Antiretroviral Resistance among HIV-Infected Persons Who Have Died in British Columbia, in the Era of Modern Antiretroviral Therapy

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Background. The prevalence of antiretroviral resistance among persons enrolled in the centralized HIV/AIDS Drug Treatment Program in British Columbia, Canada, who had died between July 1997 and December 2001, was investigated, to determine the degree to which antiretroviral resistance contributed to mortality.

Methods. During this period, 637 deaths had occurred. The last plasma sample obtained during therapy was genotyped retrospectively for treated individuals who had died of a nonaccidental cause. Samples with plasma human immunodeficiency virus (HIV) loads $<500$ copies/mL were not genotyped. Drug resistance among 1220 living HIV-infected persons who had experienced virologic therapy failure during the study period also was examined.

Results. Of 554 individuals who had died of nonaccidental causes, 58 (10.4%) were antiretroviral naive, and 99 (17.9%) had very brief exposure to antiretroviral therapy (median, 2 months). The majority of isolates from the remaining 397 individuals harbored either no major resistance mutations or represented samples with plasma HIV suppression of $<500$ copies/mL. Resistance to $\geq 1$, $\geq 2$, or 3 drug classes was observed in 76%, 42%, and 11% of individuals, respectively, in the group of 1220 living individuals experiencing virologic therapy failure, compared with only 44%, 23%, and 5% of individuals, respectively, who had died ($P < .001$).

Conclusion. Only a relatively low prevalence of multidrug resistance was observed in this cohort, indicating that the exhaustion of treatment options because of drug resistance was not a significant contributor to mortality.

Morbidity and mortality associated with HIV infection and AIDS have declined significantly in North America and Western Europe as a result of the introduction of combination antiretroviral therapies [1–6]. Despite these advances in treatment, HIV-related deaths continue to occur across the developed world [1–4, 7, 8].

Drug-resistant HIV variants are often cited as a major barrier to long-term antiretroviral efficacy and a major cause of treatment failure [9–16]. However, what proportion of recent HIV-related deaths among those with access to antiretroviral therapy is due to diminished treatment options as a consequence of multidrug resistance and what proportion may be due to other factors remain to be determined conclusively.

By use of data from the centralized HIV/AIDS Drug Treatment Program (DTP) in British Columbia, Canada, the prevalence of antiretroviral resistance among HIV-infected persons who had died between July 1997 and December 2001 was contrasted with the prevalence of resistance among living individuals who had experienced virologic therapy failure during the same study period. Our objective was to determine the degree to which antiretroviral resistance may contribute to mortality among HIV-infected individuals, in the era of highly active antiretroviral therapy (HAART).

MATERIALS AND METHODS

HIV/AIDS DTP in British Columbia. In the province of British Columbia, antiretroviral agents have been
distributed at no cost to all eligible HIV-infected individuals through the centrally administered HIV/AIDS DTP since 1986. The DTP remains the only source of free-of-charge antiretroviral therapy in the province, and pharmaceutical sales suggest that <1% of HIV-infected residents of British Columbia purchase antiretroviral agents outside the DTP [17]. The DTP database contains sociodemographic data, as well as comprehensive antiretroviral prescription and treatment data, for all those accessing care and treatment for HIV infection in British Columbia. Details on patient enrollment and DTP policies and treatment guidelines have been published elsewhere [17].

As part of routine patient monitoring, plasma HIV-1 RNA levels (i.e., plasma virus load [pVL]) and CD4 cell counts usually are measured at baseline, after 1 month of treatment, and at 3-month intervals thereafter. Portions of the plasma samples used for HIV pVL testing are archived.

**Study sample and variables of interest.** A total of 637 deaths were recorded among persons enrolled in the DTP between July 1997 and December 2001. Deaths were identified through physician reports and through linkage with the British Columbia Division of Vital Statistics (Vancouver). Causes of death were classified according to coding in the International Classification of Diseases, 9th Revision (1995–1999 [ICD-9]) and 10th Revision (2000–2001 [ICD-10]). Underlying causes of death coded under ICD-9 categories 042–044 and ICD-10 categories B20–B24 identified deaths directly caused by HIV infection. July 1997 was selected as the study start date because, at that time, HAART became universally available to all HIV-infected individuals seeking treatment in British Columbia. Subjects included in this study were part of a larger group of HIV-infected individuals who had died in British Columbia between 1995 and 2001 and whose sociodemographic characteristics, associated risk factors for HIV infection, and access to antiretroviral agents have been described elsewhere in detail [17]. Time spent undergoing antiretroviral treatment was estimated by use of a previously validated method based on the analysis of prescription-refill data [18]. Approval for this study was obtained from the institutional ethics board of Providence Health Care/University of British Columbia (Vancouver).

