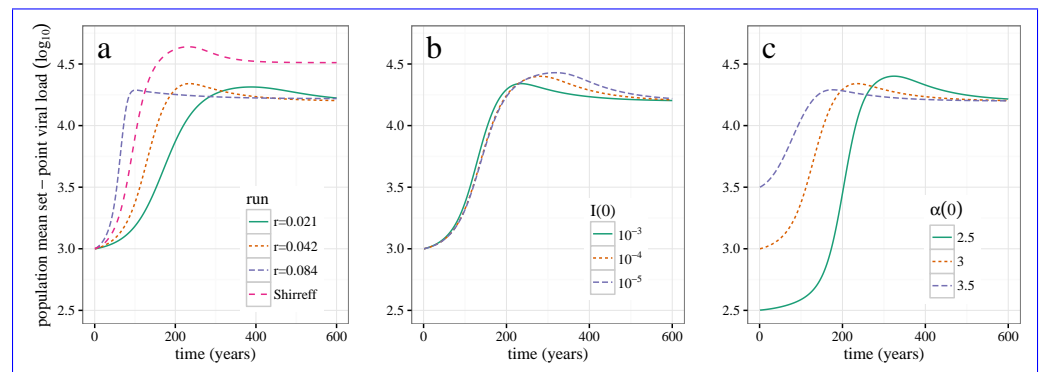


Fig 1. Baseline dynamics. Time series of mean population \log_{10} SPVL. (a) Contrast between the three-stage Shirreff model and the single-stage model calibrated to varying initial exponential growth rates, r . (b) Effects of varying initial infectious density $I(0)$. (c) Effects of varying initial mean virulence $\alpha(0)$. The $r = 0.042$ (orange, dotted) curve in panel (a), calibrated to match the epidemic dynamics of Shirreff *et al.*'s model [10], shows that our simplified model can produce similar virulence trajectories. Panels b and c illustrate the sensitivity of virulence trajectories to initial conditions $I(0)$ and $\alpha(0)$, which we hold constant in our simulations.

Mutation

Like Shirreff *et al.* [10] we incorporate a between-host mutation process in the SPVL, ~~but~~. We simplify Shirreff *et al.*'s evolutionary model by using a one-to-one genotype-phenotype mapping rather than allowing for variation in phenotypes of a single genotype. The mutational process in our model is directly taken from Shirreff *et al.*. Over the course of infection, mutation occurs within the host. However, it is assumed that SPVL of the strain transmitted by an infected individual is determined by the SPVL at the time of infection ~~(and is not further affected by within-host mutation)~~. Instead, the mutational effect takes place ~~when an infected individual transmits the virus to a susceptible individual~~ in a single step at the time of transmission. First, the distribution of \log_{10} SPVL is discretized into a vector:

$$\alpha_i = \alpha_{\min} + (\alpha_{\max} - \alpha_{\min}) \frac{(i-1)}{n-1} + \frac{i-1}{n-1} \quad i = 1, 2, 3, \dots, n. \quad (3)$$

We have experimented with varying degrees of discretization in the strain distribution (i.e., values of n); in our model runs comparing results with Shirreff *et al.* [10] (Fig 1) we use $n = 51$ (i.e. a bin width of $0.1 \log_{10}$ SPVL for α), but ~~we find only small differences when~~ reducing n to 21 (bin width = $0.25 \log_{10}$ SPVL) ~~, which we use~~ makes little difference; we use this coarser grid for all other simulations reported.

~~Baseline dynamics. Time-series of mean population virulence ($\bar{\alpha}$). (a) Shirreff model; effects of varying r . (b) Effects of varying initial infectious density $I(0)$. (c) Effects of varying initial mean virulence $\alpha(0)$.~~

We construct an n by n mutational matrix, M — which is multiplied with the transmission term — so that M_{ij} is the probability that a newly infected individual will have \log_{10} SPVL of α_j given that the infector has \log_{10} SPVL of α_i . Finally, the probabilities are normalized so that each row sums to 1:

$$M_{ij} = \frac{\Phi(\alpha_j + d/2; i) - \Phi(\alpha_j - d/2; i)}{\Phi(\alpha_{\max} + d/2; i) - \Phi(\alpha_{\min} - d/2; i)}, \quad (4)$$

where $\Phi(x; i)$ is the Gaussian cumulative distribution function with mean α_i and variance of σ_M^2 , and $d = (\alpha_{\max} - \alpha_{\min})/(n-1)$. Transmission rate and disease induced

mortality rates are discretized ~~into a vector~~ as well:

$$\begin{aligned}\beta_i &= \beta(\alpha_i), \\ \lambda_i &= \frac{1}{D_P + D_A(\alpha_i) + D_D}.\end{aligned}\tag{5}$$

Contact structure and partnership dynamics

We developed ~~six~~ seven multi-strain evolutionary models covering a gamut ~~between~~ including Champredon *et al.*'s relatively realistic [15] and Shirreff *et al.*'s relatively simple [10] epidemiological structures, each of which is based on different assumptions regarding contact structure and partnership dynamics. Specifically, we focus on the effects of the assumptions of (1) instantaneous vs. non-instantaneous partnership formation ~~and~~; (2) zero vs. positive extra-partnership sexual contact and transmission; and (3) homogeneous vs. heterogeneous levels of sexual activity on the evolution of mean \log_{10} SPVL.

Our first four models consider explicit partnership dynamics and are based on Champredon *et al.*'s model [15]. The first two (“pair-formation” or “pairform” for short) assume non-instantaneous partnership formation (i.e. individuals spend some time uncoupled, outside of partnerships) and consist of five states that are classified by infection status and partnership status. S is the number of single (uncoupled) susceptible individuals, and I is the number of single infected individuals. SS is the number of concordant negative (susceptible-susceptible) couples, SI is the number of serodiscordant (susceptible-infected) couples, and II is the number of concordant positive (infected-infected) couples. The first (“pairform+epc”) includes extra-partnership contact (with both uncoupled individuals and individuals in other partnerships) whereas the second (“pairform”) only considers within-couple transmission.

The next two models, which are intended to bridge the gap between models with fully explicit pair-formation dynamics and the simpler, implicit models used by Shirreff *et al.* [10], assume instantaneous partnership formation (“instswitch”) ~~and thus consist of~~. The compartmental structure thus omits the single states S and I , comprising only the three partnered states: SS , SI , and II . Like the first two models, ~~these models differ~~ this pair of models differs in their inclusion of extra-pair contact:

the third model (“instswitch+epc”) includes extra-partnership contact (now only with individuals in other partnerships, since uncoupled individuals ~~don’t do not~~ exist in this model) ~~and while~~ the fourth (“instswitch”) only considers within-couple transmission. Although these models can also be implemented by setting the partnership formation rate of the explicit partnership models to a high value (and we have tested that both methods in fact produce same results), we model instantaneous partnership formation models independently in order to avoid scaling of partnership formation rate during model calibration affecting the virulence trajectory.

The ~~last two models do not explicitly track sexual partnerships~~ fifth and sixth models represent extreme simplifications of sexual partnership dynamics. One (“implicit”) is an implicit serial monogamy model based on the epidemiological model used by Shirreff *et al.* [10]. It is actually a random mixing model that ~~consist of only two states, S and I , and does not consider explicit partnership dynamics~~ explicitly tracks only the total number of susceptible and infected individuals. However, to reflect the effect of ~~(instantaneously formed)~~ partnership structure, it uses an adjusted transmission rate ~~that is~~ derived from an approximation of the basic reproduction number of a serial monogamy model [18]. ~~Finally, the last model with instantaneous pair formation~~ [18]. The second model of this pair (“random”) is a simple random-mixing model.

