Management of Antiretroviral Therapy for HIV Infection: Analyzing When to Change Therapy

Rebecca M. D'Amato
Richard T. D'Aquila
Lawrence M. Wein

SWP# 4043
November 2, 1998
Management of Antiretroviral Therapy for HIV Infection: Analyzing When to Change Therapy

Rebecca M. D'Amato
Rand Corporation, Santa Monica, CA 90407

Richard T. D'Aquila
Infectious Disease Unit and AIDS Research Center, Massachusetts General Hospital, Charlestown, MA 02129

Lawrence M. Wein
Sloan School of Management, MIT, Cambridge, MA 02139

November 2, 1998

ABSTRACT

We analyze two joint decisions in the management of HIV-infected patients on antiretroviral therapy: how frequently to measure a patient's virus level and when to switch therapy. The underlying stochastic model captures the initial suppression and eventual rebound of the virus level in the blood of a typical HIV-infected patient undergoing treatment. We consider two classes of policies: a viral load policy, which triggers a change in therapy when the current virus level divided by the smallest level achieved thus far exceeds a prespecified threshold, and a proactive policy, which is similar to the viral load policy but also switches drugs at a prespecified time if no evidence of viral rebound has been seen. We find approximate analytical expressions for the probability of switching before the virus reaches its nadir (minimum value) and the mean delay in detection of viral rebound (i.e., the time interval from when the viral nadir occurs until the switch in therapy). Numerical results show that the proactive policy outperforms (i.e., a smaller detection delay for a given probability of pre-nadir switching) the viral load policy and recent recommendations by an expert AIDS panel, and may delay the onset of multidrug resistance in a significant proportion of
patients who experience drug failure.

1. INTRODUCTION

Combinations of reverse transcriptase and protease inhibitors have succeeded in suppressing the level of human immunodeficiency virus (HIV) RNA in the plasma of HIV-infected individuals to below the current level of detection (e.g., Hammer et al. 1997). The level of HIV RNA in the plasma - hereafter referred to as the viral load - has been established as the primary prognostic indicator of progression to AIDS (Mellors et al. 1996). While the majority of HIV-infected patients experience sustained viral suppression on these potent drug regimens, initial indications from controlled clinical trials suggest that after one or two years the virus becomes detectable in the plasma in roughly 10-20% of patients prescribed a combination antiretroviral regimen (e.g., Hammer et al.). The primary cause of this viral rebound is drug resistance: the high error rate of reverse transcription of viral RNA into DNA combined with the continual viral replication of HIV leads to the emergence of mutant strains of HIV that are drug resistant. Viral rebound can also be due to poor bioavailability of the drugs, nonadherence to the demanding drug regimen (up to 30 pills per day) and other factors.

Moreover, virus eradication by antiviral agents does not appear to be achievable in the foreseeable future (Finzi et al. 1997, Wong et al. 1997). In this environment, the goal of day-to-day clinical management is to delay the time until patients are resistant to all existing drug regimens. With this objective in mind, we consider how often a patient should be monitored and what changes in the viral load warrant a change in drug regimen. The crux of the tradeoff is between switching drugs too early, which risks poor adherence to a new drug reg-
imen and may prematurely exhaust the limited number of remaining salvage therapies, and
switching drugs too late, which allows for the stepwise accumulation of mutations that leads
to multidrug resistance (Molla et al. 1996). An expert panel convened by the International
AIDS Society-USA (IAS-USA) recommends switching therapy when any increase in the viral
load is observed (Carpenter et al. 1998), and the US Public Health Service (USPHS) guide-
lines (www.hivatis.org) made similar recommendations and also recommended taking viral
load measurements three or four times per year, although typical health insurance policies
may cover only two measurements per year. None of these recommendations are based on
rigorous quantitative reasoning.

In the present paper and its companion (D'Amato et al. 1998), we recommend revisions
to these practices based on mathematical modeling and analysis. D'Amato et al. use Monte
Carlo simulation to address this problem. Here, we perform a probabilistic analysis of
a somewhat simplified version of the model in D'Amato et al., which yields approximate
expressions for our performance measures and a closed-form switching policy.

The two bodies of work that relate most closely to the problem studied here are the
cancer screening (e.g., Eddy 1980 and references therein) and quality control chart design
(e.g., Porteus and Angelus 1998 and references therein) literatures. Although all three
problems focus on the tradeoff of false negatives and false positives, the HIV monitoring
problem is sufficiently distinct from the other two problems to prevent direct adoption of
existing methods. In particular, the underlying model for the viral dynamics is quite different
and more complex than the tumor growth models and product attribute models used in
cancer screening and quality control, respectively. Also, the cancer screening problem focuses
on the frequency of screening, and has no analog to the decisions of when to switch HIV therapy or when to restore a production process. See D'Amato (1998) for a more detailed discussion of the relationship among these three problems.

In §2, we formulate the viral load model, and define the two performance measures and the two classes of policies under consideration. Section 3 contains approximate analytical expressions for the two performance measures under both classes of policies. A computational study in §4 assesses the accuracy of the approximations and compares the efficacy of the two policies. Concluding remarks are provided in §5.

2. THE MODEL

2.1. The Viral Load Model. Beginning with the seminal work of Ho et al. (1995) and Wei et al. (1995), mathematical models in combination with clinical data have provided a vivid picture of the viral dynamics within an HIV-infected patient on a combination regimen of antiretroviral drugs. In D'Amato et al., these insights are incorporated into a Monte Carlo simulation model for the viral load trajectory of a HIV-infected patient on combination therapy. We begin by describing the simulation model in D'Amato et al., and then impose three simplifying assumptions to obtain the model considered here.

In D'Amato et al., the patient is administered combination therapy, and is assumed to be in a drug-sensitive stage for an exponential amount of time referred to as the time to rebound (see Figure 1). During the drug-sensitive stage, the simulation model assumes that the viral load decays in a tri-phasic manner. The first phase of exponential viral decay is due to the loss of productively-infected CD4$^+$ T cells (Ho et al., Wei et al.). This compartment of cells is typically eliminated within several weeks. The second, slower phase
of exponential viral decay is due to the depletion of an infected long-lived cell population, such as macrophages (Perelson et al. 1997), and lasts for several years. The third and slowest phase of exponential viral decay is due to the loss of a latently-infected cell population (Chun et al. 1997), and current estimates suggest that the duration of this phase is roughly a decade (Finzi et al., Wong et al.). The existence of any even slower decaying, small compartments or any sanctuaries (e.g., the brain) that are unaffected by antiretroviral agents is currently unknown. The simulation model assumes that the third phase of decay lasts until the time to rebound.

