

# Effects of Contact Structure on the Transient Evolution of HIV Virulence

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## Abstract

Early in an epidemic, high densities of susceptible hosts select for relatively high parasite virulence; later in the epidemic, lower susceptible densities select for lower virulence. Thus over the course of a typical epidemic the average virulence of parasite strains increases initially, peaks partway through the epidemic, then declines again. However, precise quantitative outcomes, such as the peak virulence reached and its timing, may depend sensitively on epidemiological details. Fraser *et al.* proposed a model for the eco-evolutionary dynamics of HIV that incorporates the tradeoffs between transmission and virulence (mediated by set-point viral load, SPVL) and their heritability between hosts. Their models use implicit equations to capture the effects of partnership dynamics that are at the core of epidemics of sexually transmitted diseases. Our models combine HIV virulence tradeoffs with a range of contact models, modeling partnership formation and dissolution and allowing for individuals to transmit disease outside of partnerships. We assess summary statistics such as the peak virulence (corresponding to the minimum expected time of progression to AIDS) across models for a range of parameters applicable to the HIV epidemic in sub-Saharan Africa. Although

virulence trajectories are broadly similar across models, the timing and magnitude of the virulence peak vary considerably. Previously developed implicit models predicted lower virulence and slower progression at the peak (a minimum of 15 years to progress to AIDS) compared both to more realistic models and to simple random-mixing models with no partnership structure at all (both with a minimum of  $\approx 7.25$  years to progress to AIDS). In this range of models, the simplest random-mixing structure best approximates the most realistic model; this surprising outcome occurs because the dominance of extra-pair contact in the realistic model swamps the effects of partnership structure.

## Author Summary

Pathogens such as HIV can evolve rapidly when the environment changes. Such changes include decreases in the probability that an infectious contact (such as a sneeze for a respiratory disease, or an unprotected sex act for a sexually transmitted disease) encounters an uninfected, susceptible person and thus has a chance to transmit the pathogen. Disease spread during an epidemic reduces the fraction of susceptible people in the population and thus changes the direction of parasite evolution. While researchers have explored these evolutionary dynamics with simulations, their models have neglected important processes such as people entering and leaving sexual partnerships. We compared several evolutionary models that include partnership dynamics and sexual contact outside of stable partnerships. Models of intermediate complexity predicted lower virulence over the course of the epidemic (a minimum of 15 years to progress to AIDS) than either more realistic models or simple models without any partnership structure at all (both approx. 7.25 years to progress to AIDS), because sexual contact outside of stable partnerships tended to wash out the effects of contact structure. The large effect of epidemiological details on evolutionary dynamics suggests that researchers trying to predict the evolution of pathogens should proceed with caution.

# Introduction

The evolution of pathogen virulence has both theoretical and, potentially, practical importance. In general, evolutionary theory suggests that pathogens with higher reproduction numbers ( $\mathcal{R}_0$ ) — that is, the number of secondary infections caused by a single infected host over the course of its infectious period — will tend to increase in prevalence relative to strains with lower reproductive ratios. Pathogens can increase their reproduction numbers 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 transmission and disease-induced mortality rates are both driven by 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 others have successfully applied it to a variety of host-pathogen systems [4–7].

Fraser *et al.* have applied these ideas to HIV, showing that the virus appears to satisfy the prerequisites of the tradeoff theory. The *set-point viral load* (SPVL: i.e., the characteristic virus load measured in blood during the intermediate stage of infection) is a measurable proxy for the rate of HIV within-host reproduction. Higher viral loads are correlated with shorter progression times (higher virulence). Studies of discordant couples — stable sexual partnerships with one infected and one uninfected partner — have shown that SPVL is (1) correlated with faster transmission (the time to infection of the uninfected partner is shorter when their partner has a higher SPVL) and (2) heritable (when the uninfected member of the couple does become infected, their SPVL is similar to their partner's). Furthermore, the rate of transmission increases with increasing SPVL (and hence with decreasing progression time) but with a decreasing slope as progression time decreases, fulfilling the requirements of the tradeoff theory [8]. Subsequent studies [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 contact structures used in these models are relatively simple.

