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

Sang Woo Park[1] Benjamin M. Bolker[2,3,4,*]

**1** Program in Health Sciences, McMaster University, Hamilton, Ontario, Canada

**2** Department of Mathematics & Statistics, McMaster University, Hamilton, Ontario, Canada

**3** Department of Biology, McMaster University, Hamilton, Ontario, Canada

**4** Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada

\* bolker@mcmaster.ca

## Abstract

The evolutionary dynamics of parasite virulence 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. In general changes in fitness landscapes over the course of an epidemic will select for higher virulence during the early, exponential-growth phase of the epidemic, but quantitative outcomes can depend sensitively on biological details and the structure of mathematical models used to capture them. Fraser, Shirreff, and co-workers have proposed a series of models for eco-evolutionary dynamics of HIV that are relatively detailed in their portrayal of the tradeoffs between transmission and virulence (mediated by set-point viral load, SPVL) and their heritability between hosts. However, these models use very simple implicit representations of the transmission process that ignore the partnership dynamics that previous research has found to be critical in predicting epidemics of sexually transmitted diseases. We explore models that 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 across all models and across a Latin hypercube sample that captures a realistic range of partnership dynamic parameters for sub-Saharan Africa. In order to account for the different interpretations of parameters across model structures, we scale all parameter sets to constrain the simulated epidemic growth rate to be identical, matching a realistic baseline value. Our primary result is that, for this particular model setting, the simplest random-mixing structure is actually the best approximation to the most realistic model; this surprising outcome occurs because the dominance of extra-pair contact in the realistic model tends to mask the effects of partnership structure.

## Author Summary

Pathogens such as HIV can evolve rapidly in response to changing conditions; such changes include both the increases in disease incidence over the course of the epidemic and treatment interventions. While researchers have successfully used computational models to explore these evolutionary dynamics, these models often neglect epidemiological processes, 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 with a range of realism and complexity in the way they modeled both partnership dynamics and the possibility of sexual contact outside of partnerships. In contrast to models of intermediate complexity, simple random-mixing models with no partnership structure at all actually gave the closest match to the most realistic and complex models; extra-pair contact tended to wash out the effects of epidemiological structure. Nevertheless, 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 both theoretical and (potentially) practical importance. The trade-off theory [1] — 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 — has been criticized [2,3], but has also been successfully applied in a variety of host-pathogen systems [4–7]. One particularly interesting application of these ideas is the work by Fraser *et al.* showing that HIV appears to satisfy the prerequisites of the tradeoff theory: in a study 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 (i.e., the characteristic virus load measured in blood during the intermediate stage of infection), which in turn predicted the probability of within-couple transmission [8,9]. Subsequent studies [10,11] 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 [XXX] 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 [12,13]. However, despite the attention to mechanistic 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.* [14]; individuals join and leave partnerships at a specified rate, and

can have sexual contact both within and outside of established partnerships. At the 32
same time, our analysis somewhat simplifies the models of Shirreff *et al.* [10], for 33
computational tractability; we check that our qualitative results are not sensitive to 34
these simplifications. In order to explore how virulence evolution depends on 35
epidemiological structure, we consider a series of models with increasing levels of 36
complexity. In order to avoid dependence of the results on a particular set of 37
parameters — as we explain below, finding matching sets of parameters across models 38
with widely differing epidemiological structures is challenging — we evaluate our models 39
across a wide range of parameters, again following Champredon *et al.* [14] in using a 40
Latin hypercube design. For each model run, we compute a set of metrics (peak 41
virulence, timing of virulence peak, equilibrium virulence) that summarize the 42
evolutionary trajectory of a simulated HIV epidemic. 43

As our primary goal is to explore how different epidemiological structures (i.e. 44
partnership dynamics and contact structures) affect our conclusions about the evolution 45
of virulence, our models use a simplified description of within-host dynamics and 46
heritability derived from Shirreff *et al.*'s multi-strain evolutionary model [10]. Like 47
Shirreff *et al.*, we use a simple susceptible-infected-susceptible demographic formulation; 48
rather than modeling birth and death (or more specifically, recruitment into the 49
sexually active population and death), we assume that whenever an individual dies from 50
infection, another enters the susceptible compartment. 51

