Received: 19 July 2017
DOI: 10.1002/mma.5237

SPECIAL ISSUE PAPER

WILEY

Extracellular dynamics of early HIV infection

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Funding information
U.S. Department of Defense, Grant/Award Number: W911NF1710414; National Science Foundation, Grant/Award Number: DMS1440386

In this paper, we explore the interplay of virus contact rate, virus production rates, and initial viral load during early HIV infection. First, we consider an early HIV infection model formulated as a bivariate branching process and provide conditions for its criticality $R_0 > 1$. Using dimensionless rates, we show that the criticality condition $R_0 > 1$ defines a threshold on the target cell infection rate in terms of the infected cell removal rate and virus production rate. This result has motivated us to introduce two additional models of early HIV infection under the assumption that the virus contact rate is proportional to the target cell infection probability (denoted by $\frac{V}{V+\theta}$). Using the second model, we show that the length of the eclipse phase of a newly infected host depends on the target cell infection probability, and the corresponding deterministic equations exhibit bistability. Indeed, occurrence of viral invasion in the deterministic dynamics depends on R_0 and the initial viral load V_0. If the viral load is small enough, eg, $V_0 \ll \theta$, then there will be extinction regardless of the value of R_0. On the other hand, if the viral load is large enough, eg, $V_0 \gg \theta$ and $R_0 > 1$, then there will be infection. Of note, $V_0 \approx \theta$ corresponds to a threshold regime above which virus can invade. Finally, we briefly discuss between-cell competition of viral strains using a third model. Our findings may help explain the HIV population bottlenecks during within-host progression and host-to-host transmission.

KEYWORDS
branching process, early infection dynamics, eclipse phase, global stability, mean field approximation

1 | INTRODUCTION

It is generally acknowledged that the fate of HIV infection is largely determined at its early or acute stage. In the absence of treatment, the outcome of the first stage of infection determines the time scale of the second one, ie, the higher/lower the target cell count at the end of the first stage, the larger/shorter the time span of the latter stage.[1] Therefore, the analysis of early HIV infection dynamics is an important problem and remains an active research area across disciplines.[2,3] It has long been argued that a large fraction (in fact, majority) of sexual contacts between infected and susceptible individuals do not result in HIV infections.[2] Broadly speaking, the virus growth process has several bottlenecks, both within hosts and when transmitted from host to host.[4] Pearson et al[3] offer a theory of stochastic viral extinction, where the virus-free state is an absorbing state. Ryser et al[5] used branching process models to argue about the key role of stochasticity in papillomavirus clearance. Joseph and Swamstrom[6] described how HIV must navigate through a low fitness landspace to initiate infection upon entering a new host. Many authors have concentrated in their analysis on intracellular virus

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competition using models taking into account multiple cell infection by virus (see for example the work of Ciupe[7] and Phan and Wodarz[8]). In contrast, it seems that extracellular competition models have received relatively little attention.

In this paper, we consider three extracellular models of invasion and early infection dynamics to study the role of virus contact rate and initial viral load in determining the persistence of the infection. In particular, we model explicitly the probability that a virus infects a cell upon contact, which leads to a model whose deterministic approximation equations exhibit bistability. We also show that, in this model, the virus-free equilibrium is locally unconditionally stable. Of note, we rely on the definition of virus dispersion to develop our models. According to Encyclopaedia Britannica,[9] " … Dispersion in biology is the dissemination, or scattering, of organisms over periods within a given area or over the earth …." Furthermore, "...there are three possible patterns of dispersion: random, aggregated or uniform … ." In the Appendix, we compute the probability that a target cell is infected as a function of the random dispersion realized by a virus. Then, we compute the probability of successful infection of a target cell integrating over all possible values of the dispersion with respect to a suitable probability density function.

This result allows one to offer a dynamical argument for the virus extinction, namely, that the between-host HIV persistence is determined by several interacting factors, like the target cell infection probability, the initial viral load, the virus contact rate, and the replication dynamics.

The paper is organized as follows. Section 2 introduces first a model of the HIV invasion defined through a bivariate branching process and we calculate the probability of extinction in terms of the kinetic constants under the condition $R_0 > 1$. Later, we introduce models of acute HIV infection with one and two viral strains under the hypothesis that the virus contact rate is proportional to the target cell infection probability. Section 3 shows through numerical simulations the dynamics of the infection as a function of the initial viral load and target cell infection probability. Our main findings in this paper are two. First, the random dispersion made by each virus to infect a target cell renders the virus-free state locally unconditionally stable. Second, the length of the eclipse phase, ie, the early phase after exposure and transmission such that virus cannot be yet detected in plasma, depends on the target cell infection probability.

2 | MATERIALS AND METHODS

2.1 | A model of HIV invasion

It has long been kown that earliest events in HIV infection are stochastic.[3,10,11] Contact between target cells and virus leads to either systemic infection or to complete extinction, the latter case being related to the low counts of free virions. In this sense, we are interested in extinction conditions in a model of HIV invasion. We propose an invasion model in terms of a bivariate branching process of virus V and infected cells I. The rationale here is that, during the early stages of invasion, the variability in the number of target cells is negligible and hence the early invasion dynamics is solely determined by the ability of both virus and infected cells to produce progenies. The model is expected to hold only for the earliest stages of infection before target cells are depleted to any noticeable extent and before immune responses are stimulated. Of note, the model introduced in this section is similar to the model of Noecker et al[12] in the sense that viral production occurs simultaneously by budding and lysis, ie, continuously or by bursting. This is reflective of different types of virus production in different target cell types.[13] The model is described by the following set of interations:

