Stochastic resetting antiviral therapies prevents drug resistance development

Angelo Marco Ramoso\textsuperscript{1}, Juan Antonio Magalang\textsuperscript{1},
Daniel Sánchez-Taltavull\textsuperscript{2}, Jose Perico Esguerra\textsuperscript{1}, and Édgar Roldán\textsuperscript{3}

\textsuperscript{1}Theoretical Physics Group, National Institute of Physics, University of the Philippines, Diliman, Quezon City 1101, Philippines
\textsuperscript{2}Department for Visceral Surgery and Medicine, Bern University Hospital, University of Bern, Switzerland
\textsuperscript{3}ICTP - The Abdus Salam International Centre for Theoretical Physics, Strada Costiera 11, 34151, Trieste, Italy

(Dated: September 16, 2020)

We study minimal mean-field models of viral drug resistance development in which the efficacy of a therapy is described by a one-dimensional stochastic resetting process with mixed reflecting-absorbing boundary conditions. We derive analytical expressions for the mean survival time for the virus to develop complete resistance to the drug. We show that the optimal therapy resetting rates that achieve a minimum and maximum mean survival times undergo a second and first-order phase transition-like behaviour as a function of the therapy efficacy drift. We illustrate our results with simulations of a population-dynamics model of HIV-1 infection.

Antiviral and antiretroviral therapies are continuously being developed to tackle viral diseases \cite{1}. Because of viral evolution, a therapy that is effective today may not remain effective forever \cite{2}. This process is known as drug resistance development and it is of special importance in chronic infections such as HIV-1 \cite{3–5}, and also for herpes and hepatitis \cite{6}. Viral evolution results into an increase in the number of infected cells, leading to a failure of the normal functions of the infected patient that can result in their death \cite{2}. Because viruses replicate and mutate rapidly, and mutation is a random process, viral evolution is intrinsically noisy \cite{7, 8}. When possible, practitioners overcome this situation by changing the therapy given to the patient. Changes in antiviral therapies can occur because of a detected viral resistance \cite{3, 9}, or for purely stochastic reasons e.g. the appearance in the market of a therapy that is cheaper or has less secondary effects. It remains an open yet challenging problem to characterize and design therapy change protocols that ensure large patient survival times that are robust to drug-resistance fluctuations.

Stochastic models have been used to study viral evolution \cite{7–11}. Examples include the usage of branching process to describe viral persistence and extinction \cite{7, 8}, and population dynamics models to assess the impact of a treatment in drug resistance development in the context of HIV-1 \cite{12}. A model that described RNA virus evolution as a diffusion process in a fitness landscape \cite{13} was able to explain the experimentally-observed rapid initial growth followed by a slower stage of linear growth in the logarithm of fitness of clone colonies of vesicular stomatitis virus \cite{14, 15}. In the same vein, the notion of a fluctuating therapy efficacy can be used to describe the evolution of therapy protocols.

Viral evolution can be modelled as a stochastic diffusion process involving incremental changes in efficacy —due to viral mutation— punctuated by sudden changes in efficacy —due to changes in therapy—. Diffusions with stochastic resetting \cite{16–27} thus provide a promising framework to model therapy evolution. This framework has been instrumental to describe biophysical processes with sudden changes, namely RNA polymerase backtracking \cite{28, 29}, receptor dynamics \cite{30}, cell crawling \cite{31}, and population dynamics \cite{32–34}, see \cite{17} for a review of applications. It remains unclear how in mul-
tiscale processes stochastic resetting of a slow variable (e.g. a therapy efficacy) affects a fast variable describing the dynamics of a time-varying population (e.g. cells and viruses).

In this Letter, we introduce a stochastic-resetting model for the evolution of the efficacy of an antiviral therapy, and study its evolution under different treatment protocols. We first describe the therapy efficacy as a one-dimensional resetting biased diffusion model with mixed absorbing and reflecting boundaries, calculate an exact analytical expression for the mean first passage time, and test our result by comparing it with Langevin dynamics simulations. We then discuss the clinical effects of our viral evolution model by coupling the stochastic resetting biased-diffusion therapy efficacy to a population dynamics model of HIV-1 chronic disease.