## Materials and Methods 52

### Infection dynamics 53

Like Shirreff *et al.* [10], we focus on the evolution of mean $\log_{10}$ set-point viral load, 54
SPVL (which we denote as $\alpha$), rather than virulence (i.e. rate of progression to AIDS) 55
itself. In contrast to Shirreff *et al.*, we use a single-stage disease model instead of 56
accounting explicitly for progression through the three main stages of HIV infection 57
(primary, asymptomatic, and disease), and we use a simple exponentially distributed 58
infectious period instead of a more realistic Weibull-distributed infectious period. We 59
account for varying transmission rates and durations of each disease stage by summing 60

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:

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

where the duration of infection ($D_P$ and $D_D$) and rate of transmission ($\beta_P$ and $\beta_D$) of

the **P**rimary and **D**isease 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 **A**symptomatic stage are Hill functions of the SPVL:

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

where $V_\alpha = 10^\alpha$. The **u**ncoupled and **e**xtra-couple transmission rates are scaled by

multiplying the **w**ithin-couple transmission rate $\beta$ by the contact ratios $c_u/c_w$ and

$c_e/c_w$.

## Mutation

Like Shirreff *et al.* [10] we incorporate a between-host mutation process in the SPVL,

but simplify Shirreff *et al.*'s evolutionary model slightly by using a one-to-one

genotype-phenotype mapping. 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 an infected individual is determined by the SPVL

at the time of infection for simplicity (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. First, the distribution of $\log_{10}$ SPVL is

discretized into a vector:

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

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 we find only small

differences when reducing $n$ to 21 (bin width 0.25 $\log_{10}$ SPVL), which we use for all

other simulations.

**Fig 1. Baseline dynamics.** Time series of mean population virulence ($\log_{10}$ SPVL). (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 $\alpha_j$ given that the infector has $\log_{10}$ SPVL of $\alpha_i$. Finally, the

probabilities are normalized so that each row sums to 1:

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

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 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 multi-strain evolutionary models, designed to cover a gamut between

Champredon *et al.*'s relatively realistic [14] and Shirreff *et al.*'s relatively simplistic [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 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 [14]. Models 1 and 2 assume non-instantaneous partnership

formation (i.e. individuals spend some time uncoupled, outside of partnerships) and ~103~

consist of five states that are classified by infection status and partnership status. $S$ is ~104~

the number of single (uncoupled) susceptible individuals, and $I$ is the number of single ~105~

infected individuals. $SS$ is the number of susceptible-susceptible couples, $SI$ is the ~106~

number of serodiscordant (susceptible-infected) couples, and $II$ is the number of ~107~

concordant positive (infected-infected) couples. Model 1 includes extra-partnership ~108~

contact (with both uncoupled individuals and individuals in other partnerships) whereas ~109~

model 2 only considers within-couple transmission. Models 3 and 4 assume ~110~

instantaneous partnership formation and thus consist of only the three partnered states: ~111~

$SS$, $SI$, and $II$. Parallel to model 1 and 2, model 3 includes extra-partnership contact ~112~

(now only with individuals in other partnerships, since uncoupled individuals don't exist ~113~

in this model) and model 4 only considers within-couple transmission. ~114~

In contrast, models 5 and 6 are not explicitly structured. Model 5 is an implicit ~115~

serial monogamy model based on the epidemiological model used by Shirreff *et al.* [10]. ~116~

It is actually a random mixing model that consist of only two states, $S$ and $I$, and does ~117~

not consider explicit partnership dynamics. However, to simulate the effect of ~118~

instantaneous partnership formation, it uses an adjusted transmission rate that is ~119~

derived from approximated basic reproduction number of a serial monogamy model [15]. ~120~

