Practice of Epidemiology

Missing Data on the Estimation of the Prevalence of Accumulated Human Immunodeficiency Virus Drug Resistance in Patients Treated With Antiretroviral Drugs in North America


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Determination of the prevalence of accumulated antiretroviral drug resistance among persons infected with human immunodeficiency virus (HIV) is complicated by the lack of routine measurement in clinical care. By using data from 8 clinic-based cohorts from the North American AIDS Cohort Collaboration on Research and Design, drug-resistance mutations from those with genotype tests were determined and scored using the Genotypic Resistance Interpretation Algorithm developed at Stanford University. For each year from 2000 through 2005, the prevalence was calculated using data from the tested subset, assumptions that incorporated clinical knowledge, and multiple imputation methods to yield a complete data set. A total of 9,289 patients contributed data to the analysis; 3,959 had at least 1 viral load above 1,000 copies/mL, of whom 2,962 (75%) had undergone at least 1 genotype test. Using these methods, the authors estimated that the prevalence of accumulated resistance to 2 or more antiretroviral drug classes had increased from 14% in 2000 to 17% in 2005 ($P < 0.001$). In contrast, the prevalence of resistance in the tested subset declined from 57% to 36% for 2 or more classes. The authors’ use of clinical knowledge and multiple imputation methods revealed trends in HIV drug resistance among patients in care that were markedly different from those observed using only data from patients who had undergone genotype tests.

antiretroviral therapy, highly active; drug resistance; genotype; HIV

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; HIV, human immunodeficiency virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside-analogue reverse transcriptase inhibitor; PI, protease inhibitor.

Missingness of data is a ubiquitous problem in epidemiologic studies and results from 2 primary causes. The first contributor is lack of response, which can result from refusal (nonresponse) or loss to follow-up (nonparticipation). Incomplete data may also occur structurally, such as when data collection is determined by clinical-care decisions. Those selected for a medical procedure, intervention, or test will contribute data, whereas those not selected or indicated for treatment will not. By definition, the selected sample will differ clinically from those who do not receive the treatment. Human immunodeficiency virus (HIV) drug resistance is one area of research in which the amount of missing data is heavily influenced by selection. Combination antiretroviral therapy (ART) has been highly successful over the past decade in reducing the morbidity and mortality associated with HIV-1 infection (1) and restoring immunologic function (2).
However, poor adherence (and subsequent virologic failure), as well as extensive treatment exposures (particularly to suboptimal treatment regimens), can result in acquired resistance to both specific HIV drugs and entire drug classes (3–5), limiting treatment options. Population trends in resistance could thus be a primary motivator for the development of new therapeutic agents and could be informative for estimating the burden of uncontrolled disease and cost of care. Furthermore, individuals with a resistant virus that is uncontrolled by their current regimens will contribute to part of a community viral load, one of the key metrics identified in the 2010 National HIV/AIDS Strategy (6).

Most data available on drug resistance status arise from genotype testing, that is, genotyping of sampled HIV strains to detect mutations that confer drug resistance. These tests have several characteristics that complicate analysis of even simple prevalence descriptions. First, standard laboratory tests measure only genotypic resistance among subjects with a high viral load. As a consequence, individuals who undergo genotype testing likely differ clinically from those who do not. Second, Department of Health and Human Services guidelines recommend that these resistance tests be used to guide the choice of ART for those who may be failing to respond to other therapies. Third, characterization of HIV drug resistance is complicated by the impact of changing drug regimens on circulating viral strains. Therapies will suppress but not eradicate an established viral strain. Such archived resistance cannot be detected by genotype testing with commercial assays but contributes to the overall burden of drug resistance because it influences treatment options and effectiveness (7).

To estimate the prevalence of latent and circulating resistance among treated populations in clinical care, approaches should be used that address the noted selection and missing data issues. Unfortunately, the majority of studies that have assessed the burden of resistance made inferences using only data from individuals who had undergone genotype tests in the course of clinical care. It is well known that the complete case analysis approach can lead to bias and diminished precision (8–10).