~~The base model (i.e. Lastly, we add a model of heterogeneity in sexual activity to the pairform+epc) for the first four models is an extension model (“hetero”).~~ Individuals are divided into different risk groups based on the sexual activity level; we scale all aspects of sexual activity, assuming that sexual activity level in both within- and extra-couple contacts is directly proportional to number of non-cohabiting (extra-couple and uncoupled) partners per year [19] (see Appendix S1). We assume random activity-weighted mixing between risk groups [20]. While this model lacks some important elements, such as age-structured mixing patterns, needed for realistic models of HIV transmission in sub-Saharan Africa, it represents a first step toward assessing the effects of epidemiological complexity. As even the models shown here push the limits of compartmental-based models (the heterogeneity model comprises 24530 coupled ordinary differential equations), adding further complexity will probably require a shift to an agent-based model framework, as well as considerable

effort in model calibration [11,21].

The pairform+epc and heterogeneous models use the basic epidemiological framework of Champredon *et al.*'s model [15]. Individuals in single compartment acquire a partner at a rate ρ , and partnerships dissolve at a rate c . Infected individuals in a discordant partnership infect their susceptible partner at a rate β (within-couple transmission rate) and susceptible individuals outside the partnership at a rate c_e (extra-couple transmission rate). Likewise, a single infected individual can infect any susceptible individuals at a rate c_u through uncoupled mixing. Extra-couple and uncoupled transmission are modeled in the same way as in Champredon *et al.*'s model. All the details have been adapted to a multi-strain scenario, so that we track (for example) a matrix II_{ij} that records the number of concordant, HIV-positive couples in which the two partners have \log_{10} SPVL of α_i and α_j . The second through fourth models (pairform, instswitch+epc, instswitch) are derived from the base model by simplifying epidemiological processes (partnership formation and uncoupled/extra-couple contact). Model details are explained in the appendix; see Appendix S1).

Latin hypercube sampling

Despite considerable effort [15,18], the parameters determining the rate and structure of sexual partnership change and contact are still very uncertain; this led Champredon *et al.* [15] to adopt a Latin hypercube sampling (LHS) strategy [22] that evaluates model outcomes over a range of parameter values. In order to make sure that our comparisons among models apply across the entire space of reasonable parameter values, and in order to evaluate the differential sensitivity of different model structures to parameter values, we follow a similar protocol and perform LHS over a parameter set including both the early- and late-stage transmission and duration parameters (β_P , D_P , β_D , D_D) and contact/partnership parameters (ρ , c , c_u/c_w , and c_e/c_w). For the heterogeneity model, the mean and squared coefficient of variation (CV) for the number of non-cohabiting partners are sampled as well. We do not allow for uncertainties in parameters that are directly related to the evolutionary process (β_{\max} , β_{50} , β_k , D_{\max} , D_{50} , D_k , σ_M), instead using Shirreff *et al.*'s point estimates throughout [10].

Latin hypercube sampling is done as in Champredon *et al.* [15]. For each parameter, z , its range is divided into $N = 1000$ equal intervals on a log scale:

$$z_i = \exp \left(\log(z_{\min}) + [\log(z_{\max}) - \log(z_{\min})] \frac{i-1}{N-1} \right) \quad i = 1, \dots, N. \quad (6)$$

Random permutations of these vectors form columns in a sample parameter matrix; each row contains a different parameter set that is used for one simulation run.

Table 1 gives the ranges of the model parameters used for LHS. Parameter ranges regarding contact and partnership dynamics (ρ , c , and c_e/c_w) are taken from Champredon *et al.* [15], whereas those regarding infection (β_P , D_P , β_D , and D_D) are taken from Hollingsworth *et al.* [18]. The remaining parameters are taken from Shirreff *et al.* [10].

~~The one completely new~~ One parameter in our model, the ratio of uncoupled to within-couple transmission c_u/c_w , is needed to more flexibly contrast uncoupled and extra-couple transmission dynamics within multi-strain models (see Appendix S1); it appears neither in either Shirreff *et al.* nor Champredon *et al.*'s models, so we need to pick a reasonable range for it. Champredon *et al.* [15] assume that the effective within-couple contact rate and effective uncoupled contact rate have the same range of 0.05 - 0.25. Given Champredon *et al.*'s parameter range, the possible maximum and minimum values of c_u/c_w are 5 and 1/5. Therefore, we use 1/5-5 as the range for the parameter c_u/c_w . Although this adds more uncertainty to the parameter c_u — Champredon *et al.*'s range implies a 5-fold difference whereas ours gives a 25-fold difference — we consider the wider range appropriate, as little is not much known about the uncoupled transmission rate.

Two parameters, mean and the squared coefficient of variation (CV) of number of non-cohabiting partners, are sampled for heterogeneity in sexual activity. To allow for a wide range of uncertainty, range for the mean number of non-cohabiting partners was taken from unmarried men, as that was the group with the largest variability [19]. Omori *et al.* [19] give a very wide range for the coefficient of variation ($\approx 0 - 20$, corresponding to squared CV range of 0-400): we narrowed this range for CV² to 0.01-100. At the bottom end of the range, estimating that a group behaves perfectly homogeneously ($CV = 0$) is likely to be a sampling artifact; at the upper end, the

Table 1. Parameter ranges/values. ~~Note that Values of c and ρ values~~ are doubled from ~~those given by~~ Champredon *et al.* because we keep track of individuals ~~in the model~~, while they keep track of couples. Starred (*) parameters (used in Fig 1), and ~~Descriptions descriptions~~ of Hill function coefficients, are taken from [10].

Notation	Description	Range/Value	Source
ρ	Partnership formation rate	1/10-2/5 <u>per year</u>	[15]
c	Partnership dissolution rate	1/15-1/5 (1.25*) <u>per year</u>	[15]
c_u/c_w	Relative contact rate for uncoupled transmission	1/5-5	Assumption
c_e/c_w	Relative contact rate extra-couple	0.01-1	[15]
β_P	Rate of transmission during primary infection	1.31-5.09 (2.76*) <u>per year</u>	[18]
β_D	Rate of transmission during high transmission disease stage	0.413-1.28 (0.76*) <u>per year</u>	[18]
D_P	Duration of primary infection	1.23/12-6/12 (0.25*) <u>years</u>	[10,18] <u>[18]</u>
D_D	Duration of high transmission disease stage	4.81/12-14/12 (0.75*) <u>years</u>	[18]
β_{\max}	Maximum rate of transmission during asymptomatic stage	0.317 <u>per year</u>	[10]
β_{50}	SPVL at which infectiousness is half maximum	13938 <u>copies per ml</u>	[10]
β_k	Hill coefficient: steepness of increase in infectiousness as a function of SPVL	1.02	[10]
D_{\max}	Duration of primary infection	25.4 <u>years</u>	[10]
D_{50}	SPVL at which duration of asymptomatic infection is half maximum	3058 <u>copies per ml</u>	[10]
D_k	Hill coefficient: steepness of decrease in duration as a function of SPVL	0.41	[10]
σ_M	Mutation standard deviation of \log_{10} SPVL	0.12	[10]
α_{\min}	Minimum \log_{10} SPVL	2	[10]
α_{\max}	Maximum \log_{10} SPVL	7	[10]
n	Number of strains	21 (51*)	Assumption
μ	<u>Mean number of non-cohabiting sexual partners</u>	<u>0.103 - 1.206</u>	<u>[19]</u>
κ	<u>Squared coefficient of variation of number of non-cohabiting sexual partners</u>	<u>0.01 - 100</u>	<u>Assumption</u>
height			

estimate is also likely to be noisy because of the low mean value among married
females (who have the largest range of CV). We assume that the number of
non-cohabiting partners follows a Gamma distribution.