As we discuss in detail below, 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* contact structure in eco-evolutionary models.

Because our main goal is to explore how conclusions about virulence evolution depend on the way in which contact structure is modeled, we consider a series of models with increasing levels of complexity in the contact structure, but simplify some of the other epidemiological processes (such as the within-host life history of HIV). We evaluate our models across a wide range of parameters, using a Latin hypercube design; for each model run, we compute a set of metrics that summarize the evolutionary trajectory of SPVL over the course of the epidemic.

## Materials and Methods

### Infection dynamics

As in Shirreff *et al.* [10], our models explicitly track the evolution of mean  $\log_{10}$  SPVL (which we denote as  $\alpha$ ), rather than the rate of progression to AIDS itself (hereafter “virulence” 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,  $\beta$ , for our models is given by:

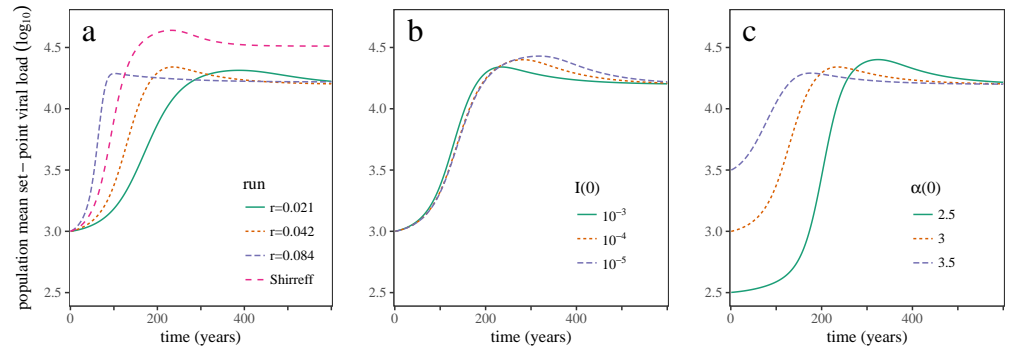
$$\beta(\alpha) = \frac{D_P\beta_P + D_A(\alpha)\beta_A(\alpha) + D_D\beta_D}{D_P + D_A(\alpha) + D_D}, \quad (1)$$

where the duration of infection ( $D_P$  and  $D_D$ ) and rate of transmission ( $\beta_P$  and  $\beta_D$ ) 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 ( $\beta_A$ ) for the Asymptomatic stage are Hill functions of the SPVL:

$$\begin{aligned} D_A(\alpha) &= \frac{D_{\max} D_{50}^{D_k}}{V_{\alpha}^{D_k} + D_{50}^{D_k}}, \\ \beta_A(\alpha) &= \frac{\beta_{\max} V_{\alpha}^{\beta_k}}{V_{\alpha}^{\beta_k} + \beta_{50}^{\beta_k}}, \end{aligned} \quad (2)$$

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  $\beta$  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 ( $\approx 200$  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. 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 in a single step at the time of transmission. First, the distribution of  $\log_{10}$  SPVL is discretized into a vector:

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

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  $\alpha$ ), but reducing  $n$  to 21 (bin width =  $0.25 \log_{10}$  SPVL) makes little difference; we use this coarser grid for all other simulations reported.

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  $\alpha_j$  given that the infector has  $\log_{10}$  SPVL of  $\alpha_i$ . 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  $\alpha_i$  and variance of  $\sigma_M^2$ , and  $d = (\alpha_{\max} - \alpha_{\min})/(n - 1)$ . Transmission rate and disease induced mortality rates are discretized as well:

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

## Contact structure and partnership dynamics

We developed seven multi-strain evolutionary models covering a gamut including Champredon *et al.*'s relatively realistic [15] and Shirreff *et al.*'s relatively simple [10] contact 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; (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”). 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, 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 do not exist in this model) 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 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 explicitly tracks only the total number of susceptible and infected individuals. However, to reflect the effect of partnership structure, it uses an adjusted transmission rate derived from an approximation of the basic reproduction number of a serial monogamy model with instantaneous pair formation [18]. The second model of this pair (“random”) is a simple random-mixing model.