Event	Change	Rate
Target cell infection	$V \to I$	$\alpha_1 = \beta T_0$
Virus removal	$V \to \varnothing$	$\alpha_2 = c$
Lysis	$I \to 2V$	$\alpha_3 = N\delta$
Budding	$I \to I + V$	$\alpha_4 = p$
Infected cell removal	$I \to \varnothing$	$\alpha_5 = \delta,$

(1)

where $\varnothing$ indicates that infected cells or virus are being removed by death or innate immune response. For simplicity and analytical tractability, we assume the constant propensity of each event α_i $i = 1, \dots, 5$ and the virus burst size of two (the effect of different burst size is similar to increasing the production rate α_3). The next generation matrix M for (1) is

$$\begin{array}{c} \\ I \\ V \end{array} \begin{array}{c} \begin{array}{cc} I & V \end{array} \\ \begin{pmatrix} 1 - \overline{N\delta} - \overline{\delta} & 2\overline{N\delta} + \overline{p} \\ \overline{\beta T_0} & 0 \end{pmatrix} \end{array} = M,$$

where the bar represents the scaled contact rates, namely, $\left(\overline{\beta T_0}, \overline{c}\right) = (\beta T_0, c) / (\beta T_0 + c)$ and $\left(\overline{N\delta}, \overline{\delta}, \overline{p}\right) = (N\delta, \delta, p)/((N+1)\delta + p)$. It is customary to define the basic reproductive number R_0, as the expected number of descendents of a virus introduced in a healthy host. Consequently, R_0 is the spectral radius of M. A necessary condition for invasion is supercriticality, ie, that the spectral radius of the next generation matrix is larger than one, or $R_0 > 1$. In the present setting, the largest eigenvalue of M is

$$R_0 = \frac{1}{2}\left(\sqrt{\left(1 - \overline{N\delta} - \overline{\delta}\right)^2 + 4\left(2\overline{N\delta} + \overline{p}\right)\overline{\beta T_0}} + 1 - \overline{N\delta} - \overline{\delta}\right), \tag{2}$$

which may be compared with the similar formulae under lysis-only and budding-only models provided in the work of Pearson et al.[3] The condition $R_0 > 1$ is then equivalent to

$$\overline{\beta T_0} > \frac{\overline{N\delta} + \overline{\delta}}{2\overline{N\delta} + \overline{p}} = \frac{1 - \overline{p}}{\overline{N\delta} + 1 - \overline{\delta}}. \tag{3}$$

Inequality (3) means that viral invasion requires the target cell infection rate $\overline{\beta T_0}$ to be larger than the infected cell removal rate $1 - \overline{p}$ divided by virus production rate $\overline{N\delta} + 1 - \overline{\delta}$. Of note, all else unchanged, a larger budding rate $\overline{p}$ makes the right-hand side smaller, thus allowing infection to occur under smaller cell infection rate $\overline{\beta T_0}$, whereas a larger lysis rate $\overline{N\delta}$ does not make the right-hand side smaller.

Let

$$\Psi = (\Psi_I, \Psi_V) = \left(\sum_{i=0}^{\infty}\sum_{j=0}^{\infty} P_I(i,j)x^i y^j, \sum_{i=0}^{\infty}\sum_{j=0}^{\infty} P_V(i,j)x^i y^j\right)$$

denote the generating function associated to process (1). Let P_I, P_V denote the probabilities of extinction of I, V, respectively. To determine P_I, P_V, we look for the smallest (in terms of its Euclidian norm) solution of equations

$$x = \Psi_I(x, y) \quad y = \Psi_V(x, y), \tag{4}$$

such that $(x, y) \in (0, 1) \times (0, 1)$. If we write down Equation (4) in terms of the contact rates, we obtain

$$\begin{aligned} x &= \overline{\delta} + \overline{N\delta}y^2 + \overline{p}xy \\ y &= \overline{c} + \overline{\beta T_0}x. \end{aligned}$$

Solving for x and y gives the extinction probabilities

$$\begin{aligned} P_I = x &= \frac{\overline{\delta} + \overline{N\delta}\overline{c}^2}{\overline{\beta T_0}\left(1 - \overline{\delta} - \overline{N\delta}\overline{c}\right)} \\ P_V = y &= \frac{\overline{\delta} + \overline{c} - \overline{\delta}\overline{c}}{1 - \overline{\delta} - \overline{N\delta}\overline{c}} = \frac{1 - \overline{\beta T_0}\left(1 - \overline{\delta}\right)}{\overline{p} + \overline{N\delta}\,\overline{\beta T_0}}. \end{aligned}$$

Note that the condition $R_0 > 1$ given by (3) holds if and only if $P_I < 1$ (and thus also $P_V < 1$). If the system has initial condition $(I, V) = (0, 1)$, then the extinction probability is

$$P(\text{Extinction of V}) = \frac{1 - \overline{\beta T_0}\left(1 - \overline{\delta}\right)}{\overline{p} + \overline{N\delta}\,\overline{\beta T_0}} = \frac{1 - \overline{\beta T_0}\left(1 - \overline{\delta}\right)}{\overline{p} + \left(1 - \overline{p} - \overline{\delta}\right)\overline{\beta T_0}}.$$

Figure 1 shows the probability of extinction of V in terms of the rates $\overline{\delta}$ and $\overline{\beta T_0}$ for a fixed value of $\overline{p}$. There is a small invasion window. The results obtained in this section motivate us to further study the role of the virus ability of infect target cells on early invasion dynamics. Consequently, in Sections 2.2 and 2.3, we introduce models of early infection dynamics, where we model explicitly the probability that a cell becomes infected upon contact with a virus, and the number of target cells depends on time.