Figure 1. A typical viral load trajectory for an HIV-infected person on combination therapy.

In the simulation model, the viral load achieves its minimum value, or nadir, at the time to rebound. After a random amount of time referred to as the time to exponential growth (typically lasting between several weeks and several months), the viral load increases
exponentially until it reaches its pre-treatment value, after which it remains constant. The viral load is assumed to be quadratic and increasing during the time interval from when the nadir is achieved until the exponential rebound begins. Also, at a random amount of time (referred to as the time to opportunistic infection) after the viral nadir is achieved, the patient is assumed to develop an opportunistic infection. When this occurs, the patient visits a medical facility and drug failure is detected.

It is common medical practice to take a viral load measurement four weeks after the initiation of treatment to confirm that a patient is adhering and responding to treatment. Hence, to eliminate nonresponders from the study, D'Amato et al. delay the start of the simulation runs until four weeks after the beginning of therapy. By the end of the fourth week, sensitive patients are assumed to be in the second (macrophage) stage of decay (Perelson et al.).

The model in this paper makes three simplifying assumptions relative to the simulation model in D’Amato et al.: (i) there is no third phase of decay, so that the second phase of decay lasts until the time to rebound, (ii) the time to exponential growth is zero, so that the viral load begins to increase exponentially when the nadir is achieved, and (iii) no opportunistic infections are incurred, so that all drug failures are detected via the monitoring policy. Although these assumptions were motivated by the desire to simplify the analysis, simulation results of this simplified model and the more realistic model in D’Amato et al. show that the three simplifying assumptions have a very minor effect on performance (D’Amato). Notice that the only randomness in the viral dynamics in our simplified model is due to the exponential time to rebound.
In our model, time is measured in weeks and the time origin \((t = 0)\) is four weeks after the initiation of treatment. Let \(\mu_0\) be the log of the viral load (in the medical literature, the viral load is typically measured in terms of RNA copies per milliliter of plasma and expressed in terms of \(\log_{10}\)) of the patient at time \(t = 0\), and let \(b\) be the \textit{baseline} log viral load, which is the log viral load before treatment. Let the time to rebound be an exponential random variable with mean \(\lambda^{-1}\). The exponential assumption implies that the time to rebound from the initiation of treatment has the same distribution as the conditional time to rebound given that a patient has not failed therapy during the first four weeks. This distributional assumption is based on a visual inspection of the data in Kempf et al. (1998). Let \(\alpha\) be the exponential rate of decay in the macrophage stage and \(\beta\) be the exponential rate of viral rebound. Hence, if the time to rebound is denoted by \(\tau\), then \(\mu_t\), the log of the true viral load at time \(t\), is given by

\[
\mu_t = \mu_0 - \alpha t \quad \text{for} \quad t \leq \tau, \quad \mu_t = \min(b, \mu_0 - \alpha \tau + \beta (t - \tau)) \quad \text{for} \quad t > \tau. \tag{1}
\]

A key feature of this problem is that the viral load measurements are noisy and left-censored. The measured log viral viral load at time \(t\) is assumed to be a normal random variable with mean \(\mu_t\) (i.e., the measurement is unbiased) and variance \(\sigma^2\). The normality assumption is justified by a chi-squared goodness-of-fit test performed by D’Amato on data from Hughes et al. (1997). The detection limit of the viral load assay is denoted by \(d\); i.e., when the measured log viral load is below \(d\), the measurement is interpreted as being equal to \(d\).
2.2. Candidate Policies. We consider two families of monitoring policies. Under the viral load policy, every $\Delta_t$ time units (starting at week four after therapy initiation), the physician measures the patient's viral load and also keeps track of the minimum measured load thus far. If the current log viral load measurement exceeds the previous minimum log viral load measurement by some switching threshold, $\Delta_v$, then therapy is changed. The proactive policy is a generalization of the viral load policy. If the changes in the viral load have not triggered a change in therapy (via $\Delta_t$ and $\Delta_v$) prior to some predetermined switching time, $T_s$, then therapy is changed at time $T_s$. Both policies are assumed to be applied indefinitely; see D'Amato for an analysis of the finite time horizon case. This paper does not explicitly model what drug regimen a patient should switch to; see Wein et al. (1997) for an analysis of this issue.

2.3. Policy Evaluation. Each patient either switches from the current therapy before the viral nadir is achieved or switches therapy some time after the viral nadir occurs. Let the detection delay be the time interval from when the viral nadir occurs until therapy is changed. This quantity is defined only for those people who remain on the current therapy until a rebound occurs. The first of our two performance measures is the mean detection delay, where the expectation is only over those patients with a defined detection delay. While the term "detection delay" is a misnomer when therapy is changed at time $T_s$ under the proactive policy (because viral rebound is not actually detected in this case), we retain this terminology to maintain consistency with related literature. The second performance measure is the probability of pre-nadir switching, which is the probability that therapy is changed before the viral nadir is achieved.
It is desirable to have a small mean detection delay (false negatives) and a small probability of pre-nadir switching (false positives). Not surprisingly, there is an inherent tradeoff between these two quantities. As the monitoring policy becomes more aggressive (i.e., smaller values of $\Delta_t$, $\Delta_v$, and $T_s$), the mean detection delay decreases because when viral rebound does occur it is caught early, but the probability of pre-nadir switching increases. This tradeoff leads us to consider the following constrained optimization problem: choose the screening interval $\Delta_t$ and the switching threshold $\Delta_v$ (and the switching time $T_s$ for the proactive policy) to minimize the mean detection delay subject to the restriction that the probability of pre-nadir switching is less than or equal to $\bar{\rho}$. Because we are interested in generating the entire efficient frontier for this tradeoff, we allow $\bar{\rho}$ to vary between 0 and 1.

