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Estimating the Rate of Accumulating Drug Resistance Mutations in the HIV Genome

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ABSTRACT

Objective: HIV mutation accumulation has great implications for pharmacoeconomics and clinical care, yet scarcity of data has hindered its representation in decision analytic models. Our objective is to determine the accuracy with which mutation accumulation and other unmeasured parameters could be estimated during model calibration.

Methods: We used a second-order Monte Carlo simulation of HIV natural history that had been calibrated by varying two unmeasured parameters (mutation accrual rate and probability of adherence) to minimize differences between estimated and observed clinical outcomes (time to treatment failure and survival). We compared these estimated values first with only those results that had been already published at the time of model calibration, and second including results that were published after model calibration.

Results: The value for mutation accrual rate assigned during calibration was 0.014 mutations per month for antiretroviral naive patients, at the lower bound of the results for nine heterogeneous studies published at the time of calibration (pooled 95% confidence interval [CI] 0.014–0.039 mutations per month). In contrast, this estimate accurately anticipated results from 11 larger and more homogeneous studies published after calibration (pooled 95% CI for antiretroviral naïve patients, 0.012–0.015 mutations per month). The value for probability of adherence assigned during calibration (75%) was also within the range of published results (pooled 95% CI 62–76%).

Conclusion: Estimates for unobserved parameters derived during model calibration were not only within the range of clinical observations, but anticipated with accuracy clinical results that were not yet available. It may be feasible to use models to estimate unobserved parameters.

Keywords: adherence, genotypic resistance, HIV, antiretroviral therapy.

Introduction

The rate at which mutations accrue in the HIV genome has great implications for the management of individuals with HIV because it impacts the effectiveness and pharmacoeconomics of combination antiretroviral therapies (CART). Resistance mutations attenuate plasma HIV suppression by CART [1], which leads to higher mortality from HIV-related causes [2,3], variations in the cost-effectiveness of CART [4], and may result in different treatment strategies being preferred [5]. Therefore, models used to predict clinical and economic outcomes for a given treatment strategy are likely to be more accurate if they include the accumulation of resistance mutations as an explicit construct.

Despite the importance of characterizing mutation accumulation, few studies have analyzed this outcome prospectively, nor have clinical and policy models of HIV disease incorporated this important attribute explicitly [4,6–10]. Until recently, data describing the accrual of resistance mutations have mostly originated from small studies with variable results [11–19], and this heterogeneity has been difficult to attribute solely to known differences among the sampled populations. Our efforts to parameterize our simulation of HIV natural history [5,20–22] were therefore hindered by uncertainty. As a consequence, we assigned estimates for the rate of mutation accumulation by choosing the value that minimized the difference between expected and observed results during its calibration.

Similar challenges in the modeling of disease natural history have been faced by investigators developing cost-effectiveness models in other domains. Researchers modeling cervical cancer and breast cancer detection strategies have employed natural history models that included preclinical stages of cancer that are not routinely detected or characterized in clinical populations [23–26]. Because these investigators were unable to estimate these parameters solely from clinical observations, they also needed to assign

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estimates for their values based on model calibration. Researchers optimizing ways to allocate livers for transplantation have pursued a similar strategy [27]. Nevertheless, despite the increasing use of this approach, there is no direct evidence that the estimation of unobserved parameters during model calibration can produce accurate parameter estimates.

Soon after we estimated values for mutation rate parameters in our HIV simulation, several studies were published, which prospectively measured these parameters in large clinical populations, focusing exclusively on populations similar to that which we were modeling [28–31]. We were therefore unwitting participants in a "natural experiment" that enabled us to compare our assigned estimates with observations from similar populations. In this report, we use the natural experiment to address the question of how our assigned estimates compared with results that were published subsequently, as well as to address the more general question of whether it is feasible to use a natural history model to estimate the value of an unobserved parameter.

