MAJOR ARTICLE

# Prevalence and Correlates of Untreated Human Immunodeficiency Virus Type 1 Infection among Persons Who Have Died in the Era of Modern Antiretroviral Therapy

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**We evaluated all human immunodeficiency virus (HIV)–related deaths over the period 1 January 1995–31 December 2001 in a Canadian province in which all HIV care and antiretroviral therapy are provided free of charge. Persons who had received antiretroviral drugs before death were compared with those who had died without ever receiving HIV treatment, by fitting a logistic model. Overall, 1239 deaths were attributed to HIV infection during the study period. Of these, 406 (32.8%) occurred among persons who had never received any HIV treatment. In adjusted analyses, aboriginal ethnicity, female sex, and lower median income were negatively associated with receiving HIV treatment before death. Furthermore, among the 833 individuals who received treatment before death, only 379 (45.5%) received antiretroviral medication ⩾75% of the time during their first year receiving therapy. The data demonstrate the need for novel interventions to expand HIV care to specific populations.**

Since its introduction in the mid-1990s, the benefits of antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) disease have been well established [1]. New ART regimens have proved to be effective in decreasing plasma HIV RNA and improving CD4 cell counts, and marked improvements in HIV-related morbidity and mortality have been documented among persons receiving ART [2, 3]. Although the adverse effects of HIV treatment present challenges [4, 5], disease progression and AIDS deaths have become so rare among persons receiving antiretrovirals that, in many areas of the world, HIV infection is increasingly being viewed as a chronic and manageable illness [6, 7].

We have previously reported that the benefits of ART are measurable at a population level [3] and we identified a significant improvement in the life expectancy of gay and bisexual males in a gay neighborhood in Vancouver [8]. These findings have emerged amid growing concerns regarding inequitable access to ART among those infected during the later stages of the HIV epidemic in North America, such as illicit drug users, ethnic minorities, and persons of lower socioeconomic status [9–11]. However, the majority of previous studies have been limited, in that they have been conducted among populations of persons still living with HIV [10, 12–16]. For this reason, it is presently not known to what extent apparent disparities in access to ART will improve as HIV disease becomes more advanced among persons who may have less access [17].

Of particular interest may be settings in which all medical care and ART are provided free of charge through a universal health-care system, because, in these settings, financial considerations may be less re-

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levant than in settings in which all or some of these services must be paid for by the patient. Therefore, the present study was conducted to evaluate access to antiretrovirals among persons who have died of HIV/AIDS in the province of British Columbia since 1995 and to determine the factors associated with receiving antiretrovirals before death.

## PATIENTS AND METHODS

***The HIV/AIDS treatment program.*** In the province of British Columbia, Canada, all anti-HIV medications have been centrally distributed at no cost to eligible HIV-infected individuals through the British Columbia Centre for Excellence in HIV/AIDS Drug Treatment Program since 1992. The treatment program remains the only source of free ART in the province, and pharmaceutical sales suggest that <1% of HIV-infected British Colombians purchase ART outside the program [17]. The center's HIV/AIDS Drug Treatment Program has received ethical approval from the University of British Columbia Ethics Review Committee, and the program conforms to the province's Freedom of Information and Protection of Privacy Act.

The center distributes antiretroviral medications on the basis of specific guidelines generated by a therapeutic guidelines committee. Since 1992, the guidelines have made available dual-nucleoside ART for people with a $CD4^+$ cell count of <350 cells/$mm^3$. In December 1995, dual therapy was made available to everyone with a $CD4^+$ cell count of <500 cells/$mm^3$. In June 1996, the center adopted plasma virus load–driven ART guidelines, consistent with those put forward by the International AIDS Society—USA [18]. In British Columbia, zidovudine has been available since 1986. The other 4 nucleoside analogues were made available over a period of 4 years: didanosine and zalcitabine in 1992, stavudine in 1993, and lamivudine in 1994. Saquinavir, indinavir, and ritonavir have been available since 1996, and nelfinavir has been available since 1998. Delavirdine and nevirapine were made available in Canada in 1998, and efavirenz became available a year later, in 1999.