Lastly, we add a model of heterogeneity in sexual activity to the pairform+epc 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.* [15]. Individuals in single compartment acquire a  
partner at a rate  $\rho$ , and partnerships dissolve at a rate  $c$ . Infected individuals in a  
discordant partnership infect their susceptible partner at a rate  $\beta$  (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  $\alpha_i$  and  $\alpha_j$ . 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: 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 ( $\beta_P$ ,  $D_P$ ,  $\beta_D$ ,  $D_D$ )  
and contact/partnership parameters ( $\rho$ ,  $c$ ,  $c_u/c_w$ , 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 ( $\beta_{\max}$ ,  $\beta_{50}$ ,  $\beta_k$ ,  $D_{\max}$ ,

$D_{50}$ ,  $D_k$ ,  $\sigma_M$ ), 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:

$$z_i = \exp \left( \log(z_{\min}) + [\log(z_{\max}) - \log(z_{\min})] \frac{i-1}{N-1} \right) \quad i = 1, 2, 3, \dots, N. \quad (6)$$

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 ( $\rho$ ,  $c$ , and  $c_e/c_w$ ) are taken from Champredon *et al.* [15], whereas those regarding infection ( $\beta_P$ ,  $D_P$ ,  $\beta_D$ , and  $D_D$ ) are taken from Hollingsworth *et al.* [18]. The remaining parameters are taken from Shirreff *et al.* [10].

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  $CV^2$  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. Values of  $c$  and  $\rho$  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 of Hill function coefficients, are taken from [10].

Notation	Description	Range/Value	Source
$\rho$	Partnership formation rate	1/10-2/5 per year	[15]
$c$	Partnership dissolution rate	1/15-1/5 (1.25*) per year	[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]
$\beta_P$	Rate of transmission during primary infection	1.31-5.09 (2.76*) per year	[18]
$\beta_D$	Rate of transmission during high transmission disease stage	0.413-1.28 (0.76*) per year	[18]
$D_P$	Duration of primary infection	1.23/12-6/12 (0.25*) years	[18]
$D_D$	Duration of high transmission disease stage	4.81/12-14/12 (0.75*) years	[18]
$\beta_{\max}$	Maximum rate of transmission during asymptomatic stage	0.317 per year	[10]
$\beta_{50}$	SPVL at which infectiousness is half maximum	13938 copies per ml	[10]
$\beta_k$	Hill coefficient: steepness of increase in infectiousness as a function of SPVL	1.02	[10]
$D_{\max}$	Duration of primary infection	25.4 years	[10]
$D_{50}$	SPVL at which duration of asymptomatic infection is half maximum	3058 copies per ml	[10]
$D_k$	Hill coefficient: steepness of decrease in duration as a function of SPVL	0.41	[10]
$\sigma_M$	Mutation standard deviation of $\log_{10}$ SPVL	0.12	[10]
$\alpha_{\min}$	Minimum $\log_{10}$ SPVL	2	[10]
$\alpha_{\max}$	Maximum $\log_{10}$ SPVL	7	[10]
$n$	Number of strains	21 (51*)	Assumption
$\mu$	Mean number of non-cohabiting sexual partners	0.103 - 1.206	[19]
$\kappa$	Squared coefficient of variation of number of non-cohabiting sexual partners	0.01 - 100	Assumption

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.

