Veering towards virulence: modelling the evolution of HIV-1 in response to prophylactic drugs

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science Graduate Department of Ecology & Evolutionary Biology University of Toronto

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Abstract

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Average virulence in HIV is on the rise in several highly treated populations. The drivers of this evolution are not known, but evolutionary theory suggests that imperfectly effective medical interventions can select for higher virulence. Previously developed mathematical models predict that HIV treatment leads to the evolution of lower virulence, but have not accounted for the fact that treated hosts sometimes transmit their infections. Here, we use an evolutionary invasion analysis to show that higher virulence evolves with the increasing use of drugs that imperfectly treat and prevent HIV infection (i.e., antiretroviral therapy and pre-exposure prophylaxis, respectively). As a consequence, untreated infections progress more rapidly to AIDS, and the prevalence of infection in host populations increases. These findings suggest that antiretroviral drugs may have under-appreciated evolutionary consequences that threaten their benefit, and we caution that virulence evolution should be closely monitored as access to these drugs continues to improve.
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And finally, to the world outside of EEB: to my friends, my family and my boyfriend, I thank you for your love, your support, and for reminding me what really matters.
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When SPVL evolves in populations that make use of both ART and PrEP, infections can persist despite the use of these drugs, and increases in the uptake rate of PrEP lead to worse outcomes for infected individuals and populations. These epidemiological outcomes depend heavily on the relative uptake rate of ART (from lightest to darkest blue, $f = 0.01, 0.1, 1$) when PrEP uptake is low, but not when PrEP uptake is high. These simulations assume high ART efficacy ($r_2 = 0.9$) and low PrEP efficacy ($r_1 = 0.2$). Left: When ART uptake is low, increases in the uptake rate of PrEP lead to the evolution of infections that progress to AIDS more rapidly. PrEP has little effect on virulence evolution when ART uptake is high. Right: The evolution of SPVL prevents PrEP from eradicating the virus from the host population. When PrEP uptake is nonexistent or very low, increases in the rate of PrEP uptake cause precipitous declines in infection prevalence, regardless of the use of ART. However, when the rate of PrEP uptake is already reasonably high ($g \gtrsim 0.1$), further increases are unable to eliminate HIV, and can actually increase the equilibrium prevalence of infection if ART uptake is low.
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1 Introduction

The evolution of parasites in response to human interventions is a fundamental challenge to public health. A growing number of parasites have evolved means of resistance to chemotherapeutic drugs and vaccines, limiting or altogether eliminating options to prevent and treat disease (reviewed in Gandon and Day 2008; Bell et al. 2014). In addition to conventional resistance mechanisms (e.g., efflux pumps to resist drugs or antigenic variation to escape vaccine-induced immunity), experiments have shown that parasite virulence can evolve in response to - and mitigate the effects of - medical interventions (e.g., virulence evolution in Marek’s disease virus in response to vaccines [Read et al. 2015], and in rodent malaria parasites in response to drugs [Schneider et al. 2012] and vaccines [Barclay et al. 2012]). The extent of this kind of evolution in non-experimental systems is poorly understood, but there is evidence of vaccine-driven virulence evolution in parasites of humans (pertussis, Mooi et al. 2009), cats (feline calicivirus, Radford et al. 2006), and poultry (Marek’s disease virus, Nair 2005; avian infectious bursal disease virus, van den Berg 2000). Using mathematical models, Gandon et al. (2001) formalized the prediction that imperfectly effective, or ‘leaky’ vaccines lead to virulence evolution. Importantly, that study also shows that evolutionary trajectories depend on vaccine targets (e.g., parasite proteins or pathways related to growth, infection or transmission) and the precise relationship between virulence and other parasite traits. Virulence may thus be expected to evolve idiosyncratically in response to different interventions in different host-parasite systems.

HIV is a parasite to which the theory of Gandon et al. (2001) has yet to be applied. No anti-HIV vaccines are currently approved for use, but other treatment strategies play functionally similar roles. Antiretroviral therapy (ART) is the use of antiretroviral drugs to suppress viral replication in infected hosts. HIV pre-exposure prophylaxis (PrEP) is a nascent prevention strategy whereby uninfected hosts take these same or similar drugs in order to prevent infection [WHO 2015]. Though not vaccines in the traditional sense, ART and PrEP are analogous to anti-growth and anti-infection vaccines, respectively (sensu Gandon et al. 2001). Thus, these interventions can be expected to elicit an evolutionary response in virulence provided that they still allow some degree of transmission, and that there are trade-offs in virulence that affect
parasite fitness (Gandon et al., 2001).

In HIV-1 infections, viral load refers to the density of virus in the blood stream (viral RNA copies/mL of blood plasma). Viral load typically spikes during primary HIV infection, when the virus first establishes itself in host CD4$^+$ cells, and at the end of infection, when CD4$^+$ cells are depleted and hosts progress to AIDS. However, during the lengthy asymptomatic phase of infection, which can last from 2 to over 20 years, viral load fluctuates about a steady value (Babiker et al., 2000). This so-called set-point viral load (SPVL) underlies a trade-off between virulence and transmission: hosts with higher SPVL progress to AIDS and death more quickly (Mellors et al., 1997), but are more infectious than those with low SPVL (Quinn et al., 2000). SPVL varies by orders of magnitude between hosts (de Wolf et al., 1997), but intermediate SPVL is predicted to maximize lifetime HIV transmission as a result of this trade-off (Fraser et al., 2007). Importantly, SPVL is heritable between infections and is in part determined by viral genes (Alizon et al., 2010; Fraser et al., 2014). Consequently, intermediate SPVL and hence intermediate virulence are believed to have evolved over the course of the HIV-1 pandemic, despite the rapid and error-prone replication that is characteristic of the virus (Fraser et al., 2007; Shirreff et al., 2011; Lythgoe et al., 2013).

It remains unknown if and how medical interventions affect the evolution of SPVL in HIV. Optimal SPVL has been quantified using data collected prior to the rollout of antiretroviral drugs (Fraser et al., 2007), which have now been circulating in various incarnations for decades (Vella et al., 2012). It has been suggested that drugs could select for higher SPVL by reducing the associated costs of higher virulence (Fraser et al., 2014), but this can only be expected to happen if treated hosts remain able to transmit. Although a meta-analysis found that average SPVL has increased in many populations since ART was first introduced (Herbeck and Müller, 2012), the drivers of this evolution are not known. Two recent studies have used mathematical models to predict how ART affects virulence evolution in HIV. Roberts et al. (2015) compared the transmission of two HIV strains of differing SPVL, and found that the use of ART generally favours the evolution of lower SPVL; Payne et al. (2014) supplemented their empirical study of HIV adaptation with a similar model and found similar results. However, both models
made two key assumptions. First, treated hosts were assumed to be unable to transmit HIV. Although it is true that ART reduces transmission risk, data demonstrate that treated hosts frequently transmit their infections (Baggaley et al., 2013; Anglemyer et al., 2013; Ratmann et al., 2016), and any viruses in infections that are able to transmit when exposed to ART will have an evolutionary advantage in highly treated populations. Second, these models assumed that more virulent infections are more likely to be treated; coupled with the first assumption, this affords a significant transmission advantage to infections with low virulence. However, the WHO now recommends the immediate initiation of ART upon HIV diagnosis, regardless of prognostic indicators such as viral load and CD4+ cell count (WHO, 2015). It is thus unclear how SPVL may be expected to evolve in populations that adhere to WHO guidelines, and where some treated hosts remain able to transmit. Further, no models of HIV virulence evolution have considered the potential influence of PrEP.

We develop a compartmental model of HIV-1 transmission to explore the phenotypic evolution of virulence in response to drugs. In contrast to past models (Payne et al., 2014; Roberts et al., 2015), we use adaptive dynamics to predict optimal transmission strategies and the expected evolutionary endpoints of SPVL evolution in response to ART. We assume that all infections are equally likely to be treated and that treated hosts transmit at a reduced rate. We introduce antiretroviral drugs and and vary their efficacy and uptake in order to determine the evolutionary consequences of different treatment and prevention scenarios. We show that higher virulence evolves when treated hosts transmit, and that this effect is greatest when ART is highly effective and widely used. We show that the use of PrEP greatly reduces infection prevalence, but amplifies virulence evolution in response to ART. Finally, we show that, in some cases, virulence evolution can erode the epidemiological and clinical benefits of interventions.
2 Mathematical model