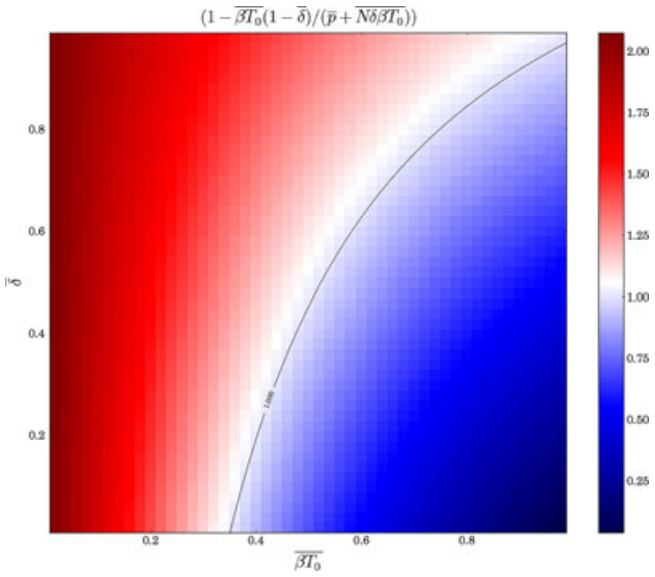

FIGURE 1 Virus extinction probability as a function of the infected cell removal rate $\overline{\delta}$ and target cell infection rate $\overline{\beta T_0}$, with constant budding rate $\overline{p} = 0.3$ and lysis rate $\overline{N\delta} = 0.5$. There is only a small region (its boundary marked in black with label 1.00), where invasion could occur with positive probability [Colour figure can be viewed at wileyonlinelibrary.com]

2.2 | A model of acute HIV infection

In this section, we shall focus on early infection with variation in the number of target cells. Thus, we have posed a model of acute HIV infection under the hypothesis that the virus contact rate is proportional to the probability of target cell infection upon contact

2.2.1 | Model formulation

Let $X_1 = X_1(t)$, $X_2 = X_2(t)$, and $X_3 = X_3(t)$ denote respectively the number of target cells, the number of infected cells, and the number of virus per milliliter (of blood or lymph) at time t. We shall use lowercase x_1, x_2, and x_3 to denote realizations of those random variables. Moreover, we denote $x = (x_1, x_2, x_3)$ the state vector. For the sake of clarity, we shall use T, I, and V respectively to name the expected value of the random variables X_1, X_2, and X_3, and at the same time, as labels for target cells, infected cells, and virus. The list of events, propensity functions $\alpha_i = \alpha_i(x)$, and change of state vectors v_i, $i = 1, \ldots, 7$, given by (5) determine both a stochastic model defined as a continuous time Markov jump process and its deterministic approximation.

Event	Change	Propensity	State change vector
Target cell birth	$\varnothing \to T$	$\alpha_1(x) = \lambda$	$v_1 = (1, 0, 0)$
Target cell infection	$V + T \to I$	$\alpha_2(x) = \beta \frac{x_3^2 x_1}{x_3 + \theta}$	$v_2 = (-1, 1, -1)$
Lysis	$I \to NV$	$\alpha_3(x) = \delta x_2$	$v_3 = (0, -1, N)$
Budding	$I \to I + V$	$\alpha_4(x) = p x_2$	$v_4 = (0, 0, 1)$
Target cell removal	$T \to \varnothing$	$\alpha_5(x) = d x_1$	$v_5 = (-1, 0, 0)$
Infected cell removal	$I \to \varnothing$	$\alpha_6(x) = \delta x_2$	$v_6 = (0, -1, 0)$
Virus removal	$V \to \varnothing$	$\alpha_7(x) = c x_3$	$v_7 = (0, 0, -1)$

(5)

The definition and name of the model contact rates are based mostly on previous HIV infection models, eg, the models of Perelson,[14] Pearson et al,[3] and Noecker et al.[12] Consequently, λ denotes the target cell production rate. Viral production occurs either by lysis or budding of the infected cell.[3] Furthermore, infected cell lysis produces N virus at rate δ, and p is the virus production rate due to budding. On the other hand, d, δ, and c are respectively target, infected, and virus removal rates. We assume the infected cell removal rate by lysis and other mechanisms to be the same for the sake of simplicity.

Of note, the propensity function $\alpha_2 = \alpha_2(x)$ corresponding to target cell infection is of the form

$$\alpha_2(x) = \beta \frac{x_1 x_3^2}{x_3 + \theta} = \beta \frac{x_3}{x_3 + \theta} x_1 x_3, \tag{6}$$

TABLE 1 Early HIV model parameters values are taken from Ho et al,[16] Perelson,[17] and Noecker et al,[12] except for θ

Parameter	Value	Dimension	Definition
λ	10	$\frac{\text{cells}}{\text{ml*day}}$	Target production rate
β	0.02	$\frac{1}{\text{virion*day}}$	Virus contact rate
p	0.583	$\frac{1}{\text{day}}$	Budding viral production rate
d	0.01	$\frac{1}{\text{day}}$	Target cell removal rate
δ	0.583	$\frac{1}{\text{day}}$	Infected cell removal rate
c	13.0	$\frac{1}{\text{day}}$	Virion removal rate
N	10	–	Number of virus produced due to lysis of one infected cell
θ	$\left[10.0^{-4}, 10.0^{0}\right]$	virions	Viral concentration at which half of the contacts of virus and target cells give rise to an infected cell

where β denotes the number of contacts per virion per day with target cells; and

$$p(x_3, \theta) = \frac{x_3}{x_3 + \theta} \tag{7}$$

is the probability of a target cell being infected upon contact with a virus. To model the contact process of a virus and a target cell giving rise to an infected cell, we have used a reasoning analogous to that of Dennis[15] to model the Allee effect through nonhomogenous Poisson process. Equation (7) arises from modeling the random dispersion realized by a virus as a pure birth process and computing the probability of a successful cell infection. Details of our derivation of Equation (7) based on population dynamics models of mating, as described in the work of Dennis,[15] are provided in Appendix . Of note, θ^{-1} may be interpreted as the expected value of the probability density function, describing the magnitude of the random dispersion realized by a single virus. We have assumed that there is no cooperation or competition in virus-to-cell binding. Model parameters and their values are summarized in Table 1.

