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. 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

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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 same time, our analysis somewhat simplifies the models of Shirreff *et al.* [10], for computational tractability; we check that our qualitative results are not sensitive to these simplifications. 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.

Materials and Methods

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.

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 virulence (i.e. rate of progression to AIDS) itself. 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 **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 (β_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 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 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] (Figure **??**) we use $n = 51$ (i.e. a bin width of 0.05 $\log_{10}$ 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.

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, designed to cover a gamut between Champredon textet 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 textet al.'s model [14]. Models 1 and 2 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 susceptible-susceptible couples, SI is the number of serodiscordant (susceptible-infected) couples, and II is the number of concordant positive (infected-infected) couples. Model 1 includes extra-partnership contact (with both uncoupled individuals and individuals in other partnerships) whereas model 2 only considers within-couple transmission. Models 3 and 4 assume instantaneous partnership formation and thus consist of only the three partnered states: SS, SI, and II. Parallel to model 1 and 2, model 3 includes extra-partnership contact (now only with individuals in other partnerships, since uncoupled individuals don't exist in this model) and model 4 only considers within-couple transmission.

In contrast, models 5 and 6 are not explicitly structured. Model 5 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 simulate the effect of instantaneous partnership formation, it uses an adjusted transmission rate that is derived from approximated basic reproduction number of a serial monogamy model [15]. Finally, model 6 is a simple random-mixing model.

The base model (i.e. model 1) for the first four models is an extension of Champredon textet 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 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 a same way as Champredon textet al.'s model. All the details have been adapted to a multi-strain scenario. Model 2, 3, and 4 are derived from the base model by removing epidemiological details (partnership formation and uncoupled/extra-couple contact). Model details are explained in the appendix.

Results

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Discussion

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Conclusion

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Supporting Information

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