In the present article, we describe methods to yield resistance-prevalence inferences for individuals who are in clinical care and engaged in treatment. Our approach centers around the idea of completing missing resistance status data by incorporating clinical knowledge of the influences of many factors (e.g., patient drug history, viral load trajectory, and past genotype testing information) on an individual’s resistance probability. Multiple-imputation methods (11) alone could be utilized to obtain an asymptotically unbiased estimate of the prevalence of resistance if missingness could be assumed random, conditional on factors measured and available to the investigator (11). However, it is unlikely that missingness of data will be conditionally independent of a strain’s being resistant, given what is known of HIV biology. For example, adherence measurements are not commonly available; however, a patient with an extensive history of poor adherence might be both less likely to have been tested (because modifying the existing regimen might not be beneficial until adherence is improved) and more likely to harbor resistance (unless adherence declines below the threshold at which there is no selective pressure on the virus to induce a resistant strain to emerge). Given that current clinical guidelines specify the consideration of factors such as drug and viral load history, as well as resistance testing in the optimization of therapy (12) (as this information best informs clinical judgment as to the potential for archived resistance and thus a therapy’s effectiveness), incorporating such clinical understanding into a data-completion algorithm could offer an alternative method for obtaining estimates of the burden of resistance.

MATERIALS AND METHODS

Study sample

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a consortium of clinical and interval HIV cohorts from Canada and the United States (13). It is 1 of 7 regional collaborations of the International Epidemiologic Databases to Evaluate AIDS that are supported by the National Institutes of Health. Genotype testing data were collected from 8 clinic-based cohorts within the NA-ACCORD during the period of interest (2000–2005), and those centers agreed to participate in the present analysis. We identified those individuals who had initiated ART before 2006 and had at least 1 clinic visit between 2000 and 2006. Participants contributed only to estimates in years in which they were actively followed (seen in the clinic at least once), as inferences were targeted at the population engaged in clinical care. Cohorts contributed data on specific genotypic resistance mutations identified by using tests conducted as part of clinical care. We included viral load information from participants with genotype data if an HIV-1 RNA measurement was available in the 6 months before the genotype test.

Study definitions and design

There are currently 5 distinct classes of antiretroviral drugs available to HIV-infected individuals in developed countries. These drugs include nucleoside-analogue reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), fusion inhibitors, and integrase inhibitors. Effective antiretroviral therapies rely on a combination of drugs, preferably from a mix of different classes. Here, we focus on the 3 major classes of drugs (PIs, NNRTIs, and NRTIs) that have been available since the late 1990s. We defined ART as a regimen including 2 or more NRTIs with at least 1 PI or NNRTI. Triple NRTI regimens with abacavir or tenofovir were also included.

Genotype mutations were analyzed using the Genotypic Resistance Interpretation Algorithm, version 4.3.6 (HIVdb Program, Stanford University, Stanford, California), which assigns inferred levels of resistance to commonly used PIs and RTIs on the basis of user-submitted protease and RT gene sequences (14). Genotypic resistance to any single drug was considered present if the algorithm assigned a score of 30 (“intermediate resistance”) or higher for the occurrence of a given mutation pattern. We defined “class” resistance as intermediate or higher resistance to any single drug in any given...
therapeutic drug class available at the time of the genotype test. Because HIV-1 RNA undergoes reverse transcription into DNA and is inserted into the host cell’s DNA, various HIV mutations are considered to be archived into the latent reservoir (7). Therefore, resistance mutations were considered to accumulate over time and were carried forward, with new resistance tests maintaining or increasing resistance scores from previous years. If results from more than 1 test were available for an individual in a given year, the scores from the last test in that year (representing the cumulative scores from all past tests) were used. Participants were considered to have viremia in a given year if they had at least 1 HIV-1 RNA measurement higher than 1,000 copies/mL after 3 continuous months on an initial antiretroviral regimen. Because genotype testing requires a high viral load for reliable results, we also considered genotype testing of a marker of viremia in the year of the test. Covariate data for those tested were taken from the visit closest to the date of the test within the previous 6 months. For participants for whom we did not have testing data, covariate information was used from the last visit with viremia (in those with viremia in a given year) or the last visit in the year (in those without viremia in a given year). These time points were selected to provide the participant with the maximum opportunity to receive genotype testing (in the former case) or become viremic (in the latter case).