Of note, the model defined by (5) is a closed system, thus the virus-free state is an absorbing state, ie, the stochastic viral extinction is possible. In Section 3, we shall explore numerically the virus extinction and the length of the infected host eclipse phase in terms of the parameter θ. On the other hand, to analyze the macroscopic dynamics of the model defined in (5), we consider the deterministic approximation, corresponding to the limit when there are no fluctuations, given by the following equations:

$$\begin{aligned} \dot{T} &= \lambda - \beta \frac{TV^2}{V + \theta} - dT \\ \dot{I} &= k \frac{TV^2}{V + \theta} - 2\delta I \\ \dot{V} &= -k \frac{TV^2}{V + \theta} + (N\delta + p)I - cV. \end{aligned} \tag{8}$$

Of note, Equations (8) reduce to the standard HIV model when $\theta = 0$. However, in the remainder of the paper, we shall show that Equations (8) couple within cell and between cell dynamics, thus allowing to study the interplay of cell infection and virus replication.

2.2.2 | Basic reproduction number and qualitative analysis

Using again the next generation matrix technique introduced by van den Driessche and Watmough,[18] we obtain the basic reproductive number

$$R_0 = \rho\left(FW^{-1}\right) = \sqrt{\frac{(p + N\delta)\beta\lambda}{2\delta(\beta\lambda + dc)}}, \tag{9}$$

where

$$F = \begin{pmatrix} 0 & \beta\frac{\lambda}{d} \\ p + N\delta & 0 \end{pmatrix}, \quad W = \begin{pmatrix} 2\delta & 0 \\ 0 & \frac{\beta\lambda}{d} + c \end{pmatrix}. \tag{10}$$

Proposition 1. (Virus free equilibrium)
The deterministic Equations (8) have a virus free equilibrium, given by $(T, I, V) = (\lambda/d, 0, 0)$*, which is locally unconditionally stable if* $\theta > 0$*, ie, if the target cell infection probability is less than 1.*

Indeed, the Jacobian of the right-hand side of Equation (8) is

$$J(T,I,V) = \begin{pmatrix} -\beta\frac{V^2}{V+\theta} - d & 0 & \beta T\frac{V^2+2V\theta}{(V+\theta)^2} \\ \beta\frac{V^2}{V+\theta} & -2\delta & -\beta T\frac{V^2+2V\theta}{(V+\theta)^2} \\ -\beta\frac{V^2}{V+\theta} & N\delta + p & \beta T\frac{V^2+2V\theta}{(V+\theta)^2} - c, \end{pmatrix}, \tag{11}$$

which evaluated at the virus free point leads to

$$J(\lambda/d, 0, 0) = \begin{pmatrix} -d & 0 & 0 \\ 0 & -2\delta & 0 \\ 0 & N\delta + p & -c \end{pmatrix}. \tag{12}$$

It follows that the disease free equilibrium is locally unconditionally stable because the Jacobian eigenvalues are in the diagonal of $J(\lambda/d, 0, 0)$. Of note, if $\theta = 0$, Equations (8) reduces to the standard case where the virus free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proposition 2. (Viral set point)
If $\theta > 0$ *and* $R_0 > 1$*, then the deterministic Equations (8) have one stable equilibrium where neither the number of virus or infected cells is zero. In the rest of this paper, we call such state the viral set point.*

To establish the stability of the viral set point, we let $\dot{T} = \dot{I} = \dot{V} = 0$ in Equation (8) and solve

$$\begin{aligned} \lambda - \beta\frac{V^2}{V+\theta}T - dT &= 0 \\ \beta\frac{V^2}{V+\theta}T - 2\delta I &= 0 \\ -\beta\frac{V^2}{V+\theta}T + (N\delta + p)I - cV &= 0, \end{aligned} \tag{13}$$

which leads to

$$\frac{\beta c}{\lambda\beta + dc}V^2 + \left[1 - R_0^2\right]V + \frac{dc\theta}{\lambda\beta + dc} = 0. \tag{14}$$

Note that (14) implies that, if $\theta > 0$, then there are two viral set points, provided $R_0 > 1$ and $\theta > 0$. In this case, we may conclude by Hurwitz theorem[19] that one of them is stable and the other one unstable.