***Study sample and variables of interest.*** For the purposes of the present study, a file was acquired from the British Columbia Ministry of Health's Vital Statistics Agency, which queried their database to extract records for all deaths that contained an *ICD-9* (1995–1999) or *ICD-10* (2000–2001) code indicating that HIV met the criteria of an underlying or associated cause of death. Vital Statistics defines a death as "HIV underlying" if the attending physician and/or coroner determines that the death was directly due to HIV infection. Alternatively, Vital Statistics defines a death as "HIV associated" if the attending physician and/or coroner determines that HIV infection was only a condition that contributed to the individual's underlying cause of death. Persons who died of accidental causes—such as illicit drug overdoses, suicides, and accidents—are not routinely tested for HIV in the province, and unless an individual is experiencing morbidity due to confirmed HIV infection, their death should not be coded as associated with HIV [19]. Nevertheless, to assess potential confounding that could stem from deaths among persons who were not eligible for ART, we evaluated the number of cases in which accidental causes of death (e.g., overdose or suicide) occurred in the data set.

For all deaths, Vital Statistics compiles several demographic characteristics, as well as the postal code of the home residence of the deceased. The demographic variables compiled included age at time of death, aboriginal ethnicity, and sex. Similar to the experience of blacks in the United States [9], aboriginal Canadians have been shown to be disproportionately affected by the HIV epidemic [20, 21]. Aboriginal Canadians also experience elevated mortality from causes of death related to poverty, compared with other ethnic groups [22]. We therefore decided to evaluate the effect of this variable on treatment access in the present study.

Because only limited sociodemographic data were available from the death records, as we and others have found previously [11, 23], we used census-based characteristics as a surrogate for socioeconomic variables. First, a profile of the province was acquired from Statistics Canada, which divided up the province into census tracts and census subdivisions and provided summary sociodemographic data for each census geographic area [24]. Second, a postal code conversion file was used to link each study subject's home residence postal code to the corresponding neighborhood-based data. This linkage enabled neighborhood median income and urban or rural status to be assigned to each individual. In addition, we determined the census tract codes for Vancouver's Downtown Eastside, a neighborhood that is well recognized as the epicenter of the province's HIV epidemic among injection drug users (IDUs) [17], and examined the impact of this variable on treatment access.

***Primary analysis of treatment access.*** We evaluated all deaths among HIV-infected persons that occurred during the period 1 January 1995–31 December 2001. We selected 1 January 1995 as the start of the study period because this is when we first observed marked declines in HIV/AIDS deaths in the province due to the increased use of stavudine and lamivudine [3, 25]. Among all subjects, we determined which individuals had ever received antiretrovirals from the treatment program through a confidential record linkage between Vital Statistics and the BC Centre for Excellence in HIV/AIDS. For the primary analysis, we conservatively assumed that an individual had accessed HIV treatment if they had ever filled $\geq 1$ prescription for antiretroviral medication from the treatment program before death. Although we restricted our analyses to persons who had died between 1995 and 2001, to be conservative, persons who received antiretrovirals at any time between 1992 and the end of 2001 were defined as having accessed treatment.

Univariate and multivariate statistical techniques were used to evaluate associations between study subject characteristics and treatment access prior to death. Variables considered in these analyses included neighborhood-based socioeconomic variables, as described above—sex, ethnicity (aboriginal vs. other), cause of death (HIV-underlying vs. HIV-associated), and age. Categorical explanatory variables were analyzed using Pearson's $\chi^2$ test, and continuous variables were analyzed using the Wilcoxon rank sum test. For the primary analysis of treatment access (ever vs. never), a logistical regression model was then fitted by including all variables that were statistically significant in univariate analyses. In addition to control for potential confounding, we decided a priori to adjust the final multivariate model for age, year of death, cause of death, and residence in the IDU HIV epicenter, regardless of whether these variables achieved statistical significance in univariate analyses.