To see how this optimization problem relates to our ultimate goal of delaying the time until the patient is not sensitive to any of the available drugs, let us suppose (although this is not included in our model) that all patients start on the same initial drug combination, and they all change to the same salvage drug combination at the time of the switch, perhaps using the "what to switch to" guidelines in Carpenter et al. In §4.3, we argue that the risks of pre-nadir switching are independent of the exact time of the switch, and hence all patients who switch before the nadir is achieved have a similar prognosis (i.e., similar time until patients fail all available drugs) under the salvage therapy. In contrast, for patients who switch therapy after the nadir, the prognosis is worse for longer detection delays because of the accumulation of drug-resistant mutants. Hence, the solution to our optimization problem leads to the goal of delaying the onset of multidrug resistance.

It is worth noting that the proactive policy "buys more time" for the patient than the
viral load policy in the cases when therapy is switched before the nadir is reached, because
the switch typically occurs during the first few visits under the viral load policy, and often
occurs at a much later time, $T_s$, under the proactive policy. Consequently, by ignoring this
issue in our optimization problem, we introduce a slight bias against the proactive policy.

Finally, our analysis does not include a cost comparison between the two classes of
policies. Although D’Amato calculates the direct testing costs of these policies, a thorough
analysis of the indirect costs warrants a separate study.

3. ANALYSIS

In this section, we analyze the two performance measures for both policies.

3.1. The Probability of Pre-nadir Switching. The Viral Load Policy. Let $P(PS)$
denote the probability of pre-nadir switching and let $P(PS \mid \tau)$ be the probability of pre-
nadir switching given that the time to rebound equals $\tau$. Then

\[ P(PS) = \int_0^{\infty} P(PS \mid \tau) \lambda e^{-\lambda \tau} d\tau. \]  

(2)

Let $P(PS \text{ at } i\Delta_t)$ be the probability of pre-nadir switching at time $i\Delta_t$ (i.e., at the time of
the $i^{th}$ measurement) given that the time to rebound is greater than or equal to $i\Delta_t$, and
let $V_i$ be the log viral load measurement at time $i\Delta_t$ for $i = 1, \ldots$, which are independent
normal random variables with variance $\sigma^2$ and mean $\mu_{i\Delta_t}$ given by equation (1).

For the viral load policy, we have

\[ P(PS \mid \tau) = \sum_{i=1}^{\lfloor \frac{\tau}{\Delta_t} \rfloor} P(PS \text{ at } i\Delta_t) \quad \text{and} \]

(3)
\[ P(PS \text{ at } i\Delta_t) = P(V_1 - V_0 \leq \Delta_v, V_2 - \min(V_0, V_1) \leq \Delta_v, \ldots, \]
\[ V_{i-1} - \min(V_0, \ldots, V_{i-2}) \leq \Delta_v, V_i - \min(V_0, \ldots, V_{i-1}) > \Delta_v). \] (4)

If we let \( \Phi \) denote the normal cdf then at the first screen,

\[ P(PS \text{ at } \Delta_t) = \Phi \left( \frac{\Delta_v - \alpha\Delta_t}{\sqrt{2\sigma}} \right) \equiv p_1. \] (5)

Equation (4), which is at the heart of the analysis of the probability of pre-nadir switching, is difficult to calculate for \( i > 1 \) because it involves the minimum of several correlated normal random variables. To obtain an approximate expression for this quantity, we make three approximations. The first approximation is to assume that the viral load measurements are nonincreasing before the nadir is achieved; i.e., \( V_0 \geq V_1 \geq \ldots \geq V_{\lfloor \frac{t}{\Delta_t} \rfloor} \Delta_t \).

By \( (1) \), we have \( E[V_0] \geq E[V_1] \geq \ldots \geq E[V_{\lfloor \frac{t}{\Delta_t} \rfloor} \Delta_t] \), so if \( \Delta_t \) is sufficiently large (which turns out to be true for practically relevant values of \( \Delta_t \)) then there is only a small probability that this assumption will be violated. Under this assumption, equation (4) becomes

\[ P(PS \text{ at } i\Delta_t) \approx P(V_1 - V_0 \leq \Delta_v, \ldots, V_{i-1} - V_{i-2} \leq \Delta_v, V_i - V_{i-1} > \Delta_v). \] (6)

The second approximation uses the following form of Slepian’s inequality (Tong 1990) to obtain an upper bound to the right side of equation (6).

Slepian’s Inequality: Let \( X \) and \( Y \) be normal \( K \)-dimensional vectors with mean vector \( \mu \) and covariance matrices \( \Theta = (\theta_{jk}) \) and \( \Gamma = (\gamma_{jk}) \), respectively. If \( \theta_{jj} = \gamma_{jj} \) for all \( j \) and
\[ \theta_{jk} \geq \gamma_{jk} \text{ for } j \neq k, \text{ then} \]

\[ P(X_1 \leq a_1, \ldots, X_K \leq a_K) \geq P(Y_1 \leq a_1, \ldots, Y_K \leq a_K). \]  

(7)

To use this inequality, we rewrite the last term of equation (6) as \( V_{i-1} - V_i \leq -\Delta_v \)
and let \( Y_j = V_j - V_{j-1} \) for \( j = 1, \ldots, i \) and \( Y_i = V_{i-1} - V_i \). Then \( Y_j \sim N(-\alpha \Delta_t, 2\sigma^2) \)
for \( j = 1, \ldots, i-1 \) and \( Y_i \sim N(\alpha \Delta_t, 2\sigma^2) \). The variable \( Y_j \) is correlated only with \( Y_{j-1} \)
and \( Y_{j+1} \) because the \( V_j \)'s are independent given the parameters and the time to rebound. 

The covariance matrix of \( Y = (Y_1, \ldots, Y_i) \) is \( \Gamma = (\gamma_{jk}) \), where \( \gamma_{jj} = 2\sigma^2 \) for \( j = 1, \ldots, i \),
\( \gamma_{j,j-1} = -\sigma^2 \) for \( j = 2, \ldots, i-1 \), \( \gamma_{j,j+1} = -\sigma^2 \) for \( j = 1, \ldots, i-2 \), \( \gamma_{i,i-1} = \gamma_{i-1,i} = \sigma^2 \) and \( \gamma_{jk} = 0 \) otherwise.