Finally, model 6 is a simple random-mixing model. ~121~

The base model (i.e. model 1) for the first four models is an extension of ~122~

Champredon *et al.*'s model [14]. Individuals in single compartment acquire a partner at ~123~

a rate, $\rho$, and partnerships dissolve at a rate, $c$. Infected individuals in a discordant ~124~

partnership infect susceptible partner at a rate $\beta$ (within-couple transmission rate) and ~125~

susceptible individuals outside the partnership at a rate $c_e$ (extra-couple transmission ~126~

rate). Likewise, a single infected individual can infect any susceptible individuals at a ~127~

rate $c_u$ through uncoupled mixing. Extra-couple and uncoupled transmission are ~128~

modeled in a same way as Champredon *et al.*'s model. All the details have been ~129~

adapted to a multi-strain scenario. Model 2, 3, and 4 are derived from the base model ~130~

by removing epidemiological details (partnership formation and uncoupled/extra-couple ~131~

contact). Model details are explained in the appendix. ~132~

## Latin hypercube sampling

Despite considerable effort by many researchers [14, 15], the parameters determining the rate and structure of sexual partnership change and contact are still very uncertain; this led Champredon *et al.* [14] to adopt a Latin hypercube sampling (LHS) strategy [16] 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 transmission and duration parameters ($\beta_P$, $D_P$, $\beta_D$, $D_D$) and contact/partnership parameters ($\rho$, $c$, $c_u/c_w$, and $c_e/c_w$). We do not allow for uncertainties in parameters that are directly related to the evolutionary process ($\beta_{\max}$, $\beta_{50}$, $\beta_k$, $D_{\max}$, $D_{50}$, $D_k$, $\sigma_M$), using Shirreff *et al.*'s point estimates throughout [10].

Latin hypercube sampling is done as in Champredon *et al.* [14]. For each parameter, $z$, its range is divided into $N = 1000$ equal intervals on a log scale:

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

For simplicity, we assume that all parameters are uniformly distributed on the log scale. Following the vectorization of a parameter range, a matrix is constructed so that each column contains a vector of a parameter series which it represents ($z_1,...z_N$). Then, each column is replaced with a random permutation series of itself. Now, each row contains a different parameter set that is used for each 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.* [14], whereas those regarding infection ($\beta_P$, $D_P$, $\beta_D$, and $D_D$) are taken from Hollingsworth *et al.* [15]. The remaining parameters are taken from Shirreff *et al.* [10].

The one completely new 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 (Appendix); we need to pick a reasonable range for it. Champredon *et al.* [14] assume that the effective within-couple contact rate and effective uncoupled contact rate have the same range of

**Table 1.** Parameter ranges/values. Note that $c$ and $\rho$ values are doubled from Champredon *et al.* because we keep track of individuals, while they keep track of couples. Starred (*) parameters (used in Figure 1) are from [10].

| Notation | Description | Range/Value | Source |
|---|---|---|---|
| $\rho$ | Partnership formation rate | 1/10-2/5 | [14] |
| $c$ | Partnership dissolution rate | 1/15-1/5 (1.25*) | [14] |
| $c_u/c_w$ | Relative contact rate for uncoupled transmission | 1/5-5 | Assumption |
| $c_e/c_w$ | Relative contact rate extra-couple | 0.01-1 | [14] |
| $\beta_P$ | Rate of transmission during primary infection | 1.31-5.09 (2.76*) | [15] |
| $\beta_D$ | Rate of transmission during high transmission disease stage | 0.413-1.28 (0.76*) | [15] |
| $D_P$ | Duration of primary infection | 1.23/12-6/12 (0.25*) | [10, 15] |
| $D_D$ | Duration of high transmission disease stage | 4.81/12-14/12 (0.75*) | [15] |
| $\beta_{\max}$ | Maximum rate of transmission during asymptomatic stage | 0.317 | [10] |
| $\beta_{50}$ | SPVL at which infectiousness is half maximum | 13938 | [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 | [10] |
| $D_{50}$ | SPVL at which duration of asymptomatic infection is half maximum | 3058 | [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 |

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 — as there is not much known about the uncoupled transmission rate, we consider the wider range appropriate.