2.1 Modelling HIV transmission

We develop a compartmental model of frequency-dependent HIV transmission to explore the epidemiological and evolutionary consequences of ART and PrEP. This system of ordinary differential equations tracks the frequencies of four host types in a population of sexually active adults: susceptible \((S)\), susceptible on PrEP \((P)\), infected \((I)\), and infected on ART \((T)\):

\[
\begin{align*}
\frac{dS}{dt} &= \theta - (\beta_I + \beta_T T)S - (\mu + g)S \\
\frac{dP}{dt} &= gS - \eta(\beta_I + \beta_T T)P - \mu P \\
\frac{dI}{dt} &= (\beta_I + \beta_T T)S - (\mu + \alpha_I + f)I \\
\frac{dT}{dt} &= fI + \eta(\beta_I + \beta_T T)P - (\mu + \alpha_T)T
\end{align*}
\]

where \(\theta\) is the rate at which individuals enter the population (and functions to maintain a constant population size), \(\beta\) is the per-capita rate of HIV-1 transmission from an infected host, \(\alpha\) is the rate of progression of an infected host to AIDS, \(\mu\) is the rate of background mortality (applied to all hosts), and \(f\) and \(g\) are rates of ART and PrEP uptake, respectively (see full list of parameters in Table 1). Subscripts indicate the host type associated with a host-specific parameter. All transmission is assumed to occur during the asymptomatic phase of infection, during which time SPVL is expressed and the majority of HIV transmission occurs \([Hollingsworth et al., 2008, Powers et al., 2011, Bellan et al., 2015]\), and excluding primary HIV infection and AIDS allows us to subsume within-host processes into the between-host vital rates. Treated hosts have reduced SPVL, and hence reduced rates of transmission and progression to AIDS (i.e., \(\beta_T \leq \beta_I; \alpha_T \leq \alpha_I\)). Hosts on PrEP move directly into the treated class upon infection, since they are assumed to continue taking their medication if unknowingly infected, and the continued use of PrEP post-infection is likely to behave functionally like ART, since similar drugs are used \([García-Lerma et al., 2008, Prada et al., 2008]\).
2.2 Modelling the SPVL trade-off

In our model, the rates of transmission and disease progression are governed by the SPVL trade-off quantified by [Fraser et al., (2007)]. By retrospectively analyzing sero-conversion and clinical outcomes in a cohort of untreated men who have sex with men (MSM) in the Netherlands, the relationship between SPVL \( V \) and the duration of untreated asymptomatic infection \( D \) was described as a decreasing Hill function,

\[
D_I[V] = \frac{D_{max}V^D_k}{V^D_k + D_{50}^D_k}
\]  

(5)

where \( D_{max} \) is the maximum duration of infection, \( D_{50} \) is the viral load at which duration is half its maximum, and \( D_k \) is a rate-determining constant (see Table 1 for parameter values). Given \( D_I[V] \) as the average duration of asymptomatic infection, and assuming exponentially-distributed wait times, then the rate of progression from asymptomatic infection to AIDS \( (\alpha) \) is represented by the inverse of equation 5,

\[
\alpha_I[V] = \frac{V^D_k + D_{50}^D_k}{D_{max}D_{50}^D_k}
\]  

(6)

and progressing to AIDS is assumed to be analogous to death (i.e., those with AIDS do not transmit).

Using known transmission pairs from a cohort of untreated sero-discordant heterosexual couples in Zambia, [Fraser et al. (2007)] also estimated HIV-1 transmission rate as a function of SPVL. A saturating relationship between transmission rate and SPVL was described using an increasing Hill function,

\[
\beta_I[V] = \frac{\beta_{max}V^\beta_k}{V^\beta_k + \beta_{50}^\beta_k}
\]  

(7)

where \( \beta_{max} \) is the maximum rate of transmission from an infected host, \( \beta_{50} \) is the viral load at which the rate of transmission is half its maximum, and \( \beta_k \) is a rate-determining constant.
The product of equations 5 and 7 is HIV-1 transmission potential, the average number of transmission events from a single infected host over the full duration of asymptomatic infection (Fraser et al., 2007). This measure is analogous to $R_0$ and approximates viral fitness as a function of SPVL. According to these functions, transmission is maximized when $V = 10^{4.52}$ virions/mL of blood plasma, which is broadly consistent with SPVL distributions observed in human populations prior to the rollout of antiretroviral drugs (Fraser et al., 2007).

### 2.3 Modelling imperfect interventions

We use the paradigm set forth by Gandon et al. (2001) to model how ART affects rates of transmission and disease progression, and how PrEP affects host susceptibility. Specifically,

\begin{align*}
\eta &= (1 - r_1) \\
\alpha_T[V] &= \alpha_I[(1 - r_2)V] \\
\beta_T[V] &= \beta_I[(1 - r_2)V]
\end{align*}

where $\eta$ represents reduced susceptibility to infection due to PrEP, and $r_1$ and $r_2$ represent the average efficacies of PrEP and ART, respectively. If $r_1 = 1$, a host using PrEP can not be infected, while PrEP has no effect if $r_1 = 0$. Similarly, ART is perfectly effective when $r_2 = 1$ and eliminates all viruses in an infection, while ART is completely ineffective when $r_2 = 0$.

Although we focus primarily on the effects of PrEP and ART, we also consider the possibility that treated hosts practice alternative means of transmission prevention. Behaviours such as increased condom use, reduced sexual contact and sero-sorting (i.e., preferentially choosing sexual partners of the same HIV infection status) are frequently observed in treated hosts (Wamoyi et al., 2011), and interventions that reduce transmission rate directly, rather than through reducing SPVL, can also affect virulence evolution (Gandon et al., 2001). We model these transmission-prevention behaviours (defined here as TPBs) as a reduction in the rate of
transmission from treated hosts,

\[ \beta_T = (1 - r_3)\beta_I[(1 - r_2)V] \]  \hspace{1cm} (11)

where \( r_3 \) represents the efficacy of TPBs.

**2.4 Parameter interpretation and estimation**

The parameters of this model are difficult to estimate and are likely highly variable in and among different host populations. We therefore consider most parameters over broad ranges when numerical predictions are made. However, some parameters can be broadly inferred from the literature. Background mortality is set at \( \mu = 0.02 \), which amounts to an average uninfected host lifespan of 50 years. This value is broadly consistent with other HIV models (Lythgoe et al., 2013; Roberts et al., 2015). ART is generally assumed to be highly effective \((r_2 > 0.8)\) because, although some hosts do not achieve viral suppression, roughly three quarters of treated infections are virologically suppressed, and many more are partially suppressed (UNAIDS, 2014). Conversely, ART uptake is assumed to be relatively low, as the UN estimates that only 40% of people living with HIV are on some form of ART (UNAIDS, 2014), and when ART efficacy is high in our model \((r_2 = 0.9)\), 40% of infections are treated at equilibrium when the drug uptake rate \( f \approx 0.07 \). Although access to ART continues to improve and \( f = 0.07 \) is likely an underestimate, our results generally consider uptake rates either below \( f = 1 \) or \( f = 2.3 \) (which indicate, respectively, that \( \sim 63\% \) and \( \sim 90\% \) of infected hosts initiate treatment in the first year of infection).

The parameter values associated with PrEP are particularly difficult to estimate. The efficacy of PrEP may exceed 99% in ideal conditions and given perfect drug adherence (Anderson et al., 2012), but realized estimates of PrEP efficacy range widely. Excluding two clinical trials discontinued due to complete non-efficacy, PrEP has been found to reduce the risk of HIV acquisition by 39 - 86% (van der Straten et al., 2012; McCormack et al., 2015). Further, since PrEP efficacy hinges vitally on drug adherence (van der Straten et al., 2012; McCormack et al., 2015).
the efficacies reported in clinical trials may be biased due to inflated access to drugs and medical care. Finally, although PrEP is a new preventive strategy with limited availability, we explore a broad range of uptake rates to predict its evolutionary implications over a broad range of rollout scenarios.
Table 1: Default variable and parameter values of the model.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description (units)</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>S</td>
<td>frequency of susceptible hosts</td>
<td>0 - 1</td>
</tr>
<tr>
<td>P</td>
<td>frequency of susceptible hosts on PrEP</td>
<td>0 - 1</td>
</tr>
<tr>
<td>I</td>
<td>frequency of infected hosts</td>
<td>0 - 1</td>
</tr>
<tr>
<td>T</td>
<td>frequency of infected hosts on ART</td>
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<td>V</td>
<td>SPVL (viral copies/mL blood plasma)</td>
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<td>rate of progression to AIDS (year$^{-1}$)</td>
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<tr>
<td>$f$</td>
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</tr>
<tr>
<td>$g$</td>
<td>PrEP uptake rate (year$^{-1}$)</td>
<td>0 - 2.3</td>
</tr>
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<td>maximum duration of asymptomatic infection (years)</td>
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<td>viral load at which D is half maximum</td>
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<tr>
<td>$\beta_k$</td>
<td>transmission rate Hill coefficient</td>
<td>1.02*</td>
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</tbody>
</table>

* parameter values obtained from Fraser et al. (2007)
3 Model Analysis

3.1 Epidemiological Equilibrium

We use an equilibrium analysis to predict how interventions affect the prevalence of infection in the host population. We find a disease-free equilibrium, DFE,

\[
\begin{align*}
\hat{S}_{DFE} &= \frac{\mu}{\mu + g} \\
\hat{P}_{DFE} &= \frac{g}{\mu + g} \\
\hat{I}_{DFE} &= 0 \\
\hat{T}_{DFE} &= 0
\end{align*}
\]

(12) (13) (14) (15)

where circumflexes denote hosts at equilibrium. When PrEP is not used, this reduces to 
\{\hat{S}_{DFE} = 1, \hat{P}_{DFE} = 0, \hat{I}_{DFE} = 0, \hat{T}_{DFE} = 0\}.

