ABSTRACT

PURPOSE: Effective antiretroviral therapies have improved the prognosis for patients infected with the human immunodeficiency virus (HIV). We aimed to estimate the likelihood that HIV-infected patients would die of comorbid disease.

METHODS: A probabilistic simulation of antiretroviral-naive HIV-infected patients in the United States was calibrated with data from an observational cohort (N=3545) and validated with data from a separate patient cohort (N=12574). The simulation explicitly represents the 2 main determinants of treatment failure and subsequent death from HIV-related causes: nonadherence to combination therapy and accumulation of phenotypic resistance to combination therapy. The likelihood of deaths not directly attributable to HIV was estimated from the Collaborations in HIV Outcomes Research-US (CHORUS) cohort.

RESULTS: For patients with newly diagnosed HIV infections, CD4 counts of 500 cells/mm³, and viral loads of 10,000 copies/mL, the median estimated survival was 26.8 years for 30-year-olds, 24.4 years for 40-year-olds and 14.6 years for 50-year-olds. The proportion of deaths not directly attributable to HIV was 36% for 30-year-olds, 53% for 40-year-olds, and 72% for 50-year-olds. For patients with characteristics similar to CHORUS participants, the median estimated survival approached 20.4 years, the mean age at death approached 60.4 years, and 41% died of illnesses not directly attributable to HIV. These estimates of non-HIV mortality were likely conservative.

CONCLUSION: As HIV-infected patients live longer, our results suggest they will experience increasing mortality from causes not directly attributable to HIV. The projected risk from comorbid disease has clinical and policy implications for future delivery of care to HIV-infected patients.

KEYWORDS: HIV; AIDS; Mortality; Computer simulation; Adherence; Resistance

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Efforts to evaluate the quality of health care for patients who are infected with the human immunodeficiency virus (HIV) have focused almost exclusively on the management of HIV-related medications and conditions. However, it is well established that increasing proportions of morbidity and mortality in HIV-infected patients are not directly attributable to HIV. With effective combination therapy, the phenomenon would have great implications for health policy because the broader aim of preventing, screening, and treating comorbid diseases would become comparably important to the aim of delivering high quality HIV care.

Forecasting the trajectory of this trend is important, but extrapolating from current data sources is unlikely to be accurate because the duration of benefit from antiretroviral therapies remains uncertain. For this reason, we have developed an HIV computer simulation that can predict the duration of effectiveness of treatment and can distinguish deaths attributable to HIV from deaths that are not attributable to HIV. This simulation differs from previously published HIV simulations because it specifically incorporates adherence and phenotypic resistance to antiretroviral therapies, the 2 factors that underlie the majority of treatment failures and subsequent deaths from HIV-related diseases. Additionally, the model’s estimates were calibrated and were validated using data from large clinical cohorts.

Methods

We simulated cohorts of 10,000 antiretroviral-naïve patients who were newly diagnosed with chronic HIV infections. For the vast majority of analyses, each hypothetical cohort consisted of identical patients who were initially equivalent with respect to a particular combination of baseline characteristics (age, CD4 count, and viral load). For the particular analysis in which we estimated causes of non–HIV-related deaths, we simulated a hypothetical cohort with characteristics similar to those of the large clinical cohort that we used to calibrate the model.

The simulation was a probabilistic, second-order Monte Carlo process that was created using Decision Maker for Windows (Version Beta 0.99.11.12a, New Brunswick, NJ). Each patient proceeded through the model separately with a distinct clinical trajectory, mirroring the heterogeneity that is present in actual patients. Patients were at risk for a variety of clinical events (eg, decrease in CD4 count, development of drug resistance, death) based on their particular time-varying characteristics. Because of the controversy concerning the optimal timing for introducing antiretroviral therapies, we made the simplifying assumption that therapy was initiated at the start of the simulation.

Overview of simulation

Variables in the simulation fall into 2 broad categories, the first representing genetic characteristics of the HIV strain, and the second representing clinical characteristics of the patient. Genetic characteristics, which reflect the acquisition of mutations, were assumed to affect clinical characteristics by altering the effectiveness of combination therapies (defined as 3 or more antiretroviral drugs prescribed simultaneously). Clinical characteristics were assumed to affect the probability of dying from HIV-related or non–HIV-related causes. Our simulation separately tracks the number of accumulated genetic mutations that may confer resistance to each of the 3 constituent drug categories in combination therapy: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. The model then uses this information to determine the likelihood of phenotypic resistance to combination therapies.

