

HIV Therapy Simulator: a graphical user interface for comparing the effectiveness of novel therapy regimens

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Associate Editor: Jeffrey Barrett

ABSTRACT

Abstract: Computer simulation models can be useful in exploring the efficacy of HIV therapy regimens in preventing the evolution of drug-resistant viruses. Current modeling programs, however, were designed by researchers with expertise in computational biology, limiting their accessibility to those who might lack such a background. We have developed a user-friendly graphical program, HIV Therapy Simulator (HIVSIM), that is accessible to non-technical users. The program allows clinicians and researchers to explore the effectiveness of various therapeutic strategies, such as structured treatment interruptions, booster therapies and induction-maintenance therapies. We anticipate that HIVSIM will be useful for evaluating novel drug-based treatment concepts in clinical research, and as an educational tool.

Availability: HIV Therapy Simulator is freely available for Mac OS and Windows at <http://sites.google.com/site/hivsimulator/>.

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Supplementary Information: Supplementary data are available at *Bioinformatics* online.

Received on April 30, 2011; revised on August 15, 2011; accepted on August 31, 2011

1 INTRODUCTION

The current standard for the management of uncomplicated HIV infection is triple-drug therapy. For patients whose therapeutic options have become limited due to the development of drug resistance, more complex regimens consisting of four to six drugs have been attempted (Martinez-Picado *et al.*, 2003; Miller *et al.*, 2000a,b). Unfortunately, efforts to improve suppressive efficacy can also increase the likelihood of adverse drug reactions and reduce patient adherence (Catanzaro *et al.*, 2004; Chesney, 2000; Claxton *et al.*, 2001). Because newly arising resistance mutations may be incorporated into the latently infected CD4+ T cell reservoir, improperly designed primary or salvage regimens may perpetuate a downward spiral of progressively more limited and poorly tolerated therapeutic options (Hosseinipour *et al.*, 2009; Izopet *et al.*, 2002). It is therefore critical to select antiviral regimens that are well tolerated and optimally tuned to achieve viral suppression and limit resistance.

Mathematical models that simulate the dynamics of viral infection are powerful tools for exploring the effects of therapy regimens on virus (Curlin *et al.*, 2007; Perelson, 2002; Rong *et al.*, 2010). Current modeling programs, however, were designed for theoretical research use, limiting their accessibility to clinical researchers and others

who might lack a computational background. To bridge this gap, we have developed HIV Therapy Simulator (HIVSIM), a graphical program that enables users to easily explore potential outcomes under different therapy strategies.

2 FEATURES

2.1 Stochastic, target-cell limited mathematical model of HIV dynamics

HIVSIM simulates viral dynamics using a previously described model (Bonhoeffer *et al.*, 1997; Curlin *et al.*, 2007; Ribeiro *et al.*, 2000). At each time step, the simulator updates the concentration of drugs, free virus particles, uninfected target cells (CD4+ T cells), and short-, medium- and long-lived infected cells in the body. The dynamics of typical primary and chronic HIV infection are accurately modeled, as is the multiphasic decline in viral load commonly observed during antiretroviral therapy. The model is target-cell limited (i.e. target cell availability limits viral load when unrestricted by antiretroviral agents) and stochastic (viral populations experience random fluctuations at low densities).

2.2 Users can alter all pharmacological and virological parameters and model new drugs

All parameters can be modified in the 'Parameters' window, allowing users to re-parameterize the model for new therapy regimens. As much as possible, default parameter values were selected based on literature-reported data (details in Supplementary Material). Parameters are separated into four categories: host/virus, drug, mutation, and simulation parameters. Up to 6 drugs and 10 mutations can be independently specified. The model allows users to specify C_{max} , half-life and baseline IC_{50} values for each drug, and changes in drug IC_{50} values caused by drug resistance mutations. Users can also define epistatic terms to account for interactions between resistance mutations. All parameters and simulation results can be saved for later retrieval and verification.

2.3 Graphical display of results

HIVSIM includes an intuitive graphical user interface that allows users to simulate a wide range of treatment scenarios. Concentrations of target cells, drugs and wild-type and mutant virus are graphed after each run. A key allows curves to be hidden if desired.