We describe the efficacy of an antiviral treatment as a bounded stochastic process $0 \leq \eta(t) \leq 1$ where $\eta = 0$ and $\eta = 1$ correspond to a completely ineffective and completely effective therapy, respectively. We assume that $\eta = 1$ is an absorbing boundary. On the other hand $\eta = 1$ is a reflecting boundary set at the maximum 100% therapy efficacy. We model the evolution of therapy efficacy $\eta(t)$ as a biased random walk or drift-diffusion process in "efficacy space" with diffusion coefficient $D$ and drift $v$. The therapy is often biased in the direction of lesser efficacy, i.e. the drift is negative $v < 0$, due to the fact that viruses develop resistance to the existing therapies that survive in the long run. Furthermore, we complement the biased diffusion model with a resetting protocol that switches the therapy efficacy to a value $\eta_0$ instantaneously at random Poissonian times with rate $r$. Such therapy "resetting" events can be due to the introduction of a new dose of drug, the discovery of more effective variants of the therapy, etc. See Fig. 1 for an illustration of the model and a sample stochastic trajectory of the therapy efficacy.

The evolution of the model can be described by the Fokker-Planck equation with source terms

$$\partial_t P + \partial_\eta (vP - D \partial_\eta P) = -rP + r\delta(\eta - \eta_0),$$

where $P \equiv P(\eta, t|\eta_0, 0)$ is the conditional probability density that the therapy is at $\eta$ at time $t$ given that its initial value (at which it is reset at rate $r$) was $\eta_0$. The dynamics is complemented by a absorbing boundary condition at $\eta = 0$, $\lim_{\eta \to 0} P(\eta, t) = 0$ and a zero-flux reflecting boundary condition at $\eta = 1$, $J(1, t) = 0$ where $J(\eta, t) = vP(\eta, t) - D \partial_\eta P(\eta, t)$ is the probability current.

In the following, we derive analytical expressions for the finite-time survival probability and the mean survival time. We denote by survival time the first-passage time of the therapy efficacy to reach the absorbing boundary $\eta = 0$. To this aim, we first make use of a relation between the finite-time survival probability with resetting $S_r(\eta_0, t)$ and the survival probability without resetting $S_0(\eta_0, t)$ [20]

$$S_r(\eta_0, t) = e^{-rt}S_0(\eta_0, t) + r \int_0^t dt e^{-\tau r} S_0(\eta_0, \tau) S_r(\eta_0, t - \tau).$$

From Eq. (2) we show that the Laplace transform of the first passage probability with resetting $\tilde{S}_r(\eta_0, s)$ and without resetting $\tilde{S}_0(\eta_0, s)$ are related through the identity (see Supplemental Material)

$$\tilde{S}_r(\eta_0, s) = \frac{(r + s)\tilde{S}_0(\eta_0, s + r)}{s + r\tilde{S}_0(\eta_0, s + r)}.$$  

We show that the Laplace transform of the first passage survival probability without resetting is given by

$$\tilde{S}_0(\eta_0, s) = e^{-\frac{2Dv}{\omega} 2Dv \cosh[\omega(\eta_0 - 1)] + v \sinh[\omega(\eta_0 - 1)]] - \frac{2Dv \cosh \omega - v \sinh \omega}{\sqrt{v^2 + 4DS}} 2Dv \cosh \omega - v \sinh \omega}$$

where $\omega = \sqrt{v^2 + 4DS}/2D$. Substituting Eq. (4) in Eq. (2) and using the relation $\langle \tau_r \rangle = \lim_{s \to 0} \partial \tilde{S}_r(\eta_0, s)/\partial s$ we obtain the following analytical expression for the mean first-passage time

$$\langle \tau_r \rangle = \frac{\phi(\Omega, \eta_0)}{r \left\{ \text{Pe} \sinh \left[ \Omega(\eta_0 - 1) \right] + \Omega \cosh \left[ \Omega(\eta_0 - 1) \right] \right\}^2},$$

where the non-trivial function $\phi(\Omega, \eta_0) = \text{Pe}^2 \{ \text{Pe} \eta_0 \cosh[\Omega(\eta_0 - 2)] - \cosh[\Omega(\eta_0 - 1)] \} + \text{Pe} \Omega \{ e^{\eta_0} \sinh[\Omega(\eta_0 - 2)] - \sinh[\Omega(\eta_0 - 1)] \} + e^{\eta_0} \cosh[\Omega(\eta_0 - 2)] - \cosh[\Omega(\eta_0 - 1)] + e^{\eta_0} \cosh[\Omega(\eta_0 - 2)] - 1$ depends on the model parameters through the dimensionless quantities $\text{Pe} = v/2D$, $\Omega = \sqrt{v^2 + 4D\xi}/2D$, and $\xi = r/2D$.

Figure 2 shows an excellent agreement between Eq. (5) and numerical Langevin-dynamics simulations of the model, for different parameter values. For positive values of $v$, the mean survival time decreases monotonously with the therapy resetting rate, hence it is beneficial to switch slowly among beneficial therapies (i.e. keeping $r$ small) in order to maximize the survival time. For small and even negative values of the efficacy drift, the mean first-passage time is non monotonous; the minimum average survival time takes place for intermediate values of $r$.

