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Using Mechanistic Models to Simulate Comparative Effectiveness Trials of Therapy and to Estimate Long-Term Outcomes in HIV Care

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Abstract

Background—In HIV care, it is difficult to decide when to initiate therapy, which drugs to use for initial treatment, and which drugs to use if drug resistance develops. With hundreds of possible drug regimens available and variable patterns of drug resistance, randomized controlled trials cannot answer all HIV treatment decisions. Mechanistic models of HIV infection can be used to conduct virtual therapeutic trials with the goal of predicting outcomes, some of which are long-term and may not fall within the time frame of a typical therapeutic trial.

Methods—We used a previously developed and validated model of HIV infection to replicate 2 arms of an HIV initial treatment trial (ACTG A5142) and predict long-term outcomes. The model incorporated data about biologic processes involved in the development of drug resistance.

Results—The model reproduced the proportion that developed AIDS (0.04 and 0.05 for the Efavirenz arm and Lopinavir arms, respectively, vs. 0.04 and 0.06 for the trial), the development of virologic failure (0.27 and 0.33 for the Efavirenz arm and Lopinavir arms, respectively, vs. 0.24 and 0.37 for the trial) and drug resistance. The hazard ratio for the time to treatment failure, a combination of resistance and other causes (0.96 for the model versus 0.75 for the trial; 95% confidence interval, 0.57-0.98), and changes in CD4 cell count, were less accurate. The model estimated longer-term life expectancy, quality-adjusted life expectancy, and HIV-related deaths.

Conclusions—Mechanistic models of HIV infections have the potential to be useful in comparative effectiveness research.

Keywords

mechanistic model; HIV infection; virtual trials

Introduction

HIV infection is a serious international public health problem that affects over 30 million people worldwide and is associated with high rates of morbidity and mortality.(1) Antiretroviral therapy (ART) is the current standard of care for HIV/AIDS. The therapy is designed to drive the replication rate of the virus as low as possible, and this involves the use of a combination of 3 or more antiretroviral drugs that affect different components of HIV replication and assembly. Although studies have shown that ART can substantially improve both the quality and length of life of HIV-infected patients,(2-4) many questions remain to be answered about its use. For example, what is the optimal time at which to initiate therapy? This remains a topic of debate, with some arguing that the benefits of early treatment are outweighed by the risks of developing drug resistance.(2, 3, 5-9) Once a patient is receiving ART, what criteria should be used to define treatment failure? And once treatment failure is declared, what new combination of drugs should the patient receive?

Given the hundreds of possible regimens available and given the variations in timing and patterns of drug resistance, it is not feasible to use randomized controlled trials (RCTs) to explore these complex issues related to HIV care. To determine the best time to initiate therapy, a controlled trial would require that patients be characterized in terms of their CD4 count and viral load and then be randomly assigned to different timing strategies. Even with simplistic stratification of these and other patient characteristics, such a trial would require over 20 arms. Questions about drug choices after treatment failure are even more complex. There are currently 6 classes of antiretroviral drugs, with multiple drugs in each class. Because the development of resistance to one drug does not confer complete resistance to other drugs in the same class, there are many possible combinations available for use if the initial treatment regimen fails.

Recognizing that RCTs cannot answer every question concerning treatment,(10, 11) some have suggested that modeling can help provide answers.(12) The use of mathematical models as a tool for medical decision making is not yet common, but several important examples provide support for their use in appropriate circumstances. Investigators working with the Scientific Registry of Transplant Recipients developed a series of simulation models that are used to predict the effects of changes in organ allocation policy before the changes are implemented.(13, 14) The Archimedes model, a complex mathematical model that represents diabetes, lipid metabolism, metabolic pathways, cardiovascular disorders, and many other interrelated aspects of human physiology and disease in a single model(15-17) has been able to reproduce the results of many clinical trials that have taken place and to accurately predict the results of some trials before the trials were completed.(18, 19) In the case of HIV treatment, many mathematical models have been designed,(20, 21) but not all of them fully represent the stochastic nature of disease progression.(22) It was this shortfall in

available HIV models that prompted us to build more mechanistically realistic representations of disease in our own mathematical models.

Our goal in this article is not to provide a specific answer to a specific question but, rather, to demonstrate that mechanistic models of HIV infection have the potential to be useful in comparative effectiveness research. To demonstrate this, we used our previously developed and validated model of HIV infection to replicate 2 arms of an HIV initial treatment trial (ACTG A5142) and predict long-term outcomes.

Methods

Description of the Model

We previously constructed a probabilistic, second-order Monte Carlo model of the progression and treatment of HIV infection. Details of the model have been published elsewhere,(23-25) and are described in more detail in an on-line appendix. Figure 1 depicts the model's basic structure and shows the ways in which the various components of the model influence one another. Patients with HIV infection are primarily characterized by a CD4 cell count and a viral load. The CD4 count is the chief predictor of HIV-related death, and the viral load is a major predictor of the rate of decline in the CD4 count. Viral load is determined not only by internal viral load “set points” unique to the individual patient but also by the presence or absence of effective ART.

At the onset of simulation, the model provides each simulated patient with a series of characteristics, including a CD4 count, a viral load, and other clinical characteristics that are important in the prediction of survival, such as comorbid diseases. The patients proceed through the model one at a time, with events occurring at daily intervals. Each day, depending on the patient's CD4 count and multiple other factors, the patient may or may not develop an AIDS-related complication, may or may not start receiving an ART regimen that is based on treatment algorithms, and may or may not experience the progression of disease as depicted by a decline in the CD4 count. If the patient is receiving ART, he or she may develop a resistance mutation, may develop toxic reactions to ART, and may or may not continue ART use, with compliance related to sociodemographic characteristics and the presence or absence of side effects. Each patient proceeds through the model until death occurs either from HIV-related complications or from non-HIV-related causes. All events are captured and recorded, providing a complete lifetime history of the patient's CD4 count, viral load, ART use, complications, and mortality burden.