***Subanalysis of time to treatment discontinuation.*** We assumed that filling ⩾1 prescription of antiretroviral medication was an imprecise measure of treatment access and therefore conducted a subanalysis to evaluate treatment access before death. Because we have previously found that receiving antiretrovirals <75% of the time during the first year of therapy is associated with mortality [26], we evaluated the proportion of patients who received antiretrovirals ⩾75% of the time during their first year of therapy and defined these patients as being consistently treated. However, because we had access to longitudinal data, we also evaluated the time to the first ⩾3-month stoppage of antiretroviral therapy before death (not restricted to the first year). Here, cumulative therapy discontinuation rates were estimated using Kaplan-Meier methods. As we have done previously, for the Kaplan Meier analysis, median income was dichotomized into those patients above and below the Canadian low-income cutoff of $14,147 CND [11, 27]. Patients who continued to receive therapy until within 3 months of their date of death were right censored at their date of death and coded as nonevents. Cox proportional-hazards regression was then used to calculate univariate and adjusted relative hazards and 95% confidence intervals (CIs), using the model-building protocol described above. Here, however, we also adjusted for year of therapy initiation, to adjust for changes in drug availability during the study period. The assumption of proportional hazards was validated by inspection of log (−log [survival function]) estimates against log time plots. All tests of significance were 2 sided, with $P < .05$ indicating that an association was statistically significant. All statistical analyses were done using SAS software (version 6.0; SAS).

## RESULTS

Overall, 1239 deaths among persons aged ⩾18 years had an *ICD-9* or *ICD-10* code indicating that HIV was either the underlying or an associated cause of death during the study period. Of these, 145 (11.7%) causes of death were deemed by the attending physician and/or coroner to be not associated with HIV, and 60 of these persons (41.4%) died without accessing treatment. Among this group, the most common underlying causes of death were various malignancies (22 [15.2%]), accidental causes (overdose, accident, and suicide) (18 [12.4%]), liver disease (15 [10.3%]), and various cardiac conditions (11 [7.6%]). Among the 18 accidental deaths, 12 (66.7%) individuals accessed therapy before death. Because of the low number of accidental deaths and the high proportion who had accessed therapy, we accepted the physician and/or coroner's judgement that HIV infection had contributed to the underlying cause of death and kept all individuals in the primary analysis. The remaining 1094 (88.3%) individuals died directly of an HIV-underlying cause (all AIDS related), among whom 346 (31.6%) died without accessing treatment. Overall, 19 (1.5%) individuals did not have a postal code that could be linked to census data, because of homelessness or other reasons, and were therefore excluded from all multivariate analyses. These 19 individuals were more likely to be aboriginal (53% vs. 12%; $P < .05$) and female (32% vs. 12%; $P < .05$).

***Primary analysis of treatment access.*** Table 1 shows the sociodemographic characteristics of the overall study population and the results of univariate comparisons of those who did ($n = 833$ [67.2%]) and did not ($n = 406$ [32.8%]) receive antiretrovirals before death. As shown here, aboriginal ethnicity (odds ratio [OR], 0.54), female sex (OR, 0.66), lower median income (OR, 0.63/$10,000 decrease), and residence in the IDU HIV epicenter (OR, 0.48) were negatively associated with accessing antiretrovirals before death. Age, urban residence, and year of death were not statistically associated with receiving ART before death.

Table 2 shows the results of the multivariate analysis of factors associated with receiving any ART before death. As shown here, aboriginal ethnicity (adjusted OR [AOR], 0.60; 95% CI, 0.41–0.87; $P = .008$), female sex (AOR, 0.68; 95% CI, 0.47–0.99; $P = .044$), and lower median income (AOR, 0.71; 95% CI, 0.54–0.92; $P = .011$/$10,000 decrease) were all negatively associated with receiving antiretrovirals prior to death in adjusted analyses.