## Simulation runs

One of the most difficult parts of model comparison is finding parameter sets that are commensurate against 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 goal, 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 in general more directly observable in real epidemics; $r$ can be estimated by simply fitting an exponential curve to the initial incidence or prevalence curves [17], while $\mathcal{R}_0$ typically requires either (1) knowledge of *all* epidemic parameters or (2) relatively sophisticated back-calculation based on $r$ and knowledge of the serial interval or generation interval of the disease [18]. Thus, we scale a parameter so that every run has the same initial exponential growth rate in the incidence.

In order to allow for all models to have equal initial exponential growth rate, $r$, we need to pick a parameter, $s$, so that $\lim_{s \to 0} r(s) = 0$ and $\lim_{s \to \infty} r(s) = \infty$. As adjusting either partnership change rate (i.e. partnership formation and dissolution rate) or transmission rate does not fulfill this requirement for certain models, we decided to scale 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 models 3, 4, and 5, all of which assume instantaneous partnership (and hence do not 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 of Shirreff *et al.*'s model.

In order to make the computation faster, we simplify the model simulations to calculate $\gamma$ for each run. While scaling the parameters to match the exponential growth rate to a target value, models are ran for only 500 years, unlike the real simulations (ran

for 4000 years) which are run after the parameters are scaled to obtain the summary statistics. Furthermore, we use Runge-Kutta method ode45 to find $\gamma$ whereas lsoda is used for the actual 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 virulence trajectory, and peak time is 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 4000 years. 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, timing of the peak virulence, and equilibrium virulence provide sufficient detail to identify the 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.

## 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 233
from the original model (Fig. 1a). However, our model produces lower peak virulence 234
($\approx 4.3$ vs. $\approx 4.6$ $\log_{10}$ SPVL) and equilibrium virulence $\approx 4.25$ vs. $\approx 4.5$ $\log_{10}$ SPVL) 235
than Shirreff's, even for matching initial incidence trajectories (i.e., $r = 0.042$ year$^{-1}$). 236

Changing the initial infectious density ($I(0)$), while it produces the expected changes 237
in the initial epidemic trajectory (Supplementary material), has little effect on the 238
virulence trajectory, making the virulence peaks slightly later and larger as $I(0)$ 239
decreases. Decreasing $I(0)$ allows a longer epidemic phase before the transition to 240
endemic dynamics (Fig. 1b). Decreasing the initial virulence similarly but more strongly 241
leads to progressively later, larger peaks in virulence (Fig. 1c). 242

Across the entire range of parameters covered by the LHS analysis, all of the classes 243
of models we considered produce qualitatively similar virulence trajectories (Fig. 2). 244
Although the speed of virulence evolution varies, leading to wide variation in the peak 245
virulence (means ranging from approximately 3.75 to 4.5 $\log_{10}$ SPVL), virulence peaks 246
in all models between 200 and 300 years. 247

**Fig 2. Envelopes of virulence trajectories 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, 248
and relative peak virulence) all vary considerably across models 3. We first consider the 249
models of intermediate realism (implicit, instantaneous-switching with and without 250
extra-pair contact ("epc" hereafter), and pair formation without extra-pair contact). 251
Some parameter sets for these models lead to low equilibrium virulence ($\approx 2.5 \log_{10}$ 252
SPVL); these same sets lead to correspondingly low peak virulence ($< 3.5 \log_{10}$ SPVL) 253
and early peak times (before 200 years), but high relative peaks ($> 1.3$) (Fig. 4, leftmost 254
column) because the equilibrium virulence is low. At the opposite extreme, parameter 255
sets that produce high equilibrium virulence also produce late peaks ($> 200$ years), high 256
peak virulence, and low relative peaks ($\approx 1.05$). The pair-formation without extra-pair 257
contact and implicit models occasionally have parameter sets that select for such low 258
virulence across the board that they never exceed their initial virulence, leading to a tail 259
of peak times near zero. 260

The most striking aspect of the univariate comparisons in Fig. 3, (and the bivariate 261

**Fig 3. Univariate distributions of summary statistics.** The distribution of equilibrium virulence for the random mixing model is very narrow, and has been replaced by a point in order to preserve the vertical axis scaling.