At the start of the simulation (Figure 1), patients have “wild-type” HIV virus. With each passing day, combination therapies may give rise to HIV mutations by means of selection pressures on viral replication. Each HIV mutation may or may not result in resistance to one or more antiretroviral drugs. As resistance accrues, the viral replication rate increases, which in turn increases the probability that subsequent mutations will develop. Adherence, viral resistance, and other patient characteristics together determine the level of effectiveness of combination therapies, as manifested by changes in CD4 count and viral load. Adherence not only affects the extent to which combination therapies reduce viral replication, but it also directly affects the selection pressures for new mutations. For this reason, patients who have poorly suppressed viral loads while taking antiretroviral drugs are likely to have more mutations accumulate, whereas patients who have undetectable viral loads or who are not taking any antiretroviral drugs are likely to have fewer mutations accumulate, concordant with clinical observations. If resistance accrues to all drugs being taken, the model will substitute another round of combination therapy with a lower likelihood of resistance based on the profile of accumulated mutations. In the present analyses, the method used to determine the composition of this new round is selection of 2 drugs from the category to which there is the lowest likelihood of phenotypic resistance and one drug from the category to which there is the second lowest likelihood of phenotypic resistance. However, the model may accommodate any preferred method for choosing subsequent rounds.

The simulation predicts mortality related to HIV separately from mortality unrelated to HIV, and both are based on clinical and epidemiologic characteristics of prognostic value across heterogeneous cohorts of patients. The methods and data sources that we used to estimate the trajectories of parameters in this simulation are described in more detail at http://www.vacohort.org.
Estimating mortality risks

The risk of mortality from HIV infection at a particular time is predicted more accurately by prognostic markers measured at that specific time than by markers measured earlier. Therefore, we used Cox proportional hazards models with time-dependent covariates to estimate mortality based on 3545 patients and 183 deaths with data eligible for analysis in CHORUS. The great majority of patients received combination therapies with 3 or more antiretroviral drugs (3202/3545 [90.3%]), and cause of death was a prospectively defined outcome. For the current analyses, we considered a death directly attributable to HIV only if study personnel judged either the immediate or the underlying cause of death to be related to the acquired immunodeficiency syndrome (AIDS). We chose this broad definition to err on the side of underestimating non–HIV-related mortality.

Deaths directly attributable to HIV

We estimated the risk for mortality directly attributable to HIV separately for patients on and off of combination therapy because their predictors of mortality appear to be different and because the smaller number of patients off therapy limited the number of variables that we could consider simultaneously. Among patients on therapy, we found clinically and statistically significant relations among age, CD4 count, and viral load (Table 1) but not among sex, race, or injection drug use. Among patients off therapy, we evaluated associations with age and CD4 count, and both were clinically and statistically significant (Table 1).

Deaths not directly attributable to HIV

We estimated the risk of mortality that was not directly attributable to HIV as a function of age, sex, race, and injection drug use. Of these variables, only age had a relation that was both plausible and statistically significant (Table 1). To estimate causes of deaths that were not directly attributable to HIV, we applied age-stratified cause-of-death data from CHORUS to the model’s projections of non–HIV-related mortality. Of the 382 deaths recorded in CHORUS to date, 126 (33%) were unrelated to AIDS. Of these deaths 28 (22%) were from cardiovascular causes, 15 (12%) were from cancer, 28 (22%) were from liver failure, and 55 (44%) were from other causes.