## 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 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  $\gamma$ :  $\beta_{\text{adj}} = \gamma\beta_{\text{base}}$ ,  $c_{\text{adj}} = \gamma c_{\text{base}}$ ,  $\rho_{\text{adj}} = \gamma\rho_{\text{base}}$ . Since transmission rate is adjusted by the scale of  $\gamma$ , 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, a value that approximates the growth rates of Shirreff *et al.*'s original models. For calibration

purposes, we run each model for only 500 years (full simulations are run for 4000 years), 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]) 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 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  $\text{years}^{-1}$ , 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 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.

Knowing the minimum progression time, timing of the minimum progression time/peak virulence, and equilibrium progression time provide sufficient detail to identify the overall shape of the virulence trajectory. 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.

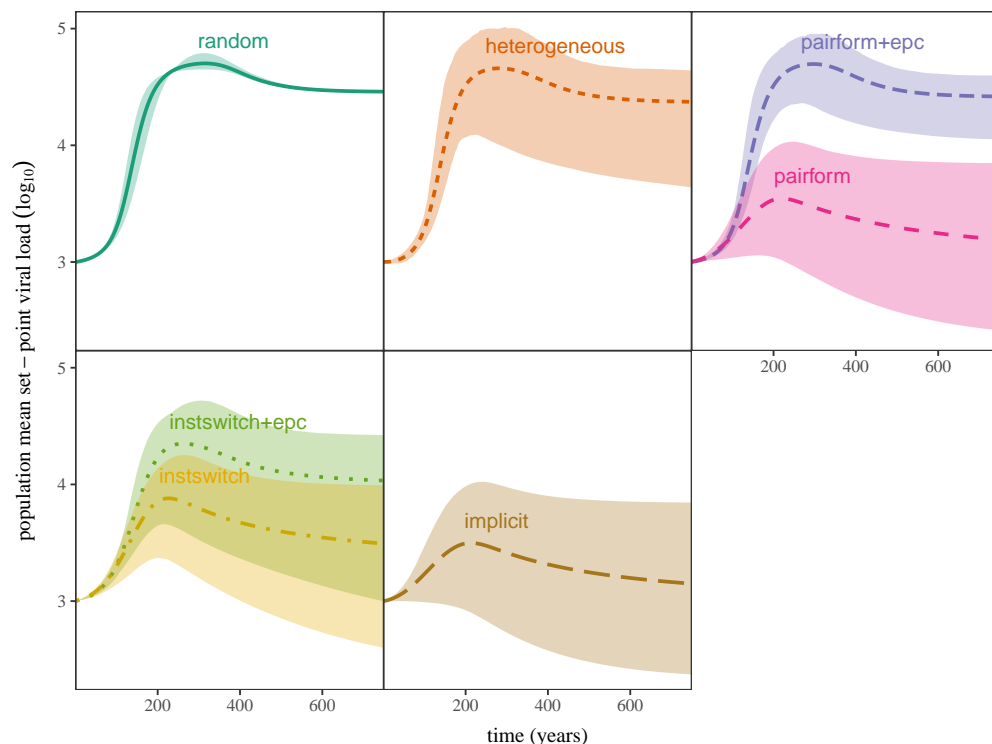
## Results

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 ( $\approx 4.3$  vs.  $\approx 4.6 \log_{10}$  SPVL) and equilibrium virulence ( $\approx 4.25$  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 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 minimum expected progression time (means ranging from approximately 6 to 12 years), virulence peaks in all models between 200 and 300 years.