Let \( X_j, j = 1, \ldots, i-1 \) be iid \( N(-\alpha \Delta_t, 2\sigma^2) \) random variables, and let \( X_i = X_{i-1} + 2\alpha \Delta_t \).

The covariance matrix for \( X = (X_1, \ldots, X_i) \) is \( \Theta = (\theta_{jk}) \), where \( \theta_{jj} = 2\sigma^2 \), for \( j = 1, \ldots, i \),
\( \theta_{i,i-1} = \theta_{i-1,i} = 2\sigma^2 \), and \( \theta_{jk} = 0 \) otherwise.

By our construction, Slepian’s inequality yields

\[ P(V_1 - V_0 \leq \Delta_v, \ldots, V_{i-2} - V_{i-1} \leq \Delta_v, V_i - V_{i-1} > \Delta_v) \]

(8)

\[ = P(Y_1 \leq \Delta_v, \ldots, Y_{i-1} \leq \Delta_v, Y_i \leq -\Delta_v) \]

(9)

\[ \leq P(X_1 \leq \Delta_v, \ldots, X_{i-1} \leq \Delta_v, X_i < -\Delta_v) \]

(10)

\[ = P(X_1 \leq \Delta_v, \ldots, X_{i-1} \leq \Delta_v, X_{i-1} \leq -\Delta_v - 2\alpha \Delta_t) \]

(11)

\[ = P(N(-\alpha \Delta_t, 2\sigma^2) \leq \Delta_v)^i \cdot P(N(-\alpha \Delta_t, 2\sigma^2) \leq -\Delta_v - 2\alpha \Delta_t). \]

(12)
If we treat Slepian’s inequality as an approximation then equations (3), (5), (6) and (12) imply that

\[ P(PS | \tau) \approx \Phi \left( \frac{-\alpha \Delta_t - \Delta_v}{\sqrt{2\sigma}} \right) \left( 1 + \sum_{i=2}^{\infty} \Phi \left( \frac{\alpha \Delta_t + \Delta_v}{\sqrt{2\sigma}} \right)^{i-2} \right) . \]  

(13)

After some simplification, equations (2) and (13) give

\[ P(PS) \approx \sum_{j=1}^{\infty} p_j e^{-\lambda j \Delta_t} , \]  

(14)

where \( p_1 \) is defined in (5) and

\[ p_j = p_1 \Phi \left( \frac{\alpha \Delta_t + \Delta_v}{\sqrt{2\sigma}} \right)^{j-2} \quad \text{for} \quad j = 2, \ldots . \]  

(15)

The terms in equation (14) eventually tend toward zero. Our third and final approximation in calculating the probability of pre-nadir switching is to truncate the terms in (14) after the true log viral load drops below \( d - 1.5\sigma \). The probability of pre-nadir switching when the log viral load drops below this value is small. The time for the load to drop below \( d - 1.5\sigma \) is \( \frac{\mu a + 1.5\sigma - d}{\alpha} \). Define \( n = \left\lfloor \frac{\mu a + 1.5\sigma - d}{\alpha \Delta_t} \right\rfloor \) to be the last screen before this time. Hence, we approximate the probability of pre-nadir switching by

\[ P(PS) \approx \sum_{j=1}^{n} p_j e^{-\lambda j \Delta_t} . \]  

(16)

We now report several structural properties of the approximation in (16). D’Amato
restricts attention to the first three terms in (16), which should not affect our qualitative conclusions. She finds that the first three terms are decreasing in the screening interval $\Delta_t$ and the switching threshold $\Delta_v$. The first two terms are convex in $\Delta_t$ and $\Delta_v$, and the third term is convex for sufficiently large $\Delta_t$ and $\Delta_v$. Hence, the first three terms in (16) are convex in our two decision variables when they are sufficiently large. We have not investigated joint convexity.

Finally, we compute the derivative of the probability of pre-nadir switching with respect to the mean time to rebound, $\lambda^{-1}$, which is the model parameter with the biggest impact on performance in the sensitivity analysis in D’Amato et al. By (16),

$$
\frac{\partial P(PS)}{\partial \lambda^{-1}} \approx \Delta_t \lambda^2 \sum_{j=1}^{n} j p_j e^{-\lambda j \Delta_t} \in [\Delta_t \lambda^2 P(PS), n \Delta_t \lambda^2 P(PS)].
$$

(17)

As expected, the first derivative with respect to the mean time to rebound is positive, because the longer the expected time to the viral nadir, the more opportunities for pre-nadir switching. However, according to the approximation in (17), the probability of pre-nadir switching is neither concave nor convex in the mean time to rebound.

The Proactive Policy. For the proactive policy,

$$
P(PS \mid \tau) = \sum_{i=1}^{\left\lfloor \frac{T_s}{\Delta_t} \right\rfloor} P(PS \text{ at } i\Delta_t) \text{ for } \tau < T_s, \quad \text{and} \quad P(PS \mid \tau) = 1 \text{ for } \tau > T_s.
$$

(18)

Let $n_T = \min\{n, \left\lceil \frac{T_s}{\Delta_t} \right\rceil\}$ denote the number of screens under the proactive policy, incorporating our truncation to $n$ screens in (16). By an argument similar to the one above (see
D’Amato), we get

\[ P(PS) = e^{-\lambda T_s} \quad \text{for} \quad n_T = 0, \]  

(19)

\[ P(PS) = p_1 e^{-\lambda \Delta_t} + (1 - p_1) e^{-\lambda T_s} \quad \text{for} \quad n_T = 1, \]  

and

(20)

\[ P(PS) \approx \sum_{j=1}^{n_T} p_j e^{-\lambda_j \Delta_t} + (1 - \sum_{j=1}^{n_T} p_j) e^{-\lambda T_s} \quad \text{for} \quad n_T = 2, \ldots \]  

(21)

As \( \Delta_t \) and \( \Delta_v \) decrease, \( \sum_{j=1}^{n_T} p_j \) decreases, and so as the likelihood of pre-nadir switching due to changes in the viral load decreases, the likelihood of pre-nadir switching due to the switching time increases. As \( T_s \) approaches infinity, (21) approaches the corresponding quantity in (16) for the viral load policy. As \( \Delta_t \) and \( \Delta_v \) approach infinity, the probability of pre-nadir switching approaches \( e^{-\lambda T_s} \), which is decreasing and convex in the switching time, \( T_s \).