**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.

comparisons in Fig. 4) is the match between the output of the least (random mixing) and the most complex (pair formation with extra-pair contact) models. The random-mixing model has lower variability, because it is unaffected by uncertainty in pair formation and extra-pair contact parameters, but otherwise the virulence dynamics of these two extreme models are remarkably similar. This phenomenon is driven by the strength of extra-pair contact in the model with explicit pair formation and extra-pair contact ("pairform+epc" in Figures 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.

**Fig 5. Sensitivity plot.** For each parameter in the Latin hypercube sample and each summary statistic, 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 (Fig. 4) shows that most of the relationships among the summary statistics are monotonic, 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 $\log_{10}$ SPVL 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 distributions. While the relationship between equilibrium virulence and peak time is similar for all model structures (top left panel), the other relationships are more separate. 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 $\mathcal{R}_0$, 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 (Fig. 5) show 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 adjusted to achieve a standard initial epidemic growth rate. Increases in the transmission rates ($\beta_P$, $\beta_D$) 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+extra-pair contact models have high, relatively constant values with respect to these parameters.

The base contact rate increases virulence and peak time in almost all cases, although the pair-formation+extra-pair contact 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 rate of partnership formation ($\rho$); the rate of uncoupled contact increases virulence and peak time in the pair-formation+epc model, which is the only model to which it applies.

## Discussion

All models must simplify the world. Many constraints — such as data availability, computation time, or 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 have led to qualitatively or quantitatively incorrect conclusions. 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, 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 used a naive random-mixing contact model. Herbeck *et al.* [11] build a network model of partnerships, but they set the "partnership" duration to 1 day — 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 extra-pair contact [19]. Adding still further realism might push the results farther away from the random-mixing model. For example, our model forms partnerships randomly, and assumes that extra-pair contact is randomly mixing across the population; one could instead implement extra-pair contact as arising from multiple concurrent partnerships (some, such as contact with sex workers, of very short duration), 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.* [14] 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]. The previous models drew their parameters from previous cohort studies from the 1990s [15, 20] rather than doing any explicit calibration to epidemic curves, but they give reasonable order-of-magnitude growth rates ($\approx 0.04$ year$^{-1}$) for the early stages of the HIV epidemic (although considerably lower than estimates of $\approx 0.07 - 0.1$ year$^{-1}$ based on population genetic reconstructions [21]). 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                347
equilibrium, but might vary over the course of an epidemic. It is not obvious whether            348
models with equal parameters but different structures should be directly compared;               349
calibration solves this problem.                                                                  350

More generally, any model that wants to be taken seriously for management and                    351
forecasting purposes should be calibrated to *all* available data, using informative priors      352
to incorporate both realistic distributions of uncertainty for all parameters from               353
independent measurements [22] and calibration from population-level observations of              354
epidemic trajectories. For practical (rather than exploratory) purposes, such a                   355
procedure would also be an improvement on the common — although not universal —                   356
practice of assessing uncertainty over uniform ranges, rather than distributions that             357
allow more continuous variation in support over the range of a parameter.                         358

Researchers have documented that HIV virulence and set-point viral load are                       359
changing, on time scales comparable to those portrayed here (e.g., compare Fig. 2 to              360
Herbeck *et al.*'s estimated rate of change of 1.3 $\log_{10}$ SPVL per century [95% CI -0.1 to   361
3] [23]), and have begun to build relatively realistic models that attempt to describe            362
how interventions such as mass antiretroviral therapy (ART) can be expected to change             363
the trajectory of virulence evolution [19, 24]. While these efforts are well-intentioned, we      364
caution that epidemiological and other structural details that are currently omitted               365
from these models could significantly change their conclusions.                                    366