A unique attribute of the simulation is the mechanism by which viral resistance to a drug is determined. The model simulates viral replication and genotype-specific mutation rates, parameters that are not typically represented in models of HIV.(20) The combination of a replication rate and a mutation rate produces mutations to various classes of ART. In a simulated patient, only through the presence of selection pressure does a mutation emerge. This means that a simulated patient can develop resistance only if he or she is receiving a drug to which the randomly occurring mutation confers resistance. Modeled this way, the development of resistance is an “emergent property” of the interrelated components of the model and is not simply a statistical estimate from an existing data source. The model is

therefore a hybrid that represents some relationships mechanistically (the development of antiretroviral resistance) and other relationships statistically (the rate of CD4 decline or mortality given CD4 count) as delineated in Figure 1.

The patient remains on the initial trial-based regimen until they either develop intolerance or the regimen fails. Failure is defined as a viral load above 2.7 log units for the initial regimen and 3.7 for subsequent regimens. Failure would most likely be caused by one or more resistance mutations which reduce the effective viral load decrement for that regimen. A new three drug regimen is then chosen. Regimens consist of either a boosted PI, Efavirenz or Nevirapine and two NRTIs. After the initial randomized treatment, the choice of and sequencing of regimens is not a fixed, pre-specified, input; rather, when a patient fails a regimen, the simulation selects a new regimen with the lowest likelihood of resistance and intolerance.

Validation of the Model

The model has been previously validated in 3 ways which are briefly described in this paper: details can be found in the referenced manuscripts.

The first validation was made by demonstrating that the model could closely reproduce the important clinical events in a dataset on which it was calibrated. The model primarily used data from the Collaborations in HIV Outcomes–US (CHORUS) cohort to calibrate the natural history of disease and the effect of treatment. In validation studies, the model was able to accurately reproduce the time to treatment failure by cycle of therapy and to reproduce the overall survival rate in the CHORUS cohort.(23)

The second validation was made by comparing the model's mortality estimates with mortality data that had not been used to calibrate the model. These mortality data were from the Antiretroviral Treatment Cohort Collaboration (ARTCC), which included 12,574 patients from 13 different cohorts.(26) The model's predictions of 3-year mortality closely matched the ARTCC data in virtually all subgroups of patient age, CD4 count, and viral load.(23)

Like the second validation, the third validation used data that had not been used to calibrate the model. In the third validation, the data were derived from 2 clinical trials that were specifically designed to investigate the relationship between adherence to treatment and resistance to drugs. One trial, the Highly Active Antiretroviral Therapy Observational Medical Evaluation and Research (HOMER) Trial, had a cohort of 1,191 individuals who were being placed on an ART regimen for the first time.(27) The other trial, the Research on Access to Care in the Homeless (REACH) Trial, had a cohort of 148 individuals, most of whom had taken ART before the study began.(28) Figure 2, adapted from one of our earlier studies,(25) demonstrates the ability of the model to predict the accumulation of antiviral resistance mutations in both cohorts, based only on the initial CD4 counts, viral loads, and medication adherence data from patients in the 2 trials.

The third validation demonstrated that the model could replicate clinically observable effects from trials and could replicate intermediate biomarkers of disease progression. Because the

effect of taking ART directly reduces viral replication in the model, the model explicitly represents the dangers of poor compliance with ART. If a simulated patient does not take his or her medication, the effect of ART on viral replication is reduced, and this in turn increases the replication rate and therefore the mutation rate. If a mutation to one drug in a particular ART regimen develops, that mutation will take hold in a particular viral population. The mutation will be based on selection pressure that favors a specific genotype and will be conferred by the presence of the drug that preferentially represses replication of a nonimmune viral strain. In this case, the model offers an appropriate representation of the relationship between adherence and resistance accumulation—i.e., it shows that a decrease in adherence leads to a cascade of increases in replication, mutations, and resistance acquisition. This validation is highlighted here because the ability of the model to predict the relationship between adherence, resistance development, and medication failure is crucial to its use in the evaluation of various strategies of when to switch therapy and what to switch to.

Virtual Replication of a Trial

To illustrate the usefulness of a mechanistic model of HIV infection in comparative effectiveness research, we chose to replicate 2 arms of the ACTG A5142 trial. The trial was designed to address the use of ART regimens with and without nucleoside reverse transcriptase inhibitors (NRTIs) in patients who had not been treated with ART previously. There were 3 arms of treatment: the efavirenz arm, which received a regimen of efavirenz plus 2 NRTIs; the lopinavir-ritonavir arm, which received a regimen of lopinavir-ritonavir plus 2 NRTIs; and the NRTI-sparing arm, which received a regimen of lopinavir-ritonavir plus efavirenz.⁽²⁹⁾ Our simulations were designed to replicate the efavirenz arm and lopinavir-ritonavir arm (i.e., the 2 NRTI-containing arms) for the average trial patient, who was 38 years old, had a CD4 count of 191 cells per microliter, and had a viral load of $10^{4.8}$ copies per milliliter. The simulations were also designed to predict long-term outcomes of overall life expectancy, quality-adjusted life expectancy, and the percentage of patients who died of HIV-related causes. In our simulations, we adjusted the model's mechanistic machinery to reflect the particularly favorable adherence rates and immunologic and virologic responses to ART that were observed in the trial.

For the current report, we incorporated adherence levels observed in ACTG 5142 (62% of patients with 100% adherence). For the remainder of patients without perfect adherence (38%), we assumed a level of adherence typical in large observational cohort studies (62% of doses taken as directed).⁽²³⁾ Sequencing of regimens is not a fixed, pre-specified, input; rather, when a patient fails a regimen, the simulation selects a new regimen with the lowest likelihood of resistance and intolerance. This flexibility is an important strength of the simulation that allows it to better approximate clinical care decisions than a simulation that hardwires particular regimens and sequences after initial failure.

While a strength of the simulation is that it has the capability to consider different scenarios regarding rate of development of new drugs and mechanistic classes, for the current analyses, we made the simplifying assumption that no new drugs or classes would be developed.