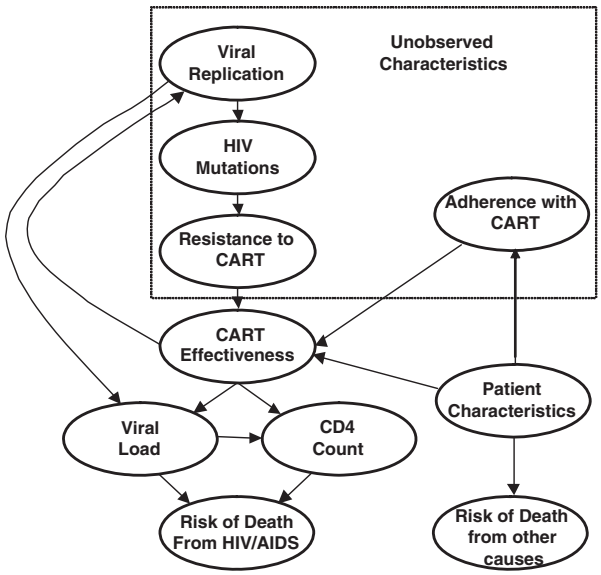

Figure 1 Influence diagram of computer simulation. The effectiveness of combination antiretroviral therapy (CART) is determined by genotypic resistance and adherence with prescribed medications, processes that are frequently unobserved. CART effectiveness influences the clinical trajectory of HIV disease, and consequently impacts survival.

Methods

We first describe our HIV model and its parameters, then how we used calibration of the model to estimate the value of the parameters that were unknown, and finally how we compared our estimated results with published results. The two parameters we estimated during calibration were the mutation accumulation rate and the level of adherence with antiretroviral therapy. Calibration was performed using the same data set that was used to estimate many important parameters in the model [21].

Model Overview

We have created a second-order Monte Carlo simulation that explicitly represents two of the processes that undermine antiretroviral effectiveness in HIV disease: development of genotypic resistance, and nonadherence to medications [5,20,21,32]. These processes influence the effectiveness of antiretroviral therapies (ARV). ARV effectiveness then determines the trajectory of clinical indices known to have prognostic significance (CD4, viral load), which are used to predict the likelihood of death. The simulation only represents those mutations that have been shown to potentially give rise to resistance to antiretroviral drugs, and does not represent naturally occurring polymorphisms or mutations that have other clinical implications.

Figure 1 is an influence diagram that describes how these constructs are integrated into the model. Resistance to CART and adherence to CART determine the level of CART effectiveness. Although greater CART effectiveness will suppress viral load more completely, it will also increase selection pressures for particular mutations that could produce resistance to one or more drugs in the round. Greater CART effectiveness reduces the rate of viral replication and therefore decreases opportunities to produce mutations overall, however, the mutations that do occur are produced in an environment of high selection pressure because of the effectiveness of the therapy against wild type virus. As resistance accrues, the viral replication rate increases, and this in turn increases the probability that subsequent mutations will develop. The effectiveness of CART influences changes in the viral load and CD4 count and also feeds back to influence the viral replication rate and selection pressures.

When there is resistance or intolerance to a particular regimen, a new regimen is chosen that includes at least two drugs from the mechanistic category with the least phenotypic resistance, and one drug from a separate category (unless all possible regimens have been exhausted). When calibrating the model, the starting regimen was assumed to include a protease inhibitor; however, the model is able to accommodate any particular choice for a starting regimen (e.g., including a non-nucleoside reverse transcriptase inhibitor).

Several additional principles are embedded in the model consistent with clinical studies of HIV mutation accumulation [11–19,28–30,33–42]. First, mutations accrue because of selection pressures. For example, if the CART round includes NNRTIs but not PIs, there is a large probability of accruing a mutation that confers resistance to an NNRTI, but a negligible probability of accruing a mutation that confers resistance to a PI