For therapies with large negative bias $v < 0$, a case that is relevant in the context of viral evolution, $\langle \tau_r \rangle$ increases monotonically with $r$, i.e. the maximum average survival is achieved switching the therapies as frequent as possible.

In a real-world scenario, practitioners have to deal with limited resources such as a finite number of therapies during the life of a patient. Within this scenario, it is important to know what is the optimal resetting rate that achieves a desired value of the mean survival time of the patient. To study this problem, we evaluate in Fig. 3
the resetting rates \( r_{\text{min}} \) and \( r_{\text{max}} \) for which the mean survival time attains respectively its minimum and maximum value, within a finite range of resetting rate. We find that \( r_{\text{min}} = 0 \) for rapidly evolving virus (\( v \) large and negative), whereas \( r_{\text{min}} \) increases monotonously with \( v \) for larger values. Notably \( r_{\text{min}} \) presents a non-analytic behaviour at a critical value of \( v \), and hence of the Peclet number, as reported by recent work on drift-diﬀusion processes with one absorbing boundary [26]. On the other hand, our results show that the ”optimal” resetting rate \( r_{\text{max}} \) achieving the maximum mean survival time displays a dependency with the therapy drift that has reminiscences of a first-order phase transition; it exhibits a sudden jump from the maximum allowed resetting rate (for rapidly evolving virus) to zero. Such transition occurs at a critical value of \( v \) that depends on the fluctuations \( D \) of the therapy eﬃcacy; it can take place at biologically relevant values (\( v \) negative) when \( D \) is large enough.

We now consider a stochastic mean-ﬁeld population-dynamics model describing a multicellular organism containing healthy \( H \), latent \( L \), and productively infective \( I \) cells by a chronic viral disease such as HIV-1. The state of the system is described by its time-dependent numbers \( H, I \) and \( L \), whose dynamics is driven by the stochastic-resetting therapy eﬃcacy \( \eta \). We remark that we include in the model a population of latent cells to account for a chronic infection, inspired in previous mathematical models of HIV-1 [4]. The dynamics of the model is given by three coupled ordinary diﬀerential equations [Eqs. (6-8) below] driven by an autonomous stochastic

\[
\begin{align*}
\frac{dH}{dt} &= \alpha - \lambda_H H - (1 - \eta)\beta HI \\
\frac{dL}{dt} &= \epsilon(1 - \eta)\beta HI + pL \left( 1 - \frac{L}{K} \right) - a_L L - \lambda_L L \\
\frac{dI}{dt} &= (1 - \epsilon)(1 - \eta)\beta HI + a_L L - \lambda_I I \\
d\eta &= (1 - \chi)(v dt + \sqrt{2D} dW) + \chi(\eta_0 - \eta).
\end{align*}
\]

Here, \( \alpha \) denotes the rate of recruitment of new healthy cells, \( \lambda_H \) is the death rate of healthy cells, \( \beta \) is the infection rate, \( \epsilon \) is the probability of an infection resulting into a latent cell, \( p \) is the proliferation rate of latent infected cells, \( K \) is the carrying capacity which introduces a logistic growth, \( a_L \) the activation rate of latent cells, \( \lambda_L \) death rate of latent cells, and \( \lambda_I \) the death rate of infected cells. Note that the infection rate \( \beta \) is multiplied by the instantaneous probability \((1 - \eta)\) of the infection to occur. Finally, \( \chi \) is a binary variable which equals to one (zero) when a reset occurs (does not occur) with probability \( r dt \) (\( 1 - r dt \)), and \( W \) is the Wiener process. Hence, Eq. (9) complemented with mixed absorbing boundary conditions describes the previously introduced therapy eﬃcacy stochastic model. Further details of the model can be found in the Supplemental Material.
Next, we illustrate the model with numerical simulations showing the impact of the therapy efficacy in the number of healthy cells of a patient. For this purpose we numerically integrate Eqs. (6-9). In this case, we only consider therapies with \( v < 0 \) because mutations beneficial to the virus are dominant in its evolution. When changes in therapy are not allowed we observe a drift in \( \eta \) through the absorbing barrier, followed by the healthy cells (Fig. 4, top). Under stochastic changes in the therapy \( \eta \) still drifts through the absorbing state barrier, however, after the stochastic reset, we often observe a period in which the healthy cells recover, delaying the absorption time of \( \eta \) (Fig. 4, bottom). We remark that, when \( \eta \) reaches the absorbing boundary at zero, the cell population still evolves, towards its fixed point. Note that, unlike in our first model, we allow here for resets from \( \eta = 0 \) to \( \eta_0 \) because even in the absence of therapy the patient can survive until their therapy changes. This motivates us to study first-passage times in the context of healthy cells. In doing so, we define the **patient survival time** as the time elapsed until \( H \leq \alpha/(2\lambda_H) \), which corresponds to the time until it falls below half of the fixed point in the absence of infection.

