Effects of Epidemiological Structure on the Transient Evolution of HIV Virulence

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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. Changes in the fitness landscape will generally select for higher virulence during the early phase of an 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 implicit representations of the transmission process that drastically simplify the partnership dynamics that previous research has found to be critical in driving epidemics of sexually transmitted diseases. We explore models that 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. 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 changes in their environments; such changes include both increases in disease prevalence 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 details such as the formation and dissolution of sexual partnerships; other research has shown that these processes can strongly affect epidemic outcomes. We built and compared models that used different methods to model both partnership dynamics and sexual contact outside of partnerships. Models of intermediate complexity predicted much lower peak virulence (15 years to progress to AIDS) compared to both more realistic models and simple random-mixing models with no partnership structure at all (both approx. 7.25 years to progress to AIDS); extra-pair contact tended to wash out the effects of epidemiological structure. The large differences in evolutionary dynamics among different epidemiological models suggests that researchers trying to predict the evolution of pathogens should proceed with caution.

Introduction

The evolution of pathogen virulence is a fundamental process in evolutionary biology, of 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 studies of discordant couples (i.e. long-term sexual partnerships with one infected and one uninfected partner), HIV virulence as measured by the rate of progression to AIDS was both heritable and covaried with the set-point viral load (i.e., the characteristic virus load measured in blood during the intermediate stage of infection), which in turn predicted the probability of 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 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 [12,13]. However, despite these studies' attention to detail at the individual or physiological level, the epidemiological structures used in these models are relatively simple.

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

We add complexity to the epidemiological model following the general approach of Champredon *et al.* [14]; individuals join and leave partnerships at a specified rate, and can have sexual contact both within and outside of established partnerships. In order to explore how virulence evolution depends on epidemiological structure, we consider a series of models with increasing levels of complexity. In order to avoid dependence of the results on a particular set of parameters — as we explain below, finding matching

sets of parameters across models with widely differing epidemiological structures is

challenging — we evaluate our models across a wide range of parameters, again

following Champredon *et al.* [14] in using a Latin hypercube design. For each model run,

we compute a set of metrics (peak virulence, timing of virulence peak, equilibrium

virulence) that summarize the evolutionary trajectory of a simulated HIV epidemic.

   As our primary goal is to explore how different epidemiological structures (i.e.

partnership dynamics and contact structures) affect our conclusions about the evolution

of virulence, our models use a simplified description of within-host dynamics and

heritability derived from Shirreff *et al.*'s multi-strain evolutionary model [10]. Like

Shirreff *et al.*, we use a simple susceptible-infected-susceptible demographic formulation;

rather than modeling birth and death (or more specifically, recruitment into the

sexually active population and death), we assume that whenever an individual dies from

infection, another enters the susceptible compartment.

Materials and Methods

Infection dynamics

Like Shirreff *et al.* [10], we focus on the evolution of mean $\log_{10}$ set-point viral load,

SPVL (which we denote as α), rather than th rate of progression to AIDS itself (we

refer to SPVL as "virulence" hereafter). 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 account for varying transmission rates and

durations of each disease stage by summing the durations of three stages (again based on

Shirreff *et al.*'s model) and taking the duration-weighted average of transmission rates

of three stages. Thus the within-couple transmission rate, β, for our models is given by:

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

where the duration of infection (D_P and D_D) and rate of transmission (β_P and β_D) of

the Primary and Disease stages of infection are independent of the host's SPVL.

Following Shirreff *et al.*, the duration of infection (D_A) and rate of transmission (β_A) for the Asymptomatic stage are Hill functions of the SPVL:

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

where $V_\alpha = 10^\alpha$. The uncoupled and extra-couple transmission rates are scaled by multiplying the within-couple transmission rate β 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 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 (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 α), 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 α_j given that the infector has $\log_{10}$ SPVL of α_i. Finally, the probabilities are normalized so that each row sums to 1:

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

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

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

Contact structure and partnership dynamics

We developed six multi-strain evolutionary models covering a gamut between Champredon *et al.*'s relatively realistic [14] and Shirreff *et al.*'s relatively simple [10] epidemiological structures, each of which is based on different assumptions regarding contact structure and partnership dynamics. Specifically, we focus on the effects of the assumptions of (1) instantaneous vs. non-instantaneous partnership formation and (2) zero vs. positive extra-partnership sexual contact and transmission 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]. 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 assume instantaneous partnership formation ("instswitch") and thus consist of only the three partnered states: SS, SI, and II. Like the first two models, these models differ in their inclusion of extra-pair contact: the third model ("instswitch+epc") includes extra-partnership contact (now only with individuals in other partnerships, since uncoupled individuals don't exist in this model) and the fourth ("instswitch") only considers within-couple transmission.