We also find an endemic equilibrium, EE (with a non-zero equilibrium proportion of infected hosts), which depends on the interventions used in the population. When neither PrEP nor ART are available \((f = g = 0)\),

\[
\begin{align*}
\hat{S}_{EE} &= \frac{\mu + \alpha I}{\beta I} \\
\hat{P}_{EE} &= 0 \\
\hat{I}_{EE} &= 1 - \frac{\mu + \alpha I}{\beta I} \\
\hat{T}_{EE} &= 0
\end{align*}
\]

(16) (17) (18) (19)

where, assuming a low background rate of mortality, the equilibrium prevalence of infection is determined largely by the trade-off between transmission rate and disease progression. When
imperfect ART ($0 < r_2 < 1$) is introduced into the population ($f > 0$), then

\begin{equation}
\hat{S}_{EE_2} = \frac{\mu + \alpha_I + f}{\beta_I + \frac{f \beta_T}{\mu + \alpha_T}} \tag{20}
\end{equation}

\begin{equation}
\hat{P}_{EE_2} = 0 \tag{21}
\end{equation}

\begin{equation}
\hat{I}_{EE_2} = \frac{(\mu + \alpha_I)(\beta_I - \alpha_I) + f(\beta_I - \alpha_I)}{\mu + \alpha_T + f \beta_T} - \mu \tag{22}
\end{equation}

\begin{equation}
\hat{T}_{EE_2} = \frac{f}{\mu + \alpha_T} \hat{I}_{EE_2} \tag{23}
\end{equation}

where increasing the rate of ART uptake ($f$) leads to an increasing proportion of treated relative to untreated infections. ART eliminates endemic infection when

\begin{equation}
f > \frac{(\beta_I - \mu - \alpha_I)(\mu + \alpha_T)}{\mu + \alpha_T - \beta_T} \tag{24}
\end{equation}

and so disease eradication depends on the relative efficacy of ART ($r_2$) and the values of $\alpha_T$ and $\beta_T$ that result.

When imperfect PrEP ($0 < r_1 < 1$) is introduced ($g > 0$) in the absence of ART ($f = 0$), analytic equilibrium expressions are intractable (i.e., few simple inferences can be drawn from them) and so are not shown. However, when PrEP always prevents infection ($r_1 = 1$), we find,

\begin{equation}
\hat{S}_{EE_3} = \frac{\mu + \alpha_I}{\beta_I} \tag{25}
\end{equation}

\begin{equation}
\hat{P}_{EE_3} = \frac{g(\mu + \alpha_I)}{\mu \beta_I} \tag{26}
\end{equation}

\begin{equation}
\hat{I}_{EE_3} = \frac{\mu(\beta_I - g - \mu) - \alpha_I (g + \mu)}{\mu \beta_I} \tag{27}
\end{equation}

\begin{equation}
\hat{T}_{EE_3} = 0 \tag{28}
\end{equation}

where, predictably, increasing the rate of PrEP uptake leads to fewer infections, and endemic infection is eliminated when

\begin{equation}
g > \frac{\mu(\beta_I - \mu - \alpha_I)}{\mu + \alpha_I}. \tag{29}
\end{equation}

When we compare this to equation 24 and consider the case that ART is also perfectly effective
$(r_2 = 1$, and therefore $\beta_T = 0$), we find that infection is eliminated for lower values of $g$ than $f$. Thus, all else being equal, preventing infection in susceptible hosts is a more effective way to control the spread of the virus than preventing transmission from infected individuals.

When both ART and PrEP are used simultaneously $(f, g > 0)$, analytic equilibrium expressions are only solvable when drugs work with perfect efficacy $(r_1 = r_2 = 1)$:

$$\hat{S}_{EE4} = \frac{\mu + \alpha_I + f}{\beta_I} \quad (30)$$

$$\hat{P}_{EE4} = \frac{g(\mu + \alpha_I + f)}{\mu \beta_I} \quad (31)$$

$$\hat{I}_{EE4} = \frac{\mu - (\mu + g)(\mu + \alpha_I + f)}{\mu + f} \beta_I \quad (32)$$

$$\hat{T}_{EE4} = \frac{f - f(\mu + g)(\mu + \alpha_I + f)}{\mu \beta_I} \quad (33)$$

In this case, endemic infection is eliminated when

$$f > \mu \left( \frac{\beta_I}{\mu + g} - 1 \right) - \alpha_I \quad (34)$$

or

$$g > \mu \left( \frac{\beta_I}{\mu + \alpha_I + f} - 1 \right) \quad (35)$$

Finally, when TPBs are used with and without other interventions, analytical equilibrium expressions are unsolvable and intractable, respectively, and are not shown.

### 3.2 Equilibrium Stability

Because equilibria were not always analytically solvable, we used numerical simulations to predict the effects of imperfect PrEP, ART and TPBs on equilibrium infection prevalence. Host frequencies only converge to equilibrium values that are locally asymptotically stable, and so a population is only infected when its EE is stable. We determine equilibrium stability...
by first decomposing our system of ODEs into its Jacobian matrix:

\[
J = \begin{pmatrix}
\frac{\partial \dot{S}}{\partial S} & \frac{\partial \dot{S}}{\partial P} & \frac{\partial \dot{S}}{\partial I} & \frac{\partial \dot{S}}{\partial T} \\
\frac{\partial \dot{P}}{\partial S} & \frac{\partial \dot{P}}{\partial P} & \frac{\partial \dot{P}}{\partial I} & \frac{\partial \dot{P}}{\partial T} \\
\frac{\partial \dot{I}}{\partial S} & \frac{\partial \dot{I}}{\partial P} & \frac{\partial \dot{I}}{\partial I} & \frac{\partial \dot{I}}{\partial T} \\
\frac{\partial \dot{T}}{\partial S} & \frac{\partial \dot{T}}{\partial P} & \frac{\partial \dot{T}}{\partial I} & \frac{\partial \dot{T}}{\partial T}
\end{pmatrix}
\]  

(36)

where the dots represent derivatives with respect to time (i.e., equations 1 - 4). The local stability matrix is the Jacobian evaluated at a particular equilibrium,

\[J \bigg|_{\hat{S}, \hat{P}, \hat{I}, \hat{T}}\]

(37)

and an equilibrium (denoted by hats) is locally asymptotically stable if all of the eigenvalues of its stability matrix, \(\lambda_J\), have negative real parts \([Otto and Day, 2008]\). If any eigenvalues are positive, then that equilibrium is found to be unstable and is not approached by nearby state space over time.

All endemic equilibria that we report were found to be stable, except for a small parameter range not shown in the main results (see Appendix A.6). An example stability calculation is provided below. When a population is infected with a virus with SPVL of 35,000 virions/mL, has a background mortality rate of 2%, and initiates ART with 90% efficacy at a rate of 0.1 per year \(\mu = 0.02, V = 35,000, r_2 = 0.9, f = 0.1\), we find numerically that two equilibria exist.

\[\{\hat{S}_{DFE}, \hat{P}_{DFE}, \hat{I}_{DFE}, \hat{T}_{DFE}\} = \{1, 0, 0, 0\}\]

(38)

is the disease free equilibrium. The eigenvalues of its Jacobian matrix are:

\[\lambda_{J_{DFE}} = \{-0.155, -0.02, -0.02, 0.015\}\]

(39)
and since one of the eigenvalues is positive, the disease-free equilibrium is unstable, meaning that an uninfected population exposed to infection will be perturbed from the DFE. The second equilibrium,

$$\{\hat{S}_{EE}, \hat{P}_{EE}, \hat{I}_{EE}, \hat{T}_{EE}\} = \{0.92, 0, 0.04, 0.04\}$$

(40)

is the endemic equilibrium. The eigenvalues of its Jacobian are:

$$\lambda_{J_{EE}} = \{-0.154, -0.032, -0.02, -0.015\}$$

(41)

and since all values are negative, the endemic equilibrium is stable, meaning that this equilibrium is an attractor and is approached by nearby state space over time. Only after an endemic equilibrium is determined to be stable can we perform an evolutionary invasion analysis.

### 3.3 Evolutionary Invasion Analysis

Evolutionary invasion analysis is a standard tool used to model phenotypic evolution in response to natural selection, and is a powerful means of understanding and predicting the evolution of virulence [Dieckmann et al. 2002; Otto and Day 2008]. This method optimizes invasion fitness, $R_m$, a measure of the growth rate of a rare mutant parasite introduced into a host population where a resident parasite is endemic and where the system is at epidemiological equilibrium. When introduced, any mutant parasite that experiences growth in abundance or density ($R_m > 0$) is assumed to outcompete and immediately replace the resident ‘strain’. Invasions occur iteratively, and host and parasite reach epidemiological equilibrium before each successive parasite invasion. When $R_m < 0$ for all possible trait values, the resident trait is evolutionarily stable and can not be invaded by any mutant. All else being equal, this is the trait value that should evolve.