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Simulation runs

One of the most difficult parts of model comparison is finding parameter sets that are commensurate with many different model structures. For the most part, our models are too complex to easily derive analytical correspondences among them. Given a numerical criterion, such as r (initial exponential growth rate) or \mathcal{R}_0 (intrinsic reproductive number), we can adjust one or more parameters by brute force to ensure that all of the models match according to that criterion. While \mathcal{R}_0 is often considered the most fundamental property of an epidemic, and might thus seem to be a natural matching criterion, here we focus on matching the initial growth rate r for several reasons. First, our primary interest is in the transient evolutionary dynamics of virulence, which are more strongly affected by r than \mathcal{R}_0 . Second, r is more directly observable in real epidemics; r can be estimated by fitting an exponential curve to the initial incidence or prevalence curves [23], while \mathcal{R}_0 typically requires either (1) knowledge of *all* epidemic parameters or (2) calculations based on r and knowledge of the serial interval or generation interval of the disease [24]. Thus, we scale parameters so that every run has the same initial exponential growth rate *of in disease incidence*.

In order to allow for all models to have equal initial exponential growth rate, r , we need to pick a parameter, s , such that $\lim_{s \rightarrow 0} r(s) = 0$ and $\lim_{s \rightarrow \infty} r(s) = \infty$. As adjusting either partnership change rate (i.e. partnership formation and dissolution rate) or transmission rate fails this requirement for some of our models, we scaled partnership change rate and dissolution rate by the same factor of γ : $\beta_{\text{adj}} = \gamma \beta_{\text{base}}$, $c_{\text{adj}} = \gamma c_{\text{base}}$, $\rho_{\text{adj}} = \gamma \rho_{\text{base}}$. Since transmission rate is adjusted by the scale of γ , uncoupled and extra-couple transmission rates are adjusted as well. For the instantaneous-switching and implicit models, none of which track single individuals, only the transmission rate and partnership dissolution rate (in this case equivalent to the partnership change rate) are adjusted.

We run each model for each of 1000 parameter sets chosen by Latin hypercube sampling, with fixed starting conditions of mean \log_{10} SPVL of 3 and epidemic size of 10^{-4} . After each run, initial exponential growth rate is calculated. Then, parameters are scaled so that the initial exponential growth rate is scaled to 0.04, *which is approximately equal to that implied by a value that approximates the growth rates of*

Shirreff *et al.*'s original models.

~~The calibration runs for each parameter set are slightly simplified. We~~
~~calibration purposes, we~~ run each model for only 500 years (full simulations are run for
 4000 years), ~~and we~~ which is always long enough to capture the exponential growth
 phase of the model. We use a 4/5 order Runge-Kutta method (ode45 from the deSolve
 package [25]) ~~, whereas we use a stiff solver (LSODA) for the full simulations.~~

~~For each model we derive the following summary statistics: peak virulence, peak~~
~~time, equilibrium virulence, and relative peak virulence. The transient phase of an~~
~~epidemic is often characterized by high virulence, and we define peak virulence as the~~
~~maximum virulence during this phase. It is simply calculated by taking the maximum~~
~~value from the~~ for all simulations. (For the heterogeneous model, approximately 10%
 of the samples failed due to numerical instability.)

Although each disease strain's core characteristic is its SPVL, the SPVL has
 one-to-one correspondences (based on eq. 2) with both the expected time to
 progression to AIDS and with the rate (probability per unit time) of HIV transmission.
 Because the time to progression (measured in years) is easier to interpret than SPVL
 (measured in \log_{10} SPVL units), we summarize the virulence ~~trajectory, and peak time~~
~~is~~ trajectories for each model run in terms of time to progression rather than SPVL.
 Because the time to progression is inversely related to SPVL (increasing SPVL
 decreases the time to progression), the time to progression is technically measuring
 inverse virulence rather than virulence (we did not think that reporting virulence as
 the rate of progression to AIDS, in units of years^{-1} , would help interpretability). For
 each model we derive the following summary statistics: minimum expected time to
 progression; time at which this minimum occurs (corresponding to peak virulence —
 this is also the time at which the maximum ~~value is reached. Once the epidemic enters~~
~~the endemic phase, evolution of virulence stabilizes and reaches equilibrium.~~
 Equilibrium virulence is calculated by taking the mean virulence at ~~rate of progression,~~
 maximum SPVL, and maximum transmission rate occur); equilibrium time to
 progression; and the ratio of progression time at its minimum to the equilibrium value.
 Equilibrium progression time is calculated after 4000 years of simulated time.

Although most simulations reach equilibrium much earlier, we set our time horizon at a
 much later date as some simulation runs have slow rate of evolution depending on the

parameter set and model assumptions.

We focus on these statistics for the following two reasons. First of all, knowing the possible ranges for the peak virulence allows us to estimate the worst-case scenario for the HIV and other sexually transmitted disease epidemics. Pathogens may already have evolved towards high virulence during the early stages of an epidemic, by the time it is observed by public health authorities. Understanding how virulent a pathogen can evolve before an epidemic begins can be helpful for controlling the disease. Furthermore, knowing the initial virulence, peak virulence, Knowing the minimum progression time, timing of the minimum progression time/peak virulence, and equilibrium virulence progression time provide sufficient detail to identify the overall shape of the virulence trajectory. ~~During an epidemic outbreak, it is difficult to observe virulence evolution. Specifically, in the case of HIV and other sexually transmitted diseases, slow evolutionary time-scale makes observing changes in the mean virulence even more challenging. Knowing the ranges of these statistics can help real-time virulence evolution prediction during an epidemic less troublesome.~~In particular, knowing the timing of the peak virulence (how many years into the epidemic the virulence peaks) can help epidemiologists guess whether the virulence of an emerging pathogen is likely (1) to have peaked early, possibly even before the pathogen is detected spreading in the population, and decline over the remaining course of the epidemic; (2) to increase, peak, and decline over the foreseeable future; or (3) to increase very slowly, peaking only in the far future. To the extent that our simplistic model for HIV reflects reality, we would take the peak time of 150-300 years (Fig 1c) to mean that, in the absence of treatment, the epidemic would probably still be increasing in virulence.

Results

Our simplifications of Shirreff *et al.*'s model [10] reproduce its qualitative behaviour — in particular, its predictions of virulence dynamics — reasonably well. As r decreases from 0.084 to 0.42 (the latter value matching the initial rate of increase in prevalence in Shirreff *et al.*'s full model) the initial trajectory of increasing virulence brackets the rate from the original model (Fig 1a). However, our model produces lower peak virulence

(≈ 4.3 vs. $\approx 4.6 \log_{10}$ SPVL) and equilibrium virulence (≈ 4.25 vs. $\approx 4.5 \log_{10}$ SPVL) than Shirreff's, even for matching initial incidence trajectories (i.e., $r = 0.042 \text{ year}^{-1}$).

Changing the initial infectious density ($I(0)$), while it produces the expected changes in the initial epidemic trajectory (Supplementary material), has little effect on the virulence trajectory, making the virulence peaks slightly later and larger as $I(0)$ decreases. Decreasing $I(0)$ allows a longer epidemic phase before the transition to endemic dynamics (Fig 1b). Decreasing the initial virulence ~~similarly but more strongly~~ also leads to progressively later, larger peaks in virulence (Fig 1c).