Because our original analyses had low power to detect other associations, because there were few nonwhites, women, and injection drug users in CHORUS, we performed an upper-bound sensitivity analysis applying the age-specific mortality rates of 19 821 HIV-negative controls in the Veterans Administration National Database who were matched to HIV-positive patients in the Veterans Aging Cohort Study by age, sex, race, and location (Table 1). This cohort was more racially diverse, had more injection drug users, and had higher levels of non–HIV-related mortality than had patients in the CHORUS study. Finally, we performed a lower-bound sensitivity analysis using low but plausible estimates for mortality not directly attributable to HIV, based on age-, sex-, and race-specific mortality in the general population (Table 1).
Causes of deaths not directly attributable to HIV
To estimate the breakdown of non–HIV-related mortality by disease category, we assigned the 126 deaths in CHORUS that were unrelated to HIV into 4 broad categories (cardiovascular, cancer, liver failure, and other) and then stratified this breakdown by age (<40 years old, 40 to 50 years old, and >50 years old). Because some deaths could have been classified in more than one way, we used the following decision rules: deaths that were attributable to hepatic tumors were categorized as liver failure rather than cancer. Deaths that were classified as “sudden death” were categorized as cardiovascular. We then applied this approach to all non–HIV-related deaths simulated by the computer model using the appropriate age strata. For these estimations, hypothetical cohorts were started in the computer simulation with the same distributions of baseline characteristics as patients in the CHORUS study.

Estimating viral load and CD4 trajectories
We estimated the suppression of viral load induced by combination antiretroviral therapies by analyzing viral load trajectories of 914 antiretroviral-naïve patients who started combination therapies in CHORUS. We used a generalized linear regression model to examine the relation of multiple variables (age, sex, race, injection drug use, baseline viral load, and CD4 count) to the change in viral load after 12 months of combination therapy. Only baseline viral load was clinically and statistically significant.

We analyzed the CD4 count trajectories of antiretroviral-naïve HIV-positive patients who started combination therapies in CHORUS by using linear regression models to test whether changes in CD4 counts varied with multiple variables (age, sex, race, injection drug use, CD4 count, viral load, sequence of treatment round, and duration of treatment round). A new round was defined as any change in two or more antiretroviral drugs. There were statistically and clinically significant relations with age, viral load, sequence of treatment round, and duration of treatment round. We further improved the model’s fit by disaggregating changes in CD4 count into within-round components that lasted only while the round was prescribed and between-round components that persisted after the round was concluded. The methods and data sources used to estimate the trajectories of viral load and CD4 count are described in more detail at http://www.vacohort.org.

Calibration and validation of simulation
We calibrated the simulation based on data from patients in CHORUS, aiming to replicate Kaplan-Meier curves describing time to cessation of rounds 1, 2, and 3 of antiretroviral therapy, as well as time to death. The only variables in the model that we adjusted during calibration were the mutation rates in the absence of any genotypic resistance to combination therapies and the probability of nonadherence to therapies. We calibrated time to cessation of treatment using data from antiretroviral-naïve patients exclusively. There was inadequate power to base the survival calibration

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Annual probability* of death in computer simulation by age, CD4 count, and viral load</th>
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<tbody>
<tr>
<td>Mortality directly attributable to HIV, on combination therapies (3203 patients, 117 deaths†)</td>
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<tr>
<td>Virus load &lt; 30 000 copies/mL</td>
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<td>CD4 &lt; 50 cells/mm³</td>
<td>0.0422</td>
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<td>CD4 50-199 cells/mm³</td>
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<td>CD4 350-499 cells/mm³</td>
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<td>CD4 ≥ 500 cells/mm³</td>
<td>0.0001</td>
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<tr>
<td>Mortality directly attributable to HIV, off combination therapies (342 patients, 14 deaths†)</td>
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<tr>
<td>CD4 &lt; 200 cells/mm³</td>
<td>0.0928</td>
</tr>
<tr>
<td>CD4 ≥ 200 cells/mm³</td>
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<tr>
<td>Mortality not directly attributable to HIV (3203 patients, 52 deaths†)</td>
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<td>Upper bound§</td>
<td>0.0040</td>
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<tr>
<td>Lower bound</td>
<td>0.0022</td>
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</tbody>
</table>

HIV = human immunodeficiency virus.
* Estimates were based on primary analyses of data from Collaborations in HIV Outcomes-US (CHORUS) except where indicated.
† Some patients who died were not included in these analyses because there was incomplete information on predictor variables. Overall there have been 256 deaths that were directly attributable to HIV and 126 deaths that were not directly attributable to HIV.
‡ There were insufficient numbers of patients in this age group to estimate mortality. Because CHORUS and general population estimates were comparable in the 2 preceding age deciles, general population data was used as an approximation.
§ From Veterans Administration data (19 821 patients, 917 deaths).
∥ From US Census Bureau estimates.
solely on data from antiretroviral-naïve patients because the number of observations declined rapidly beyond 4 years of follow-up, so we based this calibration on the survival of all participants (regardless of antiretroviral exposure), a survival that was nearly indistinguishable from the survival of antiretroviral-naïve participants during the first 4 years of follow-up.