Proposition 3. (Allee effect)
In the deterministic Equations (8), the term $\beta\frac{V}{V+\theta}TV = \beta\frac{V^2T}{V+\theta}$ *generalizes the law of mass action because* $V \ll \theta$ *implies* $\beta\frac{V^2T}{V+\theta} \approx \frac{\beta V^2T}{\theta}$*, rendering the virus free state locally unconditionally stable, as shown earlier, whereas* $V \gg \theta$ *implies* $\beta\frac{V^2T}{V+\theta} \approx \beta VT$*, approximating the law of mass action.*

1. If $0 < V \ll \theta$, or $0 < \frac{V}{\theta} \ll 1$, then

$$\frac{1}{V+\theta} = \frac{1}{\theta}\left(1 - \frac{V}{\theta} + \left(\frac{V}{\theta}\right)^2 - \cdots\right). \tag{15}$$

Consequently,

$$\begin{aligned} \beta\frac{V^2T}{V+\theta} &= \frac{\beta V^2T}{\theta}\left(1 - \frac{V}{\theta} + \left(\frac{V}{\theta}\right)^2 - \cdots\right) \\ &\approx \frac{\beta V^2T}{\theta}. \end{aligned} \tag{16}$$

In particular, if the initial viral load $V(0) = V_0$ is very small compared to θ, then system (8) is in the basin of attraction of the inconditionally stable virus free state.

2. On the other hand, if $0 < \theta \ll V$, or $0 < \frac{\theta}{V} \ll 1$, then

$$\frac{1}{V+\theta} = \frac{1}{V}\left(1 - \frac{\theta}{V} + \left(\frac{\theta}{V}\right)^2 - \cdots\right). \tag{17}$$

Consequently,

$$\begin{aligned}\beta\frac{V^2T}{V+\theta} &= \frac{\beta V^2 T}{V}\left(1 - \frac{\theta}{V} + \left(\frac{\theta}{V}\right)^2 - \cdots\right)\\ &\approx \beta VT.\end{aligned} \tag{18}$$

In other words, If V is much larger compared to θ, then system (8) behaves like the standard HIV model.

3. Finally, $V \approx \theta$ is a threshold regime characteristic of the Allee effect. Of note, invasion depends on both R_0 and the initial viral load $V(0) = V_0$. Indeed, if the initial viral load is small, eg, $V(0) = V_0 \ll \theta$, then there will be extinction reagardless of the value of R_0. On the other hand, if $V(0) = V_0 \gg \theta$ and $R_0 > 1$, there will be infection.

Model (5) is in agreement with the following argument. Individuals exposed to a larger viral load, eg, blood transfusion, arguably have a higher probability of being infected. On the other hand, individuals challenged with smaller viral loads, eg, sexual contact, have a smaller probability of being infected.

2.3 | A model of acute invasion with two HIV strains

Under the same hypotheses as in Section 2.2, a two strain model is defined by the following list of events:

Change	Propensity	State change vector
$\varnothing \to T$	$\alpha_1(x) = \lambda$	$\nu_1 = (1,0,0,0,0)$
$V_1 + T \to I_1$	$\alpha_2(x) = \beta_1 \frac{x_1 x_3^2}{x_3+\theta_1}$	$\nu_2 = (-1,1,-1,0,0)$
$V_2 + T \to I_2$	$\alpha_3(x) = \beta_2 \frac{x_1 x_5^2}{x_5+\theta_2}$	$\nu_3 = (-1,0,0,1,-1)$
$I_1 \to N_1 V_1$	$\alpha_6(x) = \delta x_2$	$\nu_6 = (0,-1,N_1,0,0)$
$I_2 \to N_2 V_2$	$\alpha_7(x) = \delta x_4$	$\nu_7 = (0,0,0,-1,N_2)$
$I_1 \to I_1 + V_1$	$\alpha_4(x) = p_1 x_2$	$\nu_4 = (0,0,1,0,0)$
$I_2 \to I_2 + V_2$	$\alpha_5(x) = p_2 x_4$	$\nu_5 = (0,0,0,0,1)$
$T \to \varnothing$	$\alpha_8(x) = dx_1$	$\nu_8 = (-1,0,0,0,0)$
$I_1 \to \varnothing$	$\alpha_9(x) = \delta x_2$	$\nu_9 = (0,-1,0,0,0)$
$I_2 \to \varnothing$	$\alpha_{10}(x) = \delta x_4$	$\nu_{10} = (0,0,0,-1,0)$
$V_1 \to \varnothing$	$\alpha_{11}(x) = cx_3$	$\nu_{11} = (0,0,-1,0,0)$
$V_2 \to \varnothing$	$\alpha_{12}(x) = cx_5$	$\nu_{12} = (0,0,0,0,-1)$,

(19)

where β_1 and β_2 are the contact rates of virions of strains 1 and 2, respectively. In Section 3, we shall explore numerically between-cell virus competition using model (19).

3 | RESULTS

First, in order to study the role of target cell infection probability on determining the length of the infected host eclipse phase, we construct of a probability density of the time it takes for the realizations of the stochastic process defined by (5) to reach 100 virions per milliliter (of blood or lymph), similar to the work of Noecker et al.[12] All probability densities were computed with 20 000 realizations of the Gillespie algorithm with initial conditions $(T, I, V) = (\lambda/d, 0, 1)$, ie, one virus per milliliter (of blood or lymph). Taking $\theta = 0, \theta = 1$, and $\theta = 10$, we have found that the mean time to reach 100 virions per milliliter was $t = 4.39$, 4.66 and 6.60 days respectively, See Figure 2. On the other hand, the number of succesful infections was 47.5%, 40%, and 14.48%, respectively. Of note, the length of the eclipse phase depends on the target cell infection probability, ie, larger values of θ correspond to smaller target cell infection probability and larger eclipse phases. The rates of virus removal $c = 5$, number of virus produced during lysis $N = 5$, and budding rate $p = 0.4$ were reduced to make more obvious the variability of the eclipse phase in Figure 2.