Across the entire range of parameters covered by the LHS analysis, all of the classes of models we considered produce qualitatively similar virulence trajectories, which we quantify in terms of the expected time of progression to AIDS (Fig 2: lower progression time corresponds to higher virulence). Although the speed of virulence evolution varies, leading to wide variation in the ~~peak virulence~~ minimum expected progression time (means ranging from approximately ~~3.75 to 4.5~~ 6 to 12 years), virulence peaks in all models between 200 and 300 years.

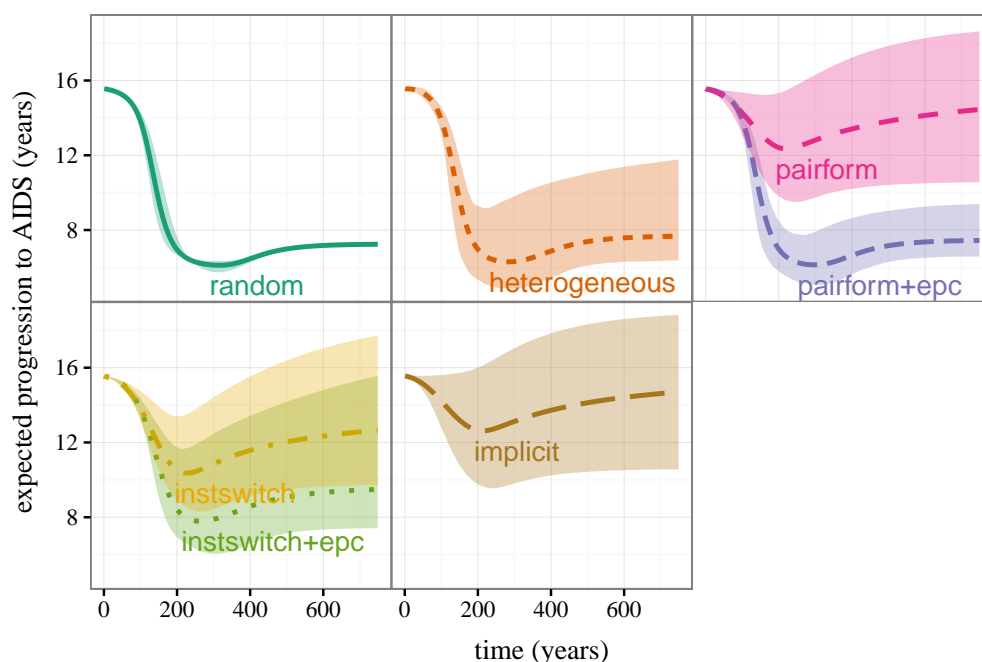


Fig 2. Envelopes of virulence trajectories (expected time of progression to AIDS) under all models. All models were run until $t = 4000$ years; truncated series are shown here.

Our chosen summary statistics (peak time, ~~peak virulence~~, ~~equilibrium~~

virulence minimum expected progression time, equilibrium expected progression time, and relative peak virulence progression time) all vary considerably across models (Fig 3). We first consider the models of intermediate realism: implicit, instantaneous-switching with and without extra-pair contact, and pair formation without extra-pair contact. Some parameter sets for these models lead to low equilibrium virulence ($\approx 2.5 \log_{10} \text{SPVL} \approx 18 \text{ years to progression}$); these same sets lead to correspondingly low peak virulence ($< 3.5 \log_{10} \text{SPVL} 16 \text{ years to progression}$) and early peak times (before 200 years), but high relative peaks (> 1.3) (Fig 4, leftmost column) because the equilibrium virulence is low). At the opposite extreme, parameter sets that produce high equilibrium virulence (8 years to progression) also produce late peaks ($> 200 \text{ years}$), $> 200 \text{ years}$ and high peak virulence, and low relative peaks (≈ 1.05 (4 years to progression)). The pair-formation without extra-pair contact and implicit models occasionally have parameter sets that select for such low virulence across the board that they never exceed their initial virulence, leading to a tail of peak times near zero.

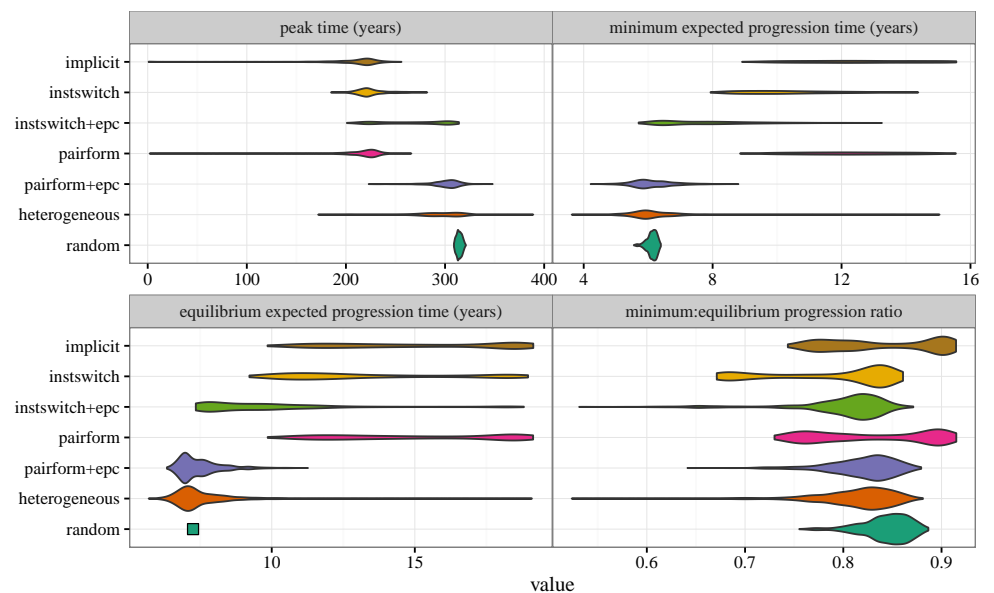


Fig 3. Univariate distributions of summary statistics. The distribution of equilibrium virulence expected progression time (lower left panel) for the random mixing model is very narrow, and has been replaced by a point in order to preserve the vertical axis scaling.

The most striking aspect of the univariate comparisons in Fig 3, (and the bivariate comparisons in Fig 4) is the similarity between the results of the least (random mixing)