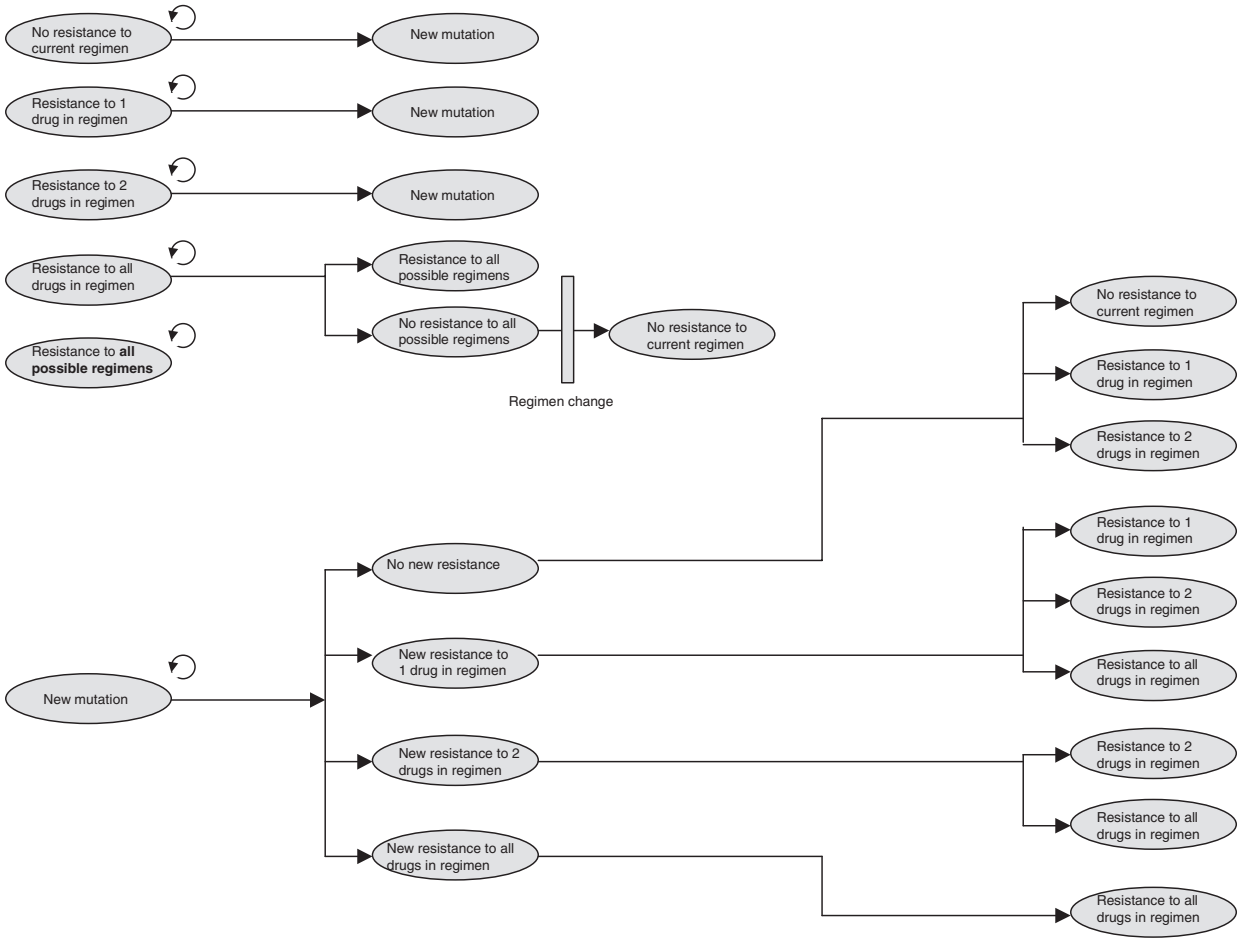

Figure 2 State transition diagram of computer simulation. A new mutation may arise during any time period, and is more likely with greater viral replication or selection pressures. Each mutation may or may not confer resistance to one or more drugs in the regimen. When there is resistance to all drugs in the regimen, the simulation will substitute a new regimen unless all possible regimens have been exhausted because of intolerance or resistance. In this example, the combination antiretroviral therapy regimen is assumed to be comprised of three drugs.

(Fig. 2). Second, the rate at which an adherent individual accrues mutations depends on the number of drugs in the CART regimen to which HIV is susceptible, because reduced susceptibility permits greater viral replication under conditions of active selection pressure. Third, the rate of accruing mutations in response to active selection pressures is never 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. Fourth, each mutation may give rise to resistance to more than one drug in a particular CART regimen (cross-resistance), and the likelihood of cross-resistance is assumed to be heterogeneous across drug classes (Table 1).