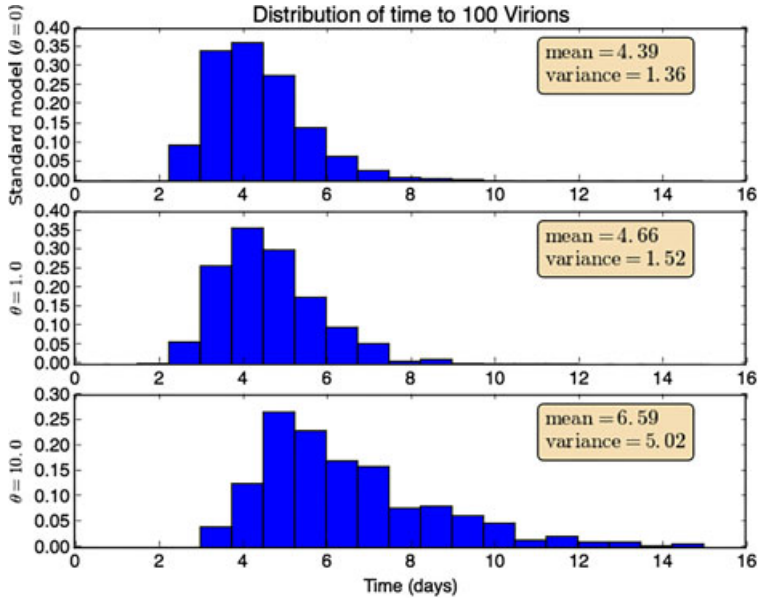

FIGURE 2 The length of the eclipse phase depends on the target cell infection probability. Top histogram corresponds to the standard model, 47.5% of simulations gives rise to an infection. Middle histogram corresponds to $\theta = 1$, 40% of simulations gives rise to an infection. Bottom histogram corresponds to $\theta = 10$, 14.48% of simulations gives rise to an infection. Larger values of θ correspond to smaller target cell infection probability and larger eclipse phases. The rates of virus removal $c = 5$, lysis production $N = 5$, and budding $M = 0.4$ were reduced to make more apparent the variability of the eclipse phase. All histograms correspond to 20 000 simulations [Colour figure can be viewed at wileyonlinelibrary.com]

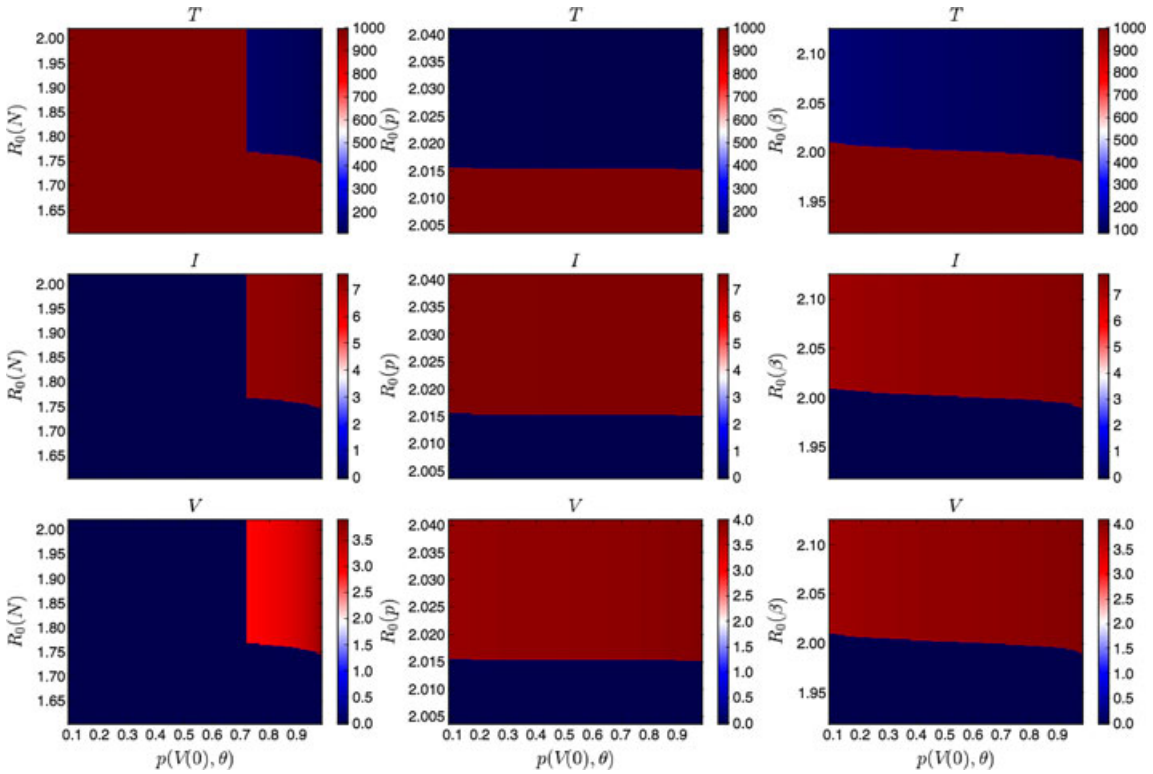

FIGURE 3 Deterministic bistability. Depending on the initial target cell infection probability, eg, the relative value of $V(0)$ and $\theta = 10^{-3}$, the system may reach the viral set point or virus extinction. In the left column, $R_0(N)$ varies as a function of the number of virus preduced during infected cell lysis. In the central column, $R_0(M)$ varies as a function of the budding rate. In the right column, $R_0(\beta)$ varies as a function of the contact rate β [Colour figure can be viewed at wileyonlinelibrary.com]