Results

In the trial and in the model, patients in the efavirenz arm were less likely than patients in the lopinavir-ritonavir arm to experience treatment failure. As shown in Table 1, the model closely reproduced the trial results in terms of the mean elevation in CD4 count, the proportion of patients who were suppressed (as indicated by viral load), the proportion who developed AIDS during the trial, the proportion who developed virologic failure, and the proportion who developed virologic failure with the presence of at least 1 relevant resistance mutation. The hazard ratio for time to treatment failure, a complex combination of virologic failure and other causes, was 0.75 in the trial, with a 95% confidence interval of 0.57-0.98, while the hazard ratio in the model was 0.96, within the confidence limits of the trial, but less accurate than the more biologically based outcomes. In addition to reproducing the trial results, the model was able to estimate long-term outcomes. As shown in Table 2, the model predicted that the efavirenz arm would have a slightly longer life expectancy, a slightly higher quality-adjusted life expectancy, and fewer HIV-related deaths than would the lopinavir-ritonavir arm.

Discussion

Our results demonstrate that a model that mechanistically represents the acquisition of resistance to antiretroviral agents by taking into account the viral replication rate, the mutation rate, and the presence of a specific selection pressure can closely reproduce the biological results of an RCT of HIV treatment. This is important to demonstrate because a variety of factors make it impossible to turn to RCTs as the sole method for completing comparative effectiveness studies concerning HIV treatment. For example, there is a limit to the number of arms that an RCT can include and a limit to the length of time that an RCT can continue. The number of arms that would be required by RCTs to truly inform the decisions made by clinicians faced with individual patients who have specific resistance patterns, CD4 counts, and viral loads is prohibitive.

As noted in Figure 1, the model contains both mechanistic and statistical relationships. The development of HIV resistance (which is measured in clinical practice) is an emergent property of the model based on the interaction of a replication rate and a mutation rate (which is not measured in clinical practice) interacting with the presence of specific selection pressure from the medications that the virtual patient is taking. However, many other components of the model are estimated statistical relationships. For example the rate of CD4 decline is estimated as a function of VL, the presence or absence of therapy, and the presence of one or more resistance mutations. The risk of death is estimated from large observational cohorts given the CD4 count, age, gender and many other clinical characteristics of the patient. Most of the data for the calibration of the statistical components of the model were derived from observational cohorts, such as the VACS and CHORUS studies. The previous validations of this model were conducted in other observational cohorts: this is the first attempt of this model to replicate the results of an RCT. It is interesting that the parameters that rely most on the mechanistic component of the model (the development of resistance and the occurrence of virologic failure) are very close to the values found in the trial, but other outcomes, such as the actual changes in CD4

counts, which are derived from statistical relationships estimated from observational cohorts, are less well reproduced. This supports, but does not prove, the notion that modeling the processes that create the data we observe in the world provides a more flexible system than modeling the relationships in the observed data themselves.

We believe that mechanistic models of HIV infection have the potential to be useful in comparative effectiveness research. While RCTs may be the best choice to answer some types of questions (Is drug A superior to drug B? Is regimen A superior to regimen B?), models may be the best choice to answer questions about optimization of treatment (What is the optimal CD4 count and viral load at which to initiate therapy? What constellation of patient characteristics can mitigate the effects of treatment?). RCTs can answer the superiority question for the “average” characteristics of the intervention and control cohorts, but RCTs are not always able to answer the superiority question for clinically encountered subgroups with different characteristics. Models have the advantage of being able to deal with the large number of variations in patients, the large and growing number of potential drug combinations used in ART regimens, and the rapidly changing landscape of resistance patterns. Moreover, whereas RCTs can answer questions about short-term outcomes, models can be used to predict long-term outcomes if the models are able to simulate important clinical events that govern transitions between states of health. In the model described here, antiretroviral resistance and ART failure are treated as emergent properties of the interactions of different components of the model. This allows the model to make estimates of outcomes under conditions and treatment choice combinations that have not been used in the model's development, and it allows for the virtual conduct of clinical trials that have far too many arms to conduct in actuality.

An example of a benefit of the model's mechanistic representation of resistance development is its ability to accurately reflect the differential effect of various patterns of lack of adherence. For example, a patient who stops taking all his medications raises viral replication and mutation, but because there is no selection pressure, no resistant strain emerges, the wild type virus simply replicates more quickly. However, in a person who discontinues one or two medications in a multi-drug regimen there is both an increase in the replication and mutation rates and the presence of selection pressure from the medication that the patient is still taking.

We believe that mechanistic models will eventually be used in comparative effectiveness research. Recognition of the limits and advantages of specific types of models is the first step in elucidating the types of roles that models will play.

Description of HIV Computer Simulation*

Our simulation separately tracks the number of accumulated genetic mutations that may confer resistance to each of the three main drug categories of HAART: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), and Protease Inhibitors (PIs). It then uses this information to determine the likelihood of phenotypic resistance to HAART. Mutations develop as a direct function of the viral replication rate and the mutation rate; whether these mutations persist in the viral

population is related to whether there is selection pressure from the presence of a particular medication in the patient's regimen. Phenotypic resistance and adherence determine the likelihood of HAART effectiveness, which then impacts the likelihood of clinical outcomes. Suppression of viral load impacts the CD4 count trajectory favorably, which in turn reduces HIV-related morbidity and mortality.

Numerous longitudinal studies have described the incidence of individual mutations in the HIV reverse transcriptase and protease genes and their correlation with phenotypic resistance and clinical characteristics.¹⁻³⁰ While their results were heterogeneous, several principles emerged. First, mutations accrue in response to selection pressures based on drugs in the antiretroviral regimen. For example, if the HAART round includes NNRTIs but not PIs, a mutation conferring resistance to an NNRTI is far more likely to accrue than is a mutation conferring resistance to a PI. Second, adherence is an important modulator of selection pressures. When adherence is low, selection pressures will decrease, so even though a high rate of viral replication may potentially give rise to a resistant mutation, this impact is mitigated as there is no selection pressure to sustain the mutation in the viral population. Third, the rate of accruing mutations depends on the number of drugs to which HIV is susceptible. The rate is lower if the number of susceptible drugs is high. Fourth, the rate of accruing mutations is unlikely to be zero, even if the round includes three or more drugs to which there is complete susceptibility of HIV and therefore maximum suppression of viral replication. Fifth, if there is resistance to all drugs in the HAART regimen, selection pressure for additional mutations will be low, and it is unlikely that additional mutations will accrue. (For this reason, even though the model does not specify a “ceiling” on the number of mutations, after patients have accumulated enough mutations to accrue resistance to all drugs in a class; it is unlikely that they will accumulate additional mutations within that class). Lastly, the cumulative incidence of resistance mutations is more clinically important than their point prevalence because accumulated resistance mutations are usually archived, and therefore may influence the effectiveness of HAART regimens even if they no longer are detected by assay. (Therefore, the simulation should represent the cumulative incidence of mutations, rather than the point prevalence.)