Statistical analysis

Estimates of the prevalences of accumulated 2- and 3-class resistance were obtained by creating a complete data set of individual resistance probabilities for each calendar year between 2000, when genotypic resistance testing became widely available in the clinic setting, and 2005. Current scientific understanding regarding the persistence of resistant viral strains and the clinical context for the development of resistance were applied to complete the missing data as follows. The accumulated 2- and 3-class-resistance data from the subset of the cohort for whom we had genotyping testing information were extended forward in time with the assumption that resistance was present indefinitely (because of the archival nature of the HIV virus). Thus, in years in which the participant was seen (contributed viral load data) but did not undergo a genotype resistance test, any past level of accumulated resistance was considered still to be present. Participants with no previous testing information who were virally suppressed (i.e., had HIV-1 RNA levels ≤1,000 copies/mL) in a given year were assumed to have no resistance in that year. Similarly, participants with viremia who later demonstrated suppression on an NNRTI or PI regimen were assumed to have accumulated no resistance to those drug classes. For the remaining participant-years with viremia but unknown resistance status, we used the multiple-imputation method (11) to estimate the probability of resistance. Five imputation data sets were created using a single-chain Markov chain Monte Carlo method with the following covariates as main terms: most recent HIV-1 RNA level and CD4+ cell count, history of injected drug use, age, prior NRTI use before ART initiation, cumulative exposure to each drug class, cumulative number of past regimen failures, cohort, year of genotype test, race, and sex. The model was fitted only in viremic participants because covariate associations were found to vary by viremia status. An expectation-maximization algorithm was used to find the posterior mode as the starting value for the chain. The final multiclass resistance prevalence estimates were determined as the average of the estimates resulting from the 5 imputation data sets. The process used to complete the data is illustrated schematically in Figure 1.

The probability of having accumulated resistance (the prevalence of accumulated resistance in the cohort) was estimated for each year in all included participants who were seen in that year. The trend in the yearly estimates was assessed by regressing the individual resistance values on the year and evaluating the significance and direction of the slope. Confidence intervals were obtained by adding the within-imputation and between-imputation variability. All analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Cohort virologic response

The analysis included 9,289 patients who participated in 1 of 8 clinic-based cohorts and who initiated ART before the end of 2005 and underwent HIV-1 RNA testing in 2000–2005. Of these patients, 3,959 (43%) had at least 1 HIV-1 RNA level greater than 1,000 copies/mL after at least 3 months of an initial therapy, and 2,962 (75% of those with viremia) had at least 1 genotype resistance test performed.

In 2000, a total of 5,004 patients treated with antiviral drugs had at least 1 strain of HIV-1 RNA measured; of these, 1,480 (30%) had at least 1 HIV-1 RNA level above 1,000 copies/mL after at least 3 months of therapy and 817 (16% of the total participants and 55% of those with viremia) underwent genotype resistance testing (Table 1). In 2005, a total of 4,653 participants who had been treated with antiretroviral drugs had at least 1 HIV-1 RNA level measured; of these, 778 (17%) had at least 1 HIV-1 RNA level above 1,000 copies/mL after at least 3 months of therapy and 486 (10% of the total participants and 62% of those with viremia) underwent genotype testing (Table 1). The proportion of treated patients who had an HIV-1 RNA level above 1,000 copies/mL declined over time ($P < 0.001$), as has been previously noted (15–18). The percentage of individuals who had genotype resistance testing out of the total number of patients on ART declined from 2000 to 2005 ($P < 0.001$), whereas the percentage of those tested out of the total number with viremia increased ($P < 0.001$).