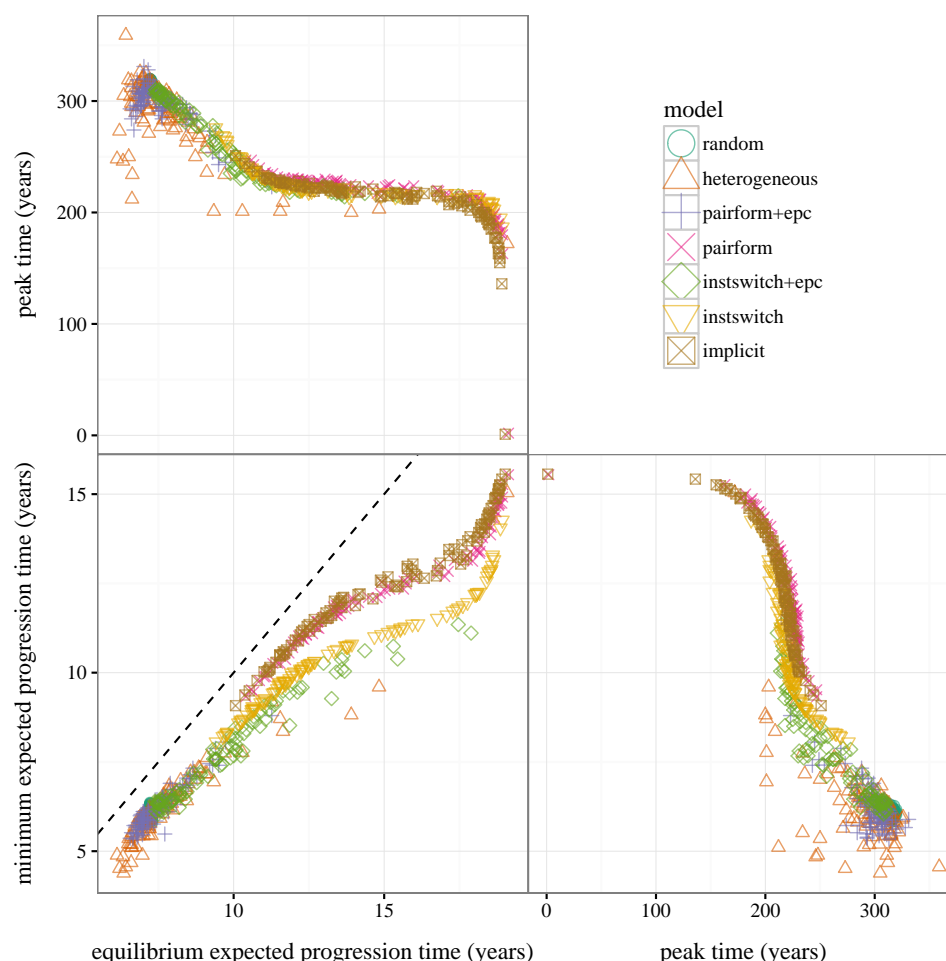


Fig 4. Pairs plot: bivariate relationships among summary statistics for each model structure. Dashed line in equilibrium vs. peak virulence plot shows 1:1 line. 100 values were sampled from each model to allow for clearer distinction between the models

and the most complex (pair formation with extra-pair contact, [pairform+epc with heterogeneity](#)) models. The random-mixing model has [lower-the lowest](#) variability, because it is unaffected by uncertainty in pair formation and extra-pair contact parameters, but otherwise the virulence dynamics of these [two-three](#) extreme models are remarkably similar. This phenomenon is driven by the strong effects of extra-pair contact in the model with explicit pair formation and extra-pair contact (“pairform+epc” in Figs 2-5). When individuals spend time uncoupled between partnerships, and when these single individuals can transmit disease to coupled individuals, the resulting unstructured mixing overwhelms the effect of structured

mixing within couples, leading to mixing that is effectively close to random. Once unstructured mixing is strong, adding realistic heterogeneity of mixing to the model has little effect other than increasing the variability in the outcomes.

~~Expressing these results in terms of more directly interpretable epidemic parameters, i.e. using the Hill functions to translate to within-couple transmission probabilities and average time of progression to AIDS, shows that these~~ These differences are practically as well as scientifically important. The random-mixing ~~and,~~ pairform+epc ~~models predict minimum times to progression (, and heterogeneous models all predict rapid progression to AIDS at the virulence peak) of 5.7~~ (median/95% CI = 6.1 (5.7-6.3) and 6.0 (5.0, 6.02 (5.04-7.7) years respectively, while, 6.03 (4.8-9.2)). In contrast, the implicit model ~~gives predicts minimum~~ progression times about twice as long: 12.5 (9.59.6-15.6) years. The corresponding differences in within-couple transmission probability are even more extreme, about a fourfold difference: 0.249 (0.24-0.26) ~~and,~~ 0.252 (0.19-0.28), and 0.252 (0.15-0.28) per year for the random and pairform+epc models vs. 0.059 (0.02-0.13) per year for the implicit model (Figs ??? show univariate distributions on the epidemiological scales of progression time ~~see Appendix S2 for plots showing univariate summaries of~~ \log_{10} SPVL and transmission probability, ~~for all summary measures and all models).~~

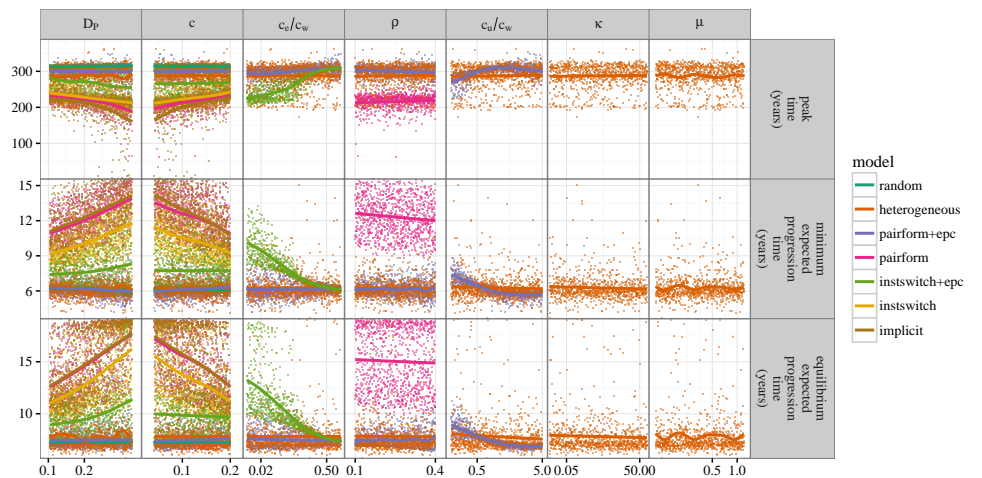


Fig 5. Sensitivity plot. For ~~each parameter most parameters~~ in the Latin hypercube sample and each summary statistic, the figure shows the distribution (points) and trend (smooth line) of the summary statistic as a function of the *unscaled* parameter value, i.e. prior to adjusting the parameters to achieve the standard initial epidemic growth rate.

~~Plotting the bivariate result distributions~~ The bivariate relationships (Fig 4) ~~shows~~

that most of the summary statistics are monotonically related, except those involving
the relative peak virulence (bottom row). Changes in parameters that increase the
equilibrium virulence initially increase the peak virulence even more, so that the
relative peak virulence increases as well, but beyond an equilibrium virulence of about
2.5 the peak virulence increases slower than the equilibrium virulence, leading to a
decrease in the relative peak virulence.

The bivariate relationships also help distinguish the results of different models with
similar univariate dynamical summaries. While the relationship between equilibrium
virulence progression time and peak time is similar for all model structures (top left
panel), the other relationships are more separate show more variation. In particular, the
implicit and pair-formation (without extra-pair contact) are very similar to each other,
but distinct from the other models. We still do not have a convincing explanation for
this distinction; we would have expected the implicit model to be most similar to the
the instantaneous-switching model without extra-pair contact, which most closely
matches its derivation. However, we note that the implicit model derivation is based on
defining the force of infection to match a scaled version of $\mathcal{R}_0 \mathcal{R}_0$, and as such would be
expected to match the equilibrium behaviour but not necessarily the epidemic-phase
behaviour of a model with explicit partnership dynamics.