We used methods of invasion analysis adapted from next-generation theory [Van Den Driessche and Watmough 2002; Hurford et al. 2010], which offer simple and biologically meaningful tools
for computing $R_m$ when a mutant virus invades a host population infected with a resident virus. First, our system of ordinary differential equations (ODEs) expands to include hosts that are infected with the mutant virus,

\begin{align*}
\frac{dS}{dt} &= \theta - (\beta I + \beta_T T + \beta' I' + \beta'_T T') S - (\mu + g) S \\
\frac{dP}{dt} &= gS - \eta(\beta I + \beta_T T + \beta' I' + \beta'_T T') P - \mu P \\
\frac{dI}{dt} &= (\beta I + \beta_T T) S - (\mu + \alpha I + f) I \\
\frac{dT}{dt} &= fI + \eta(\beta I + \beta_T T) P - (\mu + \alpha_T) T \\
\frac{dI'}{dt} &= (\beta' I' + \beta'_T T') S - (\mu + \alpha' I + f) I' \\
\frac{dT'}{dt} &= fI' + \eta(\beta' I' + \beta'_T T') P - (\mu + \alpha'_T) T'
\end{align*}

where primes denote the host classes and infection parameters associated with the mutant. Mutant ODEs can be expressed as their component parts,

\[
\frac{d\vec{x}}{dt} = A \vec{x}
\]

where $\vec{x}$ is a vector of host classes infected with the mutant virus, and $A$ is a non-singular invasion matrix describing the infection dynamics of the mutant. These terms expand to

\[
\frac{d}{dt} \begin{pmatrix} I' \\ T' \end{pmatrix} = \begin{pmatrix} \beta' S - (\mu + \alpha' I + f) & \beta'_T S \\ f + \eta \beta' P & \eta \beta'_T P - (\mu + \alpha'_T) \end{pmatrix} \begin{pmatrix} I' \\ T' \end{pmatrix}
\]

and since a negligible proportion of hosts are infected by the rare mutant, hosts are at the stable endemic equilibrium set by the resident virus. The mutant invasion dynamics $A$ can then be decomposed as $A = F - V$, where

\[
F = \begin{pmatrix} \beta' S & \beta'_T S \\ \beta' \eta P & \beta'_T \eta P \end{pmatrix}
\]
\[ V = \begin{pmatrix} \mu + \alpha_I + f & 0 \\ -f & \mu + \alpha_T \end{pmatrix}. \] (51)

\( F \) is a transmission matrix that describes the rate at which existing mutant infections generate new ones, and \( V \) is a transition matrix that describes the rate at which mutant infections move among and out of infected host classes. Therefore, \( V^{-1} \) describes the duration of time that infected and treated hosts are asymptomatically infected with mutant virus,

\[ V^{-1} = \begin{pmatrix} \frac{1}{\mu + \alpha_I'} + \frac{\mu + \alpha_T'}{f} & 0 \\ \frac{\mu + \alpha_T'}{f} & \frac{1}{\mu + \alpha_I'} \end{pmatrix}. \] (52)

The matrices \( F \) and \( V^{-1} \) satisfy the conditions of the Next-Generation Theorem (Hurford et al., 2010),

\[ \text{NGM} = FV^{-1} \] (53)

where \( \text{NGM} \) is the next-generation matrix, whose elements represent the average transmission of mutant virus from each host type. In our model,

\[ \text{NGM} = \begin{pmatrix} \frac{(\beta_I' + \frac{f\beta_T'}{\mu + \alpha_T'}) \hat{S}}{\mu + \alpha_I' + f} & \frac{\beta_T' \hat{S}}{\mu + \alpha_T'} \\ \frac{(\beta_I' + \frac{f\beta_T'}{\mu + \alpha_T'}) \eta \hat{P}}{\mu + \alpha_I' + f} & \frac{\beta_T' \eta \hat{P}}{\mu + \alpha_T'} \end{pmatrix}. \] (54)

The invasion fitness of the mutant virus is calculated from the spectral radius, \( \rho \), of the \( \text{NGM} \), (i.e., the maximum absolute value of all eigenvalues of the \( \text{NGM} \)), which approximates the total lifetime number of transmission events from a host infected with a rare mutant. Therefore,
a mutant virus is expected to invade a host population when

\[ \rho(\text{NGM}) > 1 \]  \hspace{1cm} (55)

since this indicates that an average mutant virus transmits more than once over the full duration of infection, and therefore increases in frequency when introduced into the host population. Consequently, \( \rho(\text{NGM}) \) is analogous to the basic reproduction ratio of infection, \( R_0 \) (Hurford \textit{et al.} 2010), and so, intuitively, a mutant invades the host population when its reproduction ratio \( R_0 > 1 \). According to Next-Generation Theory, this amounts to a destabilization of the endemic equilibrium of the resident virus, and the invading virus excludes the resident and reaches its own stable endemic equilibrium. Since the determinant of \( F = 0 \), it follows that the determinant of \( \text{NGM} = 0 \), and the non-zero eigenvalue of \( \text{NGM} \), or \( R_0 \), is therefore given by its trace.

In order to predict the evolution of SPVL, we find the evolutionarily stable value of SPVL, \( V^* \). This is the trait value that maximizes \( R_0 \) and hence maximizes viral fitness. When \( V^* \) is the resident trait, no mutant can destabilize the resident equilibrium. To find \( V^* \), we first calculate the selection gradient of \( R_0 \) with respect to mutant SPVL, \( V' \):

\[ \frac{\partial R_0}{\partial V'} \bigg|_{V'=V} \]  \hspace{1cm} (56)

which amounts to a linear approximation of the derivative of the invasion fitness taken about the resident trait value. A positive (negative) slope indicates that higher (lower) mutant trait values successfully invade the resident. The root of a selection gradient therefore describes the point at which neither higher nor lower \( V' \) can invade (numerical examples shown in Appendix A.1). This root is evolutionarily stable and represents \( V^* \) when it is a fitness maximum. This is true when

\[ \frac{\partial^2 R_0}{\partial V'^2} \bigg|_{V'=V=V^*} < 0 \]  \hspace{1cm} (57)
and means that mutant trait values that are either higher or lower than $V^*$ have lower fitness than $V^*$. This root is convergence stable when

$$\frac{\partial}{\partial V} \left( \frac{\partial R_0}{\partial V'} \right) \bigg|_{V'=V} \leq 0$$  \hspace{1cm} (58)$$

meaning that higher values of $V'$ invade when $V < V^*$ and lower values invade when $V > V^*$, and hence trait values converge towards $V^*$ over successive invasions (Otto and Day, 2008). All values of $V^*$ that we calculated were found to be convergence stable fitness maxima, and are thus evolutionarily stable (shown numerically in Appendix A.2).

### 3.4 Invasion Thresholds

A rare mutant invades the resident population when its $R_0 > 1$. We can therefore calculate invasion thresholds, i.e., the conditions under which a mutant virus is expected to invade. In the absence of interventions ($f = g = 0$), we recapitulate $R_0$ as in the classic $S - I$ model of parasite transmission (Otto and Day 2008), and expect a mutant to invade when

$$\beta'_I \hat{S} \mu + \alpha'_I I > \beta_I I \mu + \alpha_I I$$  \hspace{1cm} (59)$$

Substituting $\hat{S}$ from equation 16, we find

$$\frac{\beta'_I \hat{S}}{\mu + \alpha'_I} > 1.$$  \hspace{1cm} (60)$$

and so, intuitively, a mutant invades when it transmits to more hosts per infectious period than the resident.

The introduction of ART ($r_2$) alters $R_0$, such that mutant invasion occurs when

$$\frac{(\beta'_I + \frac{f \beta_I}{\mu + \alpha_I + f}) \hat{S}}{\mu + \alpha'_I + f} > 1.$$  \hspace{1cm} (61)$$
Substituting $\hat{S}$ from equation\[20\] we find:

$$\frac{\beta'_{T} + f \frac{\beta'_{T}}{\mu + \alpha'_{T} + f} > \beta_{I} + f \frac{\beta'_{T}}{\mu + \alpha_{T} + f}}{\mu + \alpha'_{T} + f}.$$ \hspace{1cm} \text{(62)}$$

Now, the expressions for $R_0$ of both the mutant and resident represent the sum of the per-host type components of $R_0$. The first term in the numerator (on either side of the inequality) describes the infection of susceptible hosts by untreated hosts; the second term describes the infection of susceptible hosts by treated hosts, and accounts for the rate at which infections progress into the treated class.

In the absence of ART, the introduction of PrEP alters $R_0$ such that invasion occurs when

$$\frac{\beta'_{T} (\hat{S} + \eta \hat{P})}{\mu + \alpha'_{I}} > 1.$$ \hspace{1cm} \text{(63)}$$

Although expressions for $\hat{S}$ and $\hat{P}$ are complex and are not shown, when they are substituted into the above equation we find

$$\frac{\beta'_{I}}{\mu + \alpha'_{I}} > \frac{\beta_{I}}{\mu + \alpha_{I}},$$ \hspace{1cm} \text{(64)}$$

which is the same invasion condition as when no interventions are used at all. Since neither the efficacy nor uptake rate of PrEP affect a mutant’s invasion fitness, PrEP has no bearing on the evolution of V when it is the only intervention being used. This is analogous to the finding in Gandon et al. (2001) that anti-infection vaccines have no impact on virulence evolution in the absence of other forces (e.g., other interventions).

When imperfect PrEP and ART are used simultaneously ($0 < r_1, r_2 < 1$), analytical expressions for equilibrium host frequencies were not found, but a mutant invasion threshold can still be
partially derived, and is given by

\[
(\beta'_I + \frac{f\beta'_I}{\mu + \alpha'_T}) \hat{S} \frac{\eta_P \beta'_T \hat{P}}{\mu + \alpha'_T} > 1. \tag{65}
\]

Again, this is interpreted as the sum of the per-host components of \( R_0 \), where the first term describes the infection of susceptible hosts, from any source (as above), and the second term describes the infection of hosts using PrEP.
4 Numerical results

4.1 Consequences of ART

Antiretroviral therapy (ART) has the expected effect of reducing the equilibrium prevalence of HIV infection (Figure 1). Given default parameter estimates (Table 1), approximately 27% of hosts become infected in a population when no treatment options are available. Increases in either the efficacy of ART ($r_2$) or its rate of uptake in untreated hosts ($f$) contribute to declines in infection prevalence. When drugs are highly effective, their introduction into the host population at low rates leads to sharp declines in equilibrium infection prevalence, and eliminates endemic HIV infection given a sufficient rate of uptake (white regions in Figure 1). However, once uptake rates are sufficiently high ($f \geq 0.5$), further increases do not have a substantial effect on infection prevalence, regardless of drug efficacy.