We now determine the impact of changes in the therapy in a region of parameters for \( v \) and \( D \). Figure 5 shows the mean survival time (left panels) and the mean patient survival time (right panels) as a function of \( v \) and \( D \) obtained from analytical and numerical calculations. For the parameter values studied here, resetting therapies increases both the mean survival time and the mean patient survival time. Their qualitative behaviour is similar: when the drug resistance develops slowly (\( v \) negative but small) the survival time and the patient survival time are large, and vice versa. The larger the resistance fluctuations \( D \), the lower the survival times, however this dependency is weaker than for \( v \). Notably,
when executing therapy resets at a rate of $(1/3)$ years$^{-1}$, the mean patient survival time can exceed 20 years for small values of $v$ and $D$ (Fig. 5D).

We have introduced a multi-scale stochastic model linking drug resistance development described by a one-dimensional stochastic resetting process with cell population dynamics. We have found that the number of healthy cells in a chronic disease such as HIV-1 display negative correlation with the drug resistance. Our analytical and numerical results quantify the beneficial aspects of therapy changes at random Poissonian times for the mean survival time of a patient as a function of the viral evolution parameters. We have derived an analytical expression for the mean survival time of the stochastic-resetting therapy efficacy as a function of its drift and diffusivity. This expression can be used to estimate patient survival times in some limits. It will be interesting to extend our work to e.g. compare different therapy resetting protocols under time constraints, account for drug resistance development which depends on the instantaneous viral load, account for multiple therapies [35], etc. We expect potential applications of our work to determine the epidemiological impact of drug resistance development, using models where the immunity to certain drugs can be transported between individuals.

[1] M. Lichterfeld and K. C. Zachary, Ther. Adv. Chronic Dis. 2, 293 (2011).
[2] D. S. Clutter, M. R. Jordan, S. Bertagnolio, and R. W. Shafer, Infect. Genet. Evol. 46, 292 (2016).
[3] D. Pillay and M. Zambon, Br. Med. J. 317, 660 (1998).
[4] A. S. Perelson and P. W. Nelson, SIAM Rev. 41, 3 (1999).
[5] D. Sanchez-Taltavull, A. Vieiro, and T. Alarcon, J. Math. Biol. 73, 919 (2016).
[6] L. Strasfeld and S. Chou, Infectious Disease Clinics 24, 809 (2010).
[7] L. G. Fabreti, D. Castro, B. Gorzoni, L. M. R. Janini, and F. Antonelli, Bulletin of mathematical biology 81, 1031 (2019).
[8] S. C. Manrubia and E. Lázaro, Phys. Life Rev. 3, 65 (2006).
[9] A. M. Wensing, V. Calvez, F. Ceccherini-Silberstein, C. Charpentier, H. F. Günthard, R. Paredes, R. W. Shafer, and D. D. Richman, Top. Antivir. Med. 27, 111 (2019).
[10] F. Tria, M. Laessig, L. Peliti, and S. Franz, J. Stat. Mech. 2005, P07008 (2005).
[11] M. I. Nelson, L. Simonsen, C. Viboud, M. A. Miller, J. Taylor, K. St George, S. B. Griesemer, E. Ghedin, N. A. Sengamalay, D. J. Spiro, et al., PLoS Pathog. 2, e125 (2006).
[12] C. Zitzmann and L. Kaderali, Front. Microbiol. 9, 1546 (2018).
[13] L. S. Tsimring, H. Levine, and D. A. Kessler, Phys. Rev. Lett. 76, 4440 (1996).
[14] I. S. Novella, E. A. Duarte, S. F. Elena, A. Moya, E. Domingo, and J. J. Holland, PNAS 92, 5841 (1995).
[15] J. J. Holland, J. C. De La Torre, D. Clarke, and E. Duarte, J. Virol. 65, 2960 (1991).
[16] M. R. Evans and S. N. Majumdar, Phys. Rev. Lett. 106, 160601 (2011).
[17] M. R. Evans, S. N. Majumdar, and G. Schehr, J. Phys. A 53, 193001 (2020).
[18] U. Bhat, C. De Bacco, and S. Redner, J. Stat. Mech. 2016, 083401 (2016).
[19] L. Kuśmierz and E. Gudowska-Nowak, Phys. Rev. E 92, 052127 (2015).
[20] A. Pal and V. Prasad, Phys. Rev. E 99, 032123 (2019).
[21] A. Pal and V. Prasad, Phys. Rev. Res. 1, 032001(R) (2019).
[22] X. Durang, S. Lee, L. Lizana, and J.-y. Jeon, J. Phys. A 52, 224001 (2019).
[23] C. Christou and A. Schadschneider, J. Phys. A 48, 285003 (2015).
[24] A. Pal and S. Reuveni, Phys. Rev. Lett. 118, 030603 (2017).
[25] A. Chechkin and I. Sokolov, Phys. Rev. Lett. 121, 042128 (2019).
[26] S. Ray, D. Mondal, and S. Reuveni, J. Phys. A 52, 255002 (2019).
[27] U. Basu, A. Kundu, and A. Pal, Phys. Rev. E 100, 022136 (2019).
[28] É. Roldán, A. Lísica, D. Sánchez-Taltavull, and S. W. Grill, Phys. Rev. E 93, 062411 (2016).
[29] G. Tucci, A. Gambassi, S. Gupta, and É. Roldán, arXiv preprint arXiv:2005.05173 (2020).
[30] T. Mora, Phys. Rev. Lett. 115, 038102 (2015).
[31] P. C. Bressloff, Phys. Rev. E 102, 022134 (2020).
[32] G. Mercado-Vásquez and D. Boyer, J. Phys. A 51, 405601 (2018).
[33] T. T. da Silva and M. D. Fragoso, J. Phys. A 51, 505002 (2018).
[34] R. García-García, A. Genthon, and D. Lacoste, Phys. Rev. E 99, 042413 (2019).
[35] D. D. Richman, D. M. Margolis, M. Delaney, W. C. Greene, D. Hazuda, and R. J. Pomerantz, Science 323, 1304 (2009).
[36] S. Redner, A guide to first-passage processes (Cambridge University Press, 2001).
[37] É. Roldán and S. Gupta, Phys. Rev. E 96, 022130 (2017).
[38] T. Pierson, J. McArthur, and R. F. Siliciano, Annu. Rev. Immunol. 18, 665 (2000).
SUPPLEMENTAL MATERIAL