The last two models do not explicitly track sexual partnerships. One ("implicit") is an implicit serial monogamy model based on the epidemiological model used by Shirreff *et al.* [10]. It is actually a random mixing model that consist of only two states, S and I, and does not consider explicit partnership dynamics. However, to reflect the effect of (instantaneously formed) partnership structure, it uses an adjusted transmission rate that is derived from an approximation of the basic reproduction number of a serial monogamy model [15]. Finally, the last model ("random") is a simple random-mixing model.

The base model (i.e. pairform+epc) for the first four models is an extension of Champredon *et al.*'s model [14]. Individuals in single compartment acquire a partner at a rate ρ, and partnerships dissolve at a rate c. Infected individuals in a discordant partnership infect their susceptible partner at a rate β (within-couple transmission rate) and susceptible individuals outside the partnership at a rate c_e (extra-couple transmission rate). Likewise, a single infected individual can infect any susceptible individuals at a rate c_u through uncoupled mixing. Extra-couple and uncoupled transmission are modeled in the same way as Champredon *et al.*'s model. All the details have been adapted to a multi-strain scenario. The second through fourth models (pairform, instswitch+epc, instswitch) are derived from the base model by simplifying epidemiological processes (partnership formation and uncoupled/extra-couple contact). Model details are explained in the appendix.

Latin hypercube sampling

Despite considerable effort [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 early- and late-stage transmission and duration parameters (β_P, D_P, β_D, D_D) and contact/partnership parameters (ρ, c, c_u/c_w, and c_e/c_w). We do not allow for uncertainties in parameters that are directly related to the evolutionary process ($\beta_{\max}$, β_{50}, β_k, $D_{\max}$, D_{50}, D_k, σ_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:

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

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

Table 1 gives the ranges of the model parameters used for LHS. Parameter ranges regarding contact and partnership dynamics (ρ, c, and c_e/c_w) are taken from Champredon *et al.* [14], whereas those regarding infection (β_P, D_P, β_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 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.

Table 1. Parameter ranges/values. Note that c and ρ 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), and Descriptions of Hill function coefficients, are taken from [10].

Notation	Description	Range/Value	Source
ρ	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]
β_P	Rate of transmission during primary infection	1.31-5.09 (2.76*)	[15]
β_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]
β_{max}	Maximum rate of transmission during asymptomatic stage	0.317	[10]
β_{50}	SPVL at which infectiousness is half maximum	13938	[10]
β_k	Hill coefficient: steepness of increase in infectiousness as a function of SPVL	1.02	[10]
D_{max}	Duration of primary infection	25.4	[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]
σ_M	Mutation standard deviation of $\log_{10}$ SPVL	0.12	[10]
α_{min}	Minimum $\log_{10}$ SPVL	2	[10]
α_{max}	Maximum $\log_{10}$ SPVL	7	[10]
n	Number of strains	21 (51*)	Assumption

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 175
more strongly affected by r than $\mathcal{R}_0$. Second, r is more directly observable in real 176
epidemics; r can be estimated by fitting an exponential curve to the initial incidence or 177
prevalence curves [17], while $\mathcal{R}_0$ typically requires either (1) knowledge of *all* epidemic 178
parameters or (2) calculations based on r and knowledge of the serial interval or 179
generation interval of the disease [18]. Thus, we scale parameters so that every run has 180
the same initial exponential growth rate of incidence. 181