The architecture of this simulation captures the interdependence of adherence and mutation accumulation that has been observed clinically (higher mutation accumulation at partial levels of adherence, and lower mutation accumulation at very high or very low levels of adherence) [19,31]. The model also considers antiretroviral regimen history because mutations are assumed to be archived. Therefore, once a regimen has incurred resistance, it loses its effectiveness permanently. Similarly, if a patient is intolerant to a regimen, this intolerance is assumed to be permanent.

Because of this design, the development of this model depends on both measured and unmeasured parameters. For example, although viral load, CD4 count and resistance patterns are measured, actual viral replication rates and mutation rates are not.

Measured Parameters

Mortality. Mortality risk for HIV-dependent causes was assumed to potentially vary with age, sex, race, risk behavior (injection drug use versus non-injection drug use), CD4, and viral load, whereas mortality risk for non-HIV dependent causes was assumed to potentially vary with age, sex, race, and risk behavior. We

Table 1 Parameters in simulation

Parameter	Value	Reference
Log decrement in viral load with combination therapy*		
Baseline log viral load <3.5	1.07	[21]
Baseline log viral load 3.5–4.5	1.96	[21]
Baseline log viral load 4.5–5.5	2.86	[21]
Baseline log viral load >5.5	3.75	[21]
CD4 change with combination therapy, valley to peak		
Round 1	164–208†	[21]
Round 2	95–139†	[21]
Round ≥3	0–119†	[21]
CD4 change with combination therapy, valley to valley		
Round 1	61	[21]
Round 2	−27	[21]
Round ≥3	−13 to −73‡	[21]
CD4 change without combination therapy (annual)		
Baseline log viral load <3.5	−22	[43]
Baseline log viral load 3.5–4.5	−55	[43]
Baseline log viral load 4.5–5.5	−89	[43]
Baseline log viral load >5.5	−122	[43]
Probability of cross-resistance§		
NRTI	0.28	[51]
PI	0.43	[51]
NNRTI	0.9	[51]
Probability mutation confers drug resistance	0.5	[11–19,28–30,33–42]
Mutation rate increase with new drug resistance (multiple)	3.16	[11–19,28–30,33–42]

*Assumes complete adherence and no resistance.
†Depending on viral load and therapy round. Range is lowered by poor adherence.
‡Depending on therapy round.
§Probability that mutation conferring resistance to one drug also confers resistance to another drug in same category.

investigated whether these relationships were clinically and statistically significant by analyzing deaths in a large multicenter observational study of HIV patients in the United States, in which cause of death (HIV-dependent versus non-HIV dependent) was a prespecified and prospectively collected outcome measure. These analyses employed Cox Proportional Hazard models with time dependent covariates, and are described in further detail elsewhere [21].

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 before starting CART 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 CART is started and that the extent of the decrease varies with the number of drugs in the CART round to which there is susceptibility and with the degree to which the patient adheres to the CART round (Table 1). 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. In accord with clinical data, the viral load will generally decrease by a larger amount if it is higher to begin with, and this relationship is instantiated in the model [29].

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. Published data before widespread adoption of CART suggest that the CD4 count declines at a rate inversely proportional to the viral load [43]. Nevertheless, published data describing this trajectory in the CART era are scarce and limited by short follow-up times, and do not suggest that a similar relationship holds. Each new therapy round typically produces an ascent in the CD4 trajectory, which is followed by a descent as the therapy becomes less effective. On initiation of a new and more effective therapy round, the CD4 count again increases until that round becomes ineffective. For this reason, each completed therapy round is typically associated with a valley (when it is started) and a peak (before its effectiveness starts to wane). To approximate these dynamics, we modeled CD4 count trajectories as consisting of two separate components: 1) a temporary valley-to-peak change, which lasts only as long as a particular CART round is actively suppressing viral replication, and 2) a permanent valley-to-valley change, which persists independently of the activity of any particular CART round (Table 1).

Unmeasured Parameters

Resistance mutations. We varied the probability that a new mutation would occur during a time cycle under circumstances that were most unlikely for inducing mutations (perfect adherence, and no baseline resistance). The simulation is specified so that this single parameter is then used as the basis for calculating the probability of developing new mutations in a wide variety of less favorable but more prevalent circumstances.