After these basic principles were used to specify the model, we calibrated it using clinical data from a large observational cohort study until time to treatment failure and survival replicated clinical observations in a large observational study.³¹ For the current report, we re-calibrated this model so that its short-term CD4 and viral load trajectories were consistent with those observed in ACTG 5142. We now describe in greater detail the simulation's specification of genotypic mutations, phenotypic resistance, viral load trajectories, CD4 trajectories, and mortality.

Genotypic Mutations

A theoretical construct entitled *optimal mutation accumulation rate* is the starting point for determining all mutation accumulation rates in the model. This construct denotes what the mutation accumulation rate would be under optimal circumstances (perfect adherence to therapy and no resistance to therapy). A different *optimal mutation accumulation rate* may be specified for each drug class; however, during our calibration of the model, we found that

it was not necessary to do this in order to yield clinically accurate projections of time to treatment failure and survival.

Starting from the *optimal mutation accumulation rate*, the model calculates the *actual mutation accumulation rate* based on the amount of viral replication (proxied by viral load) and the level of adherence:

Actual mutation accumulation rate = *optimal mutation rate* * (*replication factor* ^ (log *instantaneous viral load* – 2.31)) * (*adjustment factor for composition of regimen*) * (*adherence adjuster*)

Replication factor was set at 3.16 based on results from heterogeneous studies that measured mutation accumulation rates with varying viral loads.^{4,7-9,20,29,30} Note that the mutation rate increases as viral load (and viral replication) increases. It was not necessary to change this estimate during model calibration.

Adherence adjuster decreases the mutation accumulation rate based on the amount of nonadherence. This was specified so as to be logically consistent with other assumptions embedded in the model (e.g. if an individual is completely nonadherent to a particular drug, the impact on the accumulation of same-class mutations should be the same as if the person was not prescribed the drug at all).

Adjustment factor for composition of regimen ensures that mutations only accumulate to the drug types that are represented in the current HAART round (e.g. if an NNRTI is not included in the current HAART round, it is extremely unlikely to get an NNRTI mutation).

During calibration of our model, we found that an *optimal mutation rate* of 0.014 per month yielded the closest correlation of observed versus expected results for time to treatment failure and survival, and that any mutation rate between 0.010 per month and 0.015 per month yielded reasonably good correlations. Note that this rate reflects mutation accumulation under optimal circumstances (perfect adherence and no resistance), and therefore individuals in the model, on average, accumulate mutations more rapidly.

Phenotypic Resistance

The model considers the possibility that any one particular mutation may not induce any resistance, may engender resistance to one drug, or may engender resistance to more than one drug (because of cross-resistance). Estimates for cross resistance were based on published sources that specify the relationship of each individual mutation with each HAART drug,³² and incorporates a mathematical average of how likely any one mutation is likely to engender resistance to more than one drug in the same class. Because a separate calculation is performed for each drug class, the model captures clinically observed heterogeneity among drug classes (i.e. it is more common among NNRTIs than among PIs or NRTIs).

The model also considers the possibility that a particular mutation may or may not result in phenotypic resistance. Because this likelihood varies greatly by individual mutation, we used a simple summary estimate (0.5) which fell within the clinically observed range

(approximately 0.1 to 0.9).^{4,8,12,16,21,22,29,30} Since the rate of accumulating resistance in the model is the product of the rate of accumulating mutations and the probability that each mutation will cause resistance, any error in this estimate would have induced a compensatory error in the imputed mutation rate, and therefore would not have been expected to adversely impact its results. Because the imputed mutation rate was remarkably consistent with clinical observations, it is unlikely that this error was substantial.

Change in Viral Load

Our model assumes that the viral load for each patient has a “set point” that reflects the particular dynamics between the virulence of the HIV strain and the activity of the immune system. In the current analyses, we assume that the viral load prior to starting HAART reflects this “set-point.” (Therefore the current analyses will not apply to primary HIV infection, which is characterized by very high viral loads that are transient.) The model assumes that the viral load decreases after HAART is started and that the extent of the decrease varies with the number of drugs in the HAART round to which there is phenotypic resistance and with the degree to which the patient adheres to the HAART round. If mutations accrue and resistance develops, the viral load will start to increase and move toward its set point. Similarly, if a patient stops taking one or more drugs, the viral load will start to move toward its set point, with the speed of movement depending on the number of drugs and doses missed.

We distinguish between *steady state viral load* (a theoretical, immeasurable construct) and *instantaneous viral load* (a measurable construct). *Steady state viral load* is the viral load that would be reached at equilibrium, after an infinite amount of time, if there were no changes in any of its determinates. *Instantaneous viral load* is the true viral load at a particular time. We distinguish between these constructs because the determinates of viral load may change by clinically significant amounts over much shorter time scales (i.e. over hours) than the true viral load (i.e. usually over weeks or months). The *instantaneous viral load* moves towards the *steady state viral load*, with a delay factor that reflects its slower kinetics.

Steady-state viral load

Based on our previously reported analyses of antiretroviral naïve individuals in care,³³ and then updated to reflect short-term viral load outcomes in ACTG 5142, *steady state viral load* is determined by the following equations:

$$\text{Logsteady state viral load} = \text{Logviral load "set point"} - \text{Logviral load decrement}$$

$$\text{LogViral load decrement} = \text{Logdrug class-specific viral load decrement} * \text{scaling constant} * \text{adherence adjuster} * \text{resistance}$$

Scaling constant is based on magnitude of pre-treatment viral load in simulated cohort relative to pre-treatment viral load in source data ($\text{Log patient viral load baseline} / 4.5$). The

Log *drug class specific viral load decrements* are unboosted PI (1.84), boosted PI (2.68), efavirenz (3.09), and nevirapine (2.22).

