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

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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., 2000; 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; Iroz 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; Ron 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 Cmax, half-life and baseline IC50 values for each drug, and changes in drug IC50 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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(Supplementary Material). Simulation results suggest that SDNVP
threshold, below which associated regimen failure is unlikely.
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failure rate (Lockman et al., 2007), suggesting that a ‘washout
reverse transcriptase inhibitors (NNRTIs), including nevirapine.
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HIVSIM in elucidating complex viral dynamics and their clinical
ramifications. The results describe 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.

3 SCENARIO: NEVIRAPINE MONOTHERAPY
Maximally suppressive multi-drug antiretroviral therapy is often
unavailable in resource-constrained settings. A single dose of
nevirapine (q3NVP) 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 q3NVP 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 q3NVP, 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 q3NVP 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 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.

REFERENCES
Miller,N. et al. (2000b) Virological and immunological effects of treatment interruptions in HIV-infected patients with treatment failure. AIDS, 14, 2857–2867.