## Supporting Information                                                                          367

**S1 Appendix.   Model details.** Since we use multi-strain models, in which the                   368
distribution of $\log_{10}$ SPVL has been discretized into a vector, we use a matrix notation     369
to describe our models. The five states described in the Methods section are replaced             370
with the following notations: $S$, $I_i$, $SS$, $SI_i$, $II_{ij}$, where the subscripts denote the strain   371
that an individual is infected with. For example, $I_i$ is number of infected individuals         372
with $\log_{10}$ SPVL of $\alpha_i$, and $II_{ij}$ is the number of concordant, HIV-positive couples in    373
which the two partners have $\log_{10}$ SPVL of $\alpha_i$ and $\alpha_j$ (independent of order; $II_{ij}$ is   374
synonymous with $II_{ji}$). Below, we use the Kronecker delta (i.e. $\delta_{ij} = 1$ if $i = j$ and 1    375
otherwise) in a slightly non-standard fashion as an exponent, e.g. $2^{\delta_{ij}}$, to set a value to   376

2 when $i = j$ and 1 otherwise.

## Models 1 and 2: partnership dynamics

Single individuals acquire partners at per-person rate $\rho$. Partnership formation rate for $S$, $I_i$ are $-\rho S$ and $-\rho I_i$, 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:

$$
\begin{aligned}
\mathrm{PF}(SS) &= \frac{\rho S \cdot S}{2(S + \sum_k I_k)}, \\
\mathrm{PF}(SI_i) &= \frac{\rho S \cdot I_i}{S + \sum_k I_k}, \\
\mathrm{PF}(II_{ij}) &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{S + \sum_k I_k}.
\end{aligned}
\tag{7}
$$

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 $I$, 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):

$$
\begin{aligned}
\mathrm{DS}(S) &= 2cSS + \sum_k cSI_k, \\
\mathrm{DS}(I_i) &= cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik}.
\end{aligned}
\tag{8}
$$

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

$$S' = -\rho S + 2cSS + \sum_k cSI_k$$

$$I_i' = -\rho I_i + cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik}$$

$$SS' = \frac{\rho S \cdot S}{2(S + \sum_k I_k)} - cSS \qquad (9)$$

$$SI_i' = \frac{\rho S \cdot I_i}{S + \sum_k I_k} - cSI_i$$

$$II_{ij}' = \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{S + \sum_k I_k} - cII_{ij}$$

## Models 1 and 2: infection

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

$$\mathrm{WT}(SI_i) = -\beta_i SI_i,$$
$$\mathrm{WT}(II_{ij}) = \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij}\beta_i SI_i + M_{ji}.\beta_j SI_j) \qquad (10)$$

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

$$P = \frac{c_u I + c_e(SI + 2II)}{c_u(S + I) + 2c_e(SS + SI + II)}. \qquad (11)$$

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:

$$P = \frac{r_u I + r_e(SI + 2II)}{r_u(S + I) + 2r_e(SS + SI + II)}, \qquad (12)$$

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:

$$P_i = \frac{r_u I_i + r_e(SI_i + \sum_k(II_{ik} + \delta_{ik}II_{ik}))}{r_u(S + \sum_k I_k) + r_e(2SS + \sum_k 2SI_k + \sum_l \sum_k 2^\delta_{lk}II_{lk})}. \tag{13}$$

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: $\text{ET}(I_i) = \sum_k M_{ki} P_k U_k S$. Either partner in an $SS$ partnership can be infected, with the partnership state becoming $SI$, 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: $\text{ET}(SI_i) = \sum_k 2M_{ki} P_k E_k SS$. 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 $\log_{10}$ SPVL of a newly infected partner is not determined by its social partner but from an extra-couple partner (i.e. the term $P_i$):

$\text{ET}(II_{ij}) = (\frac{1}{2})^{\delta_{ij}}(\sum_k(M_{kj}P_k E_k SI_i + M_{ki} P_k E_k SI_j))$. Combining these equations we get the following set of equations that describe all the transmission dynamics:

$$S' = -\sum_k P_k U_k S,$$

$$I_i' = \sum_k M_{ki} P_k U_k S,$$

$$SS' = -\sum_i 2 P_i E_i SS,$$

$$SI_i' = \sum_k 2 M_{ki} P_k E_k SS - \beta_i SI_i - \sum_k P_k E_k SI_i,$$

(14)