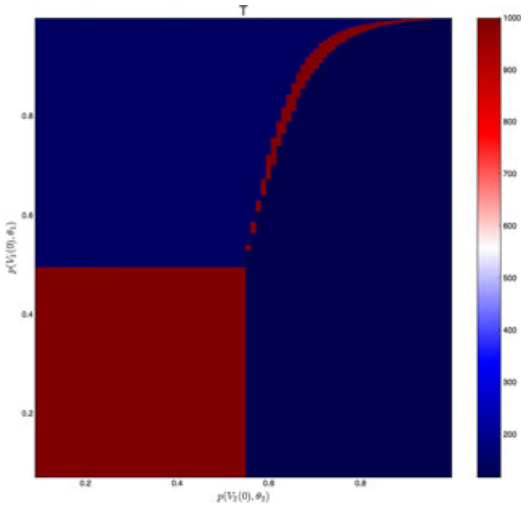

FIGURE 4 Between cell competition of two HIV strains. Invasion diagram of two competing strains V_1 and V_2 of HIV virus. We have simulated extracellular strain competition taking $N_1 = 10$ and $N_2 = 12$, whereas $\theta_1 = 10^{-3}$ and $\theta_2 = 1.3 \times 10^{-3}$. Consequently, strain V_1 has smaller R_0 but higher target cell infection probability than V_2. Of note, there is a region where both strains disappear due to the presence of the other one [Colour figure can be viewed at wileyonlinelibrary.com]

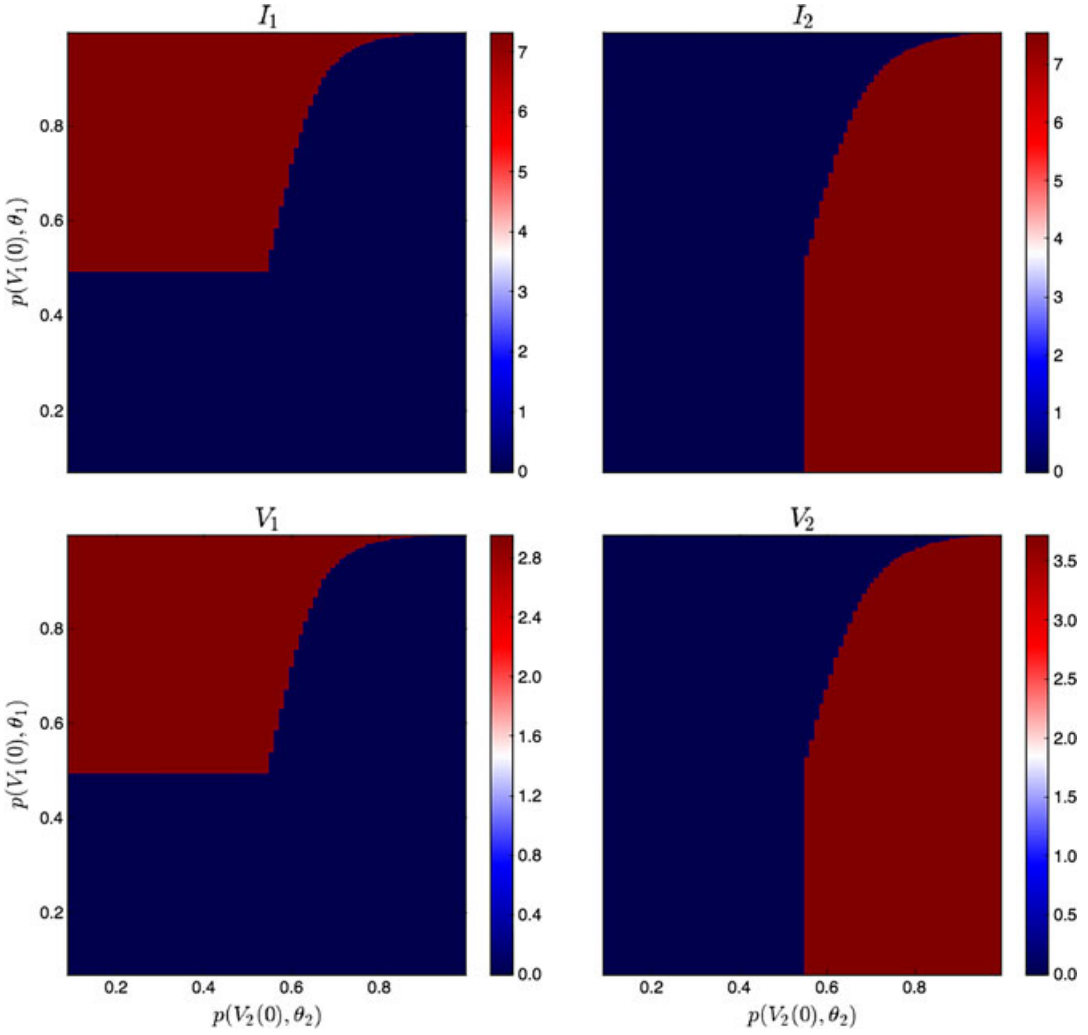

FIGURE 5 Between cell competition of two HIV strains. The basic reproduction number of strain V_2 is larger, however there is a region where strain V_1 invades and V_2 disapears provided the target cell infection probability of strain V_1 is larger [Colour figure can be viewed at wileyonlinelibrary.com]