By (21),

\[ \frac{\partial P(PS)}{\partial \lambda} = \Delta_t \lambda^2 \sum_{j=1}^{n_T} j p_j e^{-\lambda_j \Delta_t} + T_s \lambda^2 \left( 1 - \sum_{j=1}^{n_T} j p_j \right) e^{-\lambda T_s}, \]  

(22)

which is positive. Hence, the probability of pre-nadir switching under the proactive policy is increasing in the mean time to rebound. Since the switching time in practice typically occurs after the viral load drops well below the level of detection, we expect that \( n_T = n \) will often hold. In this case, a comparison of (17) and (22) shows that the sensitivity of the probability of pre-nadir switching with respect to the mean time to rebound is greater with the proactive policy than with the viral load policy.

Chapter 5 of D’Amato contains two other approximations for the probability of pre-
nadir switching for both policies. The first approximation is similar to the present one, but as its starting point considers the event that there is no pre-nadir switching. The second approximation is similar to the present one, but uses Slepian's inequality to construct a lower bound to (8) by employing perfectly inversely correlated random variables, rather than constructing an upper bound to (8) using iid random variables. The third approximation uses a different conditioning argument along with Clark's algorithm (Clark 1961), which approximates the mean and variance of correlated normal random variables. Computational results in D'Amato reveal that the first two approximations are roughly comparable to the approximation presented here, and the approximation based on Clark's algorithm is somewhat less accurate. Therefore, we omit these three approximations from the paper.

3.2. Mean Detection Delay. *Viral Load Policy.* The most direct approach to approximating the mean detection delay is to derive the pdf of the detection delay. This approach was taken by D'Amato, but the resulting expression is very unwieldy, partly because it requires knowledge of the probability of pre-nadir switching. Consequently, we make two assumptions to obtain an approximate mean detection delay. Simulation results in D'Amato show that the size of the detection delay is relatively insensitive to the magnitude of the measurement noise. In the absence of measurement noise, there is no possibility of pre-nadir switching, because $V_i = \max(\mu_i \Delta_t, d)$ and $\mu_i \Delta_t < \mu_j \Delta_t$ for $\frac{i}{\Delta_t} \geq i > j$. Our first assumption ignores the measurement noise, which leaves the time to rebound as the only remaining source of randomness. If we let $DD(\tau)$ be the detection delay given a time to rebound of $\tau$, 

16
then the mean detection delay is

\[ E(DD) = \int_0^\infty DD(\tau) \lambda e^{-\lambda \tau} d\tau. \]  \hfill (23)

The analysis of \( DD(\tau) \) is complicated by the left-censorship of the viral load assay, and we make our second approximation for ease of analysis. We assume that the time that the viral nadir is achieved happens to coincide with the time of a measurement. This approximation becomes less accurate as the screening interval \( \Delta_t \) increases. We need to consider two cases to analyze \( DD(\tau) \), depending upon whether the minimum viral load measurement is greater than or less than the detection limit, \( d \). First we consider the case where the minimum measurement is greater than \( d \). Under our two assumptions, it takes \( \frac{\Delta_v}{\beta} \) time units for the rebound of the log viral load to exceed the threshold \( \Delta_v \). Because the rebound would not be detected until the next screen after this time, we have

\[ DD(\tau) \approx \left[ \frac{\Delta_v}{\beta \Delta_t} \right] \Delta_t, \]  \hfill (24)

where, for notational convenience, we use the convention that \([0] = 1\). In the second case, where the minimum viral load measurement is less than the detection limit, the viral rebound cannot be detected until the log viral load climbs from its nadir, \( \mu_0 - \alpha \tau \), to \( d + \Delta_v \), and so

\[ DD(\tau) \approx \left[ \frac{d + \Delta_v - \mu_0 + \alpha \tau}{\beta \Delta_t} \right] \Delta_t. \]  \hfill (25)

Let \( t_d = \max\{0, \frac{\mu_0 - d}{\alpha} \} \) be the time at which the log viral load of a drug-sensitive patient
becomes undetectable. Then equations (23)-(25) imply that

\[ E(DD) \approx \int_0^{t_d} \left[ \frac{\Delta_v}{\beta\Delta_t} \right] \Delta_t \lambda e^{-\lambda\tau} d\tau + \int_{t_d}^\infty \left[ \frac{d + \Delta_v - \mu_0 + \alpha \tau}{\beta\Delta_t} \right] \Delta_t \lambda e^{-\lambda\tau} d\tau. \] (26)

The second integral in (26) needs to be split into pieces because \( \tau \) appears in the ceiling function. Let \( t_1 \) be the time such that \( \frac{d + \Delta_v - \mu_0 + \alpha(t_d + t_1)}{\beta\Delta_t} = \left\lceil \frac{d + \Delta_v - \mu_0 + \alpha t_d}{\beta\Delta_t} \right\rceil + 1 \), and let \( t_2 \) be such that \( \frac{d + \Delta_v - \mu_0 + \alpha(t_d + t_1 + t_2)}{\beta\Delta_t} = \left\lceil \frac{d + \Delta_v - \mu_0 + \alpha t_d}{\beta\Delta_t} \right\rceil + 2 \). Solving these equations gives

\[ t_1 = \frac{\beta\Delta_t}{\alpha} \left( 1 - \text{mod} \left( \frac{d + \Delta_v - \mu_0 + \alpha t_d}{\beta\Delta_t}, 1 \right) \right) \quad \text{and} \quad t_2 = \frac{\beta\Delta_t}{\alpha}. \] (27)

In the time interval \( t \in [t_d, t_d + t_1) \), we have that \( \left\lceil \frac{d + \Delta_v - \mu_0 + \alpha t_d}{\beta\Delta_t} \right\rceil = \left\lceil \frac{d + \Delta_v - \mu_0 + \alpha t_d}{\beta\Delta_t} \right\rceil = a \). For \( j = 0, 1, \ldots \), \( \left\lceil \frac{d + \Delta_v - \mu_0 + \alpha t_d}{\beta\Delta_t} \right\rceil = a + j + 1 \) in the interval \( t \in [t_d + t_1 + j t_2, t_d + t_1 + (j + 1) t_2) \).