Adherence. We defined adherence as the probability that a patient will take doses of a particular drug as directed at any particular time, irrespective of the reason for which doses may be missed ("pill fatigue," side effects, life-threatening toxicity, etc.). Our model allows individual variation in adherence from time cycle to time cycle by adding a random variation component to a baseline adherence parameter that reflects an individual's overall propensity toward adherence. The random variation component is redrawn every time a new CART round is selected. Adherence is considered "unmeasured" because although pharmacy refill databases allow estimation of adherence over time horizons of one or more months, adherence is

generally not observed over the smaller time scales that may be represented in simulations [44–47].

Estimation of Unmeasured Parameters

To test whether the model was calibrated adequately, we previously compared Kaplan Meier curves of predicted clinical outcomes (time to treatment failure and survival) based on simulation estimates with observed clinical outcomes in a large patient cohort. We performed separate analyses for separate rounds of antiretroviral therapy (first, second, and third), where a new therapy round was defined as any change in two or more antiretroviral drugs. The only variables in the model that we adjusted during calibration were the unobserved parameters that we wished to estimate (the mutation rate in the absence of genotypic resistance, and the proportion of missed medication doses). During our initial calibration (April through October, 2003), parameters were adjusted based on visual inspection of the Kaplan Meier curves; subsequently, an optimization procedure based on minimizing the sum of absolute differences was used to verify the accuracy of these values. The results of this calibration are reported in detail elsewhere [21].

Comparing Estimated Values to Subsequent Published Reports

We compared the assigned values for the unobserved variables with the range of observed values in published reports as an additional test of the model's validity, as well as to address the larger question of whether clinical models can be used to estimate the plausible range of biological parameters that are infrequently observed or measured. Assigned values were compared with the pooled 95% Confidence from published reports using the random effects method of der Simonian and Laird [48–50].

To identify articles reporting mutation rates, we searched MEDLINE from 1996 onwards (encompassing the entire era of CART). Articles were identified if they 1) were indexed by one of the following: text-words mutation, genotype, resistance or subject headings mutation; genotype; drug resistance, multiple; drug resistance, viral; drug resistance, microbial; drug resistance, multiple, viral; drug resistance; 2) were also indexed by one of the following: text words AIDS, HAART, CART, or subject headings HIV; Acquired Immunodeficiency Syndrome; Antiretroviral therapy, highly active; 3) permitted estimation of a mutation rate either from measurements of mutation prevalence at two separate times (non-naive patients) or a single measurement of mutation prevalence after starting therapy (naive patients); and 4) did not involve "salvage" therapy (a second round of combination therapy, after the failure of a first round). Articles were also identified if they were otherwise known to the authors or to experts in the field, and met conditions (3) and (4). We assumed that individuals with undetectable viral loads had no new mutations [19] and that individuals with new genotypic resistance each had one new mutation, if this number was not otherwise reported. Because our calibration focused on individuals who were initially antiretroviral naive, we separately analyzed the subgroup of studies that exclusively enrolled antiretroviral naive populations.

To identify articles reporting the proportion of medication doses that were taken as directed, we again searched MEDLINE starting with 1996. Articles were identified if they 1) were indexed by text words adherence, compliance or subject heading compliance; 2) were indexed by text words HAART, CART, or subject heading antiretroviral therapy, highly active; 3) were indexed by text word AIDS or subject headings HIV or Acquired Immunodeficiency Syndrome; and 4) permitted the estimation of the proportion of antiretroviral medication doses taken as directed (such as through pharmacy refill records, unanticipated pill counts, or directly observed therapy). We did not include estimates based exclusively on self-report because of the inherent imprecision.

Results

Our simulation produced clinically plausible outcomes for individual patients. Figure 3 shows the trajectories of CD4 count and viral load of a typical simulated patient, with superimposed displays of important events that influence the effectiveness of therapy. Changes in regimens occur because of either accumulation of phenotypic resistance or because of difficulty adhering to prescribed antiretroviral medications. After all regimens are exhausted, the CD4 count declines steadily after which this hypothetical individual dies of a HIV-related cause. Simulated individuals also may die of non-HIV related causes, and this is more likely for individuals who do not fail therapy and/or have higher CD4 counts.