**Genotypic drug-resistance testing.** Accidental deaths were assumed to be not directly related to antiretroviral resistance, and plasma samples from those individuals were not genotyped. Samples with pVLS <500 copies HIV RNA/mL were not genotyped, because of an inadequate amount of HIV in plasma. However, because these plasma samples were obtained from individuals with successful suppression of plasma HIV RNA, these samples were unlikely to contain HIV-harboring resistance mutations in sufficient quantities to compromise effectiveness of therapy.

Genotypic drug-resistance testing was restricted to those individuals who had been prescribed antiretroviral agents and who had died of nonaccidental causes (figure 1). For each subject meeting these requirements, the last plasma sample obtained during therapy was genotyped for drug resistance if the pVL was ≥500 copies HIV RNA/mL. Resistance genotyping was performed as described elsewhere [19].

Samples were considered to be “resistant” if they displayed ≥1 of the following major resistance mutations (based on the International AIDS Society USA list [20]): resistance to nucleos(t)ide reverse-transcriptase inhibitors (NRTIs)—41L, 62V, 65V, 67N, 69A/N/D or insertion, 70R, 74V, 75I, 151M, 184I/V, 210W, 215F/Y, or 219E/Q; resistance to any nonnucleoside reverse-transcriptase inhibitor (NNRTI)—100I, 103N, 106A, 108I, 181C/I, 188C/H/L/Y, 190A/S, or 236L; or resistance to any protease inhibitor (PI)—30N, 46I/L, 48V, 50L/V, 54L/M, 82A/F/S/T, 84V, or 90M.

**Drug resistance among living HIV-infected persons with virologic therapy failure.** In the evaluation of HIV-treatment outcomes, mortality often is used as an end point in the definition of therapy failure. However, surrogate markers, such as pVL and CD4 cell count, also are commonly used to define therapy failure in clinical trials and population-based studies. To provide context, the prevalence of resistance in the study group (for which therapy failure was defined as mortality [hereafter referred to as the “mortality group”]) was contrasted with the prevalence of resistance in a large group of living individuals selected on the basis of a pVL-driven definition of therapy failure (hereafter referred to as the “virologic failure group”). The virologic failure group (n = 1220), which was selected from the DTP database, included all living HIV-infected individuals in British Columbia who were experiencing therapy failure (as defined by a pVL ≥500 copies HIV RNA/mL) between the study dates of July 1997 and December 2001 and for whom a physician-requested HIV genotypic drug-resistance test had been performed. When multiple genotypic tests had been performed for an individual during the period of interest, the last available genotype obtained during therapy was selected. Genotypic drug-resistance testing and interpretation of resistance genotypes were done as described above. Individuals included in the mortality group (n = 637) and the virologic failure group (n = 1220) represent nearly 40% of the total of ~4600 patients who ever received therapy in British Columbia during this time period.

**Statistical analyses.** Categorical variables were compared between groups by use of Pearson’s χ² test. Contingency tables that contained ≥1 expected count of <5 were analyzed by means of Fisher’s exact test. The Cochran-Armitage test was used to assess resistance trends over time. Comparisons of continuous variables were done by use of the Wilcoxon rank-sum test. All reported P values are 2-sided.
RESULTS

Antiretroviral therapy and causes of mortality in the study group. A total of 637 deaths were recorded among HIV-infected individuals enrolled in the province-wide DTP between July 1997 and December 2001 (figure 1). Of these, 83 (13.0%) were attributed to accidental causes; the 2 most common causes (by ICD-9 or ICD-10 coding) were illicit-drug overdose (57.8%) and concussion (18.1%). The causes of the remaining accidental deaths included suicide, traffic accidents, assaults, and other injuries. Although HIV disease may have played an indirect role in these deaths, accidental deaths were assumed not to be directly related to antiretroviral resistance and were not included in the genotypic analyses.