Missing resistance status

Comparing those participants who did and did not have genotype testing among the participants at risk for testing (HIV-1 RNA levels >1,000 copies/mL; Table 2), we found that those receiving genotype testing had lower median HIV-1 RNA levels at the time of the test than did those who were viremic but not tested in both 2000 and 2005. Those tested in 2000 were less likely to have received NRTIs before their first combination therapy regimen (57% vs. 69%) than were those who were viremic but not tested in that same year.
In both 2000 and 2005, those not tested were more likely to report lapses in their ART regimen during the year. Median CD4<sup>+</sup> cell counts and ages were approximately the same across testing groups. Race (white vs. nonwhite), sex, and injection drug use (yes vs. no) distributions were also similar between those tested and those not tested in a given year.

Of 29,905 participant-years, we were missing genotype data for 25,774. However, only 11% were person-years with unsuppressed viral loads. Of this, 9%, 7%, 6%, 5%, 4%, and 4% had protease inhibitor-based regimens, 38% had nonnucleoside reverse transcriptase inhibitor-based regimens, 28% had viral loads >1,000 copies/mL during the year, 30% had genotype testing, 16% had viremia, and 55% had resistance testing.

Table 1. Frequency of Detectable Viremia and Genotype Testing Among Patients Treated With Antiretroviral Drugs, North American AIDS Cohort Collaboration on Research and Design, 2000–2005

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of Patients on Antiretroviral Therapy</th>
<th>No. of Patients Who Had &gt;1,000 copies/mL During the Year&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of Patients Who Had a Genotypic Resistance Test During the Year</th>
<th>% of Total&lt;sup&gt;a&lt;/sup&gt;, % of No. With Viremia&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>%</td>
<td>No. of Cases</td>
<td>%</td>
</tr>
<tr>
<td>2000</td>
<td>5,004</td>
<td>1,920</td>
<td>38</td>
<td>1,387</td>
</tr>
<tr>
<td>2001</td>
<td>5,093</td>
<td>1,850</td>
<td>36</td>
<td>1,552</td>
</tr>
<tr>
<td>2002</td>
<td>5,063</td>
<td>1,767</td>
<td>35</td>
<td>1,627</td>
</tr>
<tr>
<td>2003</td>
<td>5,052</td>
<td>1,778</td>
<td>35</td>
<td>1,688</td>
</tr>
<tr>
<td>2004</td>
<td>5,040</td>
<td>2,035</td>
<td>40</td>
<td>1,614</td>
</tr>
<tr>
<td>2005</td>
<td>4,653</td>
<td>1,817</td>
<td>39</td>
<td>1,254</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.05 for comparisons across calendar year by Cochran-Armitage trend test.

Figure 1. Diagram illustrating the use of clinical knowledge in conjunction with the multiple-imputation method to complete missing data on human immunodeficiency virus drug resistance status, North American AIDS Cohort Collaboration on Research and Design, 2000–2005. ART, antiretroviral therapy; NRTI, nucleoside-analogue reverse transcriptase inhibitor.
Table 2. Characteristics of Individuals on Combination Antiretroviral Therapy, North American AIDS Cohort Collaboration on Research and Design, 2000–2005

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2000</th>
<th></th>
<th></th>
<th>2005</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With a Genotypic Test Within Year (n = 817)</td>
<td>No Genotypic Test Within Year (n = 663)</td>
<td>With a Genotypic Test Within Year (n = 486)</td>
<td>No Genotypic Test Within Year (n = 292)</td>
<td>With a Genotypic Test</td>
<td>No Genotypic Test</td>
</tr>
<tr>
<td>Male sex</td>
<td>%</td>
<td>Median (IQR)</td>
<td>%</td>
<td>Median (IQR)</td>
<td>%</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Use of nucloside-analogue reverse transcriptase inhibitors prior to start of antiretroviral therapy</td>
<td>%</td>
<td>Median (IQR)</td>
<td>%</td>
<td>Median (IQR)</td>
<td>%</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Lapse in antiretroviral therapy during the year</td>
<td>23</td>
<td>33 (28–38)</td>
<td>16</td>
<td>26 (20–36)</td>
<td>19</td>
<td>22 (19–26)</td>
</tr>
<tr>
<td>Age years</td>
<td>40 (36–47)</td>
<td>41 (36–47)</td>
<td>43 (37–49)</td>
<td>45 (39–51)</td>
<td>44 (39–51)</td>
<td>44 (39–51)</td>
</tr>
<tr>
<td>CD4⁺, cells/mm³</td>
<td>229 (90–380)</td>
<td>221 (83–400)</td>
<td>229 (100–418)</td>
<td>224 (103–380)</td>
<td>244 (105–628)</td>
<td></td>
</tr>
<tr>
<td>Viral load, copies/mL</td>
<td>13,991 a (2,588–72,849)</td>
<td>17,000 a (3,854–72,756)</td>
<td>8,770 a (1,160–52,200)</td>
<td>24,456 a (5,575–100,010)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