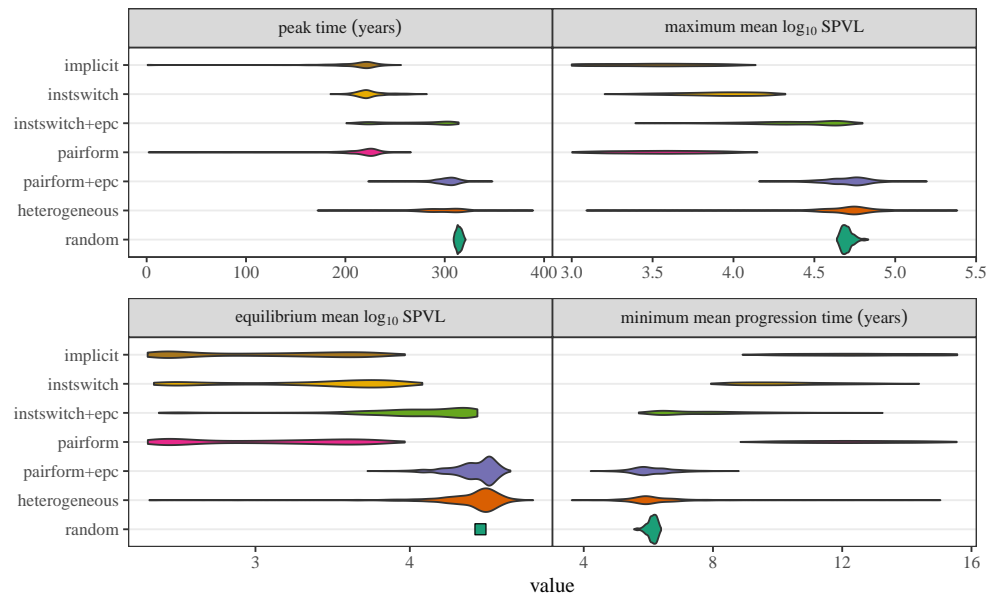
Our chosen summary statistics (peak time, minimum expected progression time, equilibrium expected progression time, and relative progression time) all vary considerably across models (Fig 3). We first consider the models of intermediate realism: implicit, instantaneous-switching with and without extra-pair contact, and pair formation without extra-pair contact. Some parameter sets for these models lead to low equilibrium virulence ( $\approx 18$  years to progression); these same sets lead to correspondingly low peak virulence (16 years to progression) and early peak times



**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.

(before 200 years: Fig 4). At the opposite extreme, parameter sets that produce high equilibrium virulence (8 years to progression) also produce late peaks ( $> 200$  years) and high peak virulence (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.

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) and the most complex (pair formation with extra-pair contact, pairform+epc with heterogeneity) models. The random-mixing model has the lowest variability, because it is unaffected by uncertainty in pair formation and extra-pair contact parameters, but otherwise the virulence dynamics of these 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



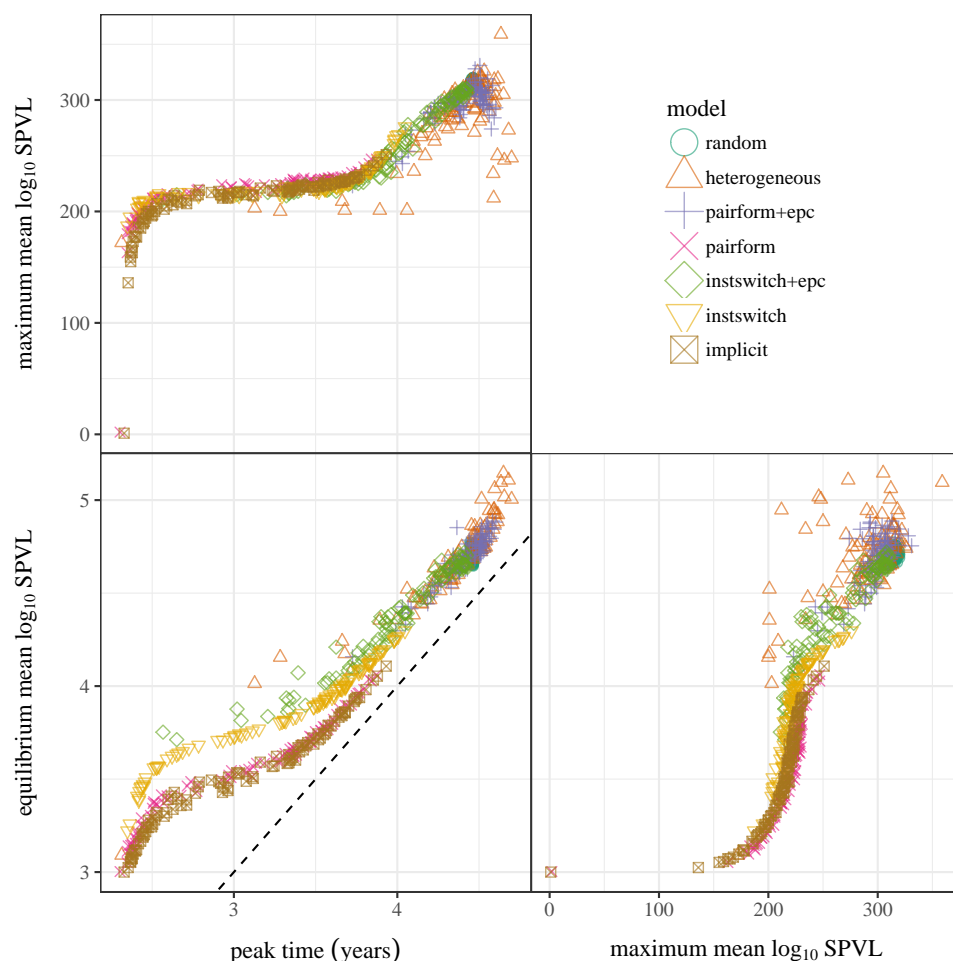
**Fig 3. Univariate distributions of summary statistics.** The distribution of equilibrium expected progression time (lower left panel) for the random mixing model is very narrow, and has been replaced by a point in order to preserve the vertical axis scaling.