The remaining 554 deaths (87.0%) were attributed to nonaccidental causes. These deaths included 383 (69.1%) directly related to HIV infection (ICD-9 categories 042–044 and ICD-10 categories B20–B24) and 34 (6.1%) related to liver disease, 25 (4.5%) to various cardiac conditions, 20 (3.6%) to viral and/or bacterial infections, 18 (3.2%) to malignant neoplasms, 43 (7.8%) to other causes, and 31 (5.6%) to unknown causes.

Of the 554 individuals who had died of nonaccidental causes, 58 (10.5%) had enrolled in the province’s DTP but had never been dispensed any antiretroviral agents. Plasma samples from these individuals were not genotyped, since resistance mutations were not likely to have been present. The remaining 496 individuals (89.5%) had had at least some exposure to antiretroviral agents.

The number of nonaccidental deaths per year among treated individuals increased slightly over the period of interest (table 1). In this cohort, the median time elapsed between initiation
of antiretroviral therapy and date of death increased over the study period, from 28 months for those who had died in the last half of 1997 to 47 months for those who had died in 2001 (P<.001). The median time actually spent receiving antiretroviral therapy increased, from 11 months of antiretroviral exposure for those who had died in the last half of 1997 to 28 months of antiretroviral exposure for those who had died in 2001. Similarly, the median time spent receiving HAART increased from 4 to 15 months over the study period. The median time elapsed between the discontinuation of therapy and death remained constant over the study period, with death occurring a median of 2 months after discontinuation of therapy (interquartile range [IQR], 0.5–7.4 months). Although the reasons for discontinuation of therapy are unknown, the majority of individuals with successful suppression of plasma HIV RNA (pVL <500 copies HIV RNA/mL; drug-resistance genotyping was successful for 232 [92.8%] of these 250 samples).

The majority of the last plasma samples obtained during therapy (212 [55.9%] of 379 samples) either represented in quantities sufficient to compromise therapy. Of interest, 60 (41%) of these 147 individuals had discontinued antiretroviral therapy for unknown reasons shortly after this pVL measurement and, therefore, were not receiving any antiretroviral agents at time of death. The remaining 250 deaths (63.0%) had occurred among individuals whose last pVL measurement during therapy was ≥500 copies HIV RNA/mL; drug-resistance genotyping was performed in quantities sufficient to compromise therapy. Of interest, 60 (41%) of these 147 individuals had discontinued antiretroviral therapy for unknown reasons shortly after this pVL measurement and, therefore, were not receiving any antiretroviral agents at time of death. The remaining 250 deaths (63.0%) had occurred among individuals whose last pVL measurement during therapy was ≥500 copies HIV RNA/mL; drug-resistance genotyping was successful for 232 (92.8%) of these 250 samples.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of deaths</th>
<th>Between start of therapy and death</th>
<th>Undergoing any antiretroviral therapy</th>
<th>Undergoing HAART</th>
<th>Between cessation of therapy and death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 (July–December)</td>
<td>45</td>
<td>28 (8–54)</td>
<td>11 (4–33)</td>
<td>4 (0–8)</td>
<td>2.5 (0.6–4.4)</td>
</tr>
<tr>
<td>1998</td>
<td>90</td>
<td>32 (19–60)</td>
<td>18 (7–33)</td>
<td>6 (0–13)</td>
<td>2.8 (0.6–8.0)</td>
</tr>
<tr>
<td>1999</td>
<td>105</td>
<td>35 (17–56)</td>
<td>15 (6–34)</td>
<td>8 (3–14)</td>
<td>1.8 (0.6–8.0)</td>
</tr>
<tr>
<td>2000</td>
<td>135</td>
<td>44 (28–71)</td>
<td>20 (8–44)</td>
<td>10 (4–22)</td>
<td>2.0 (0.5–8.5)</td>
</tr>
<tr>
<td>2001</td>
<td>121</td>
<td>47 (20–68)</td>
<td>28 (10–48)</td>
<td>15 (5–33)</td>
<td>1.6 (0.5–6.0)</td>
</tr>
<tr>
<td>Overall</td>
<td>496</td>
<td>40 (19–62)</td>
<td>19 (7–41)</td>
<td>8 (2–18)</td>
<td>2.0 (0.5–7.4)</td>
</tr>
</tbody>
</table>

**NOTE.** The considerable discrepancy between the median time between start of therapy and death and the median time actually spent receiving antiretroviral therapy suggests that, for many individuals, use of antiretroviral agents was intermittent. HAART, highly active antiretroviral therapy; IQR, interquartile range.