a P < 0.05 by χ² test or Wilcoxon rank sum test comparing those with and without genotype tests among those at risk for testing (viral load < 1,000 copies/mL).

Incorporation of best clinical knowledge accounted for the completion of 5% of the missing data and had the remaining missingness in the cohort. In contrast, using only clinical knowledge to complete the remaining missingness resulted in lower estimates for the prevalence of class resistance to 2 or more classes of drugs declined over time (22% and 17% in 2000 and 2005, respectively; Table 3). The observed prevalences in those with testing. There was a slight increase in the estimated accumulated prevalence (as a result of multiple-imputation method to complete the remaining missing data), estimated to be 2% and the relative increase in variance (as a result of the completion of 93% of the missing data and had the largest impact on estimates of the prevalence of resistance. When data from those in the cohort with missing geno-type testing were ignored, the observed prevalences in those with testing were 57%, 50%, 49%, 44%, 37%, 36%, respectively, after the algorithm was applied to complete the data. Following clinical knowledge was used as the sole means of completing the missing data, the relative efficiency of the imputation estimator based on the remaining missingness resulted in lower estimates for the prevalence of accumulated resistance to 2 or more classes of drugs in the cohort were 51%, 61%, 65%, 66%, 66%, and 66% for the years 2000–2005, respectively. The prevalence of observed resistance remained stable, at 12% in 2000 and 13% in 2005. The prevalence of observed resistance increased from 5% to 7% in 2000 to 2001 (P < 0.001 for trend; Table 3). We estimated the prevalences of accumulated resistance to 2 or more classes of drugs in the cohort were 51%, 61%, 65%, 66%, 66%, and 66% for the years 2000–2005, respectively. The prevalence of observed resistance remained stable, at 12% in 2000 and 13% in 2005. The prevalence of observed resistance increased from 5% to 7% in 2000 to 2001 (P < 0.001 for trend; Table 3).
information. However, future suppression on a PI or NNRTI regimen does not fully exclude the possibility of resistance to those classes. Excluding the regimen information resulted in minor upward shifts of the estimated prevalences of 1%–2%.

**DISCUSSION**

In the present article, we used a modified multiple-imputation method that augmented the statistical approach with current clinical and scientific knowledge. The application of this method to the study of antiretroviral drug resistance enabled us to consider a large body of clinical knowledge concerning archiving of resistance, drug cross-class resistance, and future likelihood of viral suppression. The evolving epidemiology of antiretroviral drug resistance in clinical practice has not been fully described, as inferences have relied on data from resistance tests performed during the course of routine clinical practice. Thus, a large percentage of missing data has been routinely ignored in studies characterizing the magnitude and trends in resistance. By estimating the prevalence of accumulated resistance using data from a representative sample of North American patients who had been treated in clinical care, we found contrasting inferences regarding the trend in 2- and 3-class resistance compared with those in the genotype-tested subset. The prevalences of 2- and 3-class resistance in the entire cohort remained essentially stable except in 2000, which accounted for the significant trend test. This trend, compared with the dramatic decreases in class resistance observed among the tested subset, speaks to 2 factors: first, the inability of testing to capture the persistence of mutant viral strains in the latent reservoir; and second, selection factors that determine who is tested. Although the observed estimates do attempt to correct for the latent reservoir by summing past resistance scores over repeated tests, patients who were subsequently doing well on therapy (with a suppressed viral load) after a past failure did not undergo subsequent tests. Using the methods presented here, we were able to infer the likely resistance level for such individuals based on their past testing results (e.g., PI-class resistant in 2000), an assumption of archived resistance (e.g., PI-class resistant in all subsequent years), and knowledge of their viral load trajectory (e.g., suppressed viral load since 2000 and thus no additional acquired resistance). Such scientific knowledge regarding the development and persistence of resistance took precedence over a random draw from a multivariate normal distribution for completing the missing resistance data.