S1. Analytical expression for the mean survival time

In this section we provide additional details about the derivation of Eq. (5) in the Main Text for the mean absorption time for the one-dimensional stochastic-resetting process that we use to describe the therapy efficacy. The derivation proceeds as follows: First, we derive an analytical expression for the survival probability in the absence of resetting \( r = 0 \). Next, we use a known relation to derive the Laplace transform of survival probability with resetting from the survival probability without resetting. Third, we derive the mean survival time from the Laplace transform of the survival probability with resetting.

First passage without resetting

We first consider for the ease of analytical calculations the case \( r = 0 \) in which the therapy efficacy is a drift diffusion process. We denote by \( P(\eta,t) \) the conditional probability density that the efficacy of the therapy is \( \eta \) at time \( t \), given that its initial value at time \( t = 0 \) was \( \eta_0 \). It obeys the Fokker-Planck equation that results from taking \( r = 0 \) in Eq. (1) in the Main Text

\[
\frac{\partial P(\eta,t)}{\partial t} + \frac{\partial J(\eta,t)}{\partial \eta} = 0, \tag{S10}
\]

where \( J(\eta,t) \) is the probability current defined in this case as

\[
J(\eta,t) \equiv vP(\eta,t) - D \frac{\partial P(\eta,t)}{\partial \eta}. \tag{S11}
\]

Equations (S10) and (S11) are complemented with the initial and boundary conditions of the process

\[
P(\eta,t=0) = \delta(\eta - \eta_0), \tag{S12}
\]

\[
\lim_{\eta \to 0^+} P(\eta,t) = 0, \tag{S13}
\]

\[
J(\eta = 1,t) = 0. \tag{S14}
\]

Here, Eq. (S12) accounts for the initial condition \( \eta(0) = \eta_0 \), Eq. (S13) for the absorbing boundary at \( \eta = 0 \), and Eq. (S14) for the reflecting boundary condition at \( \eta = 1 \). Taking the Laplace transform on Eq. (S10), we get

\[
sP(\eta,s) - P(\eta,t=0) + vP'(\eta,s) - DP''(\eta,s) = 0, \tag{S15}
\]

where the prime denotes derivative with respect to \( \eta \) and we have introduced the notation

\[
P(\eta,s) \equiv \int_0^\infty e^{-st} P(\eta,t) \, dt, \tag{S16}
\]

for the Laplace transform of the propagator. Applying the initial condition (S12) into Eq. (S15), we obtain

\[
sP(\eta,s) - \delta(\eta - \eta_0) + vP'(\eta,s) - DP''(\eta,s) = 0. \tag{S17}
\]