RNA/mL suggests that drug-resistance mutations were not present in quantities sufficient to compromise therapy. Of interest, 60 (41%) of these 147 individuals had discontinued antiretroviral therapy for unknown reasons shortly after this pVL measurement and, therefore, were not receiving any antiretroviral agents at time of death. The remaining 250 deaths (63.0%) had occurred among individuals whose last pVL measurement during therapy was ≥500 copies HIV RNA/mL; drug-resistance genotyping was successful for 232 (92.8%) of these 250 samples.

The majority of the last plasma samples obtained during therapy (212 [55.9%] of 379 samples) either represented in quantities sufficient to compromise therapy. Of interest, 60 (41%) of these 147 individuals had discontinued antiretroviral therapy for unknown reasons shortly after this pVL measurement and, therefore, were not receiving any antiretroviral agents at time of death. The remaining 250 deaths (63.0%) had occurred among individuals whose last pVL measurement during therapy was ≥500 copies HIV RNA/mL; drug-resistance genotyping was successful for 232 (92.8%) of these 250 samples.

### Genotypic drug-resistance testing.** Of the 397 treated individuals for whom plasma samples were available (table 2), 147 deaths (37.0%) occurred among individuals whose last pVL measurement during therapy was <500 copies HIV RNA/mL. Although genotyping of these samples was not possible, the fact that plasma HIV RNA was suppressed to <500 copies HIV RNA/mL suggests that drug-resistance mutations were not present in quantities sufficient to compromise therapy. Of interest, 60 (41%) of these 147 individuals had discontinued antiretroviral therapy for unknown reasons shortly after this pVL measurement and, therefore, were not receiving any antiretroviral agents at time of death. The remaining 250 deaths (63.0%) had occurred among individuals whose last pVL measurement during therapy was ≥500 copies HIV RNA/mL; drug-resistance genotyping was successful for 232 (92.8%) of these 250 samples.

The major cause of death among individuals with successful suppression of plasma HIV RNA (pVL <500 copies HIV RNA/mL; n = 147) or contained HIV harboring no major antiretroviral resistance mutations (n = 65). The proportion of isolates with or without resistance-associated mutations remained relatively stable over the course of the study period (figure 2A). A total of 167 samples (44.1%) harbored HIV with ≥1 major resistance mutation (figure 2A), an observation strongly driven by resistance to NRTIs (142 samples [37.4%]) and, specifically, by resistance to lamivudine arising from the M184I/V mutation (101 samples [26.6%]). A total of 83 (21.9%) and 53 (13.9%) samples had mutations conferring resistance to NNRTIs and PIs, respectively (data not shown). Isolates harboring HIV with mutations conferring resistance to drugs from ≥2 classes and drugs from all 3 classes were observed relatively infrequently (23.4% and 5.8% of isolates, respectively; figure 2A).