![Figure 1](image-url)

Figure 1: The equilibrium prevalence of HIV infection ($\hat{I} + \hat{T}$) decreases with both the efficacy and rate of uptake of ART. Lighter regions indicate lower infection prevalences, and the white region indicates that drugs have eradicated HIV from the host population. Approximately 27% of hosts are infected when ART is unavailable ($f = 0$), and low efficacy ART ($r_2 < 0.5$) has little epidemiological effect, regardless of its uptake rate. However, infection prevalence declines rapidly with increasing drug efficacy, and highly effective drugs ($r_2 > 0.8$) eradicate HIV over a broad range of uptake rates.
The use of ART favours the evolution of increased SPVL (Figure 2). By suppressing viral load, ART reduces rates of transmission and disease progression in treated hosts. This generates selection for the compensatory evolution of higher SPVL, as infections that retain higher viral loads when treated are more likely to transmit. However, the value of SPVL that maximizes overall viral fitness (evolutionary stable SPVL, $V^*$) represents a compromise between the divergent values of SPVL that maximize transmission from untreated versus treated hosts. As one host type becomes more common, it comes to represent a greater potential source of HIV transmission, and weighs more heavily on the optimization of SPVL. The relative proportions of untreated and treated infections are therefore integral to virulence evolution in this system, which is reflected by strong selection for increasing SPVL as the rate of drug uptake increases (see Appendix A.4).

The value of SPVL that evolves generally increases as drugs become more effective, but when uptake rates are low, and above a particular efficacy threshold ($f \lesssim 0.1, r_2 \gtrsim 0.9$), further increases in drug efficacy lead to the evolution of lower SPVL. Since treated hosts are very unlikely to transmit when drugs approach perfect efficacy, the evolution of SPVL becomes governed largely by the tradeoff expressed in untreated hosts, and so selection for higher SPVL is reduced. However, this only occurs when there is a sufficiently high proportion of infections left untreated. When the rate of drug uptake is high, few infections remain untreated, and highly effective drugs lead to the evolution of very high SPVL in order to increase the likelihood of transmission from what is effectively the only source of transmission, i.e., treated hosts.

The evolution of SPVL in response to ART leads to worse outcomes for hosts. Higher SPVL leads to higher intrinsic virulence (i.e., faster progression to AIDS in untreated hosts) than in the absence of evolution (Figure 3, left panel). In the absence of evolution in response to interventions and given default parameter estimates, asymptomatic infections persist for approximately 6.7 years before progressing to AIDS (which is slightly lower than the $\sim 6.9$ years calculated in [Fraser et al., 2007], due to our inclusion of a background mortality rate; see Appendix A.3). However, when SPVL evolves to maximize transmission in a population with highly effective and rapidly initiated ART, an adapted virus causes untreated hosts to
progress to AIDS in as few as 3.5 years.

While epidemiological parameters affect the evolution of SPVL, SPVL evolution also has implications for epidemiology (Figure 3, right panel). In the absence of evolution, increasing the uptake rate and efficacy of ART reduces the proportion of hosts infected with HIV. However, the evolution of SPVL leads to increased rates of transmission and hence increased prevalence in a treated population. When we calculate evolutionary stable SPVL for a given set of parameters and plug this evolved virus back into its corresponding epidemiological model, we find that the equilibrium prevalence of HIV infection increases dramatically. Paradoxically, when the rate of ART uptake exceeds $\sim 0.2$, further increasing the availability of drugs leads to a higher prevalence of infection. When drug uptake is high and treated hosts become the dominant selective environment for HIV, and when SPVL evolution favours optimizing transmission from these hosts, then increasing the rate of ART uptake increases the frequency of viruses encountering this environment to which they are adapted.
Figure 3: When SPVL evolves in response to highly effective ART (from lightest to darkest red, $r_2 = 0.7, 0.8, 0.9$), increasing the uptake rate of drugs leads to worse outcomes for infected individuals and populations. **Left:** In the absence of evolution (solid line), untreated HIV infections progress to AIDS in approximately 6.7 years. When SPVL evolves in response to different drug treatment scenarios (dashed lines), hosts without access to ART progress to AIDS more quickly. **Right:** In the absence of evolution (solid lines), increasing the uptake rate of ART reduces the prevalence of infection, and can eliminate HIV from the population when drugs are highly effective (e.g., the dark red line demonstrates HIV elimination at uptake rates at or above 0.2). SPVL evolution in response to drugs leads to higher infection prevalences at equilibrium (dashed lines) than when SPVL does not evolve. When the rate of drug uptake is high enough that the majority of infections are treated at equilibrium ($f \gtrsim 0.2$), SPVL evolves to maximize transmission from treated hosts, and further increases in the rate of drug uptake counterintuitively increase the proportion of hosts infected with HIV.

### 4.2 Consequences of PrEP

The prevalence of HIV infection declines rapidly when pre-exposure prophylaxis (PrEP) is introduced into an infected population at endemic equilibrium and without access to ART (Figure 4, left). When PrEP is highly effective ($r_1 \approx 0.8$), the virus does not persist if PrEP is initiated by as few as $\sim 1\%$ of susceptible hosts per year. Combining PrEP and ART, unsurprisingly, offers additional epidemiological benefits. When ART is available, even entirely ineffective PrEP ($r_1 = 0$) leads to elimination of HIV when the rate of PrEP uptake is as low as 0.006 (Figure 4, right). This occurs because hosts on PrEP are immediately treated upon HIV infection, and thus the proportion of infections that are treated increases as PrEP...
becomes more widely used (even when PrEP does not actually function as prophylaxis), which contributes to reductions in infection prevalence. These results assume that SPVL is optimized to transmit from untreated hosts (i.e., before we allow SPVL to evolve in the face of widespread and highly effective ART).

Figure 4: The equilibrium prevalence of HIV infection declines with both the efficacy of PrEP ($r_1$) and its rate of uptake in susceptible hosts ($g$). **Left:** When ART is not used, the use of PrEP eliminates endemic HIV infection (white region) at low uptake rates when PrEP has middling or high efficacy. **Right:** If PrEP is used in conjunction with ART ($r_2 = 0.9, f = 0.1$), endemic HIV infection is eliminated at very low uptake rates (note the differences in y-axis scale), regardless of the efficacy of PrEP.

PrEP prevents infection without affecting a mutant’s invasion fitness. Therefore, in the absence of ART, PrEP bears no consequence on the evolution of SPVL. However, when some infections are treated with ART, the use of PrEP contributes to the evolution of higher SPVL (Figure 5). This only occurs when PrEP efficacy is low, as effective PrEP eliminates endemic HIV infection whether or not SPVL evolution is allowed to occur, in which case no values of SPVL are evolutionarily stable. We therefore consider the evolutionary consequences of low efficacy PrEP ($r_1 = 0.2$). Since the use of PrEP increases the proportion of infections that are treated, increasing the uptake rate of PrEP concomitantly increases the proportion of infections exposed to ART. When PrEP uptake is very low, the relative uptake rate of ART drives the value of...
SPVL that is predicted to evolve: at a high rate of ART uptake, most infections are treated at equilibrium and the addition of PrEP has little epidemiological or evolutionary effect; at a low ART uptake rate small increases in the use of PrEP lead to large increases in the proportion of treated hosts, which drives the evolution of higher SPVL. In contrast, when PrEP uptake is high, the majority of infections are treated and SPVL evolution is governed by the transmission tradeoff in treated hosts, regardless of the rate of ART uptake.

Figure 5: When both ART and PrEP are used, evolutionarily stable SPVL ($V^*$) increases with the rate of PrEP uptake ($g$). Given low rates of PrEP uptake, the value of SPVL that evolves depends largely on the rate at which infected hosts initiate ART (from lightest to darkest blue, $f = 0.01, 0.1, 1$). However, as PrEP uptake increases, the vast majority of infections occur in hosts on PrEP. Consequently, more infections are immediately treated, and very high SPVL evolves regardless of the actual rate of ART uptake. The case is shown where ART is highly effective ($r_2 = 0.9$) but PrEP has low efficacy ($r_1 = 0.2$), because endemic HIV can not persist when PrEP is highly effective, even when SPVL evolves.

PrEP can have unintended consequences on host health and the spread of HIV in a population that already has access to ART (Figure 6). When SPVL evolves in response to PrEP, untreated hosts progress to AIDS more quickly. This effect of PrEP is greatest when ART uptake is low, because increasing the uptake of PrEP entails a sharp increase in the proportion of treated infections, which drives the evolution of very high SPVL and thus very high virulence. Furthermore, the evolution of SPVL allows endemic HIV infection to persist where it would otherwise be eliminated by PrEP (Figure 6). If PrEP uptake is low when introduced in
a host population, the model predicts considerable declines in infection prevalence; however, these returns are diminished or disappear altogether if PrEP uptake increases from a low to a medium or high rate. When PrEP is highly used and SPVL evolves, the prevalence of infection converges at around 10%, regardless of the uptake rate of ART, and therefore the prevalence of HIV is largely predicted by the use of preventive HIV drugs.