The *viral “set point”* is the equilibrium viral load after the primary phase of HIV infection has concluded. *Adherence adjuster* attenuates the decrease in viral load as individuals are more nonadherent to therapy. Adherence is defined as the proportion of antiretroviral doses taken as directed. We assume a linear relationship between adherence and the logarithm of the decrease in viral load, a reasonable approximation as verified by a later analyses of 6,394 antiretroviral naïve patients for which adherence information was available.³³

Resistance adjuster attenuates the decrease in viral load if patients have resistance to one or more antiretroviral drugs. We assume a linear relationship between the proportion of drugs to which there is resistance, and the logarithm of the decrease in viral load (i.e. if viral load decrease would be X log units with resistance to no drugs, it would be $\frac{2}{3} * X$ log units with resistance to 1 drug, and $\frac{1}{3} * X$ log units with resistance to 2 drugs). While this is clearly a simplification, there is a growing literature to support a rough rule of thumb that, under favorable circumstances (the absence of resistance and high levels of adherence), one-drug regimens drop log viral loads by approximately 1 log, two drug regimens drop log viral loads by approximately 2 logs, and three drug regimens drop log viral loads by approximately 3 logs.^{7,9,11,13,18,20,29} Over time, we may be able to make this relationship more precise.

Instantaneous viral load

The formula for this variable is straightforward, specifying an exponential convergence towards the *steady state viral load*:

Log *Instantaneous viral load* at time t = Log *Instantaneous viral load* at time t-1 + (Log *instantaneous viral load* at time t - Log *instantaneous viral load* at time t-1)/*viral load delay constant*.

Viral load delay constant was set at 1.5 months, reflecting observed kinetics of viral load fluctuations.

Change in CD4 Count

The CD4 count plays a crucial role in determining the risk of HIV-related mortality, and therefore estimating its trajectory is essential for predicting this mortality risk over long time periods.

Similarly to how viral load is represented, CD4 count is also represented by a steady state variable and an instantaneous variable.

Steady State

The representation of CD4 is more complicated than viral load because there is no “set point.” Published data prior to widespread adoption of HAART suggests that the CD4 count declines at a rate inversely proportional to the viral load.³⁴ However, HAART may change

this relationship substantially. We therefore analyzed the CD4 count trajectories of the anti-retroviral naïve HIV-positive patients starting HAART in the same observational cohort that was used to analyze viral load. We analyzed this data in accord with the conceptual framework that changes in CD4 count during HAART may be disaggregated into two separate components: a *trough to peak* change in CD4 (representing the rise in CD4 count from when a round is started, to the highest level that will be obtained during that round) and a *trough to trough* change in CD4 (representing the change in CD4 count from the start of first HAART round to the start of each subsequent round), which occurs as patients develop resistance or have worsening of nonadherence. The “peak” CD4 for a particular HAART round was approximated by the value 1 year after that round was initiated. (This is only a gross approximation, as data show that CD4 counts continue to increase as long as regimens are effective. However, the rate of increase diminishes dramatically after 1 year, and therefore the 1 year value can be used as a proxy for the plateau.) Based on our previously reported analyses of antiretroviral naïve individuals in care,³³ and then updated to reflect short-term CD4 outcomes in ACTG 5142, *CD4 trajectory* is determined by the following equations:

If off HAART

$$CD4_{at\ time\ t} = CD4_{at\ time\ t-1} - \text{time interval (in months)} * (1.78 + 2.8 * (\log \text{instantaneous viral load} - 3)).$$

If on HAART and resistant to one or fewer drugs in the regimen)

$$\begin{aligned} CD4 = & +2 * (\text{if patient on haart for at least one year}) \\ & +23 * (\text{if patient on haart for at least two years}) \\ & +10 * (\text{if patient on haart for at least three years}) \\ & +14 * (\text{if patient on haart for at least four years}) \\ & +10 * (\text{if patient on haart for at least five years}) \\ & +0 * (\text{if patient age at reg baseline} < 30) \\ & +26 * (\text{if } 30 \leq \text{patient age at reg baseline} < 40) \\ & +18 * (\text{if } 40 \leq \text{patient age at reg baseline} < 50) \\ & +16 * (\text{if } 50 \leq \text{patient age at reg baseline} < 60) \\ & +6 * (\text{if } 60 \leq \text{patient age at reg baseline} < 70) \\ & -15 * (\text{if patient age at reg baseline} \geq 70) \\ & +1 * (\text{if } CD4_{at\ reg\ baseline} \leq 200) \\ & +0 * (\text{if } 200 < CD4_{at\ reg\ baseline} < 350) \\ & -6 * (\text{if } 350 \leq CD4_{at\ reg\ baseline} < 500) \\ & -48 * (\text{if } CD4_{at\ reg\ baseline} \geq 500) \\ & +3.3 \\ & +0 * (\text{if patient adherence} > 0.8) \\ & +0 * (\text{if } 0.6 \leq \text{patient adherence} < 0.8) \\ & -6 * (\text{if } 0.4 \leq \text{patient adherence} < 0.6) \\ & -31 * (\text{if } 0.2 \leq \text{patient adherence} < 0.4) \\ & -51 * (\text{if patient adherence} < 0.2) \\ & +43 * \text{Change in viral load from baseline (scaled according to max possible change in viral load)} \end{aligned}$$

+“noise”component without between – regimen correlation
 +“noise”component with between – regimen correlation

If on HAART (and resistant to 2 or more drugs in the regimen)

We based the following equations from data from PLATO, a joint analysis of 13 13 HIV cohorts from Europe, North America, and Australia, involving patients who had had multi-class virological failure:³⁵

If viral load ≥ 4.0 ,

$$CD4_{at \text{ time } t} = CD4_{at \text{ time } t-1} + (50 * pat - > VL_{real} + 200) / \text{time interval};$$

Otherwise,

$$CD4_{at \text{ time } t} = CD4_{at \text{ time } t-1}$$

Instantaneous

Instantaneous CD4 incorporates a delay factor (3 months), analogous to *instantaneous viral load*. It also incorporates a “noise” factor to reflect unexplained variance in the CD4 count (a far lower proportion of CD4 count variance is explained by covariates). The delay factor was specified based on observed CD4 kinetics, and the noise factor was specified during the verification of the model to result that clinically plausible CD4 trajectories were produced for simulated individual patients.