Next, we explore whether the deterministic Equation (8) reaches extinction or the viral set point as we vary both, ie, the initial viral infection probability $\frac{V_0}{V_0+\theta}$ and the basic reproduction number R_0. Figure 3 represents a virus invasion diagram as follows, in the left column, $R_0(N)$ varies as a function of the number of virus N produced during lysis of an infected cell. In the central column, $R_0(p)$ varies as a function of the budding rate p. In the right column, $R_0(\beta)$ varies as a function of the contact rate β. Parameter values correspond to Table 1. In each case, varying parameters were changed by ±25%. On the other hand, $\theta = 10^{-3}$ was kept fixed, whereas the initial viral load was varied in $V_0 \in \left[10^{-4}, 10^{-1}\right]$. On the other hand, the first row shows the number of target cells T, whereas the second row shows the number of infected cells I and the third row shows the number of virions V in the system final state. It is apparent that there is a deterministic threshold for the virus reaching either extinction or the viral set point. Of note, there is a trade-off between R_0 and the initial target infection probability $\frac{V_0}{V_0+\theta}$, which however is not symmetric with respect to lysis, budding, and viral contact rate. In particular, with the current parameter setting, a large enough lysis production is necessary to avoid within host virus extinction. It is apparent that there is a regime where extinction is possible although $R_0 > 1$.

Finally, we have considered a model of early HIV infection with two strains given by Equation (19). Parameters correspond to Table 1. However, we have simulated extracellular strain competition taking $N_1 = 10$ and $N_2 = 12$, whereas $\theta_1 = 10^{-3}$ and $\theta_2 = 1.3 \times 10^{-3}$. Consequently, strain V_1 has smaller R_0 but higher target cell infection probability than V_2. Figures 4 and 5 show the invasion diagram for the competing virus strains. Of note, there is a region where both strains disappear due to the presence of the other one. Note that the figure is not symmetric. As expected, having a larger R_0 gives a larger competitive advantage to strain 2. However, there is a region where having a larger target cell infection probability gives strain 1 a larger competitive advantage.

4 | CONCLUSIONS

It has long been argued that virus populations undergo bottlenecks as they progress within a host or when they are transmitted from one host into another. In this paper, we have analyzed models of virus invasion and early infection dynamics to explore the role of the virus ability to attach itself to a target cell, and its relation with virus replication dynamics. Using standard modeling techniques, we have offered evidence that invasion depends upon both, the target cell infection probability and the replication dynamics as measured by R_0. All three models introduced here have allowed us to conclude that the confluence of these factors is required for a successful invasion and that only in the specific regions of parameter space the viral population will overcome the bottleneck phenomenon. This conclusion from the models analysis seems to be in good agreement with similar experimental findings, as discussed, eg, in the work of Pearson et al.[3]

ACKNOWLEDGEMENTS

The initial work on this project was started during GAR visit to the Centro de Investigación en Matemáticas (CIMAT) A.C. in Guanajuato, Mexico and the subsequent visit of MC to the Mathematical Biosciences Institute (MBI) at the Ohio State University. All authors graciously acknowledge support from CIMAT and MBI. MBI receives its major funding through the National Science Foundation under grant DMS 1440386. MN-L acknowledges the financial support from the Asociación Mexicana de Cultura, A.C. MAC acknowledges partial support from DoD, contract W911NF1710414 (USA). All authors would like to extend their thanks to the anonymous reviewer whose comments helped them improve the original manuscript.

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How to cite this article: Capistrán MA, Núñez-López M, Rempala GA. Extracellular dynamics of early HIV infection. *Math Meth Appl Sci*. 2018;1–12. https://doi.org/10.1002/mma.5237

APPENDIX

FIRST PRINCIPLES MODELING OF TARGET CELL INFECTION PROBABILITY

To model the contact process of a virus and a target cell giving rise to an infected cell, we use a reasoning analogous to that of Dennis[15] to model the Allee effect through stochastic mating encounters. According to Dennis, " … *Stochastic fluctuations in mating encounters should affect reproduction in sparse populations* … ." It appears that this is precisely the case in early HIV infection, when there is a low virus load within a host. To apply Dennis reasoning, we shall assume that, once a virus is found inside a host, it will be subject to random biological dispersion.[9]

Denoting the virus realized dispersion by $a \geq 0$ (a might, eg, account for the area of spatial domain visited by the virus, we assume herein that a is continuous and nondecreasing), the successful infection encounter per virus may be modeled by the binary random variable $X(a)$ that satisfies equation akin to the chemical reaction with a acting as time

$$X(a) = X(0) + Y(abV(1 - X(a))),$$

where $X(0) = 0$ and $Y(s)$ is a standard (unit) Poisson process (see. eg, Gardner[20] or Karlin[21]). The assumptions about the aforementioned reaction process as a function of nondecreasing a are as follows, see also Ponciano and Capistrán.[22] (1) the system is well mixed. (2) In the early stage of HIV infection, we neglect variations in the number of target cells and assume that only a tiny fraction of target cells need to be infected to ensure the infection; consequently, the probability

that a virus contacts a target cell is proportional to the abundance of virus, denoted V with the proportionality constant denoted $b > 0$. From the equation earlier, it follows in particular that

$$P(X(a) = 1) = 1 - \exp(-abV). \tag{A1}$$

If we model $\lambda = ab$ as a continuos random variable Λ whose probability density function $f_\Lambda(\lambda)$ has support on $(0, \infty)$, then

$$P\left(\sup_{a>0} X(a) = 1\right) = \int_0^\infty (1 - \exp(-\lambda V)) f_\Lambda(\lambda) d\lambda, \tag{A2}$$

Note that the density $f_\Lambda(\lambda) = \theta\exp(-\lambda\theta)$ with $0 < \lambda < \infty$ is monotonically decreasing and has support on the nonnegative real numbers. Based on (A2), the probability that the contact of a virus and a target cell gives rise to an infected cell can be expressed in closed form

$$P\left(\sup_{a>0} X(a) = 1\right) = \frac{V}{V + \theta}. \tag{A3}$$