In order to allow for all models to have equal initial exponential growth rate, r, we 182
need to pick a parameter, s, such that $\lim_{s \to 0} r(s) = 0$ and $\lim_{s \to \infty} r(s) = \infty$. As 183
adjusting either partnership change rate (i.e. partnership formation and dissolution 184
rate) or transmission rate fails this requirement for some of our models, we scaled 185
partnership change rate and dissolution rate by the same factor of γ: $\beta_{\text{adj}} = \gamma \beta_{\text{base}}$, 186
$c_{\text{adj}} = \gamma c_{\text{base}}$, $\rho_{\text{adj}} = \gamma \rho_{\text{base}}$. Since transmission rate is adjusted by the scale of γ, 187
uncoupled and extra-couple transmission rates are adjusted as well. For the 188
instantaneous-switching and implicit models, none of which track single individuals, 189
only the transmission rate and partnership dissolution rate (in this case equivalent to 190
the partnership change rate) are adjusted. 191

We run each model for each of 1000 parameter sets chosen by Latin hypercube 192
sampling, with fixed starting conditions of mean $\log_{10}$ SPVL of 3 and epidemic size of 193
10^{-4}. After each run, initial exponential growth rate is calculated. Then, parameters 194
are scaled so that the initial exponential growth rate is scaled to 0.04, which is 195
approximately equal to that implied by Shirreff *et al.*'s original models. 196

The calibration runs for each parameter set are slightly simplified. We run each 197
model for only 500 years (full simulations are run for 4000 years), and we use a 4/5 198
order Runge-Kutta method (`ode45` from the `deSolve` package [19]), whereas we use a 199
stiff solver (LSODA) for the full simulations. 200

For each model we derive the following summary statistics: peak virulence, peak 201
time, equilibrium virulence, and relative peak virulence. The transient phase of an 202
epidemic is often characterized by high virulence, and we define peak virulence as the 203
maximum virulence during this phase. It is simply calculated by taking the maximum 204
value from the virulence trajectory, and peak time is the time at which the maximum 205
value is reached. Once the epidemic enters the endemic phase, evolution of virulence 206

stabilizes and reaches equilibrium. Equilibrium virulence is calculated by taking the 207

mean virulence at 4000 years. Although most simulations reach equilibrium much 208

earlier, we set our time horizon at a much later date as some simulation runs have slow 209

rate of evolution depending on the parameter set and model assumptions. 210

We focus on these statistics for the following two reasons. First of all, knowing the 211

possible ranges for the peak virulence allows us to estimate the worst-case scenario for 212

the HIV and other sexually transmitted disease epidemics. Pathogens may already have 213

evolved towards high virulence during the early stages of an epidemic, by the time it is 214

observed by public health authorities. Understanding how virulent a pathogen can 215

evolve before an epidemic begins can be helpful for controlling the disease. Furthermore, 216

knowing the initial virulence, peak virulence, timing of the peak virulence, and 217

equilibrium virulence provide sufficient detail to identify the shape of the virulence 218

trajectory. During an epidemic outbreak, it is difficult to observe virulence evolution. 219

Specifically, in the case of HIV and other sexually transmitted diseases, slow 220

evolutionary time-scale makes observing changes in the mean virulence even more 221

challenging. Knowing the ranges of these statistics can help real-time virulence 222

evolution prediction during an epidemic less troublesome. 223

Results 224

Our simplifications of Shirreff *et al.*'s model [10] reproduce its qualitative behaviour — 225

in particular, its predictions of virulence dynamics — reasonably well. As r decreases 226

from 0.084 to 0.42 (the latter value matching the initial rate of increase in prevalence in 227

Shirreff *et al.*'s full model) the initial trajectory of increasing virulence brackets the rate 228

from the original model (Fig. 1a). However, our model produces lower peak virulence 229

(≈ 4.3 vs. $\approx 4.6 \log_{10}$ SPVL) and equilibrium virulence (≈ 4.25 vs. $\approx 4.5 \log_{10}$ SPVL) 230

than Shirreff's, even for matching initial incidence trajectories (i.e., $r = 0.042$ year^{-1}). 231