While calibrating the simulation, we estimated values for two parameters: the rate of accumulating resistance mutations, and the likelihood of adherence with antiretroviral therapies.

Resistance Mutations

We first compare our imputed estimate to results for the studies that were available at the time of calibration, which usually did not focus exclusively on an antiretroviral naive population, and were often relatively small. Then, we compare our estimate to results for the studies that were available after the time of estimation, which did focus on an antiretroviral naive population, and were commonly larger.

We estimated that individuals starting their first CART round would accrue new mutations in the reverse transcriptase and protease genes at a combined

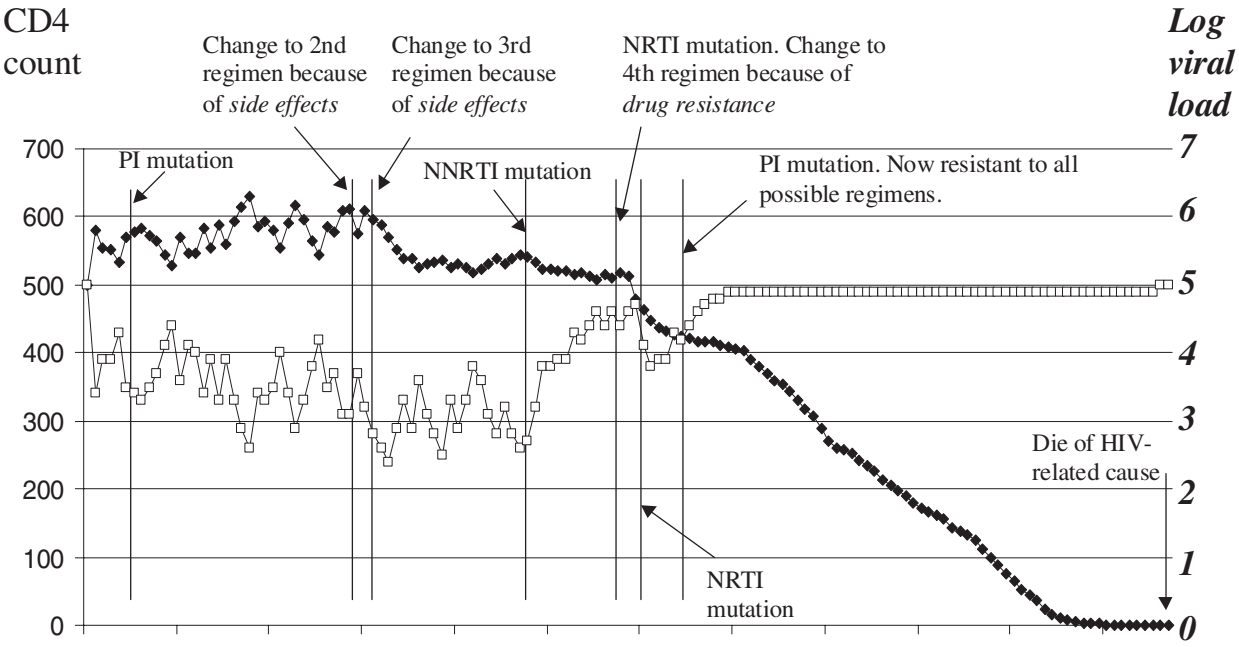

Figure 3 Example of CD4 (filled diamond) and viral load (clear box) trajectories of one simulated patient. This patient started the simulation with a CD4 count of 500 and a viral load at a "set-point" of 100,000. After starting combination antiretroviral therapy (CART), the CD4 count rose and the viral load declined. As time passed, the patient developed genotypic and phenotypic resistance to all possible CART rounds, mitigating the favorable effects of CART on CD4 count and viral load. Finally, the patient developed resistance to all possible rounds. Changes in regimens occur because of either accumulation of phenotypic resistance or because of difficulty adhering to prescribed antiretroviral medications. Not every mutation will lead to an adverse change in CD4 or viral load immediately, but after several mutations phenotypic resistance is likely to accumulate and consequently there will be a need to change regimens. Later rounds are less effective at suppressing viral load and elevating CD4 count compared with earlier rounds, mirroring widely observed patterns. After all regimens are exhausted, the CD4 count declines steadily after which this hypothetical individual dies of a HIV-related cause. Simulated individuals also may die of non-HIV related causes, and this is more likely for individuals who do not fail therapy and/or have higher CD4 counts.