Individuals who had started receiving monotherapy or dual therapy were significantly more likely to harbor resistant HIV than were individuals who had received HAART exclusively (figure 2B). Resistance to ≥1 class of drugs was observed for 138 (54.5%) of 253 individuals who had started receiving monotherapy or dual therapy, compared with 29 (23.0%) of 126 in-
Table 2. Comparison between HIV-infected individuals who had died with and those who had died without any antiretroviral resistance.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No antiretroviral resistance (n = 68)</th>
<th>Virologic suppressiona (n = 147)</th>
<th>Any antiretroviral resistance (n = 167)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>39.6 (9.3)</td>
<td>42.4 (10.3)</td>
<td>39.2 (9.1)</td>
<td>.039 .767 .002</td>
</tr>
<tr>
<td>At start of therapy</td>
<td>42.3 (8.8)</td>
<td>45.8 (10.6)</td>
<td>43.2 (8.9)</td>
<td>.008 .247 .031</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>81.2</td>
<td>87.2</td>
<td>87.4</td>
<td>.263 .230 .944</td>
</tr>
<tr>
<td>IDU, %</td>
<td>31.3</td>
<td>30.4</td>
<td>29.3</td>
<td>.903 .777 .837</td>
</tr>
<tr>
<td>CD4 cell count, median (IQR), cells/mm³</td>
<td>30 (10–160)</td>
<td>200 (70–370)</td>
<td>50 (10–200)</td>
<td>&lt;.001 .207 &lt;.001</td>
</tr>
<tr>
<td>pVL, median (IQR), copies HIV RNA/mL</td>
<td>109,000 (3185–416,000)</td>
<td>200 (&lt;500)</td>
<td>49,000 (5100–272,000)</td>
<td>&lt;.001 .250 &lt;.001</td>
</tr>
<tr>
<td>Time undergoing therapy, median (IQR), months</td>
<td>15 (7–62)</td>
<td>31 (13–47)</td>
<td>32 (16–52)</td>
<td>&lt;.001 &lt;.001 .153</td>
</tr>
<tr>
<td>Adherence to therapyb</td>
<td>78 (33–100)</td>
<td>100 (73–100)</td>
<td>83 (58–100)</td>
<td>&lt;.001 .084 .006</td>
</tr>
</tbody>
</table>

NOTE. IDU, injection drug use; IQR, interquartile range; pVL, plasma virus load.

a Defined as pVL <500 copies HIV RNA/mL.

b Defined as percentage (IQR) of prescriptions refilled during first 12 months of therapy.

dividuals who had received HAART exclusively (P < .001). Similarly, resistance to ≥2 classes of drugs was observed for 77 individuals (30.4%) who had started receiving monotherapy or dual therapy, compared with 12 (9.5%) of 126 individuals who had received HAART exclusively (P < .001). Of interest, not a single individual who received HAART as their first therapy harbored HIV with resistance to all 3 classes of antiretroviral agents. All individuals with resistance to 3 drug classes initially had received monotherapy or dual therapy before receiving HAART (22 [10.4%] of 210 individuals) (P < .001).

Individuals with confirmed resistance mutations had had a significantly longer median duration of therapy (32 months [IQR, 16–52 months]), compared with individuals confirmed to have had no resistance mutations (15 months [IQR, 7–62 months]) (P < .001). There were no other significant differences between these 2 groups (table 2).

Antiretroviral resistance among individuals living with HIV infection who had experienced virologic therapy failure. To put these observations in perspective, a virologic failure group was selected, which included all living DTP participants with a pVL ≥500 copies HIV RNA/mL over the same study period and for whom a physician-requested genotypic drug-resistance test had been performed (n = 1220). We observed a dramatically higher prevalence of antiretroviral resistance in the virologic failure group than in the mortality group. Of the 1220 individuals in the virologic failure group, 924 (75.7%) harbored HIV with resistance to ≥1 drug class, compared with only 167 (44.1%) of the 379 individuals in the mortality group (P < .0001). Similarly, the prevalence of resistance to ≥2 and 3 drug classes also was significantly higher in the virologic failure group (42.3% and 11.1% of isolates, respectively) than in the mortality group (23.4% and 5.8% of isolates, respectively) (P < .001). Resistant isolates in the mortality and virologic failure groups were similar with regard to the number of resistance mutations detected. Isolates from the virologic failure group that were resistant to a single drug class had a median of 2 major resistance mutations, compared with a median of only 1 major resistance mutation in isolates from the mortality group that were resistant to a single drug class. The number of resistance-associated mutations in isolates with antiretroviral resistance to 2 or 3 drug classes was the same for both groups (median, 4 and 8 mutations, respectively).

In contrast to the relatively stable prevalence of antiretroviral resistance in the mortality group (figure 2A), we observed a dramatic increase in the proportion of isolates in the virologic failure group with resistance to ≥2 classes of drugs over the study period (figure 3). This was primarily due to an increase in NNRTI resistance in this group: in 1997, only 5.9% of isolates displayed NNRTI resistance, which increased to 38% of isolates by 2001 (data not shown).