To check the validity of the mortality estimates in the model, we compared them with the mortality rates reported in the largest published analysis of mortality in HIV in the era of current therapies (ie, the Antiretroviral Treatment Cohort Collaboration [ARTCC]), consisting of 13 separate patient cohorts and a total of 12,574 patients. This sample differed substantially from the sample that we used for model calibration, because fewer than 5% (n = 553) of these patients originated from the CHORUS cohort. Individual mortality estimates from the computer simulation for each of 20 possible combinations of baseline age, CD4 count, and viral load strata were compared with corresponding stratified estimates from the ARTCC for 3-year survival (the longest follow-up time reported by the collaboration). Stratified ARTCC results were only reported with an additional stratification based on Centers for Disease Control and Prevention clinical stage. Our simulation does not stratify on this basis, so we made the simplifying assumption that all simulation strata with CD4 counts less than 50 cells/mm³ were compared with corresponding ARTCC strata with a clinical stage suggestive of AIDS, otherwise they were compared with corresponding ARTCC strata with clinical stages not suggestive of AIDS. After verifying that the simulation was adequately calibrated and validated, we simulated the survival of hypothetical cohorts of antiretroviral-naïve patients with HIV. Cohorts with different combinations of age, CD4 count, and viral load strata were analyzed separately.

Figure 2  Calibration of computer simulation. Dashed lines represent computer simulation estimates, and solid lines represent clinical data from the Collaborations in HIV Outcomes Research–US (CHORUS) cohort. Graphs depict the proportion of patients starting a round of combination therapy who still remain on round one (A), two (B), and three (C), and the proportion of patients who remain alive (D). HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome.
Results

Calibration and validation of simulation

The computer simulation closely replicated Kaplan-Meier curves depicting the duration of combination therapy for antiretroviral-naïve patients in a large cohort of HIV-infected patients, demonstrating that the simulation was well calibrated (Figure 2, A-C). It was also able to approximate the survival curve for this cohort (Figure 2, D).

When 3-year mortality estimates for each of 20 possible combinations of baseline age, CD4 count, and viral load strata were compared with corresponding data from 12,574 antiretroviral-naïve patients from a distinct patient sample, the majority of simulation estimates were within the 95% confidence limits of the observed outcomes, suggesting that the simulation has external validity (Figure 3).

Simulation estimates

Life expectancy

Estimated median survival decreased with age and varied substantially with baseline viral load and CD4 count within each age stratum (Table 2). Generally, estimated median survival increased with higher CD4 counts and decreased with higher viral loads. For 30-year-old patients with CD4 counts of 800 cells/mm³ and viral loads of 10,000 copies/mL, median life expectancy was 31.3 years. In contrast, for patients of the same age with CD4 counts of 200 cells/mm³ and viral loads of 100,000 copies/mL, estimated median life expectancy was only 12.2 years.

Proportion of deaths unrelated to HIV

The projected proportion of deaths that were not directly attributable to HIV increased with age and varied substantially with baseline viral load and CD4 count within each age stratum. Generally, patients with less advanced stages of HIV disease (higher CD4 counts or lower viral loads) were predicted to have greater proportions of deaths from non–HIV-related causes. For 30-year-olds with favorable prognostic indicators (CD4 counts of 800 cells/mm³ and viral loads of 10,000 copies/mL), an estimated 45% of patients would die of causes that were not directly attributable to HIV. In contrast, for patients of the same age with unfavorable prognostic indicators (CD4 counts of 200 cells/mm³ and viral loads of 100,000 copies/mL), only an estimated 6% of patients would die of causes that were not attributable to HIV. For 50-year-olds, the corresponding estimates were 82% for favorable prognostic indicators and 20% for unfavorable prognostic indicators. If the viral load was 10,000 copies/mL, a majority of deaths among 50-year-olds would be due to causes that are not attributable to HIV, regardless of CD4 count.