rate of 0.014 per month during the first year based on our calibration of the model. Nine studies were published before this calibration (Table 2). Only three involved antiretroviral naive populations exclusively, and the majority involved fewer than 100 individuals. The pooled results from these studies yielded a 95% confidence interval (CI) extending from 0.014 mutations per month to 0.039 mutations per month, which was too wide to permit an inference with a satisfactory degree of certainty. Pooled results from the studies that enrolled samples more similar to the target population (exclusively antiretroviral naive patients) yielded an even wider 95% CI from 0.001 mutations per month to 0.029 mutations per month, extending well over one order of magnitude.

An additional 11 studies were published after our simulation was calibrated (Table 2). All of them focused on antiretroviral-naive patients exclusively, and all but two enrolled at least 100 patients. When these studies were incorporated into our quantitative summary, the 95% CI for the mutation rate became dramatically narrower, decreasing to between 0.017 and 0.021 mutations per month. When we restricted pooling to those studies that exclusively involved antiretroviral naïve patients (more closely resembling our target population), the 95% confidence remained narrow, varying from 0.013 mutations per month to 0.017 mutations per month. This range closely bracketed our imputed estimate obtained during calibration (0.014 mutations per month) Furthermore, our imputed value was identical to the result from the largest study that enrolled similar patients.

Adherence

During our calibration of the simulation, we estimated that individuals would have a baseline probability of adhering to 75% of antiretroviral medication doses as prescribed. Seven studies were published before our calibration with results ranging from 45% to 91% (Table 3). Their pooled 95% CI (65–77%) was reasonably narrow and contained our imputed estimate.

An additional four studies were published after our calibration (Table 3). When these results were incorporated into the pooled estimate, the 95% CI did not change appreciably (62–76%), and continued to contain our imputed estimate.

Discussion

Our HIV simulation was constructed during the current treatment era of highly active antiretroviral

Table 2 Estimates for mutation rate published before versus after imputation of the corresponding model parameter

Author	Year	N	Median follow-up (months)	Antiretroviral naive exclusively?	Mutation incidence (per month)
Studies published before model calibration					
Race et al. [11]	1998	25	11	No	0.018
Michelet et al. [12]	1999	16	11	No	0.017
Gulick et al. [13]	2000	33	36	No	0.014
Maguire et al. [52]	2000	105	9	Yes	0.020
Pellegrin et al. [53]	2002	48	16	No	0.022
Walmsley et al. [54]	2002	653	11	Yes	0.003
Von Vaerenbergh et al. [55]	2002	25	36	Yes	0.022
Bangsberg et al. [19]	2003	148	6	No	0.073
Squires et al. [14]	2003	552	6	No	0.049
Cumulative 95% confidence interval, all studies pooled					0.014–0.039
Cumulative 95% confidence interval, antiretroviral naive studies pooled					0.001–0.029
Studies published after model calibration					
Weidle et al. [56]	2003	399	6	Yes	0.025
Vergne et al. [57]	2003	66	18	Yes	0.012
Martinez-Picado et al. [58]	2003	99	11	Yes	0.018
Ferrer et al. [59]	2003	100	11	Yes	0.011
Demeter et al. [60]	2004	517	6	Yes	0.015
Gallant et al. [61]	2004	600	33	Yes	0.005
Kemp et al. [28]	2004	653	15	Yes	0.018
Bocket et al. [29]	2004	165	10	Yes	0.012
MacManus et al. [30]	2004	649	11	Yes	0.010
Harrigan et al. [31]	2005	1191	12	Yes	0.014
Laurent et al. [62]	2005	176	30	Yes	0.0035
Cumulative 95% confidence interval, all studies pooled					0.017–0.021
Cumulative 95% confidence interval, antiretroviral naive studies pooled					0.012–0.015

The target population consists of individuals who were antiretroviral naïve before the initiation of therapy.

treatments, and therefore it was designed "from the ground up" to consider the most important processes that limit the effectiveness and duration of this treatment: genotypic resistance and nonadherence to therapy. One difficulty we encountered while developing our simulation is that genotypic mutations are not measured at regular intervals as part of routine clinical care. For this reason, these parameters are often unobserved, and it was difficult to derive estimates for their values from clinical data sources. Soon after we estimated values for these parameters during model calibration, several large studies were published which prospectively measured the rate of accumulating resistance mutations. The validity of the model is enhanced by the observation that that our estimated values were well within the confidence limits of pooled analyses of these studies. Indeed, the results from the largest and most comparable populations (antiretroviral naive individuals) were only available after we calibrated the simulation, yet offered the strongest evidence that its estimates were accurate.