Reliability of using a single plasma sample for resistance testing. For the mortality group, resistance data were obtained from the last plasma sample obtained during therapy, prior to death. However, resistance-associated mutations may have been present in earlier samples. In an attempt to determine the reliability of using this single sample, we analyzed retrospective data to assess the presence of resistance-associated mutations in earlier samples, if available. Earlier genotype data were available for approximately one-half of the patients. Despite this nonrandom sample, patterns of previous antiretroviral resistance were mostly consistent with results of genotyping the last plasma sample obtained during therapy, with resistance to 2 or 3 drug classes observed at some point in the individual’s history in only 7% of those that were classified as "not resistant" and in 12% of
resistance test had been requested during the same study period (for whom therapy failure was defined as a pVL $\geq 500$ copies HIV RNA/mL [the virologic failure group]). Specifically, we wished to determine whether mortality in this population was primarily due to an exhaustion of available treatment options, arising as a direct result of multidrug resistance.

The majority of individuals (56%) in the mortality group who had received antiretroviral therapy had harbored HIV with either no major resistance mutations or had had pVL suppression of $<500$ copies HIV RNA/mL, suggesting that drug resistance was not sufficient to compromise therapy. Less than 25% of the individuals in the mortality group had harbored HIV with mutations conferring resistance to antiretroviral agents from $\geq 2$ drug classes, whereas only a minority (~5%) had harbored HIV with mutations conferring resistance to drugs from all 3 classes. Of interest, resistance to 3 drug classes was not observed for any individual who had received HAART exclusively. In the larger population, we estimate that resistance to all 3 classes of drugs was present in $<4\%$ of the 554 individuals who had died of nonaccidental causes, regardless of access to therapy.

These results clearly suggest that exhaustion of available and effective treatment options, arising as a direct result of multidrug resistance, was not a driving factor in the majority of deaths in this cohort. These results contrast somewhat with those from a recent study of 29 HIV-related deaths, which reported mutations conferring resistance to both HIV reverse-transcriptase inhibitors and PIs in isolates from 10 individuals (34%) [21].

The relatively low level of antiretroviral resistance observed in the mortality group contrasts with the high level of resistance observed in the virologic failure group. Consistent with the increased prevalence of antiretroviral resistance in 2 groups was investigated. The 2 groups were selected on the basis of 2 independent definitions of antiretroviral therapy failure: a group composed of all HIV-infected individuals who had died between July 1997 and December 2001 (for whom therapy failure was defined as mortality [the mortality group]) and a group composed of all living individuals for whom a genotypic drug-resistant mutations or represented individuals with successful pVL all 3 drug classes. Overall, the majority of isolates either contained no major resistance mutations or represented individuals with successful pVL suppression of $<500$ copies HIV RNA/mL; resistance to drugs from all 3 classes was rarely observed. Individuals who had received monotherapy ("mono") or dual therapy ("dual") at some point in their treatment history were significantly more likely to have harbored HIV with resistance mutations than were individuals who had received highly active antiretroviral therapy (HAART) only. None of the patients who had received HAART only had mutations conferring resistance to all 3 drug classes.

**DISCUSSION**

To determine the degree to which antiretroviral resistance may contribute to mortality among HIV-infected individuals in a province where antiretroviral medications and HIV care are provided at no cost through a government-sponsored program, the prevalence of antiretroviral resistance in 2 groups was investigated. The 2 groups were selected on the basis of 2 independent definitions of antiretroviral therapy failure: a group composed of all HIV-infected individuals who had died between July 1997 and December 2001 (for whom therapy failure was defined as mortality [the mortality group]) and a group composed of all living individuals for whom a genotypic drug-
creased use of triple-drug combination therapies over the period of interest, rates of resistance to 2 and 3 drug classes had increased dramatically in the virologic failure group, whereas levels of multidrug resistance had remained relatively stable in the mortality group over the same period.