Causes of deaths unrelated to HIV

Using baseline estimates obtained from CHORUS, the projected median age at death was 60.4 years, and an estimated 41% of patients eventually die of non–HIV-related causes.
Of these patients, 35% were estimated to die of cardiovascular causes, 26% of cancer, 12% of liver failure, and 28% of other causes.

### Sensitivity analyses

Age-, sex-, and race-adjusted mortality rates in the general population were sometimes lower than the mortality rates observed in CHORUS that were used for our baseline analyses (Table 1). However, applying these general population mortality data in our simulation as a lower-bound estimate for mortality that was not attributable to HIV yielded no substantive differences in results regardless of the age, CD4, and viral load stratum examined. No median survival estimate differed by more than 1.2 years, and no estimate for non-HIV-related deaths differed by more than 2%.

In contrast, using higher-bound estimates for mortality not attributable to HIV obtained from the Veterans Administration National Database resulted in decreased median survival estimates and increased proportions of estimated deaths due to non–HIV-related causes, particularly for patients with less advanced stages of HIV disease (higher CD4 counts or lower viral loads). For 30-year-old patients with CD4 counts of 800 copies/mm$^3$ and viral loads of 10 000 copies/mL, the estimated proportion of deaths not directly attributable to HIV increased from 46% to 59%. For 50-year-old patients, the estimated proportion of deaths not directly attributable to HIV increased from 82% to 87%.

### Discussion

HIV is increasingly a disease that people die with rather than a disease that people die from. The results of our simulation suggest that a substantial proportion of deaths among HIV-infected patients in the current treatment era will not be directly attributable to HIV. Indeed, for many of the groups examined, the simulation estimates that a majority of deaths will be from nonattributable causes. If the age, CD4 count, and viral load distributions of antiretroviral-naïve patients entering the CHORUS study are assumed to be representative of newly diagnosed HIV-infected patients in the United States, our model predicts that HIV-infected patients will have a median survival of 20.4 years, die at a median age of 60.4 years, and have 41% of deaths not directly attributable to HIV. These projections are likely underestimates because we calibrated the simulation using a strict definition for non–HIV-related deaths.

Because our data and model clearly indicate that comorbid disease will become an important determinant
of survival, many policy questions are raised, including how comorbid disease should be managed among HIV-infected patients and who should perform this management. Because patients with HIV are living longer, the need to prevent, screen, and manage comorbid diseases is becoming increasingly important. Remaining life expectancy is a critical determinant of the overall benefit and the cost-effectiveness of prevention and screening, and HIV continues to lower the life expectancies substantially in most infected patients. Furthermore, if HIV or HIV therapies alter the risks for specific comorbid diseases substantially, guidelines will need to be tailored specifically.

We strongly argue that the most important question is not who should prevent, screen, and manage comorbid diseases but whether high-quality management is provided. First, we propose that guidelines for the prevention, screening, and management of common comorbid conditions should be tailored as necessary for patients with HIV. Second, once these guidelines are in place, the primary providers of HIV care should be responsible for ensuring that these guidelines are met, if necessary by involving an appropriate colleague through referral or comanagement. Third, measuring adherence with these guidelines could provide an objective way of evaluating the quality of the care that is delivered by particular providers or groups of providers.

This study has several important limitations. Projections regarding cause of death were based upon a relatively small number of non–HIV-related deaths (n = 126), and few of these deaths occurred among patients over 50 years old, a group in which the simulation predicted that most future deaths will occur. These projections were based on data from a cohort with low prevalences of injection drug use and hepatic disease, and therefore projections based on other cohorts of HIV-infected patients would likely yield far higher estimates for the proportion of deaths due to liver failure. For these reasons, our cause-of-death projections must be interpreted with extreme caution while awaiting confirmation by other data sources.

Newer combination therapy regimens, such as those containing “boosted” protease inhibitors, may induce different resistance patterns or have greater efficacy than the regimens on which the calibration and validation of the simulation was based. However, underestimating the efficacy of HIV regimens would only serve to strengthen the main conclusion of this analysis, namely, that large proportions of patients with HIV will die of causes that are not directly attributable to HIV.

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References