$$II_{ij}' = \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij} \beta_i SI_i + M_{ji}, \beta_j SI_j) + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \left(\sum_k (M_{kj} P_k E_k SI_i\right.$$

$$\left. + M_{ki} P_k E_k SI_j)\right).$$

## Model 1 and 2 - Disease induced mortality

430

The disease induced mortality (DM) rate, $\lambda$, is given by taking the reciprocal of the 431

total duration of the infection: $\lambda_i = 1/(D_A + D_P(\alpha_i) + D_D)$. Since we assume an SIS 432

formulation, where infected individuals that die from infection are immediately replaced 433

by an individual in the single susceptible compartment, we obtain the following 434

equation for single infected individuals: 435

$$DM(S) = \sum_k \lambda_k I_k,$$

(15)

$$DM(I_i) = -\lambda_i I_i.$$

If an infected individual in a partnership dies, the partnership dissolves. Thus, an 436

$SI_i$ partnership dissolves at a rate $-\lambda_i$, and the susceptible partner enters the single 437

susceptible compartment at rate $\lambda_i SI_i$ (due to the SIS formulation the the infected 438

partner that dies also gives rise, at an equal rate, to an individual entering the single 439

susceptible compartment): 440

$$DM(S) = \sum_k 2\lambda_k SI_k,$$

(16)

$$DM(SI_i) = -\lambda_i SI_i.$$

Similarly, $II_{ij}$ partnerships dissolve at a rate $-(\lambda_i + \lambda_j)$, but two cases, when $i \neq j$ 441

and $i = j$, must be considered separately. When an $II_{ij}$ partnership dissolves due to 442

disease-induced mortality, where $i \neq j$, the death of the partner with strain $i$ causes its 443

partner to enter $I_j$ compartment at rate $\lambda_j II_{ij}$, and vice versa. When an $II_i i$ <span style="float:right">444</span>

partnership dissolves, the death of either partner causes the other partner to enter the <span style="float:right">445</span>

$I_i$ compartment at rate $\lambda_i II_{ii}$, which sums up to $2\lambda_i II_{ii}$. Combining these dynamics <span style="float:right">446</span>

yields: <span style="float:right">447</span>

$$\mathrm{DM}(S) = \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk},$$

$$\mathrm{DM}(I_i) = \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \tag{17}$$

$$\mathrm{DM}(II_{ij}) = -(\lambda_i + \lambda_j)II_{ij}.$$

Finally, combining all these equations give us the full model, which is Model 1. We <span style="float:right">448</span>

can simply drop the uncoupled and extra-couple transmission terms to obtain equation <span style="float:right">449</span>

2: <span style="float:right">450</span>

$$
\begin{aligned}
S' =& -\rho S + 2cSS + \sum_k cSI_k - \sum_k P_k U_k S + \sum_k \lambda_k I_k \\
&+ \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk} \\
I_i' =& -\rho I_i + cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} + \sum_k M_{ki} P_k U_k S - \lambda_i I_i \\
&+ \sum_k 2^{\delta_{ik}} \lambda_k II_{ik} \\
SS' =& \frac{\rho S \cdot S}{2(S + \sum_k I_k)} - cSS - \sum_i 2P_i E_i SS \\
SI_i' =& \frac{\rho S \cdot I_i}{S + \sum_k I_k} - cSI_i - \beta_i SI_i + \sum_k 2M_{ki} P_k E_k SS - \sum_k P_k E_k SI_i \\
&- \lambda_i SI_i \\
II_{ij}' =& \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{(S + \sum_k I_k)} - cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij}\beta_i SI_i + M_{ji}\beta_j SI_j) \\
&+ \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (\sum_k (M_{kj} P_k E_k SI_i + M_{ki} P_k E_k SI_j)) - (\lambda_i + \lambda_j)II_{ij}
\end{aligned}
\tag{18}
$$