These results represent an interesting paradox: drug resistance in HIV infection, especially resistance to multiple classes of drugs, is common and increasingly prevalent over time among individuals experiencing virologic therapy failure who remain alive but is relatively uncommon among those who have died. Although the inverse association between antiretroviral resistance and mortality may seem counterintuitive, the duration of antiretroviral therapy in the mortality group suggests that the low level of drug resistance was mainly driven by insufficient antiretroviral exposure. Among individuals who had died, the median time elapsed between initiation of therapy and death was >3 years; however, the time actually spent undergoing antiretroviral therapy was only 19 months. Given the large number of treatment possibilities today, 19 months is not long enough to have attempted and failed all possible therapy combinations. The discrepancy between these times indicates that, for many individuals, antiretroviral therapies were used only intermittently or were discontinued. In fact, the majority of the study population (including ~40% of individuals whose last pVL measured during therapy was <500 copies HIV RNA/mL) were not receiving any antiretroviral agents at the time of death, having discontinued therapy for unknown reasons a median of 2 months previously. For 10% of the study population, there was no antiretroviral exposure at all.

Consistent with these observations are the results of a recent study of HIV-infected individuals in British Columbia, which reported a positive association between intermittent use of antiretroviral therapy and mortality [22], and of a recent study of 88 HIV-related deaths occurring in 1999–2000, which reported that the majority of patients who had died were not receiving HAART, despite access to care [8]. In the latter study [8], an inability to tolerate HAART, because of side effects or therapy toxicity, and nonadherence were cited as the major reasons that patients were not receiving antiretroviral agents at time of death. In addition, a recent study investigating barriers to antiretroviral access among 1239 HIV-infected individuals in British Columbia who had died between 1995 and 2001 (which included our cohort) identified female sex, aboriginal ethnicity, and low socioeconomic status as the strongest predictors of lack of therapy access, intermittent therapy use, and/or discontinuation of therapy, despite the availability of antiretroviral agents at no cost through a government-funded treatment program [17]. Although reasons for intermittent use of therapy are not known for the individuals in our study, side effects, illness, toxicity, and other factors are highly likely to have played a large role.

Finally, a large study estimating the prevalence of antiretroviral resistance in the United States reported that ~78% of HIV-infected individuals with pVLs >500 copies HIV RNA/mL harbored resistant HIV [23]; this result is entirely consistent with the observed prevalence of antiretroviral resistance in our virologic failure group. Most notably, these investigators also reported a positive correlation between drug resistance and antiretroviral exposure; in this previous study, the prevalence of drug resistance was significantly associated with greater access to treatment [23].

A limitation of this study is the fact that no pVL data or plasma samples were available for ~20% of treated individuals who had died. Although we cannot exclude the possibility that these individuals may have harbored drug-resistant HIV, the fact that these individuals had received only a median of 2 months of therapy strongly suggests that drug resistance did not play a large role in their deaths. Additional limitations of this study include its retrospective nature and the fact that reasons for interruption and/or discontinuation of therapy are mostly unknown. Finally, it is important to note that the 2 different end points used (clinical therapy failure as defined by mortality and virologic therapy failure as determined by pVL >500 copies HIV RNA/mL) resulted in groups that were not directly comparable. The mortality group included all individuals who had died, regardless of whether they had received antiretroviral agents, whereas the virologic failure group included all individuals who had received therapy and had experienced at least one pVL >500 copies HIV RNA/mL. The total prevalence of resistance among all living HIV-infected individuals in British Columbia is likely to be much lower than that in the virologic failure group in this study, since this latter group excluded those who had consistently maintained a pVL <500 copies HIV RNA/mL (~1000 individuals), those with ≥1 pVL >500 copies HIV RNA/mL but for whom a genotypic drug-resistance test had not been requested by their physicians (~1700 individuals), those lost to follow-up (~30 individuals), and those who had never received antiretroviral agents (number unknown). However, the data show the tremendous difference in resistance prevalence and trends for these 2 different definitions of treatment failure.

In conclusion, the results of this study strongly indicate that treatment failure due to antiretroviral resistance was not a major factor influencing mortality in this cohort, which was composed of individuals for whom antiretroviral agents were available at no cost. For most of the individuals studied, insufficient and/or intermittent exposure to antiretroviral agents, comorbidities, and other factors likely played a larger role.

References

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