Finally, the sensitivity plots plot (Fig 5) show shows the effects of each parameter
on the summary statistics. In almost every case the effects of the parameters are
monotonic; note that the plot shows the effects of the *unscaled* parameters, i.e. before
they have been calibrated to achieve a standard initial epidemic growth rate. Increases
in the transmission rates (β_P , β_D) and durations (D_P , D_D) in the primary and disease
stages generally decrease the equilibrium virulence, peak virulence, and peak time,
although the random and pair-formation+epc models have high, relatively constant
values with respect to these parameters (because the patterns are so similar across this
set of parameters. Fig 5 shows only D_P).

The partnership dissolution rate (c), which essentially acts as a contact rate in the
model, increases virulence and peak time in almost all cases, although the
pair-formation+epc model is again relatively insensitive. The ratio of extra-pair to
within-pair contact (c_e/c_w) affects virulence in the instantaneous-switching+epc model,
but not the pair-formation+epc model (probably because the uncoupled individuals

present in the pair-formation+epc model make extra-pair contact by coupled individuals less important). Surprisingly, ~~neither of the pair-formation models is particularly sensitive to the~~ once calibration is taken into account, the remaining parameters have little effect overall. The rate of partnership formation (ρ) ~~the~~ has little impact on the models with finite pair-formation times. The relative rate of uncoupled contact ~~increases virulence and~~ (c_u/c_w) slightly decreases the minimum and equilibrium progression time and delays the peak time in the pair-formation+epc model, ~~which is the only model to which it applies~~ but neither the uncoupled contact rate nor the mean (μ) or CV^2 of the number of non-cohabiting sexual partners has much systematic effect in the heterogeneous model.

Discussion

All models must simplify the world. Many constraints — ~~such as among them~~ data availability, computation time, ~~or and~~ code complexity — drive the need for parsimony, with different constraints applying in different contexts. The critical question that modelers must ask is whether the simplified model gives adequate answers, or whether the simplifications lead to qualitative or quantitative errors. This question is especially important for modelers who are hoping that their conclusions will guide management decisions.

In the particular example of HIV virulence eco-evolutionary dynamics and ~~epidemiological,~~ the complexity of epidemiological structures we reach the slightly ironic conclusion that the effort put into building a more realistic model essentially cancels out, ~~leaving us in the same position as if we had ignored the problem of epidemiological complexity entirely and~~ putting us back where we started when used a naive random-mixing contact model. ~~In Herbeck *et al.*'s [11] network model of partnerships, the partnership duration is set to 1 day~~ However, we are not quite back where we started, as the complex models lead to wider, presumably more realistic confidence intervals on the predictions. In general, unstructured mixing — very unrealistic in epidemic terms, but perhaps actually more true to real-world HIV epidemiological dynamics than a model with realistic partnership durations that neglects whether occurring through purely random mixing, or through extra-pair

contact ~~[-?]. Making~~ and contact among people outside of stable partnerships — tends to drive faster virulence evolution, leading to higher peak virulence and lower times to progression at the peak time.

Taking further steps to make the model even more realistic might ~~make~~ add further structure, making the random-mixing model ~~less appropriate~~ predictions less accurate.

For example, our model forms partnerships randomly, and assumes that extra-pair contact is randomly mixing across the population; one could instead model extra-pair contact as arising from multiple concurrent partnerships (some, such as contact with sex workers, of very short duration) and/or more structured partnership formation (by age, ethnicity, or behaviour group). The effects of other realistic complications such as explicit modeling of two sexes (both in contact structure and differential transmission probabilities), temporal and spatial variation in epidemic processes, or presence of genetic variation in hosts are harder to predict.

Parameterization is one of the biggest challenges of epidemiological modeling. In addition to following Champredon *et al.* [15] by doing Latin hypercube sampling across a wide range of epidemiological parameters, we calibrated each set of parameters to the same initial epidemic growth rate, chosen to match the results of previous models [10]. Previous models in this area have drawn their parameters from cohort studies from the 1990s [18, 26] rather than doing any explicit calibration to epidemic curves, but they give reasonable order-of-magnitude growth rates ($\approx 0.04 \text{ year}^{-1}$) for the early stages of the HIV epidemic (although considerably lower than estimates of $\approx 0.07 - 0.1 \text{ year}^{-1}$ based on population genetic reconstructions [27]). However, our reason for calibrating was not to match any specific observed epidemic, but rather to make sure that we were making meaningful comparisons across a range of models with radically different epidemiological structures, and hence involving different interpretations of the same quantitative parameters. For example, in models with instantaneous switching the partnership dissolution rate c is identical to the partnership formation rate; in models with explicit partnership formation, the partnership formation rate is also c at equilibrium, but might vary over the course of an epidemic. It is not obvious whether models with equal parameters but different structures should be directly compared; calibration solves this problem.

More generally, any model that wants to be taken seriously for management and

forecasting purposes should be calibrated to *all* available data, using informative priors to incorporate both realistic distributions of uncertainty for all parameters from independent measurements [28] and calibration from population-level observations of epidemic trajectories. Such a procedure would also be an improvement on the common — although not universal — practice, which we have followed here, of assessing uncertainty over uniform ranges rather than using distributions that allow more continuous variation in support over the range of a parameter.

Researchers have documented that HIV virulence and set-point viral load are changing, on time scales comparable to those portrayed here (e.g., compare Fig 2 to Herbeck *et al.*'s estimated rate of change of $1.3 \log_{10}$ SPVL per century [95% CI -0.1 to 3] [29]), and have begun to build relatively realistic models that attempt to describe how interventions such as mass antiretroviral therapy (ART) can be expected to change the trajectory of virulence evolution [?,30,31] [12,30,31]. While these efforts are well-intentioned, we caution that epidemiological and other structural details that are currently omitted from these models could significantly change their conclusions.

Acknowledgements

We would like to thank Christophe Fraser and David Champredon for access to simulation code; this work was funded by NSERC Discovery Grant 386590-2010.

Supporting Information

Appendix S1: ~~model details~~Model Details Since we use multi-strain models in which the distribution of ~~has been discretized into a vector~~, we use a matrix notation to describe our models. The five states described in the *Methods* section are replaced with the following notations: $S, I_i, SS, SI_i, II_{ij}$, where the subscripts denote the strain with which an individual is infected. For example, I_i is number of infected individuals with ~~of α_i~~ , and II_{ij} is the number of concordant, HIV-positive couples in which the two partners have ~~of α_i and α_j~~ (independent of order; II_{ij} is synonymous with II_{ji}). Below, we use the Kronecker delta (i.e. $\delta_{ij} = 1$ if $i = j$ and 1 otherwise) in a slightly non-standard fashion as an exponent, e.g. $2^{\delta_{ij}}$, to set a value to 2 when $i = j$

and 1 otherwise.