Figure 6: When SPVL evolves in populations that make use of both ART and PrEP, infections can persist despite the use of these drugs, and increases in the uptake rate of PrEP lead to worse outcomes for infected individuals and populations. These epidemiological outcomes depend heavily on the relative uptake rate of ART (from lightest to darkest blue, $f = 0.01, 0.1, 1$) when PrEP uptake is low, but not when PrEP uptake is high. These simulations assume high ART efficacy ($r_2 = 0.9$) and low PrEP efficacy ($r_1 = 0.2$). **Left:** When ART uptake is low, increases in the uptake rate of PrEP lead to the evolution of infections that progress to AIDS more rapidly. PrEP has little effect on virulence evolution when ART uptake is high. **Right:** The evolution of SPVL prevents PrEP from eradicating the virus from the host population. When PrEP uptake is nonexistent or very low, increases in the rate of PrEP uptake cause precipitous declines in infection prevalence, regardless of the use of ART. However, when the rate of PrEP uptake is already reasonably high ($g \gtrsim 0.1$), further increases are unable to eliminate HIV, and can actually increase the equilibrium prevalence of infection if ART uptake is low.
4.3 Consequences of TPBs

Although not a main focus of our study, we also considered how transmission-prevention behaviours (TPBs) affect the evolution of SPVL (elaborated in Appendix A.5). Briefly, we found that lower SPVL evolves when highly effective TPBs are used by hosts on ART. Since TPBs act as a barrier to transmission from treated hosts, they relax selection generated by ART and favour the evolution of lower SPVL in order to maximize transmission from untreated hosts. TPBs thus mitigate virulence evolution in response to drugs.
5 Discussion

It is believed that HIV-1 has evolved intermediate virulence to maximize population-level transmission, but it is poorly understood if or how the use of antiretroviral drugs affects this evolution (Fraser et al. 2014). There is growing experimental and observational support for the prediction that imperfect drugs and vaccines can lead to the evolution of higher virulence (Gandon and Day 2008; Barclay et al. 2012; Schneider et al. 2012; Read et al. 2015), and HIV-1 conforms to the preconditions necessary for this kind of evolution (Gandon et al. 2001): HIV-1 is an obligate endoparasite where virulence and transmission both increase with viral density, and where medical interventions imperfectly reduce viral replication. Here, we used an invasion analysis to predict evolutionary end-points of set-point viral load (SPVL, a proxy measure for virulence), and found that higher SPVL is expected to evolve in response to imperfect, or ‘leaky’ antiretroviral therapy (ART). This evolution can allow the persistence of highly virulent HIV infections in conditions where drugs would otherwise eliminate the virus from a host population. However, selection for high virulence is at least somewhat alleviated when treated hosts practice behaviours that reduce their likelihood of transmission (see Appendix A.5). In addition, preventive HIV drugs (pre-exposure prophylaxis, or PrEP) are shown to be highly capable of reducing the prevalence of HIV, but exacerbate the evolution of SPVL in response to ART. When SPVL is allowed to evolve, we show that higher uptake rates of ART or PrEP can be accompanied, counterintuitively, by higher HIV infection prevalence. These findings build on the predictions of Gandon et al. (2001), who found that leaky interventions can lead to virulence evolution, but that evolutionary outcomes depend critically on the type of interventions used and the fitness trade-offs inherent to different host and parasite species.

ART has turned HIV infection from a death sentence into a manageable, lifelong condition (Ray et al. 2011), but only 40% of infections are currently treated (UNAIDS 2014). While this suggests that the average rate of ART uptake is relatively low, access to treatment continues to improve in populations worldwide, leading to significant reductions in HIV-1 incidence and AIDS-related mortality (UNAIDS 2014). However, our results show that increasing the uptake of ART may have unforeseen evolutionary consequences. Although we predict modest evolution
in SPVL when drug uptake is low, evolutionarily optimal SPVL is expected to increase by orders of magnitude if imperfect ART becomes very highly used. Intriguingly, average SPVL has increased in several European countries since the rollout of ART ([Dorrucci et al., 2007 Müller et al., 2009 Gras et al., 2009 Potard et al., 2009]. Although the causes of this evolution are unknown, our results suggest that the use of ART and PrEP drugs may play a role in SPVL evolution in such highly treated populations.

Our findings contrast with two previously published mathematical models that predicted the evolution of lower SPVL when ART is used ([Payne et al., 2014 Roberts et al., 2015]. These studies assumed that treated hosts do not transmit HIV. It is true that, in ideal conditions, infections undergoing ART are virologically suppressed (i.e., viral load declines below 400 copies/mL of blood plasma) and the risk of sexual transmission is negligible ([Vernazza et al., 2008]. However, viral load is not suppressed in approximately 24% of treated infections worldwide ([UNAIDS, 2014], and ART has been shown to reduce average HIV-1 transmission risk by 58 - 92% (reviewed in [Attia et al., 2009 Anglemyer et al., 2013 and Baggaley et al., 2013]. Furthermore, [Ratmann et al., 2016] recently found that 6% of infections in the Netherlands were transmitted from treated hosts. Regardless of its causes, this observed leakiness in ART is likely to elicit an evolutionary response in HIV if some treated infections are more likely to transmit than others because of viral traits.

The modelling studies of [Payne et al., 2014] and [Roberts et al., 2015] also assumed that less virulent infections are less likely to receive treatment. Historically, the initiation of ART was delayed until the onset of AIDS (i.e., when CD4+ cell density declines below 200 cells/mm³; [WHO, 2010]). Since infections with high SPVL progress to AIDS more quickly, it has been suggested that this treatment strategy disproportionately truncates the transmission window of infections with high SPVL, and generates a transmission advantage for low SPVL infections because they remain untreated for longer. Administering treatment to some hosts over others is no longer standard practice, and the WHO recommends the immediate initiation of ART upon HIV diagnosis ([WHO, 2015], which obviates this mechanism of selection. However, universal treatment is not always possible, and there are likely to be treatment biases in some settings.
For example, in Botswana, where Payne et al. (2014) observed the evolution of lower SPVL in comparison to neighbouring South Africa, prevention projects explicitly target ART towards those with the highest viral loads (Cohen et al., 2013). In consideration of this, we adjusted our model so that infections with higher viral load initiate ART at a higher rate, and found that this selects for the evolution of even higher SPVL than when all infections are treated equally (results not shown). However, it should be reiterated that our approach estimates evolutionarily stable viral phenotypes, and is not directly comparable to the transient evolution of competing strains observed in Payne et al. (2014) and Roberts et al. (2015).

We simplified the transmission dynamics of HIV in our epidemiological model in order to make broad evolutionary and epidemiological predictions. First, we assumed only horizontal HIV transmission. Second, we assumed no heterogeneity in hosts aside from their use of interventional. Third, apart from the constraints imposed by the virulence-transmission trade-off, we assumed that there are no additional limits to the evolution of SPVL. Although large variation in SPVL is observed, there are likely biological constraints such as host cell availability that preclude the evolution of extremely high SPVL. However, highly virulent HIV genotypes exist, and the full range of values of evolutionary stable SPVL predicted by our results has been observed in host populations (de Wolf et al., 1997; Fraser et al., 2007). Fourth, we simplified HIV-1 infection as being wholly represented by the stable viral dynamics of asymptomatic infection. Although viral load and transmission rate surge during primary HIV-1 infection (reviewed in Boily et al. 2009), the relative contribution of transmission during this brief period is contested. A recent study found that less transmission occurs during primary infection than previously thought (Bellan et al., 2015), and a separate review suggests that early infection may be less likely to play a significant role in populations where HIV is endemic (Miller et al., 2010). We do not expect the inclusion of primary HIV-1 infection to qualitatively change our findings.

Perhaps the most vital assumption of our model is that viral suppression scales with baseline SPVL, such that infections with high SPVL remain more infectious than those with low SPVL when ART is used. It is not known the extent to which this is true, but there are a number of
observations that support this assumption. In particular, infections with higher SPVL retain a
higher viral load when treated (Maldarelli et al., 2007), require a longer duration of treatment
to achieve virologic suppression (Paredes et al., 2000; Rizzardi et al., 2000; Phillips et al.,
2001; Matthews et al., 2002; Manegold et al., 2004; European Collaborative Study, 2007), are
less likely to achieve complete virologic suppression (Bratt et al., 1998; Paredes et al., 2000;
Chaisson et al., 2000; Knobel et al., 2001), and are more likely to experience virologic failure
(i.e., viral rebound despite adherence to ART) (Egger et al., 2002; van Leth et al., 2005).
Furthermore, SPVL rebounds rapidly when treatment is stopped (Davey et al., 1999; García
et al., 1999; Ruiz et al., 2000), and typically to pre-treatment levels (Hatano et al., 2000;
Oxenius et al., 2002; Hamlyn et al., 2012). Prolonged breaks in adherence may thus represent
islands of infectivity where host infectiousness relates positively to pre-treatment SPVL. Finally,
viral ‘blips’ (brief and intermittent periods of detectable viral load despite adherence to ART)
are observed more often in hosts with high baseline SPVL (Havlir et al., 2001; Leierer et al.,
2015), and infections with large or frequent blips are more likely to experience virologic failure
(Easterbrook et al., 2002; Grennan et al., 2012; Laprise et al., 2013) and achieve higher viral
rebound upon treatment interruption (Castro et al., 2013). These observations span drug
types, host populations, and viral clades, but collectively support the intuitive assumption that
infections with high SPVL are more infectious than those with low SPVL when imperfectly
treated.