***Subanalysis of treatment consistency.*** Overall, among the 833 individuals who received ART before death, only 379 (45.5%) received antiretroviral medication ⩾75% of the time during their first year of therapy, and 454 (54.5%) received antiretrovirals <75% of the time. Among the 81 aboriginal persons who accessed therapy, only 23 (28.4%) received antiretrovirals ⩾75% of the time, and, among the 90 women who accessed treatment, only 32 (35.6%) received antiretrovirals ⩾75% of the time. The median neighborhood income of those who were consistently treated was $19,890, and it was $18,976 among those who re-

**Table 1. Univariate analyses of sociodemographic and neighborhood-based characteristics, with regard to ever accessing human immunodeficiency virus (HIV) treatment before death.**

| Characteristic | Accessed treatment | | Unadjusted OR (95% CI) | *P* |
|---|---|---|---|---|
| | No | Yes | | |
| Ethnicity | | | | |
| Other | 338 (83.3) | 752 (90.3) | | |
| Aboriginal | 68 (16.8) | 81 (9.7) | 0.54 (0.38–0.76) | .001 |
| Sex | | | | |
| Male | 343 (84.5) | 743 (89.2) | | |
| Female | 63 (15.5) | 90 (10.8) | 0.66 (0.47–0.93) | .018 |
| Median income, $[a] (IQR) | 18.1 (13.6–21.0) | 19.4 (15.5–22.0) | 0.63 (0.50–0.79) | .001 |
| Cause of death | | | | |
| HIV-associated | 60 (14.8) | 85 (10.2) | | |
| HIV-underlying | 346 (85.2) | 748 (89.8) | 1.53 (1.07–2.18) | .019 |
| Age, median years (IQR) | 41 (34–48) | 41 (36–47) | 1.00 (0.89–1.12) | .480 |
| IDU HIV epicenter | | | | |
| No | 364 (89.7) | 789 (94.7) | | |
| Yes | 42 (10.3) | 44 (5.3) | 0.48 (0.31–0.75) | .001 |
| Urban | | | | |
| No | 45 (11.3) | 73 (8.9) | | |
| Yes | 354 (88.7) | 748 (91.1) | 1.30 (0.92–1.53) | .186 |
| Year of death, median (IQR) | 1997 (1995–1999) | 1997 (1996–1999) | 1.03 (0.98–1.09) | .301 |

**NOTE.** Data are no. (%) of subjects except where noted. Odds ratios (ORs) for continuous variables are as follows. Age, per 10 years older; median income, per $10,000 decrease. CI, confidence interval; IDU, injection drug use; IQR, interquartile range.

[a] Income in thousands $CND.

ceived antiretrovirals <75% of the time. All comparisons were statistically significant ($P < .05$) when the above variables were associated with receiving consistent treatment.

Figure 1 shows the cumulative therapy discontinuation (≥3 months) rates among the patients who accessed therapy, stratified by ethnicity, sex, and socioeconomic status. As shown here, aboriginal persons, women, and persons in the lower income strata had statistically elevated rates of therapy discontinuation (all log rank $P < .05$). The curves do not drop until 1 month after the initiation of therapy, because all individuals are initially dispensed 1 month's worth of ART.

Table 3 shows the univariate and adjusted relative hazards (ARHs) of therapy discontinuation for those who accessed therapy prior to death. As shown here, in adjusted analyses, women (ARH, 1.33; 95% CI, 1.00–1.77; $P = .049$) and persons of lower socioeconomic status (ARH, 1.41; 95% CI, 1.16–1.72 per $10,000 decrease; $P < .001$) experienced statistically elevated rates of therapy discontinuation. In the adjusted analysis, ethnicity did not achieve statistical significance.

## DISCUSSION

Even in a setting where all health care is provided free of charge by the state, high HIV/AIDS death rates persist because of the lack of, or only marginal access to, antiretrovirals. In the present study, one-third of HIV-related deaths occurred among untreated individuals, and those who died without ever receiving HIV treatment were more likely to be aboriginal, to be female, and to reside in a neighborhood with a lower median income. Among those who accessed treatment, fewer than half received consistent treatment before death, and similar sociodemographic characteristics were associated with elevated rates of treatment discontinuation before death.

In North America, aboriginal persons (including American Indians and Alaska natives) may be at elevated risk of HIV in-

**Table 2. Logistical regression analysis of factors associated with ever receiving antiretroviral treatment before death.**

| Variable | Adjusted OR (95% CI) | *P* |
|---|---|---|
| Aboriginal ethnicity, yes vs. no | 0.60 (0.41–0.87) | .008 |
| Sex, female vs. male | 0.68 (0.47–0.99) | .044 |
| Median income, per $10,000 decrease | 0.71 (0.54–0.92) | .011 |

**NOTE.** The model was also adjusted for year of death, residence in the injection-drug use human immunodeficiency virus epicenter, age, and cause of death. CI, confidence interval; OR, odds ratio.