We now concentrate our efforts in obtaining an analytical solution to Eq. (S17). First we express \( P(\eta,s) \) as a piecewise continuous function:

\[
P(\eta,s) = \begin{cases} 
P_<(\eta,s) & \text{when } \eta < \eta_0 \\
P_>(\eta,s) & \text{when } \eta > \eta_0, \end{cases} \tag{S18}
\]

for \( \eta \neq \eta_0 \). Both \( P_< \) and \( P_> \) obey Eq. (S17) in \( \eta < \eta_0 \) and \( \eta > \eta_0 \) respectively, i.e.

\[
DP''_<(\eta,s) - vP'_<(\eta,s) - sP_<\eta(\eta,s) = 0, \tag{S19}
\]

\[
DP''_>(\eta,s) - vP'_>(\eta,s) - sP<_\eta(\eta,s) = 0. \tag{S20}
\]
The solutions of Eqs. (S19-S20) are given by sums of exponential functions

\[
\mathcal{P}_<(\eta, s) = a_+ e^{\alpha_+ \eta} + a_- e^{\alpha_- \eta}, \quad (S21)
\]
\[
\mathcal{P}_>(\eta, s) = b_+ e^{\alpha_+ \eta} + b_- e^{\alpha_- \eta}. \quad (S22)
\]

Plugging in Eq. (S21) in (S19) and Eq. (S22) in (S20) yields the second order equation

\[
D\alpha_{\pm}^2 - v\alpha_{\pm} + s = 0, \quad (S23)
\]

whose solutions are given by

\[
\alpha_{\pm} = \frac{v}{2D} \pm w, \quad (S24)
\]

where

\[
w = \sqrt{v^2 + 4Ds}. \quad (S25)
\]

The parameters \(a_+, a_-, b_+,\) and \(b_-\) can be determined using the boundary conditions. Applying the absorbing boundary condition (S13) into Eq. (S21) we get \(a_+ + a_- = 0\), hence defining \(a \equiv a_+\), we find that \(\mathcal{P}_<\) has the form

\[
\mathcal{P}_<(\eta, s) = a \begin{bmatrix} e^{\alpha_+ \eta} - e^{\alpha_- \eta} \end{bmatrix}. \quad (S26)
\]

Next, we use the reflecting boundary condition (S14) in (S22) which implies \(v \mathcal{P}_>(\eta = 1, s) = DP_>'(\eta = 1, s)\). This results in the following relation \(v \begin{bmatrix} b_+ e^{\alpha_+ \eta} + b_- e^{\alpha_- \eta} \end{bmatrix} = D \begin{bmatrix} \alpha_+ b_+ e^{\alpha_+ \eta} + \alpha_- b_- e^{\alpha_- \eta} \end{bmatrix}\), or equivalently \((v - D\alpha_+)e^{\alpha_+ b_+} = (D\alpha_- - v)e^{\alpha_- b_-} \equiv b\). Thus we get

\[
\mathcal{P}_>(\eta, s) = b \begin{bmatrix} e^{\alpha_+ (\eta - 1)} - e^{\alpha_- (\eta - 1)} \end{bmatrix} \begin{bmatrix} v - D\alpha_+ & v - D\alpha_- \end{bmatrix}. \quad (S27)
\]

The continuity condition of \(\mathcal{P}(\eta, s)\) at \(\eta = \eta_0\) in Eqs. (S26-S27) implies that

\[
b \begin{bmatrix} e^{\alpha_+ (\eta_0 - 1)} - e^{\alpha_- (\eta_0 - 1)} \end{bmatrix} \equiv a \begin{bmatrix} e^{\alpha_+ \eta_0} - e^{\alpha_- \eta_0} \end{bmatrix} \equiv c \quad (S28)
\]

therefore

\[
\mathcal{P}_<(\eta, s) = c \begin{bmatrix} e^{\alpha_+ \eta} - e^{\alpha_- \eta} \end{bmatrix} \begin{bmatrix} e^{\alpha_+ \eta_0} - e^{\alpha_- \eta_0} \end{bmatrix}, \quad (S29)
\]
\[
\mathcal{P}_>(\eta, s) = c \begin{bmatrix} e^{\alpha_+ (\eta - 1)} - e^{\alpha_- (\eta - 1)} \end{bmatrix} \begin{bmatrix} v - D\alpha_+ & v - D\alpha_- \end{bmatrix}. \quad (S30)
\]

To solve for \(c\), we solve the differential equation (S17) at \(\eta = \eta_0\),

\[
DP_>'(\eta, s) = v \mathcal{P}'(\eta, s) + s\mathcal{P}(\eta, s) - \delta(\eta - \eta_0). \quad (S31)
\]