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.

These differences are practically as well as scientifically important. The random-mixing, pairform+epc, and heterogeneous models all predict rapid progression to AIDS at the virulence peak (median/95% CI = 6.1 (5.7-6.3), 6.02 (5.04-7.7), 6.03 (4.8-9.2)). In contrast, the implicit model predicts minimum progression times about twice as long: 12.5 (9.6-15.6) years. The corresponding differences in within-couple transmission probability are even more extreme, about a fourfold difference: 0.249 (0.24-0.26), 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 (see Appendix S2 for plots showing univariate summaries of  $\log_{10}$  SPVL and transmission probability).

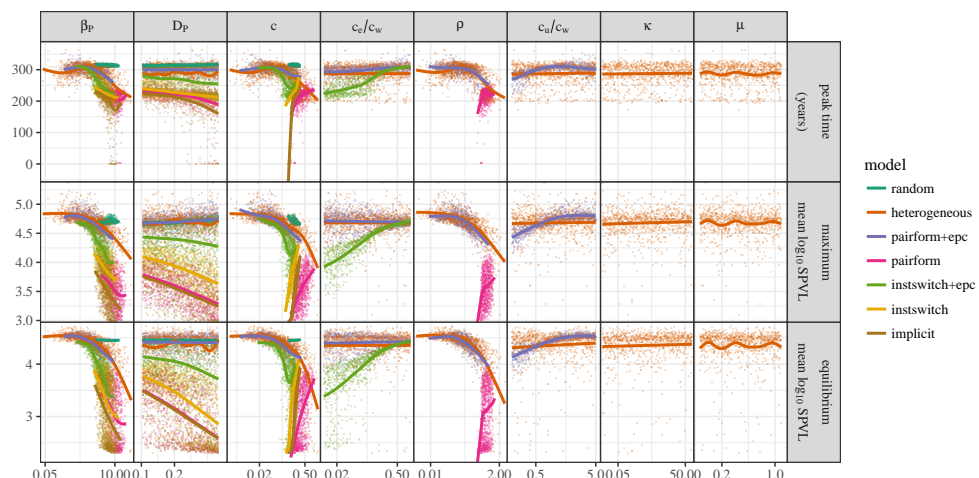
The bivariate relationships (Fig 4) help distinguish the results of different models with similar univariate dynamical summaries. While the relationship between equilibrium progression time and peak time is similar for all model structures (top left





**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

panel), the other relationships 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 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  $\mathcal{R}_0$ , 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.