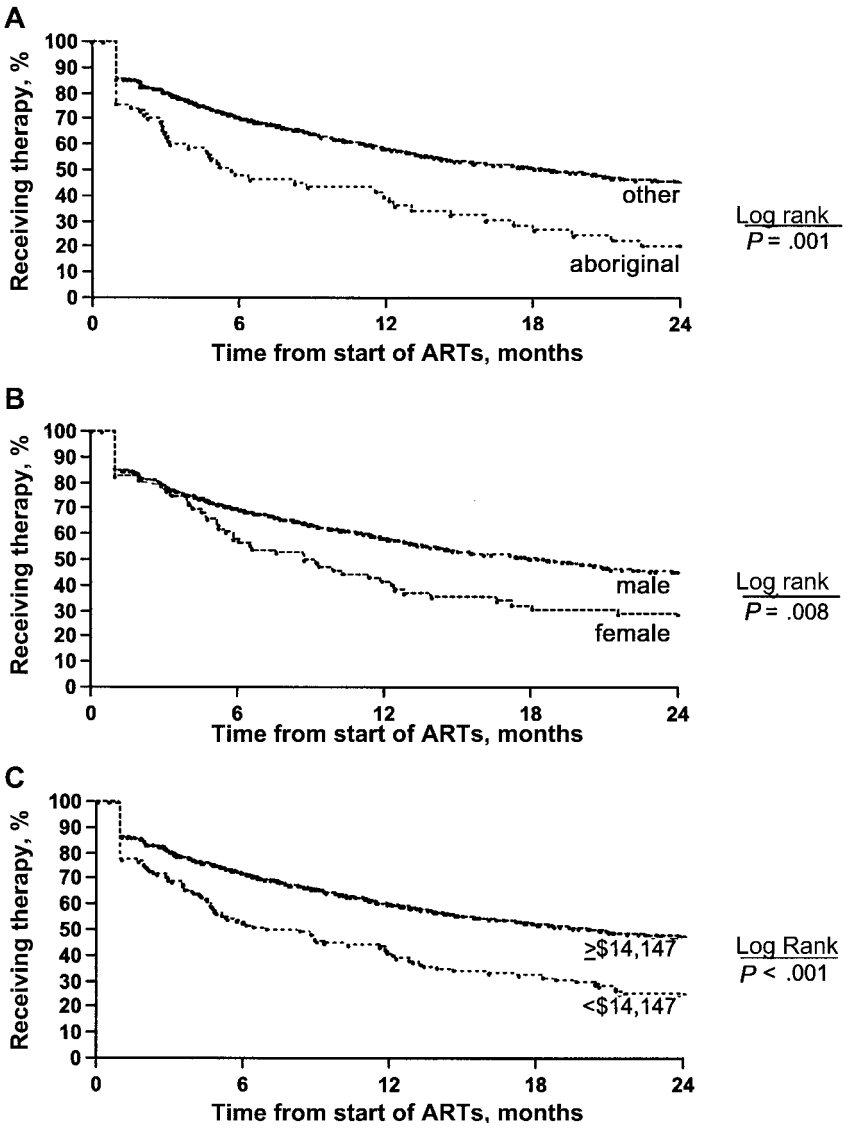


**Figure 1.** Product limit estimates of cumulative therapy discontinuation for ⩾3 months among human immunodeficiency virus (HIV)–infected subjects who died between 1 January 1995 and 31 December 2001, stratified by ethnicity *(A),* sex *(B),* and socioeconomic status *(C),* are shown. Note that the curves do not drop until 1 month after the initiation of antiretroviral therapy (ART), because all individuals are initially dispensed 1 month's worth of treatment.

fection [20, 21, 28]. For this reason, it is particularly worrisome that the present study identified strong associations between aboriginal ethnicity and not receiving antiretroviral therapy. These data demonstrate that culturally sensitive interventions aimed at improving access to antiretrovirals among HIV-infected aboriginal persons is an urgent priority. Although previous studies of access to antiretrovirals have tended to be conducted among living populations, these findings are also consistent with the experience of other HIV-positive ethnic minorities in other settings [10, 13, 14].

