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Stochastic Dynamics Between HIV-1 Latent Infection and cART Efficacy within the Brain Microenvironment

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The authors sincerely congratulate Prof. Zhien Ma on his 90th birthday and to celebrate his long-lasting impact on the field of mathematical biology and differential equations.

Abstract. We develop a stochastic human immunodeficiency virus type 1 (HIV-1) infection model to analyze combination antiretroviral therapy (cART) dynamics in the brain microenvironment, explicitly accounting for two infected cell states: (1) productively infected and (2) latently infected populations. The model introduces two key epidemiological thresholds – $\overline{\mathcal{R}}_{c1}$ (productive infection) and $\overline{\mathcal{R}}_{c2}$ (latent infection) – and defines the stochastic control reproduction number as $\overline{\mathcal{R}}_c = \max\{\overline{\mathcal{R}}_{c1}, \overline{\mathcal{R}}_{c2}\}$. Our analysis reveals three distinct dynamical regimes: (1) viral extinction ($\overline{\mathcal{R}}_c < 1$): the infection clears exponentially with probability one; (2) latent reservoir dominance ($\overline{\mathcal{R}}_c = \overline{\mathcal{R}}_{c2} > 1$): the system almost surely converges to a purely latent state, characterizing stable viral reservoir formation; (3) persistent productive infection ($\overline{\mathcal{R}}_c = \overline{\mathcal{R}}_{c1} > 1$): the infection persists indefinitely with a unique stationary distribution, for which we derive the exact probability density function. And numerical simulations validate these theoretical predictions, demonstrating how environmental noise critically modulates HIV-1 dynamics in neural reservoirs. Our results quantify the stochastic balance between productive infection, latency establishment, and cART efficacy, offering mechanistic insights into viral persistence in the brain.

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1 Introduction

The brain serves as a major reservoir for human immunodeficiency virus type 1, harboring populations of long-lived infected brain macrophages that contribute to the persistence of viral infection and pose significant challenges for viral eradication [36]. Substantial evidence indicates that HIV-1 crosses the blood-brain barrier (BBB) through either free viral particles or infected macrophages, establishing cerebral infection within two weeks of initial exposure [29]. Within the central nervous system (CNS), viral infection primarily targets long-lived myeloid cells, including perivascular macrophages, microglia, and astrocytes [33,34]. Current clinical management relies on combination antiretroviral therapy to suppress viral load, slow disease progression, and reduce the size of latent viral reservoirs [5,8,37].

However, the efficacy of cART in the brain is significantly constrained by two major factors: (1) BBB restricts drug penetration, and (2) diminished immune surveillance creates a potential viral sanctuary [36,51]. Both experimental and clinical studies demonstrate that while cART effectively suppresses HIV-1 RNA production, it shows limited impact on viral DNA levels within the brain [22,38,59]. This suggests that cART primarily targets productive infection while failing to eliminate latent viral reservoirs.

Latently infected cells are currently defined as cells harboring integrated, intact proviruses capable of reversible viral production arrest [18, 34]. However, this definition remains largely theoretical. To date, only resting CD4+ T cells fully satisfy this criterion, while the virological characteristics of other cell types require further validation [18, 19, 50]. Notably, cells of the monocyte/macrophage lineage exhibit distinct behavior – they maintain low-level viral replication rather than complete transcriptional silence [19, 50]. Emerging evidence indicates that latently infected brain macrophages may retain minimal but detectable infectivity, distinguishing them from truly healthy cells [25,28,41].

Recent experimental evidence demonstrates that HIV-1-infected macrophages/microglia can survive acute infection and establish latent infection by 21 days post-infection, with retained capacity for viral reactivation [10]. A dynamic equilibrium exists between productively and latently infected brain macrophages, characterized by continuous stochastic transitions between activated and deactivated states [10, 20, 36, 51]. While cART exhibits variable penetration efficacy in brain macrophages and tissues [2, 10], it effectively reduces both cerebrospinal fluid (CSF) viral load and cerebral viral RNA levels [59]. This reduction likely reflects decreased populations of activated brain macrophages [21], suggesting that cART may significantly alter the baseline equilibrium between activation states, favoring deactivation [24, 41]. Conversely, latency reversing agents (LRAs)