Thus, the second integral in (26) becomes

\[ \Delta \left[ a \left( e^{-\lambda t_d} - e^{-\lambda(t_d + t_1)} \right) + \sum_{j=0}^{\infty} (a+j+1)(e^{-\lambda(t_d + t_1 + j t_2)} - e^{-\lambda(t_d + t_1 + (j+1) t_2)}) \right] = \Delta \left[ ae^{-\lambda t_d} + \frac{e^{-\lambda(t_d + t_1)}}{1 - e^{-\lambda t_2}} \right]. \] (28)

Hence, by (26) and (28), our estimate for the mean detection delay is

\[ E(DD) = \Delta_t \left[ \left\lceil \frac{\Delta_v}{\beta\Delta_t} \right\rceil \left( 1 - e^{-\lambda t_d} \right) + e^{-\lambda t_d} \left( a + \frac{e^{-\lambda t_1}}{1 - e^{-\lambda t_2}} \right) \right]. \] (29)

In the practically interesting case where \( \Delta_v = 0 \) (therapy is switched in the face of any
increase in the viral load), we have \( a = 1, t_1 = t_2 = \frac{\beta \Delta_t}{\alpha} \), and (29) simplifies to

\[
E(DD) = \Delta_t \left[ 1 + \frac{e^{-\lambda(t_d + t_2)}}{1 - e^{-\lambda t_2}} \right].
\]  

(30)

To better understand the structure of the mean detection delay, D’Amato developed a very accurate (see Figures 4-9 to 4-12 of that paper) approximation to (30) that is increasing and piecewise linear in \( \Delta_u \). The slope of both pieces is the same and there is a jump when \( \Delta_u = \beta \Delta_t \). She also developed an accurate (Figures 4-13 to 4-16) approximation to (30) that is increasing and linear in \( \Delta_t \) with a slope that is independent of \( \Delta_u \). Finally, D’Amato showed that \( E(DD) \) in (30) is increasing in the switching time \( T_s \), but is neither convex nor concave in \( T_s \).

If \( t_d > 0 \) and we use the approximation \( e^{-\lambda t_2} \approx 1 - \lambda t_2 \) (\( \lambda t_2 \) is much less than unity in most practical situations), then

\[
\frac{\partial E(DD)}{\partial \lambda^{-1}} \approx \Delta_t \left( \frac{e^{-\lambda(t_d + t_1)}(\lambda(t_d + t_1 - t_2) + 1)}{t_2} \right)
\]

(31)

This expression is positive, so our analysis suggests that the mean detection delay increases with the mean time to rebound, but is neither concave nor convex in the mean time to rebound.

**Proactive Policy.** The mean detection delay for the proactive policy can be approximated by a similar, but slightly more involved, argument; details can be found in D’Amato. Let \( t_3 \) be the smallest time \( t \) such that \( T_s - t < \left[ \frac{d + \Delta_t - \mu_0 + \alpha t}{\beta \Delta_t} \right] \Delta_t \) and \( T_s \geq t \geq t_d \). Further, let \( l \) be
the smallest nonnegative integer such that \( t_d + t_1 + (l - 1)t_2 > t_3 \). These two quantities are computed in D'Amato. Then we can approximate the mean detection delay by

\[
E(DD) \approx \left[ \frac{\Delta_v}{\beta \Delta_t} \right] \Delta_t (1 - e^{-\lambda t_d}) + \Delta_t \left[ ae^{-\lambda t_d} + e^{-\lambda(t_d+t_1)} \left( \frac{1 - e^{-\lambda t_2}}{1 - e^{-\lambda t_2}} \right) - (a + l)e^{-\lambda t_3} \right] + T_s(e^{-\lambda t_3} - e^{-\lambda T_s}) - \frac{1}{\lambda}(e^{-\lambda t_3}(\lambda t_3 + 1) - e^{-\lambda T_s}(\lambda T_s + 1)).
\]

(32)

The expression in (32) displays the same qualitative dependence on the screening interval, switching criteria, and time to rebound as does the detection delay for the viral load policy. The mean detection delay in (32) is increasing in \( T_s \), but is neither concave nor convex. Using (32), we can compute \( \frac{\partial E(DD)}{\partial \lambda} \), but we have not been able to establish analytically whether this derivative is larger or smaller than the corresponding quantity in (31). But numerical results in D'Amato et al. reveal that the proactive policy's mean detection delay is less sensitive than the viral load policy's mean detection delay with respect to changes in the mean time to rebound.

3.3. Optimization. Part of our aim in developing the simplified expressions above was to be able to explicitly solve the optimization problem

\[
\min_{\Delta_t > 0, \Delta_v \geq 0, T_s > 0} E(DD)
\]

subject to \( P(PS) \leq \bar{p} \). (34)

However, the ceiling function and mod functions appearing in \( E(DD) \) prevent us from per-
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial load at 4 weeks, $\mu_0$</td>
<td>$3.7 \log$ copies/mL</td>
<td>Deeks et al. 1997</td>
</tr>
<tr>
<td>Time to rebound</td>
<td>exponential, mean 35 wk</td>
<td></td>
</tr>
<tr>
<td>Decay rate, $\alpha$</td>
<td>$0.3 \text{ wk}^{-1}$ with prob. 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$0.1 \text{ wk}^{-1}$ with prob. 0.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$0.08 \text{ wk}^{-1}$ with prob 0.75</td>
<td></td>
</tr>
<tr>
<td>Rebound rate, $\beta$</td>
<td>$0.2519 \text{ wk}^{-1}$ with prob. 0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$0.1149 \text{ wk}^{-1}$ with prob. 0.5</td>
<td></td>
</tr>
<tr>
<td>Load measurement noise</td>
<td>normal($0,\sigma=0.19$)</td>
<td>Hughes et al.</td>
</tr>
<tr>
<td>Detection limit, $d$</td>
<td>20 copies/mL</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Viral load model parameters.

forming an explicit Lagrangian analysis. Furthermore, ignoring these functions is too crude an approach. Because a brute force search for the optimal proactive policy is somewhat burdensome, we consider two simpler approaches in §4.

4. COMPUTATIONAL STUDY

The goals of the computational study are to assess the accuracy of our analytical approximations and to compare the performance of the two classes of policies.