**Fig 5. Sensitivity plot.** For 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.

Finally, the sensitivity plot (Fig 5) shows the effects of each parameter on the summary statistics. The most notable difference can be observed by comparing the scaled parameters (e.g.  $\beta_P$ ,  $\beta_D$ ,  $c$ ,  $\rho$ ) with the unscaled parameters (e.g.  $D_P$ ,  $D_D$ ,  $c_e/c_w$ ,  $c_u/c_w$ ,  $\kappa$ ,  $\mu$ ); note that the effects of  $\beta_D$  and  $D_D$  are not shown in Fig 5 as their patterns are so similar to  $\beta_P$  and  $D_P$ , respectively.

One of the distinguishing features of the scaled parameters (in comparison to the unscaled parameters) is that the range of the parameters is compressed (relative to other models) for models without extra-pair contact as those models require parameters to be scaled by a large value in order to achieve a given  $r$  of 0.04. Models with extra-pair contact show wide range parameters as they can display a wide range of dynamics depending on  $c_e/c_w$  (as well as  $c_u/c_w$  for models with uncoupled mixing) and thus require wide range of scaling factors to achieve the target  $r$ . Parameter range for random-mixing model is severely compressed because latin hypercube sampling does not affect the prevalence trajectory very much, and scaling factor does not vary much across parameters.

For parameters involved in partnership turnover ( $c$  and  $\rho$ ), main distinction is between models with and without extra-pair contact. With extra-pair contact, we get gradual decrease in peak time, maximum  $\log_{10}$  SPVL, and equilibrium  $\log_{10}$  SPVL with increasing turnover rates; Otherwise we get increase in summary statistics. Although we

have not verified this idea analytically, we speculate that increase in turnover rates diminishes the effect of epc (equivalently increasing relative importance of within-partnership contact), therefore selecting for lower  $\log_{10}$  SPVL. For models without epc, increased rates of partnership change decrease the level of structured mixing (mimicing epc models), resulting in selection for higher  $\log_{10}$  SPVL.

We also note that the implicit model and the instantaneous partnership formation model show similar patterns in scaled parameters. In fact, we can see that the effect of partnership dissolution rate,  $c$ , on equilibrium  $\log_{10}$  SPVL of the two models are almost identical (in Fig 4, they have distinguishing features). Lastly, we note that increase in transmission rates ( $\beta_P$  and  $\beta_D$ ) has a decreasing effect on summary statistics for all models except for random mixing model.

Surprisingly, once calibration is taken into account, the unscaled parameters have little to no effect overall. Increase in duration ( $D_P$ ,  $D_D$ ) in the primary and disease stages generally decrease the equilibrium virulence, peak virulence, and peak time, although the models with uncoupled mixing and random mixing model have high, relatively constant values with respect to these parameters. The ratio of extra-pair to within-pair contact ( $c_e/c_w$ ) affects summary statistics 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). Similarly, increasing the ratio of uncoupled to within-pair contact,  $c_u/c_w$ , increases peak and equilibrium  $\log_{10}$  SPVL and delays peak time of the pair-formation+epc model but has almost no effect on the heterogeneous model. Neither the uncoupled contact rate nor the mean ( $\mu$ ) 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 — among them data availability, computation time, 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 the complexity of contact structures we reach the slightly ironic conclusion that the effort put into building a more realistic model essentially cancels out, putting us back where we started when used a naive random-mixing contact model. 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 — whether occurring through purely random mixing, or through extra-pair contact 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 add further structure, making the random-mixing model 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 contact 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 [12,30,31]. While these efforts are well-intentioned, we caution that structural details that are currently omitted from these models could significantly change their conclusions.

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## Supporting Information

**Appendix S1: Model Details**

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**Appendix S2: Dynamics of Transmission and Virulence**

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