Changing the initial infectious density ($I(0)$), while it produces the expected changes 232

in the initial epidemic trajectory (Supplementary material), has little effect on the 233

virulence trajectory, making the virulence peaks slightly later and larger as $I(0)$ 234

decreases. Decreasing $I(0)$ allows a longer epidemic phase before the transition to 235

endemic dynamics (Fig. 1b). Decreasing the initial virulence similarly but more strongly 236

leads to progressively later, larger peaks in virulence (Fig. 1c).   237

Across the entire range of parameters covered by the LHS analysis, all of the classes   238
of models we considered produce qualitatively similar virulence trajectories (Fig. 2).   239
Although the speed of virulence evolution varies, leading to wide variation in the peak   240
virulence (means ranging from approximately 3.75 to 4.5 $\log_{10}$ SPVL), virulence peaks   241
in all models between 200 and 300 years.   242

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,   243
and relative peak virulence) all vary considerably across models 3. We first consider the   244
models of intermediate realism (implicit, instantaneous-switching with and without   245
extra-pair contact ("epc" hereafter), and pair formation without extra-pair contact).   246
Some parameter sets for these models lead to low equilibrium virulence ($\approx 2.5 \log_{10}$ 247
SPVL); these same sets lead to correspondingly low peak virulence ($< 3.5 \log_{10}$ SPVL)   248
and early peak times (before 200 years), but high relative peaks (> 1.3) (Fig. 4, leftmost   249
column) because the equilibrium virulence is low. At the opposite extreme, parameter   250
sets that produce high equilibrium virulence also produce late peaks (> 200 years), high   251
peak virulence, and low relative peaks (≈ 1.05). The pair-formation without extra-pair   252
contact and implicit models occasionally have parameter sets that select for such low   253
virulence across the board that they never exceed their initial virulence, leading to a tail   254
of peak times near zero.   255

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.

The most striking aspect of the univariate comparisons in Fig. 3, (and the bivariate   256
comparisons in Fig. 4) is the match between the output of the least (random mixing)   257
and the most complex (pair formation with extra-pair contact) models. The   258
random-mixing model has lower variability, because it is unaffected by uncertainty in   259
pair formation and extra-pair contact parameters, but otherwise the virulence dynamics   260

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 (β_P, β_D) and durations (D_P, D_D) in the primary and disease stages

generally decrease the equilibrium virulence, peak virulence, and peak time, although

the random and pair-formation+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 (ρ);

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 [20]. 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, 21] rather than doing any explicit calibration to epidemic curves, but they give reasonable order-of-magnitude growth rates (≈ 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 [22]). However, our reason for calibrating was not to match any specific observed epidemic, but rather to make sure that we were making meaningful comparisons across a range of models with radically different epidemiological structures, and hence involving different interpretations of the same quantitative parameters. For example, in models with instantaneous switching the partnership dissolution rate c is identical to the partnership formation rate; in models with explicit partnership formation, the partnership formation rate is also c at equilibrium, but might vary over the course of an epidemic. It is not obvious whether models with equal parameters but different structures should be directly compared; calibration solves this problem.

More generally, any model that wants to be taken seriously for management and forecasting purposes should be calibrated to *all* available data, using informative priors to incorporate both realistic distributions of uncertainty for all parameters from independent measurements [23] and calibration from population-level observations of epidemic trajectories. For practical (rather than exploratory) purposes, such a

procedure would also be an improvement on the common — although not universal — 351

practice of assessing uncertainty over uniform ranges, rather than distributions that 352

allow more continuous variation in support over the range of a parameter. 353

Researchers have documented that HIV virulence and set-point viral load are 354

changing, on time scales comparable to those portrayed here (e.g., compare Fig. 2 to 355

Herbeck *et al.*'s estimated rate of change of 1.3 $\log_{10}$ SPVL per century [95% CI -0.1 to 356

3] [24]), and have begun to build relatively realistic models that attempt to describe 357

how interventions such as mass antiretroviral therapy (ART) can be expected to change 358

the trajectory of virulence evolution [20, 25]. While these efforts are well-intentioned, we 359

caution that epidemiological and other structural details that are currently omitted 360

from these models could significantly change their conclusions. 361

Supporting Information 362

S1 Appendix. Model details. Since we use multi-strain models, in which the 363

distribution of $\log_{10}$ SPVL has been discretized into a vector, we use a matrix notation 364

to describe our models. The five states described in the Methods section are replaced 365

with the following notations: S, I_i, SS, SI_i, II_{ij}, where the subscripts denote the strain 366

that an individual is infected with. For example, I_i is number of infected individuals 367

with $\log_{10}$ SPVL of α_i, and II_{ij} is the number of concordant, HIV-positive couples in 368

which the two partners have $\log_{10}$ SPVL of α_i and α_j (independent of order; II_{ij} is 369

synonymous with II_{ji}). Below, we use the Kronecker delta (i.e. $\delta_{ij} = 1$ if $i = j$ and 1 370

otherwise) in a slightly non-standard fashion as an exponent, e.g. $2^{\delta_{ij}}$, to set a value to 371