Appendix S2: Dynamics of Transmission and Virulence

Models 1 (“pairform+epc”) and 2 (“pairform”)

Partnership dynamics

Single individuals acquire partners at per-person rate ρ . Partnership formation rate for S, I_i are ρS and ρI_i , respectively. We follow Champredon *et al.*’s results and assume that single individuals are distributed into coupled states with pair-formation (PF) rates as follows:

$$\begin{aligned} \text{PF}(SS) &= \frac{\rho S \cdot S}{2(S + \sum_k I_k)}, \\ \text{PF}(SI_i) &= \frac{\rho S \cdot I_i}{S + \sum_k I_k}, \\ \text{PF}(II_{ij}) &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{S + \sum_k I_k}. \end{aligned}$$

Partnerships dissolve at per-partnership rate c : the dissolution rates for SS, SI_i , and II_{ij} pairs are cSS, cSI_i , and cII_{ij} respectively. Unlike single strain model, where both individuals leaving the II partnership would enter I_i , we have to account for strains which the individuals in concordant partnership are infected with (i.e. both partners in II_{ii} enter I_i whereas one partner in II_{ij} enters the I_i compartment while the other enters I_j). Thus, coupled individuals are distributed into single states through partnership dissolution (DS):

$$\begin{aligned} \text{DS}(S) &= 2cSS + \sum_k cSI_k, \\ \text{DS}(I_i) &= cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik}. \end{aligned}$$

Combining the partnership formation and dissolution processes yields the following equation:

$$\begin{aligned}
 S' &= -\rho S + 2cSS + \sum_k cSI_k \\
 I'_i &= -\rho I_i + cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} \\
 SS' &= \frac{\rho S \cdot S}{2(S + \sum_k I_k)} - cSS \\
 SI'_i &= \frac{\rho S \cdot I_i}{S + \sum_k I_k} - cSI_i \\
 II'_{ij} &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{S + \sum_k I_k} - cII_{ij}
 \end{aligned}$$

Pair-formation models: infection dynamics

Within-couple transmission (WT) occurs in both models. An infected partner in SI partnership transmits virus to a susceptible partner, and partnership state becomes II : $WT(SI_i) = -\beta_i SI_i$. Since we assume that mutation occurs, II_{ij} , where $i \neq j$, can be formed from both SI_i and SI_j partnership: $WT(II_{ij}) = M_{ij}\beta_i SI_i + M_{ji}\beta_j SI_j$. On the other hand, II_{ii} can only be formed from an SI_i partnership: $WT(II_{ii}) = M_{ii}\beta_i SI_i$. Using the Kronecker delta notation, we obtain the following set of equations that describes within-couple transmission dynamics:

$$\begin{aligned}
 WT(SI_i) &= -\beta_i SI_i, \\
 WT(II_{ij}) &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij}\beta_i SI_i + M_{ji}\beta_j SI_j)
 \end{aligned}$$

Champredon *et al.* define the proportion of infectious extra-couple and uncoupled contact through the following term:

$$P = \frac{c_u I + c_e (SI + 2II)}{c_u (S + I) + 2c_e (SS + SI + II)}.$$

The effective uncoupled, c_u , and extra couple, c_e , contact rates are the product of two terms: uncoupled/extra-couple contact rate \times rate of transmission per contact. Therefore, the transmission rate per contact term in c_u and c_e is canceled out in the equation above. Using this property, we modify the equation above as follows:

$$P = \frac{r_u I + r_e (SI + 2II)}{r_u (S + I) + 2r_e (SS + SI + II)},$$

where $r_u = c_u/c_w$ and $r_e = c_e/c_w$ are the relative uncoupled/extra-couple contact rates. This simplification is useful in a multi-strain model since we cannot multiply a vector with a single value (e.g. $c_u S$ in denominator) if we use Champredon *et al.*'s equation in its original form. Extending the above equation to multi-strain model so that P_i represents the proportion of the extra-couple and uncoupled contact of an infected individual with strain i , we obtain:

$$P_i = \frac{r_u I_i + r_e (SI_i + \sum_k (II_{ik} + \delta_{ik} II_{ik}))}{r_u (S + \sum_k I_k) + r_e (2SS + \sum_k 2SI_k + \sum_l \sum_k 2I_{lk}^{\delta} II_{lk})}.$$

Using the equation above, we can model extra-pair transmission (ET). For convenience, uncoupled and extra-couple transmission rates, c_u and c_e , will be replaced with $U_i = r_u \beta_i$ and $E_i = r_e \beta_i$ hereafter.

Single susceptible individuals become infected and enter single infected compartment at the total rate of $\sum_k P_k U_k S$. Through mutation, newly infected individuals are distributed into single infected compartments with different strains: $ET(I_i) = \sum_k M_{ki} P_k U_k S$. Either partner in an SS partnership can be infected, with the partnership state becoming SI_i , at the total rate of $\sum_i 2P_i E_i SS$. The formation of SI_i partnerships is similar to the process through which single susceptible individuals are distributed into single infected compartments: $ET(SI_i) = \sum_k 2M_{ki} P_k E_k SS$. Lastly, the susceptible partner in an SI partnership can be infected due to uncoupled/extra-couple contacts and partnership can change to an II partnership. As in the previous cases, SI_i partnerships are lost at a rate of $\sum_k P_k E_k SI_i$. The mutation process is similar to that of within-couple transmission. The only difference is that the of a newly infected partner is not determined by its social partner but from an extra-couple partner (i.e. the term P_i):

$$ET(II_{ij}) = \left(\frac{1}{2}\right)^{\delta_{ij}} \left(\sum_k (M_{kj} P_k E_k SI_i + M_{ki} P_k E_k SI_j)\right).$$

Combining these equations we get the following set of equations that describe all the transmission dynamics:

$$\begin{aligned}
 S' &= - \sum_k P_k U_k S, \\
 I'_i &= \sum_k M_{ki} P_k U_k S, \\
 SS' &= - \sum_i 2P_i E_i SS, \\
 SI'_i &= \sum_k 2M_{ki} P_k E_k SS - \beta_i SI_i - \sum_k P_k E_k SI_i, \\
 II'_{ij} &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij} \beta_i SI_i + M_{ji} \beta_j SI_j) + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \left(\sum_k (M_{kj} P_k E_k SI_i \right. \\
 &\quad \left. + M_{ki} P_k E_k SI_j) \right).
 \end{aligned}$$

Pair formation models: Disease induced mortality

The disease induced mortality (DM) rate, λ , is given by taking the reciprocal of the total duration of the infection: $\lambda_i = 1/(D_A + D_P(\alpha_i) + D_D)$. Since we assume an SIS formulation, where infected individuals that die from infection are immediately replaced by an individual in the single susceptible compartment, we obtain the following equation for single infected individuals:

$$\begin{aligned}
 \text{DM}(S) &= \sum_k \lambda_k I_k, \\
 \text{DM}(I_i) &= -\lambda_i I_i.
 \end{aligned}$$

If an infected individual in a partnership dies, the partnership dissolves. Thus, an SI_i partnership dissolves at a rate $-\lambda_i$, and the susceptible partner enters the single susceptible compartment at rate $\lambda_i SI_i$ (due to the SIS formulation the the infected partner that dies also gives rise, at an equal rate, to an individual entering the single susceptible compartment):

$$\begin{aligned}
 \text{DM}(S) &= \sum_k 2\lambda_k SI_k, \\
 \text{DM}(SI_i) &= -\lambda_i SI_i.
 \end{aligned}$$

Similarly, II_{ij} partnerships dissolve at a rate $-(\lambda_i + \lambda_j)$, but two cases, when $i \neq j$ and $i = j$, must be considered separately. When an II_{ij} partnership dissolves due to

disease-induced mortality, where $i \neq j$, the death of the partner with strain i causes its partner to enter I_j compartment at rate $\lambda_j II_{ij}$, and vice versa. When an II_i partnership dissolves, the death of either partner causes the other partner to enter the I_i compartment at rate $\lambda_i II_{ii}$, which sums up to $2\lambda_i II_{ii}$. Combining these dynamics yields:—

$$\begin{aligned} \text{DM}(S) &= \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk}, \\ \text{DM}(I_i) &= \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \\ \text{DM}(II_{ij}) &= -(\lambda_i + \lambda_j) II_{ij}. \end{aligned}$$