Adherence

The model permits the user to specify an overall predisposition towards adherence to therapy, defined as the proportion of antiretroviral doses taken as directed. Because adherence often varies greatly from time to time (both within regimens, and because of differing regimen characteristics, between regimens), we modify this predisposition via two “noise” terms, one of which is drawn anew with each time period, and the other of which is drawn anew each time a new regimen starts. The noise factors were specified during the verification of the model to result in clinically plausible viral load and CD4 trajectories for individual patients.

The model incorporates the observation that nonadherence to one drug in a HAART regimen is often highly correlated with nonadherence to other HAART drugs in the regimen (i.e. if you miss one drug, chances are relatively high that you also will miss the other drugs at the same dosing time). To represent this correlation, the model permits the user to select a correlation factor. Because there are insufficient clinical data on which to base estimates for this correlation, we arbitrarily set it at 0.9 for all of our analyses. This setting was consistent with satisfactory performance on our calibration and validation exercises.³¹

For the current report, we incorporated adherence levels observed in ACTG 5142 (62% of patients with 100% adherence). For the remainder of patients without perfect adherence (38%), we assumed a level of adherence typical in large observational cohort studies (62% of doses taken as directed).³³

Mortality

Mortality is partitioned into *HIV-related* and *non-HIV-related* sources of death. *HIV-related mortality* is a function of age, CD4 count, viral load, and presence of HAART (to consider the salutary effects of maintaining less “fit” viral strains, independent from its beneficial impact on CD4 count and viral load). Estimates were based on our analyses of observational data of HIV+ individuals for which cause of death was a prospectively defined and measured outcome. Detailed tables are available from the authors on request; summary tables were published previously.³¹

Non-HIV related mortality is a function of age, sex, and race, and was based on same observational cohort above. These results were indexed to published life tables of all-causes mortality in the United States by age, race, and sex to extrapolate beyond the age groups that were represented in this population.³⁶ Detailed tables are available from the authors on request; summary tables were published previously.³¹

Appendix Reference List

1. Ross L, Johnson M, DeMasi R *et al.* Viral genetic heterogeneity in HIV-1-infected individuals is associated with increasing use of HAART and higher viremia. *AIDS* 14(7): 813-9, 2000;
2. Gulick RM, Mellors JW, Havlir D *et al.* 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Annals of Internal Medicine* 2000; 133: 35-39
3. Lawrence J, Schapiro J, Winters M *et al.* Clinical resistance patterns and responses to two sequential protease inhibitor regimens in saquinavir and reverse transcriptase inhibitor-experienced persons. *Journal of Infectious Diseases* 179(6):1356-64, 1999;
4. Gatanaga H, Aizawa S, Kikuchi Y *et al.* Anti-HIV effect of saquinavir combined with ritonavir is limited by previous long-term therapy with protease inhibitors. *AIDS Research & Human Retroviruses* 15(17):1493-8, 1999;
5. Gulick RM, Mellors JW, Havlir D *et al.* Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection: 100-week follow-up. *JAMA* 280(1):35-41, 1998;
6. Piketty C, Race E, Castiel P *et al.* Efficacy of a five-drug combination including ritonavir, saquinavir and efavirenz in patients who failed on a conventional triple-drug regimen: phenotypic resistance to protease inhibitors predicts outcome of therapy. *AIDS* 1999; 13: F71-77

7. Garcia F, Romeu J, Grau I *et al.* A randomized study comparing triple versus double antiretroviral therapy or no treatment in HIV-1-infected patients in very early stage disease: the Spanish Earth-1 study. *AIDS* 13(17):2377-88, 1999;
8. Lorenzi P, Yerly S, Abderrakim K *et al.* Toxicity, efficacy, plasma drug concentrations and protease mutations in patients with advanced HIV infection treated with ritonavir plus saquinavir. Swiss HIV Cohort Study. *AIDS* 11(12):F95-9, 1997;
9. Tebas P, Patick AK, Kane EM *et al.* Virologic responses to a ritonavir--saquinavir-containing regimen in patients who had previously failed nelfinavir. *AIDS* 1999; 13: F23-28
10. Mouroux M, Yvon-Groussin A, Peytavin G *et al.* Early virological failure in naive human immunodeficiency virus patients receiving saquinavir (soft gel capsule)-stavudine-zalcitabine (MIKADO trial) is not associated with mutations conferring viral resistance. *Journal of Clinical Microbiology* 38(7):2726-30, 2000;
11. Montaner JS, Reiss P, Cooper D *et al.* A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA* 1998; 279: 930-937
12. Harrigan PR, Hertogs K, Verbiest W *et al.* Baseline HIV drug resistance profile predicts response to ritonavir-saquinavir protease inhibitor therapy in a community setting. *AIDS* 1999; 13: 1863-1871
13. Deeks SG, Grant RM, Beatty GW, Horton C, Detmer J, Eastman S. Activity of a ritonavir plus saquinavir-containing regimen in patients with virologic evidence of indinavir or ritonavir failure. *AIDS* 1998; 12: F97-102
14. Descamps D, Flandre P, Calvez V *et al.* Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072) Study Team). *JAMA* 2000; 283: 205-211
15. Coakley EP, Gillis JM, Hammer SM. Phenotypic and genotypic resistance patterns of HIV-1 isolates derived from individuals treated with didanosine and stavudine. *AIDS* 2000; 14: F9-15
16. Casado JL, Hertogs K, Ruiz L *et al.* Non-nucleoside reverse transcriptase inhibitor resistance among patients failing a nevirapine plus protease inhibitor-containing regimen. *AIDS* 2000; 14: F1-F7
17. Hanna GJ, Johnson VA, Kuritzkes DR *et al.* Patterns of resistance mutations selected by treatment of human immunodeficiency virus type 1 infection with zidovudine, didanosine, and nevirapine. *J Infect Dis* 2000; 181: 904-911
18. Kuritzkes DR, Sevin A, Young B *et al.* Effect of zidovudine resistance mutations on virologic response to treatment with zidovudine-lamivudine-ritonavir: genotypic analysis of