2 when $i = j$ and 1 otherwise. 372

Models 1 and 2: partnership dynamics 373

Single individuals acquire partners at per-person rate ρ. Partnership formation rate for 374

S, I_i are $-\rho S$ and $-\rho I_i$, respectively. We follow Champredon *et al.*'s results and 375

assume that single individuals are distributed into coupled states with pair-formation 376

(PF) rates as follows: 377

$$\text{PF}(SS) = \frac{\rho S \cdot S}{2(S + \sum_k I_k)},$$

$$\text{PF}(SI_i) = \frac{\rho S \cdot I_i}{S + \sum_k I_k},$$

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

(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):

$$\text{DS}(S) = 2cSS + \sum_k cSI_k,$$

$$\text{DS}(I_i) = cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik}.$$

(8)

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

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

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

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

(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: $\text{WT}(SI_i) = -\beta_i SI_i$. Since we assume that mutation occurs, II_{ij}, where $i \neq j$, can be formed from both SI_i and SI_j partnership: $\text{WT}(II_{ij}) = M_{ij}\beta_i SI_i + M_{ji}\beta_j SI_j$. 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:

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

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

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

The effective uncoupled, c_u, and extra couple, c_e, contact rates are the product of two terms: uncoupled/extra-couple contact rate × 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:

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

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:

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

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:

$\mathrm{ET}(I_i) = \sum_k M_{ki} P_k U_k S$. 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: $\mathrm{ET}(SI_i) = \sum_k 2M_{ki} P_k E_k SS$. 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):

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

$$
\begin{aligned}
S' &= -\sum_k P_k U_k S, \\
I_i' &= \sum_k M_{ki} P_k U_k S, \\
SS' &= -\sum_i 2P_i E_i SS, \\
SI_i' &= \sum_k 2M_{ki} P_k E_k SS - \beta_i SI_i - \sum_k P_k E_k SI_i, \\
II_{ij}' &= \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij} \beta_i SI_i + M_{ji}, \beta_j SI_j) + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (\sum_k (M_{kj} P_k E_k SI_i \\
&\quad + M_{ki} P_k E_k SI_j)).
\end{aligned}
\tag{14}
$$

Model 1 and 2 - Disease induced mortality

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

$$
\begin{aligned}
\mathrm{DM}(S) &= \sum_k \lambda_k I_k, \\
\mathrm{DM}(I_i) &= -\lambda_i I_i.
\end{aligned}
\tag{15}
$$

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

$$\mathrm{DM}(S) = \sum_k 2\lambda_k SI_k,$$
$$\mathrm{DM}(SI_i) = -\lambda_i SI_i. \tag{16}$$

Similarly, II_{ij} partnerships dissolve at a rate $-(\lambda_i + \lambda_j)$, but two cases, when $i \neq j$ and $i = j$, must be considered separately. When an II_{ij} partnership dissolves due to disease-induced mortality, where $i \neq j$, the death of the partner with strain i causes its partner to enter I_j compartment at rate $\lambda_j II_{ij}$, and vice versa. When an $II_i i$ partnership dissolves, the death of either partner causes the other partner to enter the I_i compartment at rate $\lambda_i II_{ii}$, which sums up to $2\lambda_i II_{ii}$. Combining these dynamics yields:

$$\mathrm{DM}(S) = \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk},$$
$$\mathrm{DM}(I_i) = \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}, \tag{17}$$
$$\mathrm{DM}(II_{ij}) = -(\lambda_i + \lambda_j) II_{ij}.$$

