ABSTRACT

Background: Viral latency prevents timely HIV cure. Thus, cure efforts have focused on eliminating the reservoir of latently infected CD4+ T cells in which HIV has integrated into human chromosome DNA. However, substantial controversy surrounds a fundamental question: what sustains the reservoir—ongoing viral replication and infection of new cells or proliferation of surviving latent cells? Given that antiretroviral therapy (ART) rapidly decreases measurable viral loads in the blood, ongoing viral replication on ART could occur only if ART was not reaching the infected cells producing new infection, implying the presence of a drug sanctuary. Recently, we described the development of a mathematical model of HIV latent infection dynamics which stands in contrast to prior studies that demonstrated minimal evolution of pro-viral DNA in HIV infected cells. According, these prior results support the role of latent cell proliferation (antigen-driven and homeostatic) as the mechanism sustaining the latent reservoir.

Methods: Using a mathematical model of HIV dynamics, we explored the possible role of drug sanctuaries and proliferation of latent cells in HIV persistence. Our model uses published estimates of the three phases of viral decay on ART to define three infected cell states: productive infection, pre-integration latency and post-integration latency and measures the degree of viral diversity expected as a function of time on ART. The model also incorporates prior statements of HIV reservoir subsets including central memory, effector memory and naive CD4+ T cells as well as known decreases in the number of activated CD4+ T cells accessible to infection on ART.

Results: The model predicts that the percentage of latently infected cells born of new infection rather than proliferation decreases dramatically as time on ART increases. While we are able to reproduce realistic viral load data with a model that includes a drug sanctuary during the early months of ART, its importance in sustaining chronic HIV infection diminishes over time due to a decrease in activated CD4+ T cells on ART.

Conclusions: Given that drug sanctuaries—and thus, ongoing viral evolution—do not sustain chronic HIV infection on ART, enhancing ART delivery to drug sanctuary sites would not decrease the number of activated CD4+ T cells on ART.

INTRODUCTION

THE HIV RESERVOIR

The HIV reservoir is a group of HIV-infected cells that are in a state of latency, or rest. When patients on ART stop their medications, viral rebound typically occurs in 2 weeks due to reactivation of resting cells and subsequent viral production. Cells must be activated to become infected. Latency is thought to arise when a cell that was infected during acute infection was never activated to become infected. Accordingly, these prior results support the role of latent cell proliferation as the mechanism sustaining the latent reservoir.

ANTIRETROVIRAL THERAPY (ART)

Viral loads decrease quickly during the first 10-14 days on effective ART as the shortest-lived infected cells die. A second group of cells dies more slowly. We hypothesize that these cells have undergone infection but not integration at the time of ART initiation. Clinical viral suppression is reached by end of 2nd phase.

METHODS

PHASES OF VIRAL AND RESERVOIR DECLINE ON ART

Using single copy assays, Palmer et al. measured viral loads in patients suppressed on ART for several years and found that there is a 1/2 more phases of viral decay. Using OVOA, the estimated half-life of the reservoir is 44 months. We adopt a model of 3-phase infected cell decay to model the first two phases of viral decay and combine the third and fourth phases into a third latent phase with half-life 44 months. In our model, we expect the infected cell compartment of a standard system of ordinary differential equations into 3 non-sanctuary infected cell types to reflect the three phases of viral decay and add a small, sanctuary infected cell type.

RESULTS

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