- human immunodeficiency virus type 1 isolates from AIDS clinical trials group protocol 315. ACTG Protocol 315 Team. *J Infect Dis* 2000; 181: 491-497
19. Bachelier LT, Anton ED, Kudish P *et al.* Human immunodeficiency virus type 1 mutations selected in patients failing efavirenz combination therapy. *Antimicrobial Agents & Chemotherapy* 2000; 44: 2475-2484
20. Atkinson B, Isaacson J, Knowles M, Mazabel E, Patick AK. Correlation between human immunodeficiency virus genotypic resistance and virologic response in patients receiving nelfinavir monotherapy or nelfinavir with lamivudine and zidovudine. *J Infect Dis* 2000; 182: 420-427
21. Havlir DV, Marschner IC, Hirsch MS *et al.* Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. AIDS Clinical Trials Group Study 343 Team. *New England Journal of Medicine* 1998; 339: 1261-1268
22. Zolopa AR, Shafer RW, Warford A *et al.* HIV-1 genotypic resistance patterns predict response to saquinavir-ritonavir therapy in patients in whom previous protease inhibitor therapy had failed. *Annals of Internal Medicine* 1999; 131: 813-821
23. Race E, Gilbert SM, Sheldon JG *et al.* Correlation of response to treatment and HIV genotypic changes during phase III trials with saquinavir and reverse transcriptase inhibitor combination therapy. *AIDS* 12(12):1465-74, 1998;
24. Michelet C, Bellissant E, Ruffault A *et al.* Safety and efficacy of ritonavir and saquinavir in combination with zidovudine and lamivudine. *Clinical Pharmacology & Therapeutics* 65(6):661-71, 1999;
25. Maguire M, Gartland M, Moore S *et al.* Absence of zidovudine resistance in antiretroviral-naïve patients following zidovudine/lamivudine/protease inhibitor combination therapy: virological evaluation of the AVANTI 2 and AVANTI 3 studies. *AIDS* 2000; 14: 1195-1201
26. Pellegrin I, Breilh D, Montestruc F *et al.* Virologic response to nelfinavir-based regimens: pharmacokinetics and drug resistance mutations (VIRAPHAR study). *AIDS* 2002; 16: 1331-1340
27. Walmsley S, Bernstein B, King M *et al.* Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *New England Journal of Medicine* 2002; 346: 2039-2046
28. Squires K, Pozniak AL, Pierone G, Jr. *et al.* Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. *Annals of Internal Medicine* 2003; 139: 313-320
29. Katlama C, Clotet B, Plettenberg A *et al.* The role of abacavir (ABC, 1592) in antiretroviral therapy-experienced patients: results from a randomized, double-blind, trial. CNA3002 European Study Team. *AIDS* 2000; 14: 781-789

30. Miller V, it-Khaled M, Stone C *et al.* HIV-1 reverse transcriptase (RT) genotype and susceptibility to RT inhibitors during abacavir monotherapy and combination therapy. *AIDS* 14(2):163-71, 2000;
31. Braithwaite RS, Justice AC, Chang CC *et al.* Estimating the proportion of patients infected with HIV who will die of comorbid diseases. *American Journal of Medicine* 2005; 118: 890-898
32. Johnson VA, Brun-Vezinet F, Clotet B *et al.* Update of the Drug Resistance Mutations in HIV-1: 2005. *Topics in HIV Medicine* 2005; 13: 51-57
33. Braithwaite RS, Kozal MJ, Chang CC, *et al.* Adherence, Virologic and Immunologic Outcomes for HIV-infected Veterans Starting Combination Antiretroviral Therapies. *AIDS* 2007; 21:1579-1590.
34. Cook J, Dasbach E, Coplan P *et al.* Modeling the long-term outcomes and costs of HIV antiretroviral therapy using HIV RNA levels: application to a clinical trial. *AIDS Research & Human Retroviruses* 15(6):499-508, 1999;
35. Ledergerber B and the PLATO collaboration. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*, 2004; 364, 51 - 62
36. Vital Statistics in the United States: Mortality, Part B; Various Years Through 1991. 1995. US Dept of Health and Human Services, National Center for Health Statistics. Vital Statistics in the United States.
37. Braithwaite RS, Shechter S, Roberts MS, Schaefer A, Bangsberg D, Harrigan R, Justice A. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. *J Antimicrob Chemother* 2006; 58:1036-1043.

References

1. WHO. [Accessed 7/28/2009] Global Summary of the AIDS epidemic, December 2007. 2009. Available at: http://www.who.int/hiv/data/2008_global_summary_AIDS_ep.png
2. Ho DD. Time to hit HIV, early and hard. *N Engl J Med.* 1995; 333:450–451. [PubMed: 7616996]
3. Sterling TR, Chaisson RE, Keruly J, et al. Improved outcomes with earlier initiation of highly active antiretroviral therapy among human immunodeficiency virus-infected patients who achieve durable virologic suppression: longer follow-up of an observational cohort study. *J Infect Dis.* 2003; 188:1659–1665. [PubMed: 14639536]
4. Sterling TR, Chaisson RE, Moore RD. Initiation of highly active antiretroviral therapy at CD4+ T lymphocyte counts of >350 cells/mm³: disease progression, treatment durability, and drug toxicity. *Clin Infect Dis.* 2003; 36:812–815. [PubMed: 12627368]
5. Cohen CJ, Boyle BA. Antiretroviral therapy: the “when to start” debates. *Clin Infect Dis.* 2004; 39:1705–1708. [PubMed: 15578374]
6. Phillips AN, Lepri AC, Lampe F, et al. When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies *Aids.* 2003; 17:1863–1869. [PubMed: 12960818]
7. Lane HC, Neaton JD. When to start therapy for HIV infection: a swinging pendulum in search of data. *Ann Intern Med.* 2003; 138:680–681. [PubMed: 12693893]

8. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*. 2004; 364:51–62. [PubMed: 15234856]
9. Hertogs K, Bloor S, Kemp SD, et al. Phenotypic and genotypic analysis of clinical HIV-1 isolates reveals extensive protease inhibitor cross-resistance: a survey of over 6000 samples. *Aids*. 2000; 14:1203–1210. [PubMed: 10894285]
10. Volpp KG, Das A. Comparative effectiveness--thinking beyond medication A versus medication B. *N Engl J Med*. 2009; 361:331–333. [PubMed: 19625714]
11. Luce BR, Kramer JM, Goodman SN, et al. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. *Ann Intern Med*. 2009; 151:206–209. [PubMed: 19567619]
12. Basu A, Meltzer D. Modeling comparative effectiveness and the value of research. *Ann Intern Med*. 2009; 151:210–211. [PubMed: 19652188]
13. Schaubel DE, Dykstra DM, Murray S, et al. Analytical approaches for transplant research, 2004. *Am J Transplant*. 2005; 5:950–957. [PubMed: 15760420]
14. Wolfe RA, Schaubel DE, Webb RL, et al. Analytical approaches for transplant research. *Am J Transplant*. 2004; 4(9):106–113. [PubMed: 15113359]
15. Eddy DM, Schlessinger L. Validation of the archimedes diabetes model. *Diabetes Care*. 2003; 26:3102–3110. [PubMed: 14578246]
16. Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. *Diabetes Care*. 2003; 26:3093–3101. [PubMed: 14578245]
17. Schlessinger L, Eddy DM. Archimedes: a new model for simulating health care systems--the mathematical formulation. *J Biomed Inform*. 2002; 35:37–50. [PubMed: 12415725]
18. Stern M, Williams K, Eddy D, et al. Validation of prediction of diabetes by the Archimedes model and comparison with other predicting models. *Diabetes Care*. 2008; 31:1670–1671. [PubMed: 18509203]
19. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. *Ann Intern Med*. 2005; 143:251–264. [PubMed: 16103469]
20. Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med*. 2001; 344:824–831. [PubMed: 11248160]
21. Richter A, Hauber B, Simpson K, et al. A Monte Carlo simulation for modelling outcomes of AIDS treatment regimens. *Pharmacoeconomics*. 2002; 20:215–224. [PubMed: 11950379]
22. Shechter SM, Bailey MD, Schaefer AJ, et al. The Optimal Time to Initiate HIV Therapy Under Ordered Health States. *Operations Research*. 2008; 56:20–33.
23. Braithwaite RS, Justice AC, Chang CC, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. *Am J Med*. 2005; 118:890–898. [PubMed: 16084183]
24. Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. *Aids*. 2007; 21:1579–1589. [PubMed: 17630553]
25. Braithwaite RS, Shechter S, Roberts MS, et al. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. *J Antimicrob Chemother*. 2006; 58:1036–1043. [PubMed: 17023498]
26. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*. 2002; 360:119–129. [PubMed: 12126821]
27. Bangsberg DR, Charlebois ED, Grant RM, et al. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *Aids*. 2003; 17:1925–1932. [PubMed: 12960825]
28. Harrigan PR, Hogg RS, Dong WW, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naïve cohort initiating triple antiretroviral therapy. *J Infect Dis*. 2005; 191:339–347. [PubMed: 15633092]
29. Riddler SA, Haubrich R, DiRienzo AG, et al. Class-sparing regimens for initial treatment of HIV-1 infection. *N Engl J Med*. 2008; 358:2095–2106. [PubMed: 18480202]

Figure 1.

Influence diagram and structure of the simulation model. This model includes 2 parameters that are typically not measured or observed in other models: viral replication and the rate of mutations within the viral genome (shaded box). These combine with selection pressure to produce viral resistance, which constitute the mechanistic component of the model, other components represent relationships statistically. HAART indicates highly active antiretroviral therapy. This model is a hybrid in that it contains mechanistic components (resistance acquisition) and statistical components (e.g. the risk of death by CD4 count, the relationship of viral load to CD4 count)

Figure 2.

Comparison of trial-based results and model-based results concerning the relationship between adherence to treatment and the accumulation of antiviral resistance mutations. The top panel compares results from the Highly Active Antiretroviral Therapy Observational Medical Evaluation and Research (HOMER) Trial(27) with results from the model (simulation). The bottom panel compares results from the Research on Access to Care in the Homeless (REACH) Trial(28) with results from the model (simulation). This figure is modified and reproduced, with permission, from Braithwaite RS, Shechter S, Roberts MS, et al. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. *J Antimicrob Chemother.* 2006;58:1036-43.

Table 1
A Comparison of Trial-Based Results and Model-Based Results*

Variable	Trial-Based Results		Model-Based Results	
	Efavirenz Arm	Lopinavir-Ritonavir Arm	Efavirenz Arm	Lopinavir-Ritonavir Arm
Elevation in CD4 cell count, mean (range) of cells per μL	230 (142–353)	287 (176–419)	254	235
Proportion of patients who were suppressed, as indicated by viral load	0.89	0.77	0.86	0.79
Proportion of patients who developed AIDS	0.04	0.06	0.04	0.05
Proportion of patients who developed virologic failure	0.24	0.37	0.27	0.33
Proportion of patients who developed virologic failure and had at least 1 mutation	0.09	0.06	0.08	0.06
Hazard ratio for time to treatment failure: efavirenz arm vs. lopinavir-ritonavir arm	0.75, with 95% confidence interval of 0.57–0.98		0.96	

* The results shown are for data derived from 2 arms of the ACTG A5142 trial.²⁹

The efavirenz arm received a regimen of efavirenz plus 2 nucleoside reverse transcriptase inhibitors (NRTIs). The lopinavir-ritonavir arm received a regimen of lopinavir-ritonavir plus 2 NRTIs.

Table 2
Model-Based Long-term Predictions*

Outcome	Efavirenz Arm	Lopinavir-Ritonavir Arm
Five-year outcomes		
Median elevation in CD4 cell count, expressed as no. cells per μL	276	269
Median change in viral load, expressed in log units	-4.32	-4.20
Mean no. resistance mutations	0.36	0.29
Mean no. antiretroviral therapy regimens used	1.54	1.53
Mortality	0.020	0.021
Lifetime outcomes		
Life expectancy, expressed in years	35.55	35.50
Quality adjusted life expectancy (QALY), expressed in adjusted years	31.41	31.36
HIV deaths, expressed as a percent	9.0	9.2

* The results shown are for data derived from 2 arms of the ACTG A5142 trial.²⁹

The efavirenz arm received a regimen of efavirenz plus 2 nucleoside reverse transcriptase inhibitors (NRTIs). The lopinavir-ritonavir arm received a regimen of lopinavir-ritonavir.