The results using data from the subset of individuals who underwent genotype resistance testing were generally consistent with trends observed in several recent European cohorts (13, 19–21). This apparent decline in resistance in the subset of genotyped patients could be attributed to several factors, including an earlier use of genotype testing among those failing to respond to ART (22), low adherence to the prescribed therapeutic regimen (23–25), or the increased use of regimens that are less likely to select for drug resistance (23, 26). All of these factors could affect the percentages of mutations detected in the circulating virus. Comparisons between those who did and did not undergo genotype testing revealed clear contrasts that suggested that inferences concerning resistance trends cannot be extrapolated from the tested subset to the clinical-care population. Further, testing results alone do not capture the reservoir of archived resistance in the larger cohort of HIV-infected patients (unless frequent testing is used throughout follow-up). The multiple imputation method, along with assumptions about the structure of the resistance data, provided 1 potential methodological approach to quantifying the burden of resistance in the population over time in lieu of universal repeated testing data. It should be noted that this approach still requires conditional independence to hold in the partially completed data (after clinical knowledge-based imputation) (10, 27). The validity of the individual resistance probability estimates for those not tested relies upon the predictive strength of the covariates.
included in the multiple-imputation model, which may not comprise the optimal set of explanatory factors. In the present example, however, only approximately 6% of the data arose from multiple-imputation models as a result of our use of clinical knowledge to inform the data collection.

The greatest influence on the estimated prevalences and subsequent trend arose from the integration of current scientific knowledge about resistance. In particular, the assumption concerning the persistence of resistant strains in an individual over time defined a data structure that treated resistance as a monotonically increasing function. The assumption that despite a positive response to new regimens and an absence of detectable drug-resistant viremia, an individual continues to harbor resistant viral strains reflects current understanding and evidence (28) and was incorporated into methods used to compute both the observed prevalence and the estimated cohort prevalence, though it was much more influential on cohort inferences for which the assumed structure was used to complete missing data. Thus, the prevalence of resistance we observed in any year was likely higher than what would be expected from a cross-sectional survey of resistance. However, because the earliest genotype testing data we have are from 1997, the accumulation of resistance only pertains to resistance captured after this time. Further, resistant variants fade as selective pressure is removed, such as during a period of poor or interrupted adherence to therapeutic regimes. Therefore, our estimates of the prevalence of accumulated resistance likely represent a lower bound for the true prevalence.

A limitation of the analysis was the simplifying assumption that genotype testing results, when available, were an accurate reflection of phenotypic drug susceptibility. Genotype tests have a limited ability to detect resistant circulating strains at low viral loads and thus might result in falsely classifying an individual as not harboring resistant viral strains. Of additional concern are tests that are administered after therapy has been discontinued. With selective pressure no longer present, resistant variants fade as selective pressure is removed, such as during a period of poor or interrupted adherence to therapeutic regimens. Therefore, our estimates of the prevalence of accumulated resistance likely represent a lower bound for the true prevalence.

Of further interest is the generalizability of the estimates presented. The target population in this study was HIV-infected individuals engaged in clinical care. The source population was an open cohort of participants initiating ART treatment who were observed during the year for which they contributed to the prevalence estimate. We capture primarily durable viral suppression (3, 31–36). The contrast in inferences presented here between the tested sample and the entire cohort highlights the value of appropriate handling of missing data in informing clinical practice and policy.

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REFERENCES