Investigators who have used models to answer pharmacoeconomic and other questions in health care

Table 3 Estimates for medication adherence published before versus after imputation of the corresponding model parameter. Nonadherence is defined as the proportion of doses taken as prescribed

Author	Year	N	Median follow-up (months)	Proportion of doses taken as directed (%)
Studies published before model calibration				
Haubrich et al. [44]	1999	173	1	91
Paterson et al. [45]	2000	99	6	75
Howard et al. [46]	2002	161	1	45–64
Arnsten et al. [47]	2002	85	5	53
Golin et al. [63]	2002	140	11	71
Van Wijngaerden et al. [64]	2002	43	3	86
Bangsberg et al. [19]	2003	148	12	65
Cumulative 95% confidence interval				65–77
Studies published after model calibration				
Halkitis et al. [65]	2003	68	1	82–91
Remien et al. [66]	2005	109	2	39
Rathbun et al. [67]	2005	17	6	51
Harrigan et al. [31]	2005	1130	12	84*
Cumulative 95% confidence interval				62–76

*Approximated based on adherence that was reported in discrete strata.

commonly need to estimate the value of unobserved parameters by calibrating model output to separate, observed outcomes of interest. Goldie et al. have developed a natural history model of cervical cancer to estimate the cost-effectiveness of various screening strategies for human papilloma virus infection, in which they estimated the likelihood of transitioning from premalignant to malignant lesions based on the observed incidence of these lesions [23–25]. Fryback et al. has developed a natural history model of breast cancer, in which they estimated the proportion of breast cancer precursors that are unlikely to transition from premalignant to malignant lesions based on the incidence of malignant lesions [26]. Although the current simulation does not involve cancer, it involves analogous clinical constructs in the natural history of HIV. An unobserved event (mutation rate) gives rise to an observed event (failure of antiretroviral therapy), and inferences about the unobserved event are made based on characterizations of the observed event. Furthermore, the likelihood of antiretroviral failure is also dependent on a partially observed parameter, the compliance. Our results provide support to the assertion that it is feasible to estimate the values of selected simulation parameters as long as there are substantial additional checks on the simulation's calibration and validity.

This natural experiment occurred because of a confluence of circumstances. Assays for genotypic mutations did not have great clinical utility until the advent of the current CART regimens, which have only been in use for less than a decade. Even after the potential utility of these tests were clear, their great expense made frequent and prospectively scheduled testing prohibitively expensive, thereby discouraging their systematic use. For this reason, much of the initial mutation accumulation data was on small groups of patients, and often was retrospective. This led to substantial time lag between when the clinical importance of modeling resistance became apparent, and when large prospective data sources became available.

Our study has several limitations. Some of the published reports used outcome metrics that were not identical to those used in our simulation. The simulation does not yet discriminate between individual drugs within any one antiretroviral category, and does not discriminate between individual mutations that may confer resistance to any one antiretroviral drug category, and therefore more in depth validation of estimated parameter results is not possible. Finally, although we demonstrate that it is possible to use imputation to produce accurate parameter estimates, the generalizability of this finding is unclear, because it would not be expected to apply to models with great structural or parameter uncertainty.

In conclusion, we have created a computer simulation of HIV disease in the era of CART that represents the unobserved processes that are the main determinants of treatment failure: antiretroviral adherence and the accrual of mutations that confer genotypic resistance. While calibrating the simulation, we estimated values for these variables. These estimates not only were well within the range of clinical observations, but anticipated with accuracy clinical results that were not yet available. It may be feasible to use models to estimate the values of unobserved biological parameters.

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