Take the integral both sides with respect to \(\eta\) from \(\eta_0 - \epsilon\) to \(\eta_0 + \epsilon\) and then the limit of \(\epsilon\) to 0 we obtain

\[
D \begin{bmatrix} \mathcal{P}'_>(\eta_0, s) - \mathcal{P}'_<(\eta_0, s) \end{bmatrix} = v \begin{bmatrix} \mathcal{P}_>(\eta_0, s) - \mathcal{P}_<(\eta_0, s) \end{bmatrix} - 1 \quad (S32)
\]

The first term at the right-hand side vanishes due to the continuity condition, therefore

\[
\mathcal{P}'_>(\eta_0, s) - \mathcal{P}'_<(\eta_0, s) = -\frac{1}{D}, \quad (S33)
\]
Using Eqs. (S29) and (S30) in (S33) and solving for $c$ we get, after some cumbersome simplifications,

$$
c = \frac{2 \left( \sqrt{v^2 + 4Ds} \cosh \left( \frac{\sqrt{v^2 + 4Ds} \eta_0 - 1}{2D} \right) + v \sinh \left( \frac{\sqrt{v^2 + 4Ds} \eta_0 - 1}{2D} \right) \right)}{(v^2 + 4Ds) \cosh \left( \frac{\sqrt{v^2 + 4Ds}}{2D} \right) - v \sqrt{v^2 + 4Ds} \sinh \left( \frac{\sqrt{v^2 + 4Ds}}{2D} \right)}.
$$

(S34)

The Laplace transform of the first-passage (survival) time probability at $\eta = 0$ without resetting is given by [36]

$$
\mathcal{F}_0(s) = D \frac{\partial}{\partial \eta} \mathcal{P}_< (\eta, s) \bigg|_{\eta = 0} - v \mathcal{P}_<(\eta, s) \bigg|_{\eta = 0},
$$

(S35)

where the second term at the right-hand side vanishes because of the absorbing boundary condition. Note that here we have introduced the subscript 0 to emphasize that this first-passage statistic refers to the case $r = 0$. Since $c$ does not depend on $\eta$, Eq. (S35) together with Eq. (S29) imply that

$$
\mathcal{F}_0(s) = cD \frac{\alpha_+ - \alpha_-}{e^{\alpha_+ \eta_0} - e^{\alpha_- \eta_0}}.
$$

(S36)

Substituting the values of $\alpha_+$ and $\alpha_-$ [Eq. (S24)] and $C$ [Eq. (S34)] in Eq. (S36) we arrive at the analytical expression for the Laplace transform of the first-passage-time probability for the drift-diffusion process with mixed boundary conditions:

$$
\mathcal{F}_0(s) = \frac{\sqrt{v^2 + 4Ds} \left( \frac{\sqrt{v^2 + 4Ds} \eta_0 - 1}{2D} \right) + v \sinh \left( \frac{\sqrt{v^2 + 4Ds} \eta_0 - 1}{2D} \right)}{\exp \left[ \frac{\eta_0 v}{2D} \right] \left( \frac{\sqrt{v^2 + 4Ds} \eta_0 - 1}{2D} \right) - v \sqrt{v^2 + 4Ds} \sinh \left( \frac{\sqrt{v^2 + 4Ds}}{2D} \right)}. \quad (S37)
$$

From Eq. (S37) we can also derive an analytical expression for the Laplace transform of the survival probability, which is defined as follows

$$
\mathcal{S}_0(s) = \int_{0^+}^1 d\eta \mathcal{P}(\eta, s)
$$

(S38)

$$
= \int_{0^+}^{\eta_0} \mathcal{P}_<(\eta, s) \, d\eta + \int_{\eta_0}^{1} \mathcal{P}_>(\eta, s) \, d\eta,
$$

(S39)

where in the second line we have used Eq. (S18). We now recall the relation (valid for any $\eta_0 > 0$) between the survival probability and the first passage probability $F_0(t) = -\partial_t S_0(t)$ which takes the form $\mathcal{F}_0(s) = -[s \mathcal{S}_0(s) - S_0(t = 0)]$ upon taking the Laplace transform, or equivalently

$$
\mathcal{F}_0(s) = 1 - s \mathcal{S}_0(s).
$$

(S40)

Here we have used the fact that at time $t = 0$, the process has not been absorbed by the absorbing boundary $\eta = 0$, i.e. $\eta_0 > 0$.