4.1. Experimental Design. A simulation model provides a benchmark for our approximations in §3. The parameter values for our study can be found in Table 1. These values are derived from clinical data and are discussed in detail in D'Amato et al; here we only make several comments about Table 1. In D'Amato et al., we consider two different patient types, drug-naive and drug-experienced. The present paper only considers the latter type, who have already undergone antiviral therapy. These patients tend to have a larger initial viral load and a shorter time to viral rebound than patients who have not been exposed to antiviral agents. The mean time to rebound is based on an uncontrolled clinical environment, which
is the targeted setting for our analysis. Although the decay and rebound rates are assumed to be known constants in the analytical model, they are discrete probability distributions (derived from a regression analysis of clinical data) in the simulation model, in an attempt to make the model more realistic. To compute our analytical results, we took the mean of these distributions as our known values. Simulation results not shown here reveal that the difference between using constant and random $\alpha$ and $\beta$ is negligible. Finally, the detection limit of 20 copies/mL corresponds to the bDNA assay, which is currently the most sensitive viral assay in widespread use.

In the simulation study, we discretized the switching threshold $\Delta_v$ by tenths and the screening interval $\Delta_t$ and switching time $T_s$ by weeks. For each policy and choice of decision variables, the number of simulated patients was chosen so that, for performance measure $Y$, we have $\frac{\bar{Y} - \text{lower } 95\% \text{ CI endpoint}}{\bar{Y}} \leq 0.16$ for all $Y$, and $\leq 0.03$ on average. This condition resulted in the simulation of between 20,000 and 40,000 patients for each policy discussed below. In addition, we chose a monitoring horizon of 15 years to guarantee that few patients ($< 0.02\%$) remain on the original therapy at the end of a simulation run.

4.2. Results. Accuracy of Analysis. Figures 2 and 3 plot the simulated and estimated probability of pre-nadir switching and mean detection delay as a function of $\Delta_v$ and $\Delta_t$, respectively, for the viral load policy. Figure 4 plots the simulated and estimated probability of pre-nadir switching and mean detection delay versus the switching time for the proactive policy. For all proactive policies, the values of the screening interval $\Delta_t$ and the switching threshold $\Delta_v$ were chosen so that the corresponding viral load policy results in a probability of pre-nadir switching of about 0.02. See D'Amato for additional plots (using other policy
Figure 2. Viral Load Policy: Estimated and simulated performance measures when $\Delta_t = 4$ weeks, $\Delta_v$ varies.

Figure 3. Viral Load Policy: Estimated and simulated performance measures when $\Delta_v = 0.6$, $\Delta_t$ varies.
parameter values) that are similar to those in Figures 2-4.

The estimated pre-nadir switching probabilities are very accurate: the average absolute error is 0.0041 under the viral load policy, and 0.0011 under the proactive policy. As predicted by our analysis, all the probability of pre-nadir switching curves in Figures 2 and 3 are decreasing and convex.

![Graph showing estimated and simulated performance measures](image)

Figure 4. Proactive Policy: Estimated and simulated performance measures when $\Delta_t = 2$ weeks, $\Delta_v = 0.6$, $T_s$ varies.

The approximate mean detection delays typically underestimate the true delays, but are reasonably accurate: the average absolute error is 0.58 weeks for the viral load policy and 0.75 weeks for the proactive policy. As predicted, the mean detection delay is increasing in $\Delta_t$, $\Delta_v$ and $T_s$, is roughly linear in $\Delta_t$, and is neither convex nor concave in $T_s$.

Optimization. To address the optimization problem in (33)-(34), we compute three trade-
off curves of the simulated values of the probability of pre-nadir switching and the mean detection delay; see Figure 5. The middle curve in Figure 5 uses the optimal viral load policy derived by an exhaustive search of the discretized control space $\Delta_v = (0, 0.1, 0.2, \ldots)$, $\Delta_t = (1, 2, 3, \ldots)$. The other two curves use fixed values of $\Delta_v$ and $\Delta_t$, and then find the optimal value of $T_s$. The lower curve in Figure 5 uses $\Delta_t = 1$ week and $\Delta_v = 0.8$, which corresponds to the optimal viral load policy when $\bar{p} = 0.02$ (see the leftmost point in the middle curve). The values of $T_s$ on the lower curve were calculated via simulation, although nearly identical values can be derived using (19)-(21).

Figure 5. Simulated tradeoff curves for the optimal viral load policy, the proactive policy with $\Delta_t = 1$ week and $\Delta_v = 0.8$, and the proactive policy with $\Delta_t = 13$ weeks and $\Delta_v = 0$. The numbers next to each point on in the middle curve are the corresponding screening interval, $\Delta_t$ (in weeks), and the switching threshold, $\Delta_v$. The number next to each point on the upper and lower curves is the corresponding switching time, $T_s$ (in weeks).
The upper curve in Figure 5 represents an attempt to derive a closed-form expression for the switching time that might be useful in practice. Current clinical guidelines (Carpenter et al.) suggest a viral load policy with $\Delta_v = 0$ and $\Delta_t \approx 13$ weeks. The upper curve in Figure 5 uses these values, equations (21) and (34) and the approximation $n_T = \min\{n, \left\lfloor \frac{T_s}{\Delta t} \right\rfloor \} \approx n$ (which holds exactly in most cases) to obtain the switching time

$$T_s \approx \frac{1}{\lambda} \ln \left( \frac{1 - \sum_{j=1}^{n} p_j}{\bar{p} - \sum_{j=1}^{n} p_j e^{-\lambda j \Delta t}} \right). \quad (35)$$

Figure 5 shows that the proactive policy with $\Delta_t = 1$ week and $\Delta_v = 0.8$ outperforms the optimal viral load policy, under the same risk of pre-nadir switching. When the probability of pre-nadir switching is restricted to 3%, the proactive policy can achieve a detection delay which is 2.2 weeks shorter (18.5% reduction over the viral load delay), when the probability is 10%, the proactive policy saves 3.8 weeks (34.9%), and when the probability is 20%, it saves 4.5 weeks (45.9%). In contrast, the closed-form proactive policy in (35) does not perform as well as the optimal viral load policy. However, relative to the current clinical guidelines, which corresponds to $(\Delta_v = 0, \Delta_t = 13, T_s = \infty)$ and achieves a mean detection delay of 20.53 (±0.16) weeks and zero probability of pre-nadir switching, the closed-form proactive policy can reduce the detection delay considerably; e.g., it can cut the delay in half when a 20% probability of pre-nadir switching is allowed.