Finally, combining all these equations give us the full model, which is Model 1. We can simply drop the uncoupled and extra-couple transmission terms to obtain equation 2:—

$$\begin{aligned} S' &= -\rho S + 2cSS + \sum_k cSI_k - \sum_k P_k U_k S + \sum_k \lambda_k I_k \\ &\quad + \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk} \\ I_i' &= -\rho I_i + cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} + \sum_k M_{ki} P_k U_k S - \lambda_i I_i \\ &\quad + \sum_k 2^{\delta_{ik}} \lambda_k II_{ik} \\ SS' &= \frac{\rho S \cdot S}{2(S + \sum_k I_k)} - cSS - \sum_i 2P_i E_i SS \\ SI_i' &= \frac{\rho S \cdot I_i}{S + \sum_k I_k} - cSI_i - \beta_i SI_i + \sum_k 2M_{ki} P_k E_k SS - \sum_k P_k E_k SI_i \\ &\quad - \lambda_i SI_i \\ II_{ij}' &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{(S + \sum_k I_k)} - cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij} \beta_i SI_i + M_{ji} \beta_j SI_j) \\ &\quad + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \left(\sum_k (M_{kj} P_k E_k SI_i + M_{ki} P_k E_k SI_j)\right) - (\lambda_i + \lambda_j) II_{ij} \end{aligned}$$

Models 3 (“instswitch”) and 4 (“instswitch”)

Partnership dynamics

Since model 3 and 4 assume instantaneous partnership formation, there are only three states: SS , SI_i , and II_{ij} . Partnership dissolution rates are equal to those of model 1 and 2: $DS(SS) = -cSS$, $DS(SI_i) = -cSI_i$, and $DS(II_{ij}) = -II_{ij}$. Once individuals leave a partnership, they enter temporary compartments and are distributed into a partnership as follows:—

$$\begin{aligned} X &= 2cSS + \sum_k cSI_k \\ Y_i &= cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} \\ SS' &= -cSS + \frac{X^2}{2(X + \sum_k Y_k)} \\ SI'_i &= -cSI_i + \frac{XY_i}{X + \sum_k Y_k} \\ II'_{ij} &= -cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \frac{Y_i Y_j}{X + \sum_k Y_k}. \end{aligned}$$

Instantaneous-switching models: Infection dynamics

Model 3 and 4 share the within-couple transmission term with model 1 and 2. Since there is no single (uncoupled) state, only extra-couple transmission exists:—

$$P_i = \frac{r_e(SI_i + \sum_k (II_{ik} + \delta_{ik} II_{ik}))}{r_e(2SS + \sum_k 2SI_k + \sum_l \sum_k (2^{\delta_{kl}} II_{lk}))}.$$

Movement from SS state to SI state and SI to SS is modeled through the same equation that is used in model 1 and 2.—

Instantaneous-switching models: Disease induced mortality

Disease induced mortality is modeled similar to model 1 and 2. However, as single state does not exist in model 3 and 4, individuals that has left their partnerships due to death of their partners enter temporary compartments and form partners instantly:—

$$\begin{aligned}
 X &= \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk}, \\
 Y_i &= \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \\
 SS' &= \frac{X^2}{2(X + \sum_k Y_k)}, \\
 SI'_i &= -\lambda_i SI_i + \frac{XY_i}{X + \sum_k Y_k}, \\
 II'_{ij} &= -(\lambda_i + \lambda_j) II_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{Y_i Y_j}{X + \sum_k Y_k}.
 \end{aligned}$$

Combining all these dynamics, we have equation 3. If we remove extra-couple transmission, we have equation 4.

$$\begin{aligned}
 X &= 2cSS + \sum_k cSI_k + \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk}, \\
 Y_i &= cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} + \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \\
 SS &= -cSS + \frac{X^2}{2(X + \sum_k Y_k)} - \sum_i 2P_i E_i SS, \\
 SI_i &= -cSI_i + \frac{XY_i}{X + \sum_k Y_k} - \beta_i SI_i + \sum_k 2M_{ki} P_k E_k SS \\
 &\quad - \sum_k P_k E_k SI_i - \lambda_i SI_i, \\
 II_{ij} &= cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \frac{Y_i Y_j}{X + \sum_k Y_k} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij} \beta_i SI_i + M_{ji} \beta_j SI_j) \\
 &\quad + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \left(\sum_k (M_{kj} P_k E_k SI_i + M_{ki} P_k E_k SI_j)\right) - (\lambda_i + \lambda_j) II_{ij}.
 \end{aligned}$$

Implicit model

Following [10], Model 5 is an implicit instantaneous partnership formation model that uses an adjusted transmission rate, β'_i , that is derived from [18]'s approximate basic reproduction number:-

$$\beta'_i = \frac{c\beta_i}{c + \beta_i + \lambda_i}.$$

Thus, we get the following model:-

$$S' = \sum_k \lambda_k I_k - \sum_k \beta'_k S I_k.$$

$$I_i = \sum_k M_{ki} \beta'_k S I_k - \lambda_i I_i.$$

Random-mixing model

Model 6 is a random mixing model. It is modeled in a same way as model 5 without the adjusted transmission rate:-

$$S' = \sum_k \lambda_k I_k - \sum_k \beta_k S I_k,$$

$$I_i = \sum_k M_{ki} \beta_k S I_k - \lambda_i I_i.$$

Initial distribution of infected individuals

We follow Champredon *et al.*'s result to calculate the initial distribution of infected individuals. For model 1 and 2, we have disease equilibrium state of $S^* = \frac{c}{c+\rho}$ and $SS^* = \frac{1-S^*}{2}$. We let $\epsilon = 10^{-4}$, which is the total number of infected individuals in the beginning of simulation and D be the vector such that D_i represent the proportion of individuals with i . Y_i is taken from normal distribution with mean 3 and is normalized so that $\sum_i D_i = 1$. Then, we have the following initial distribution of each states:-

$$S(0) = (1 - \epsilon)S^*,$$

$$SS(0) = (1 - \epsilon)^2 SS^*,$$

$$SI_i(0) = 2\epsilon(1 - \epsilon)SS^*D_i,$$

$$I_i(0) = \epsilon S^* D_i,$$

$$II_{ij}(0) = \left(\frac{1}{2}\right)^{\delta_{ij}} 2\epsilon^2 SS^* D_i D_j.$$

Since model 3 and 4 do not have single state, $SS^* = 1$ at the disease free equilibrium and the initial distribution becomes as follows:-

$$\begin{aligned}
 SS(0) &= (1 - \epsilon)^2 SS^*, \\
 SI_i(0) &= 2\epsilon(1 - \epsilon)SS^*D_i, \\
 II_{ij}(0) &= \left(\frac{1}{2}\right)^{\delta_{ij}} 2\epsilon^2 SS^*D_iD_j.
 \end{aligned}$$

Lastly, as model 5 is an implicit model, which does not consider different stages of partnership, we have the following initial distribution:—

$$\begin{aligned}
 S(0) &= 1 - \epsilon, \\
 I_i(0) &= \epsilon D_i.
 \end{aligned}$$

Model 6 has the same distribution of initial infected individuals as model 5.—

Appendix S2: dynamics of transmission and virulence This section presents—

Envelopes of transmission trajectories under all models. This figure matches Fig 2, but displays the envelope of population-mean transmission probabilities rather than over time for each model.

Envelopes of progression trajectories under all models. This figure matches Fig 2, but displays the envelope of population-mean expected time of progression to AIDS (i.e., length of intermediate HIV phase) rather than over time for each model.

Univariate distributions of transmission probabilities and progression. This figure matches Fig 3, but displays the univariate distributions for the transmission probability and progression time at the virulence peak and at the epidemiological equilibrium, rather than the distributions of.

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