We have modelled the evolution of SPVL without explicit consideration of host and viral ge-
netics. Although SPVL is a heritable viral trait (Hecht et al., 2010; Hollingsworth et al., 2010;
Alizon et al., 2010; Müller et al., 2011) and is broadly linked to viral replication capacity and
mechanisms that modulate immune activation (Trkola et al., 2003; Miura et al., 2010; Fraser
et al., 2014), the precise genetic machinery underlying SPVL is not clear. While our results
predict the effects of ART on evolutionarily stable SPVL, the evolution of SPVL-related genes
is likely to be affected by many additional factors, such as genetic correlations with other
phenotypes, standing viral genetic variation, the types of drugs used, and host genetic factors
such as variation in HLA haplotypes and CD4 co-receptors. In particular, correlations between
SPVL and drug resistance may have important ramifications on SPVL evolution. ART resis-
tance has evolved in response to all drugs currently used to treat HIV (Johnson et al., 2013), and resistance mutations tend to carry fitness costs associated with viral replication (Back et al., 1996; Little et al., 2002; Wheeler et al., 2010). ART may thus be expected to indirectly drive the evolution of lower SPVL when it selects for drug resistance. Although transmitted drug resistance remains an important clinical and epidemiological problem (Vercauteren et al., 2009; Wheeler et al., 2010), resistance mutations generally revert to wild-type when not directly selected for by ART, and modern combination therapies and drug cycling mitigate the within-host evolution of drug resistance (Clavel and Hance, 2004; Siliciano and Siliciano, 2013). Strikingly, recent studies show that the prevalence of drug resistance is decreasing in high-resource areas, despite increasing access to ART (Bontell et al., 2013; De Luca et al., 2013; Charpentier et al., 2013; Theys et al., 2013; Vercauteren et al., 2013). If antiretroviral drugs continue to impose strong selection upon HIV infections, and if modern treatment strategies successfully combat the evolution of resistance, then selection on other viral traits that benefit transmission in the face of treatment may become more apparent.

Our evolutionary framework necessitated the assumption that HIV exists at epidemiological equilibrium with its host. Although it has been hypothesized that the advent of ART is pushing HIV to extinction (Granich et al., 2009), HIV infection is endemic and infection prevalence is stable in many host populations, despite the widespread use of ART (Sullivan et al., 2009; Beyrer et al., 2012; De Cock et al., 2012). When calculating evolutionary stable SPVL, we also assumed that only one resident and one mutant SPVL phenotype exist in a population at any given time. This does not reflect the reality that SPVL varies by orders of magnitude across infected hosts (de Wolf et al., 1997; Fraser et al., 2007). However, given that viral genes are likely to underlie much of this variation (Alizon et al., 2010; Bonhoeffer et al., 2015), the wide distribution of extant SPVL does not preclude its evolution towards a new optimum.

Models of adaptive dynamics (i.e., evolutionary invasion analyses) usually assume that evolutionary change is slow relative to ecological change, since host populations reach epidemiological equilibrium before each successive mutant evolves and invades. However, because a broad range of SPVL phenotypes already exist, the evolution of SPVL does not require the gradual evolu-
tion of incrementally changing trait values. Finally, in calculating evolutionary endpoints of SPVL evolution, we are unable to predict the timescales over which SPVL evolution may be expected to occur. However, we have estimated how long it takes for interventions to eradicate HIV infection from host populations, and find that more effective and more highly used drugs lead to more rapid viral extinction, but that even highly effective and prevalent drugs take decades if not centuries to eliminate HIV (see Appendix A.7). This could potentially provide sufficient time for the widespread transmission of viral genotypes that transmit well from imperfectly treated hosts.

Intermediate SPVL has evolved to maximize HIV-1 transmission, but there is evidence that average SPVL is increasing in many populations (reviewed in Herbeck and Müller 2012). We have shown for the first time that higher virulence can be expected to evolve in HIV-1 when antiretroviral drugs imperfectly suppress viral growth and lead to the preferential transmission of infections with high SPVL. We also show that this evolution makes untreated HIV infection more severe, and makes the virus more difficult to eliminate from host populations. These predictions are theoretical, and although treated infections are observed to transmit (reviewed in Anglemyer et al. 2013 and Baggaley et al. 2013), it has not been shown whether baseline SPVL affects transmission rate from those undergoing ART. Isolating transmission pairs in HIV is notoriously difficult, and the transmission of complex viral phenotypes like SPVL can be obscured by host immunity, rapid within-host evolution, stochasticity and the immediate effects of antiretroviral drugs. More broadly, the HIV-1 pandemic is a dynamic assemblage of host populations infected with diverse viral subtypes, some of which may behave idiosyncratically and evolve in different ways. Not surprisingly, there are conflicting reports of the strength and directionality of SPVL evolution among these host populations and the proposed mechanisms that drive it (Herbeck and Müller 2012; Fraser et al. 2014; Roberts et al. 2015). However, we show that the use of antiretroviral drugs as treatment and as prevention can play important roles in this evolution. These results suggest that HIV interventions may have underappreciated consequences on the evolution of virulence, and that monitoring SPVL evolution should be a high priority as access to lifesaving antiretroviral drugs continues to improve.
A Appendix

A.1 Calculating the selection gradient

Selection gradients indicate the direction of evolution expected when a resident trait value is not evolutionarily stable and can be invaded by a mutant. Positive (negative) selection gradient values indicate that mutants with higher (lower) trait values invade the corresponding resident. When the selection gradient equals zero, neither higher nor lower trait values invade (except in the special case of evolutionary branching, see Appendix A.2). We calculate these gradients numerically and find that they vary depending on the parameter inputs of the model. We show an example of how the SPVL selection gradient changes with an increasing uptake rate of ART (Figure A.1). The root of the selection gradient increases with $f$, meaning that increasing the use of drugs leads to the evolution of higher SPVL.

Figure A.1: SPVL selection gradients vary with the parameter estimates of the model. Here, when ART is highly effective ($r_2 = 0.9$), the roots of the selection gradients increase with the uptake rate of ART ($f = 0$, black dashed line; $f = 0.05$, pink line; $f = 0.2$, red line), indicating that higher values of SPVL are expected to evolve as drugs become more widely used.
A.2 Determining evolutionary and convergence stability

Evolutionary and convergence stability are easiest to infer from pairwise-invadibility plots (PIPs), which, for a given resident trait value, show the range of mutant trait values that can invade and those that can not. A resident trait value is evolutionarily stable when no mutant can invade, and is convergence stable when iterative invasions of incrementally changing trait values lead towards the evolutionarily stable point, and not away from it (satisfying, respectively, conditions 57 and 58 in the main text). PIPs are calculated numerically and vary depending on the parameters of the model. We show PIPs for the same parameter combinations that were used to generate the fitness gradients above (Figure A.2).

![Figure A.2: Three pairwise-invasibility plots demonstrating convergence and evolutionary stability, and showing how evolutionarily stable SPVL increases with the uptake rate of ART (from left to right, \( f = 0, 0.05, 0.2 \)). Green regions indicate where mutants invade the corresponding resident trait, and purple regions indicate mutants that do not invade. White regions indicate where no stable endemic equilibrium exists.](image-url)

In order to confirm that all of our calculated values of \( V^* \) are evolutionarily stable, we found the second derivative condition at the root of each selection gradient and plotted these values over the efficacy and uptake rates of drugs (Figure A.3). We show over a broad range of parameter combinations that the second derivative condition (inequality 57) is met, meaning that all of our predicted values of \( V^* \) are fitness maxima and are evolutionarily stable. Conversely, when the second derivative condition is positive, evolutionary branching occurs, i.e. multiple stable trait values can evolve from one monomorphic parasite population. This is sometimes observed in models of virulence evolution when different virulence traits evolve that are specialized to
different host types (Otto and Day, 2008). However, despite the differences between untreated and treated hosts in our model, we do not find this result. Even when treatment status is irreversibly determined prior to infection (i.e., infections are always either treated or untreated and hence any given HIV infection experiences only one host environment, as in Figure A.3D), evolutionary branching is not observed to occur.

Figure A.3: In our model, the second derivative conditions of selection gradient roots are always negative, and the corresponding roots are thus evolutionarily stable trait values. A: ART only, \( r_2 = 0.9 \); B: ART only, \( f = 0.1 \); C: ART + PrEP, \( r_1 = 0.2, r_2 = 0.9, f = 0.1 \) and ; D: ART + PrEP, \( r_1 = 0.2, r_2 = 0.9, f = 0 \).

