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Quantifying the treatment efficacy of reverse transcriptase inhibitors: new analyses of clinical data based on within-host modeling

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Abstract

Background: Current measures of the clinical efficacy of antiretroviral therapy (ART) in the treatment of HIV include the change in HIV RNA in the plasma and the gain in CD4 cells.

Methods: We propose new measures for evaluating the efficacy of treatment that is based upon combinations of non-nucleoside and nucleoside reverse0imtanscriptsed i

that further characterization of ART outcomes could differentiate among the vast majority of patients who achieve viral suppression but do not reach the immunologic reconstitution that matches their reduction in viral replication. Such characterizations may help further refine the guidelines for monitoring ART response.

Within-host HIV modeling has been a cornerstone for understanding HIV dynamics. Within this modeling paradigm, every patient is described by a set of fixed immune and viral parameters. The dynamics of HIV infection take place on two different timescales: fast viral and CD4 cell population dynamics that change on the timescale of months, and slower dynamics on the timescale of years that describe the decay of the patient's immune system. For the past decade, a vast amount of modeling work has been dedicated to understanding the interaction between the human immune system and HIV. Studies have been devoted to fitting models to within-host data and building models to provide both quantitative and qualitative answers. The principles of the within-host HIV fast dynamics are now relatively well-understood [2-6]. Further developments have focused on incorporating other elements of interaction between HIV and the immune system, such as cytotoxic T lymphocytes [4,7-9] and latently infected T cells [10-13].

Much effort has also been devoted to modeling the impact of treatment on the within-host HIV infection [2-4,14-26]. Major topics have been optimizing treatment for viral load reduction and CD4 increase [18-20], HIV drug resistance [15,16,24-26], adherence to therapy [15,16,20], structured treatment interruptions [21-23] and others. However, clinical applications of the understanding of fast dynamics have been limited because the necessary analyses, based upon these models, require detailed data that are difficult to obtain in large amounts from clinical trials or routine clinical care.

Here, we show how a mathematical model can be used to characterize a patient's response to a common ART regimen, the combination of nucleoside plus non-nucleoside reverse transcriptase inhibitors (NRTI/NNRTI). We use our model and novel data analysis techniques to analyze data from large longitudinal HIV clinical cohorts in order to characterize treatment efficacy. We quantify treatment efficacy by developing new surrogate markers for measuring ART outcomes. Specifically, we quantify the pace of immune destruction and the impact of therapy on the viral reproduction number. We discuss the implications of our analyses for clinical decision making.

Materials and methods

Patients and sampling

We analyzed data from a random group of 83 ART naïve patients receiving initial treatment with a NNRTI/NRTI regimen. Each patient had viral load and CD4 counts measured both before treatment and after approximately one year of treatment. Data were collected through the San Francisco General Hospital AIDS Program Database that was contained in the Healthcare Electronic Record Organizer (HERO) and from the UNC CFAR HIV Clinical Cohort Study. We defined the threshold of viral suppression to be 400 HIV RNA copies/ml.

Mathematical methods

We consider a simple mathematical model that characterizes the fast viral dynamics of HIV infection

where denotes the number of uninfected CD4 cells, denotes the number of infected CD4 cells and

The system described by model (2) has two time inde-

and the intercept of the CD4/viral-load linear relation

inated; see Figure 2. A fair amount of correlation is observed between the potential for CD4 count reconstitution and the logarithm of the CD4 gain per virion eliminated (Pearson correlation coefficient ~0.675). Patients could be divided into four categories: (a) patients with a potential for both a high CD4 count reconstitution and a high CD4 gain per virion eliminated, (b) patients with a potential for only a low CD4 count reconstitution but a high CD4 gain per virion eliminated, (c) patients with a potential for a high CD4 count reconstitution but only a low CD4 gain per virion eliminated, and (d) patients with a potential for only a low CD4 count reconstitution and a low CD4 gain per virion eliminated. Surprisingly, many patients who attained viral suppression did not have high CD4 cell recovery profiles (the blue dots in the regions (b) and (d) of Figure 2). The other data (red dots) in Figure 2 also show substantial heterogeneity in our efficacy measures among the patients who were not virally suppressed. The red points are spread throughout the plane of potential of CD4 count reconstitution - CD4 gain per virion eliminated. This spread indicates that our new efficacy measures are not correlated with viral suppression. Most