2.4 Flexible therapy editor

A graphical therapy editor enables users to define and simulate arbitrary therapy regimens. Multiple start and end times per drug

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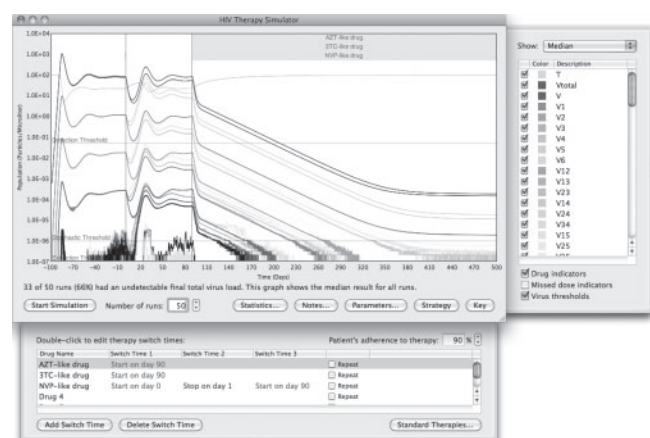


Fig. 1. HIVSIM user interface (Mac version).

are supported, including regularly repeating patterns (e.g. cycles of 30 days on followed by 30 days off). Regimens are shown as horizontal bars in the results graph, enabling easy correlation of treatment conditions to simulation results. We have predefined seven three-drug therapy strategies that have been reported in the literature, allowing users to evaluate for themselves the relative strengths and weaknesses of commonly discussed strategies.

3 SCENARIO: NEVIRAPINE MONOTHERAPY

Maximally suppressive multi-drug antiretroviral therapy is often unavailable in resource-constrained settings. A single dose of nevirapine ($_{SDNVP}$) has been shown to effectively prevent mother-to-child HIV transmission (Guay *et al.*, 1999), but is associated with the appearance of mutations conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine. When $_{SDNVP}$ patients are placed on NNRTI-based regimens within the following 6 months, significantly higher virological failure rates were observed. However, when NNRTI-based therapy is started more than 6 months after $_{SDNVP}$, there is no longer an increased failure rate (Lockman *et al.*, 2007), suggesting that a 'washout period' may enable drug-resistant strains to fall below a critical threshold, below which associated regimen failure is unlikely.

This scenario can easily be modeled in HIVSIM (see Supplementary Material). Simulation results suggest that $_{SDNVP}$ is least successful when the washout period lasts 30–45 days, but the probability of clinical success (undetectable plasma viral load) increases as the washout period lengthens, and exceeds 90% when it is 270 days or longer. These results closely agree with the clinical results described by Lockman *et al.* (2007). A deeper examination of the results suggests that the optimal washout period length is closely linked to nevirapine efficacy, as small changes in the parameters used to model nevirapine can cause substantial changes in the washout dynamics observed. This scenario illustrates the potential utility of HIVSIM in elucidating complex viral dynamics and their clinical ramifications.

4 DISCUSSION

Mathematical models can be used to examine the impact of antiretroviral therapies on HIV infection. We have developed an intuitive graphical program, HIV Therapy Simulator, which allows users without a technical background to compare the efficacy of standard and novel HIV therapy regimens in suppressing viral replication and the emergence of drug-resistant strains. HIVSIM may be useful as an educational tool for illustrating the strengths and weaknesses of various HIV therapy strategies, as well as teaching evolutionary concepts such as genetic drift and epistasis.

HIVSIM may also enable clinical researchers to evaluate the logic of novel treatment strategies such as cycling or recycling pharmacologic agents, and structured treatment interruptions of various lengths and frequencies. This approach may be particularly helpful in planning for and evaluating clinical trials in which it is not possible for ethical reasons to have a true placebo arm. However, we caution against using HIVSIM to inform individual treatment decisions, as simulation models are necessarily simplified and cannot substitute for the judgment of a trained clinician. Potential future directions for HIVSIM include porting to additional platforms, adding additional biological features and extending the program to other infections such as hepatitis C.

Conflict of Interest: none declared.

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