A.3 Evolutionary consequences of background mortality

Fraser et al. (2007) estimated that the SPVL trade-off in HIV-1 maximizes transmission potential when \( V = 10^{4.52} \) virions/mL. However, this optimal trait value was calculated using ‘transmission potential’ (i.e., transmission rate multiplied by the duration of infection) as a proxy for fitness, which ignores alternative sources of mortality and demographic feedbacks. Background mortality rate is a standard term in epidemiological models, and increasing this rate (\( \mu \)) selects for an increasing rate of host exploitation, which leads to the evolution of higher
virulence \cite{Anderson1981, Williams2001}. This is recapitulated in our model, where $R_0$ is maximized at $V = 10^{4.52}$ when $\mu = 0$, but at increasing $V$ as $\mu$ increases (Figure A.4). This means that the evolutionary stable viral load that we calculate in an untreated population is slightly higher than that calculated by Fraser et al. \cite{Fraser2007}. However, since our rate of background mortality is low ($\mu = 0.02$) and consistent across all host types, the inclusion of this parameter does not qualitatively influence our results.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figureA4}
\caption{Contour plot showing the viral reproduction ratio ($R_0$) as a function of SPVL ($V$) and the background mortality rate ($\mu$). The value of $V$ that maximizes ‘transmission potential’ was calculated by Fraser et al. \cite{Fraser2007} as $V = 10^{4.52}$ (black dashed line). However, the value of $V$ that maximizes lifetime HIV transmission (as given by our invasion analysis) increases with $\mu$ (red solid line), and so the inclusion of a background mortality rate leads to the evolution of higher SPVL.}
\end{figure}

\subsection*{A.4 Evolutionary consequences of the ART uptake rate}

The SPVL tradeoff is optimized differently in untreated and treated infections due to the efficacy of drugs, but the value of SPVL that evolves depends on the relative contribution to transmission of these two host types. In this way, the efficacy and uptake rate of ART are both key drivers of SPVL evolution in our model. We show how increasing the rate of ART uptake increases the value of SPVL that is expected to evolve (Figure A.5).
Figure A.5: Evolutionarily stable SPVL increases precipitously with the rate of drug uptake in the population, and more effective drugs magnify this effect (from lightest to darkest purple, $r_2 = 0.7, 0.8, 0.9, 0.95$).

### A.5 Elaborated consequences of TPBs

We consider the case that TPBs are used as an intervention strategy in addition to ART and PrEP. The inclusion of TPBs elicits no change in the model’s base ODEs, and $R_0$ remains unchanged:

$$R_0 = \frac{(\beta_I + \frac{f\beta_T}{\mu + \alpha_T})\hat{S}}{\mu + \alpha_I + f} + \frac{\beta_T\eta P\hat{P}}{\mu + \alpha_T}$$  \hspace{1cm} (66)$$

except that $\beta_T$ now depends on the efficacy of $r_3$ in addition to $r_2$.

In a population where antiretroviral drugs are unavailable, increasing both the efficacy and uptake rate of TPBs leads to sharp declines in infection prevalence, and infection can be eliminated altogether when TPBs have a relatively high efficacy and uptake rate (Figure A.6). When treatment consists of both highly effective ART and the adoption of TPBs, increasing the uptake rate of treatment leads to substantial declines in infection prevalence, but increasing the efficacy of TPBs does not have much effect.

Although TPBs reduce transmission rate, they do not affect the optimization of the transmission-virulence trade-off within a host, i.e. transmission potential is maximized at the same value
Figure A.6: The use of TPBs leads to declines in equilibrium infection prevalence. **Left:** when TPBs are the only intervention available, the equilibrium prevalence of infection declines as the efficacy and uptake rate of TPBs increase. The virus is eliminated from the host population when both the uptake rate and efficacy of TPBs \( \geq 0.4 \). **Right:** When treatment consists of both effective ART \( (r_2 = 0.9) \) and TPBs, increasing the uptake of treatment leads to rapid declines in infection prevalence, but increasing the efficacy of TPBs does not have a substantial effect.

of SPVL regardless of any linear coefficient depressing transmission rate. However, the use of TPBs affects evolutionary stable SPVL due to evolutionary-epidemiological feedbacks (Figure A.7). Increasing the efficacy of TPBs prevents HIV transmission, thereby increasing the proportion of susceptible hosts in the population and, consequently, increasing the value of SPVL that evolves. However, when treatment includes both ART and TPBs, increasing the effectiveness of TPBs leads to the evolution of lower virulence than when TPBs are not used. TPBs block treated hosts from transmitting, which relaxes the selective effect imposed by ART and favours the optimization of SPVL to maximize transmission from untreated infections. As TPBs become more effective, treated hosts account for less transmission, and lower SPVL evolves as compared to when no TPBs are used. Although it is very difficult to gauge the realized uptake rates and prevention efficacy of different TPBs used across different populations (Albarracin et al., 2005), we show that they are broadly predicted to have both epidemiological and evolutionary benefits.
Figure A.7: The use of TPBs can have opposing effects on the evolution of SPVL. **Left:** when TPBs are the only intervention available, evolutionary stable SPVL increases somewhat with TPB efficacy, and this effect increases as the rate of TPB uptake increases (from lightest to darkest red, $f = 0.01, 0.05, 0.1, 0.3$). As drug efficacy increases, endemic equilibrium becomes less likely to persist, and so $V^*$ does not exist at high TPB efficacy and uptake rates. **Right:** When hosts are treated with effective ART, increasing the rate of treatment uptake leads to the evolution of much higher SPVL (dotted black line, $r_2 = 0.9$). However, the use of TPBs reduces the value of SPVL that evolves, and as TPBs become more effective, evolutionary stable SPVL becomes lower (from lightest to darkest purple, $r_3 = 0.3, 0.5, 0.7$).

### A.6 Hysteresis in infection prevalence

Given baseline parameter estimates, stability analyses confirmed that when endemic equilibria (EE) are locally asymptotically stable, disease-free equilibria (DFE) are unstable. However, over a very small range of parameters it was observed that stable EE and DFE can sometimes coexist and are separated by an unstable EE (Figure A.8). The backwards bifurcations that result from these simultaneously stable states were only observed when PrEP, ART and TPBs were all used simultaneously, and occur as the prevalence of infection approaches zero. These backwards bifurcations are indicative of hysteresis. The unstable EE acts as a repeller, and the DFE and the stable EE are simultaneous attractors. The attractor towards which the host population moves depends on the initial conditions of the system. If HIV is already endemic when EE and DFE are both stable, then EE should persist; conversely, if a population at DFE is exposed to infection, they can be expected to stay at DFE. As hysteresis was very rarely
observed, it does not contribute substantially to our main findings.

Figure A.8: An example of a backwards bifurcation observed as endemic equilibria approach zero. These were rarely observed and only over narrow parameter ranges (here, $f = 0.05$, $g = 0.01$, $\mu = 0.015$), but indicate that three equilibria can sometimes exist simultaneously: a stable EE (solid lines), an unstable EE (dashed lines), and a stable DFE (not shown, but observed wherever stable and unstable EE exist simultaneously). Where a backwards bifurcation occurs, we show how the equilibrium infection prevalence shifts as we increase the efficacy of PrEP (blue line, $r_2 = 0, r_3 = 0.45$), the efficacy of ART (red line, $r_1 = 0.25, r_3 = 0.45$), or the efficacy of TPBs (orange line, $r_1 = 0.25, r_2 = 0$).

A.7 Estimating the time to viral extinction

We predicted the duration of time over which HIV interventions lead to the elimination of infection from the host population. In doing so, we assume that SPVL does not evolve. We first infect a naïve population with default virus ($V = 38,465$) and let it reach its endemic equilibrium

$$\{\hat{S}_{EE}, \hat{P}_{EE}, \hat{I}_{EE}, \hat{T}_{EE}\} = \{0.729, 0, 0.271, 0\}. \quad (67)$$

We then introduce an intervention at time zero. In the case that the endemic equilibrium is destabilized by the intervention, we determine how long it takes for the virus to go extinct by plotting the population dynamics over time and determining when no more transmission
occurs, or when

\[ \beta_I I + \beta_T T \approx 0. \]  

(68)

Disease eradication happens more quickly as the efficacy and uptake rate of ART increase, but it can still take decades if not centuries for the virus to be eliminated (Figure A.9). For example, when ART is highly effective and initiated at a relatively high rate \( (r_2 = 0.9, f = 0.5) \), HIV is predicted to go extinct in 324 years. In a more optimistic scenario, when drugs are 99% effective and are initiated by 90% of infected hosts within the first year of infection \( (f \approx 2.3) \), it still takes an estimated 80 years for transmission to be altogether eliminated from the population. For analogous parameter estimates, the use of PrEP leads to more rapid disease elimination than ART (Figure A.10). HIV goes extinct within 51 years when PrEP is highly effective and widely used \( (r_1 = 0.9, g = 0.5) \), and in only 29 years when PrEP has near perfect efficacy and achieves very high uptake \( (r_1 = 0.99, g \approx 2.3) \). Finally, combination interventions lead to the most rapid disease elimination, and we show how changing the uptake rates of PrEP and ART affect the time until viral extinction (Figure A.11). Taken together, these plots demonstrate that the efficacies of interventions play a more substantial role than drug uptake rates in reducing infection prevalence.
Figure A.9: Contour plot showing the estimated number of years until HIV is eradicated when ART is used to treat infections. As drugs become more potent and more widely used, HIV is eradicated more quickly. The upper limit of ART uptake in this plot is $f = 2.3$, which translates to $\sim 90\%$ of hosts initiating ART in the first year of infection.

Figure A.10: Contour plot showing the estimated number of years until HIV is eradicated when PrEP is used to prevent infections. As the efficacy and uptake rate of PrEP increase, the virus is eliminated more quickly.
Figure A.11: Contour plot showing the estimated number of years until HIV is eradicated when both ART and PrEP are used. Here, we use the same efficacy estimates as many of our main results ($r_1 = 0.2, r_2 = 0.9$) and show that the rates of drug uptake have relatively little effect on the length of time until HIV is eliminated. In the best case scenario in this plot ($f = g = 2.3$), HIV is eliminated in 128 years.
References