4.3. Discussion. The computational results confirm that our analytical approximations for the mean detection delay and probability of pre-nadir switching are accurate, and the derived structural results are valid. They also reveal that the proactive policy outperforms
the viral load policy, and the simple proactive switching policy in (35) can significantly reduce the mean detection delay relative to that achieved by current clinical guidelines.

Our computational results are difficult to interpret without an assessment of the risks of pre-nadir switching and a long detection delay. The risks of pre-nadir switching are not well understood. Many practitioners are reluctant to "use up" a drug regimen too quickly during the long course of HIV infection. However, anecdotal evidence suggests that if a patient is switched before the nadir, then the patient may be able to re-use the original drug regimen months or even years later against the still susceptible virus, although this has yet to be confirmed in clinical trials. Also, a switch in therapy introduces the possibility that the patient may not successfully tolerate, comply and respond to the new regimen, which can lead to the emergence of drug-resistant virus. As mentioned in §2, these risks are not likely to depend on the exact time before the nadir when therapy is switched. The primary risk of a long detection delay is the stepwise acquisition of drug-resistant mutants. Typically three mutations in the protease gene confer resistance to protease inhibitors and five mutations generate widespread cross-resistance (Molla et al., Condra et al. 1995). The speed at which the mutations accumulate varies widely, with a rate ranging from 0.3 to 2.0 mutations per month (Molla et al.).

We are now in a position to interpret the tradeoff curves in Figure 5. The reductions in detection delay achieved by the proactive policy (lower curve) relative to the optimal viral load policy (middle curve) occur in the time window where mutations are likely to accumulate for drug-experienced patients. The same is true for the closed-form proactive policy (upper curve) relative to the current clinical guidelines. Hence, proactive switching is
likely to delay the onset of multidrug resistance, which is the ultimate goal in this analysis. See D'Amato et al. for a more in-depth discussion of the comparison of the viral load and proactive policies.

D'Amato et al. perform a sensitivity analysis, where most of the model parameters are altered. These results reveal that the main qualitative conclusions of our studies are insensitive to the exact values of the various model parameters. These results also show that the sensitivity of the probability of pre-nadir switching (mean detection delay, respectively) with respect to changes in the mean time to rebound is larger (smaller, respectively) for the viral load policy than the proactive policy, thereby confirming our comparison of (17) and (22).

5. CONCLUDING REMARKS

Although the success of recently developed antiretroviral therapy is promising, viral rebound – caused primarily by drug resistance, poor bioavailability, high toxicity and non-compliance – remains a concern. This study has focused on two specific aspects of therapy management: how frequently to monitor patients and when to change therapy. Given the small number of salvage therapies currently available, these decisions are likely to have a significant clinical impact.

In this paper, we derive analytical estimates for the mean detection delay and the probability of pre-nadir switching, and discuss the relationship between these two measures and the development of multidrug resistance. Computational results reveal that our analytical approximations are accurate and that the proactive policy, where therapy is switched before viral rebound is detected, outperforms any policy – including the current IAS-USA guide-
lines – that bases the switching decision only on the detection of a viral rebound. We believe that clinical trials should be performed to validate the superiority of proactive switching.

Readers are referred to D'Amato et al. for a detailed discussion of the shortcomings of the virological and clinical aspects of the model. The policies considered in our studies are rather simple, and dynamic programming could be used to develop more sophisticated policies where $\Delta_r$ and $\Delta_v$ vary over time, as in the quality control literature (Porteus et al.). Also, subsequent modeling work should incorporate an important issue that has just emerged: the late effects due to the long-term use of protease inhibitors (Carr et al. 1998). To the extent that different drug combinations have complementary toxicity profiles with respect to these late effects, proactive switching should delay the onset of late effects.

This paper and its companion (D'Amato et al.) provide a systematic framework with which to view the “when to change therapy” decision. While the introduction of new antiretroviral agents and improved monitoring tools in the coming years are likely to change the relative risks of our two primary outcome measures, and hence make some of the specific conclusions in this paper and D'Amato et al. obsolete, the framework presented here should remain intact. According to this framework, an optimal monitoring policy requires an explicit assessment and tradeoff of the risk of multidrug resistance due to a long detection delay versus the risk of multidrug resistance caused by pre-nadir switching (via poor bioavailability, toxic side effects, noncompliance, and the possible reduction in the number of remaining salvage therapies). Further research to better quantify these risks, particularly the risks of pre-nadir switching, are required. These risks – and some key parameters in our model, such as the mean time to rebound (see Kempf et al.) – depend on a variety of
virological, immunological and psychological factors that vary from patient to patient, such as the initial viral load, initial CD4+ count, the presence of pre-existing viral mutants, and antiretroviral drug history. Hence, a simple mathematical model such as ours is necessarily a caricature of the actual disease and monitoring processes. Consequently, our model should only be used as an aid in the decision-making process, and the explicit assessment and tradeoff (i.e., where to reside on the tradeoff curve depicted in Figure 5) of these risks need to be addressed by the medical practitioner and patient on a case-by-case basis.

Finally, our computational results reveal that the relatively high detection limit of the viral load assay prevents the optimal monitoring of viral rebound. A similar situation has occurred in cancer treatment, where a significant proportion of patients are expected to develop resistance to chemotherapeutic agents, but the tumors are too small to monitor the effect of treatment. The state-of-the-art chemotherapy protocols use fixed cycles of drugs, which are designed to have complementary toxicity profiles and resistance patterns (Norton 1997). The HIV antiretroviral community may find it worthwhile to adopt this paradigm in the future, when a set of drugs that are less toxic and less vulnerable to cross-resistance are introduced.

ACKNOWLEDGMENT

We thank Ed Kaplan and a number of anonymous clinicians for suggesting the proactive switching policy, and thank Jonathan Cohen for helping to generate the figures. Rebecca D'Amato received partial support from a National Defense Science and Engineering Graduate Fellowship. Richard T. D'Aquila received grant support from AI29193.
References


