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 of 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 genotypic 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, NNRTs, 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

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
In both 2000 and 2005, those not tested were more likely to report lapses in their ART regimen during the year. Median CD4⁺ 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% were associated with protease inhibitor-based regimens, nonnucleoside reverse transcriptase inhibitor-based regimens, and both types of regimens, respectively. A total of 2,951 viremic (viral load >1000 copies/mL) participant-years with no genotype testing were included in the analysis.

**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>Protease Inhibitor-Based Regimen</th>
<th>Nonnucleoside Reverse Transcriptase Inhibitor-Based Regimen</th>
<th>No. of Patients Who Had &gt;1,000 copies/mL During the Year*</th>
<th>No. of Patients Who Had a Genotypic Resistance Test During the Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>%</td>
<td>No. of Cases</td>
<td>%</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>2000</td>
<td>5,004</td>
<td>1,920</td>
<td>38</td>
<td>1,387</td>
<td>28</td>
</tr>
<tr>
<td>2001</td>
<td>5,093</td>
<td>1,850</td>
<td>36</td>
<td>1,552</td>
<td>30</td>
</tr>
<tr>
<td>2002</td>
<td>5,063</td>
<td>1,767</td>
<td>35</td>
<td>1,627</td>
<td>32</td>
</tr>
<tr>
<td>2003</td>
<td>5,052</td>
<td>1,778</td>
<td>35</td>
<td>1,688</td>
<td>33</td>
</tr>
<tr>
<td>2004</td>
<td>5,040</td>
<td>2,035</td>
<td>40</td>
<td>1,614</td>
<td>32</td>
</tr>
<tr>
<td>2005</td>
<td>4,653</td>
<td>1,817</td>
<td>39</td>
<td>1,254</td>
<td>27</td>
</tr>
</tbody>
</table>

*P < 0.05 for comparisons across calendar year by Cochran-Armitage trend test.
### Table 2.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Genotypic Test</th>
<th>With Genotypic Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral Load &gt; 1000 copies/mL</td>
<td>n = 1,554</td>
<td>n = 1,480</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
</tr>
<tr>
<td>% Male</td>
<td>52</td>
<td>57</td>
</tr>
<tr>
<td>White</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Age, years</td>
<td>48 (43–53)</td>
<td>43 (39–47)</td>
</tr>
<tr>
<td>CD4 (+), cells/mm(^3)</td>
<td>336 (244–580)</td>
<td>230 (160–370)</td>
</tr>
<tr>
<td>Viral load, copies/mL</td>
<td>11,932 (2,388–72,346)</td>
<td>2,996 (824–7,963)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

- \( P < 0.008 \)

5% of the data on the accumulation of 2 or more classes of resistance remained missing for years 2000 through 2005, respectively, after the algorithm based on clinical knowledge was applied to complete the data. Following the multiple-imputation method to complete the remaining missing resistance data, the relative increase in variance (as a result of the remaining missingness) was estimated to be 2% and the relative efficiency of the imputation estimator based on the 5 imputation data sets was 99%. Results were similar for 3-class resistance data.

### Class resistance over time

When data from those in the cohort with missing genotype testing were ignored, the observed prevalence of class resistance to 2 or more antiretroviral drug classes decreased \( P < 0.001 \) for trend; Table 3). The observed prevalences in the tested subgroup were 57%, 56%, 49%, 34%, 37%, and 36% for the years 2000–2005, respectively. Likewise, the observed prevalence of class resistance to 3 antiretroviral drug classes declined over time (22% and 17% in 2000 and 2005, respectively; \( P < 0.001 \) for trend). The level of observed wild-type (i.e., those without any detected drug resistance) remained stable, at 12% in 2000 and 13% in 2005.

When combining estimated resistance (in those who were viremic but not tested) with observed resistance (in those who were tested), we found that the prevalence of accumulated resistance in the entire cohort was much lower than the observed prevalence in those with testing. There was a slight increase in the estimated accumulated prevalence over time, mostly from 2000 to 2001 \( P < 0.001 \) for trend; Table 3). We estimated the prevalences of accumulated resistance to 2 or more classes to be 14%, 17%, 18%, 17%, 17%, and 17% for the years 2000 through 2005, respectively. The prevalence of accumulated 3-class resistance also slightly increased from 6% in 2000 to 7% in 2005 \( P = 0.008 \).

### Sensitivity analyses

Incorporation of best clinical knowledge accounted for the completion of 93% of the missing data and had the largest impact on estimates of the prevalence of resistance. When the algorithm for completing missing data using clinical knowledge was ignored and the multiple-imputation method was used as the sole means of completing the missing data, the estimates for the prevalence of accumulated resistance to 2 or more classes of drugs in the cohort were 51%, 61%, 64%, 64%, 65%, and 66% for 2000–2005, respectively. The estimates for the prevalence of accumulated 3-class resistance in the cohort were 32%, 41%, 45%, 46%, 48%, and 50%, respectively. In contrast, using only clinical knowledge to complete missing data and ignoring the remaining missingness resulted in lower estimates for the prevalence. For example, the prevalences of accumulated resistance to 2 or more classes of drugs were estimated to be 10%, 13%, 15%, 14%, 14%, and 14% and to 3 classes were estimated to be 4%, 5%, 5%, 5%, 5%, and 5% for 2000–2005, respectively.

Regimen and viral load data were used to inform individual resistance probability estimates as a surrogate for testing.
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 miss...
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 completion.

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 regimens. 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 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 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 the burden of acquired resistance arising from treatment exposure. The overall pool of resistance also includes community-acquired resistance, which could not be adequately addressed in the present study because of the limited numbers of pre-ART genotype tests. The prevalence of community-acquired multiclass resistance in North America is estimated to be 6%–17% (29, 30).

Patients who exhibit virologic failure (the result of either nonadherence or resistance) on antiretroviral therapy tend to have worse long-term outcomes than do those who achieve 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