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

$$S' = -\rho S + 2cSS + \sum_k cSI_k - \sum_k P_k U_k S + \sum_k \lambda_k I_k$$

$$+ \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk}$$

$$I'_i = -\rho I_i + cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} + \sum_k M_{ki} P_k U_k S - \lambda_i I_i$$

$$+ \sum_k 2^{\delta_{ik}} \lambda_k II_{ik}$$

$$SS' = \frac{\rho S \cdot S}{2(S + \sum_k I_k)} - cSS - \sum_i 2P_i E_i SS \qquad (18)$$

$$SI'_i = \frac{\rho S \cdot I_i}{S + \sum_k I_k} - cSI_i - \beta_i SI_i + \sum_k 2M_{ki} P_k E_k SS - \sum_k P_k E_k SI_i$$

$$- \lambda_i SI_i$$

$$II'_{ij} = \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \frac{\rho I_i \cdot I_j}{(S + \sum_k I_k)} - cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij}\beta_i SI_i + M_{ji}\beta_j SI_j)$$

$$+ \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot \left(\sum_k (M_{kj} P_k E_k SI_i + M_{ki} P_k E_k SI_j)\right) - (\lambda_i + \lambda_j)II_{ij}$$

Models 3 and 4: Partnership dynamics

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

$$X = 2cSS + \sum_k cSI_k$$

$$Y_i = cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik}$$

$$SS' = -cSS + \frac{X^2}{2(X + \sum_k Y_k)} \qquad (19)$$

$$SI'_i = -cSI_i + \frac{XY_i}{X + \sum_k Y_k}$$

$$II'_{ij} = -cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \frac{Y_i Y_j}{X + \sum_k Y_k}.$$

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:

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

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

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

$$X = 2cSS + \sum_k cSI_k + \sum_k 2\lambda_k SI_k + \sum_l \sum_k 2^{\delta_{lk}} \lambda_k II_{lk},$$

$$Y_i = cSI_i + \sum_k 2^{\delta_{ik}} cII_{ik} + \sum_k 2^{\delta_{ik}} \lambda_k II_{ik},$$

$$SS = -cSS + \frac{X^2}{2(X + \sum_k Y_k)} - \sum_i 2P_i E_i SS,$$

$$SI_i = -cSI_i + \frac{XY_i}{X + \sum_k Y_k} - \beta_i SI_i + \sum_k 2M_{ki} P_k E_k SS \tag{22}$$

$$- \sum_k P_k E_k SI_i - \lambda_i SI_i,$$

$$II_{ij} - cII_{ij} + \left(\frac{1}{2}\right)^{\delta_{ij}} \frac{Y_i Y_j}{X + \sum_k Y_k} + \left(\frac{1}{2}\right)^{\delta_{ij}} \cdot (M_{ij}\beta_i SI_i + M_{ji}\beta_j SI_j)$$

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

Model 5

Following [10], Model 5 is an implicit instantaneous partnership formation model that uses an adjusted transmission rate, β', 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:

$$S' = \sum_k \lambda_k I_k - \sum_k \beta_k' SI_k.$$

$$I_i = \sum_k M_{ki} \beta_k' SI_k - \lambda_i I_i. \tag{24}$$

Model 6

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

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

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

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:

$$
\begin{aligned}
S(0) &= (1 - \epsilon)S^*, \\
SS(0) &= (1 - \epsilon)^2 SS^*, \\
SI_i(0) &= 2\epsilon(1 - \epsilon)SS^* D_i, \\
I_i(0) &= \epsilon S^* D_i, \\
II_{ij}(0) &= \left(\frac{1}{2}\right)^{\delta_{ij}} 2\epsilon^2 SS^* D_i D_j.
\end{aligned}
\tag{26}
$$

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

$$
\begin{aligned}
SS(0) &= (1 - \epsilon)^2 SS^*, \\
SI_i(0) &= 2\epsilon(1 - \epsilon)SS^* D_i, \\
II_{ij}(0) &= \left(\frac{1}{2}\right)^{\delta_{ij}} 2\epsilon^2 SS^* D_i D_j.
\end{aligned}
\tag{27}
$$

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

$$
\begin{aligned}
S(0) &= 1 - \epsilon, \\
I_i(0) &= \epsilon D_i.
\end{aligned}
\tag{28}
$$

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

Acknowledgments

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