**First passage with resetting**

Following [20, 37], the survival probability with resetting (denoted here with subscript $r$) obeys a renewal equation together with the survival probability without resetting

$$
S_r(t) = e^{-rt} S_0(t) + r \int_0^t d\tau e^{-r\tau} S_0(\tau) S_r(t - \tau).
$$

(S41)

Taking the Laplace transform on both sides of Eq. (S41), we get $\mathcal{S}_r(s) = \mathcal{S}_0(s + r) + r \mathcal{S}_0(s + r) \mathcal{S}_r(s)$, which solving for $\mathcal{S}_r(s)$ yields

$$
\mathcal{S}_r(s) = \frac{\mathcal{S}_0(s + r)}{1 - r \mathcal{S}_0(s + r)}.
$$

(S42)
Therefore, the Laplace transform of the first-passage-time probability with resetting can be expressed in terms of the Laplace transform of the survival probability without resetting as follows

\[ \mathcal{F}_r(s) = 1 - \frac{s \mathcal{S}_0(s + r)}{1 - r \mathcal{S}_0(s + r)}. \]  

(S43)

Shifting the relation (S40) from \( s \) to \( s + r \), i.e. using \( \mathcal{S}_0(s + r) = (1 - \mathcal{F}_0(s + r)) / (s + r) \) in Eq. (S43) we obtain after some simplifications

\[ \mathcal{F}_r(s) = \frac{(r + s) \mathcal{F}_0(s + r)}{s + r \mathcal{F}_0(s + r)} \]  

(S44)

After some algebra, in using Eq. (S37) in (S44) and the relation \( \langle \tau_r \rangle = -\lim_{s \to 0} \partial_s \mathcal{F}_r(s) \) we derive Eq. (5) in the Main Text for the mean first-passage time, copied here for convenience

\[ \langle \tau_r \rangle = \frac{\text{Pe}^2 + \text{Pe} \Omega + \text{Pe} \Omega}{\left( \text{Pe} \sinh \left[ 2\Omega (\eta_0 - 1) \right] \right)^2} \left( \begin{array}{c} 1 + \cosh \left[ 2\Omega (\eta_0 - 1) \right] \\ \cosh \left[ 2\Omega (\eta_0 - 1) \right] \\ \cosh \left[ 2\Omega (\eta_0 - 1) \right] \\ -\exp \left[ \text{Pe} \eta_0 \right] \cosh \left[ \Omega \eta_0 \right] \\ -\exp \left[ \text{Pe} \eta_0 \right] \cosh \left[ \Omega \eta_0 \right] \\ \text{Pe} \sinh \left[ 2\Omega (\eta_0 - 1) \right] \\ -\exp \left[ \text{Pe} \eta_0 \right] \cosh \left[ \Omega \eta_0 \right] \\ -\exp \left[ \text{Pe} \eta_0 \right] \cosh \left[ \Omega (\eta_0 - 2) \right] \end{array} \right) \]  

(S45)

where we have introduced the variables

\[ \Omega = \sqrt{v^2 + 4Dr} \quad ; \quad \text{Pe} = \frac{v}{2D} \quad ; \quad \xi = \frac{r}{2D}. \]  

(S46)

S2. Details of the biophysical model

Our biological model [Eqs. (6-9) in the Main Text] is an adaptation of that reported in Ref. [4] and describes the evolution of three different cell populations in blood: healthy cells \( H \) which are susceptible to be infected, infected cells \( L \) which are in a latent state, and productively infected cells \( I \) which can infect healthy cells. The dynamics is described by the reactions described below, where the chronic feature is modelled by adding a latent population with a logistic growth. Such dynamics have been hypothesized in [38] and used to model HIV-1 dynamics in [4, 5].

- Recruitment of a new healthy cell by the organism at a rate \( a \): \( \emptyset \to H \).
- Death of a healthy at a rate \( \lambda_H \): \( H \to \emptyset \).
- A healthy cell being infected, which we assume it is proportional to the number of infected cells, \( I \), and inversely proportional to the efficacy of the therapy \( \eta \), at a rate \( \beta \). With probability \( \epsilon \) the resulting cell will be a latent cell: \( H \to L \), and with probability \( 1 - \epsilon \) the resulting cell will be a productively infected cell: \( H \to I \).
- Proliferation of a latent cell with rate \( p \): \( L \to L + L \).
- Death of latent cells by competition for resources, with rate \( \frac{p}{\pi} \): \( L + L \to \emptyset \). This is an artificial reaction to mimic the logistic growth, see [5] for details in HIV-1 modeling.
- Activation of a latent cell resulting into a productively infected cell at rate \( a_L \): \( L \to I \).
- Death of a latent cell at rate \( \lambda_L \): \( L \to \emptyset \).
- Death of a productively infected cell at rate \( \lambda_I \): \( I \to \emptyset \).

A mean-field formulation of the dynamics of the system leads to the ordinary differential equations (6-8) in the Main Text.