## Models 3 and 4: Partnership dynamics <span style="float:right">451</span>

Since model 3 and 4 assume instantaneous partnership formation, there are only three <span style="float:right">452</span>

states: $SS$, $SI_i$, and $II_{ij}$. Partnership dissolution rates are equal to those of model 1 <span style="float:right">453</span>

and 2: $\mathrm{DS}(SS) = -cSS$, $\mathrm{DS}(SI_i) = -cSI_i$, and $\mathrm{DS}(II_{ij}) = -II_{ij}$. Once individuals <span style="float:right">454</span>

leave a partnership, they enter temporary compartments and are distributed into a

partnership as follows:

$$
\begin{aligned}
X &= 2cSS + \sum_k cSI_k \\
Y_i &= cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} \\
SS' &= -cSS + \frac{X^2}{2(X + \sum_k Y_k)} \\
SI_i' &= -cSI_i + \frac{XY_i}{X + \sum_k Y_k} \\
II_{ij}' &= -cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \frac{Y_i Y_j}{X + \sum_k Y_k}.
\end{aligned}
\tag{19}
$$

## Model 3 and 4 - Infection

Model 3 and 4 share the within-couple transmission term with model 1 and 2. Since

there is no single state, only extra couple transmission exists:

$$
P_i = \frac{r_e(SI_i + \sum_k(II_{ik} + \delta_{ik}II_{ik}))}{r_e(2SS + \sum_k 2SI_k + \sum_l \sum_k(2^{\delta}_{kl} II_{lk}))}.
\tag{20}
$$

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.

## Model 3 and 4 - 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:

$$
\begin{aligned}
X &= \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk}, \\
Y_i &= \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \\
SS' &= = \frac{X^2}{2(X + \sum_k Y_k)}, \\
SI_i' &= -\lambda_i SI_i + \frac{XY_i}{X + \sum_k Y_k}, \\
II_{ij}' &= -(\lambda_i + \lambda_j)II_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{Y_i Y_j}{X + \sum_k Y_k}.
\end{aligned}
\tag{21}
$$

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

$$
\begin{aligned}
X =& 2cSS + \sum_k cSI_k + \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk}, \\
Y_i =& cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} + \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \\
SS =& -cSS + \frac{X^2}{2(X + \sum_k Y_k)} - \sum_i 2P_i E_i SS, \\
SI_i =& -cSI_i + \frac{XY_i}{X + \sum_k Y_k} - \beta_i SI_i + \sum_k 2M_{ki} P_k E_k SS \\
& - \sum_k P_k E_k SI_i - \lambda_i SI_i, \\
II_{ij} & - cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \frac{Y_i Y_j}{X + \sum_k Y_k} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij} \beta_i SI_i + M_{ji} \beta_j SI_j) \\
& + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \left(\sum_k (M_{kj} P_k E_k SI_i + M_{ki} P_k E_k SI_j)\right) - (\lambda_i + \lambda_j) II_{ij}.
\end{aligned}
\tag{22}
$$

## Model 5

Following [10], Model 5 is an implicit instantaneous partnership formation model that uses an adjusted transmission rate, $\beta'$, that is derived from [15]'s approximate basic reproduction number:

$$
\beta_i' = \frac{c\beta_i}{c + \beta_i + \lambda_i}.
\tag{23}
$$

Thus, we get the following model:

$$
\begin{aligned}
S' &= \sum_k \lambda_k I_k - \sum_k \beta_k' SI_k. \\
I_i &= \sum_k M_{ki} \beta_k' SI_k - \lambda_i I_i.
\end{aligned}
\tag{24}
$$

## Model 6

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

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

$$I_i = \sum_k M_{ki} \beta_k S I_k - \lambda_i I_i. \tag{25}$$

## 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 $\log_{10}$ SPVL of $i$. $Y_i$ 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:

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

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

$$SI_i(0) = 2\epsilon(1-\epsilon)SS^* D_i, \tag{26}$$

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

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

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

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

$$SI_i(0) = 2\epsilon(1-\epsilon)SS^* D_i, \tag{27}$$

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

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

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

$$I_i(0) = \epsilon D_i. \tag{28}$$

Model 6 also shares the same distribution of initial infected individuals as model 5.

# Acknowledgments

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