In addition, we found associations between lower income and female sex and not receiving antiretrovirals, as well as receiving inconsistent treatment, prior to death. These findings are also consistent with the results of previous studies that have found lower socioeconomic status and female sex to be associated with worse access to health care [10, 12, 29, 30], and interventions aimed at improving access to antiretrovirals among women and lower income persons must also be made a priority [10, 13, 31].

Although in urgent need of further study, strategies that may improve access and adherence to antiretrovirals among HIV-infected IDUs include improved access to illicit drug treatment, directly observed therapy programs, access to medical services without appointment, and onsite pharmacists at medical clinics

**Table 3. Univariate and multivariate Cox proportional-hazards regression of factors associated time to antiretroviral therapy discontinuation of >3 months.**

| Characteristic | Unadjusted RH (95% CI) | Adjusted RH (95% CI) |
|---|---|---|
| Ethnicity, aboriginal vs. other | 1.56 (1.18–2.06) | 1.19 (0.87–1.61) |
| Sex, female vs. male | 1.41 (1.09–1.84) | 1.33 (1.00–1.77) |
| Median income, per $10,000 decrease | 1.55 (1.31–1.84) | 1.41 (1.16–1.72) |

**NOTE.** The model was also adjusted for year of death, residence in the injection-drug use human immunodeficiency virus epicenter, age, and cause of death. CI, confidence interval; RH, relative hazard.

[13, 32–37]. Conversely, lower levels of HIV-related experience have been associated with worse access to antiretroviral therapy [12].

There are several features of our study that should be highlighted. First, it is important to stress that the data were gathered in a setting in which all HIV/AIDS care, antiretrovirals, and laboratory monitoring are available free of charge and where, as previous studies have shown, virtually all patients acquire antiretrovirals through a centralized source [12]. Second, the centralized death registry enabled complete population-level data on HIV/AIDS deaths and causes of death for the entire province. Finally, because a complete prospective record of antiretroviral dispensation was maintained, it was possible to determine precisely each individual's level of treatment before death. For these reasons, our results were not influenced by selection factors that may compromise the interpretation of other cohort studies.

Conversely, although previous studies have suggested that ecological measures may result in an underestimation of the true relationship between socioeconomic status and health outcomes [11, 38], we should stress that there was potential for misclassification, because an ecological measure of socioeconomic status was used. Similarly, although we adjusted our analyses for residence in the neighborhood in which the majority of IDUs are concentrated, a major limitation of data from death registries is that they do not contain data regarding behaviors such as the use of illicit drugs. A multitude of studies have found addiction to be a barrier to accessing adequate HIV treatment [12, 34, 39], and, were these data available, it is likely that our models would have been affected. This is because IDUs tend to reside in lower income areas and because, in comparison to other risk groups, women are more likely to have been infected through illicit drug use or through sexual contact with IDUs [40, 41]. Nevertheless, it should be noted that such an adjustment, if possible, would not change the underlying fact that women and persons of lower socioeconomic status have markedly worse access and higher therapy discontinuation rates in our setting. We should also note that lower income neighborhoods may also be associated with higher levels of crack cocaine or other non–injection drug use, as well as a higher prevalence of mental illness, including depression, all of which have been associated with a higher risk of HIV infection as well as lower access to antiretrovirals [40, 42].

In summary, we found that one-third of HIV-related deaths occurred among untreated individuals and that aboriginal ethnicity, female sex, and lower socioeconomic status were all associated with dying without treatment. Among those who accessed treatment before death, fewer than half received consistent treatment, and similar sociodemographic factors were associated with higher rates of therapy discontinuation. Given that these data were derived in a universal health care setting in which all HIV/AIDS care and antiretrovirals are available free of charge, it is likely that similar problems exist in many other settings in the developed world. To prevent ongoing levels of HIV/AIDS mortality, novel health care interventions and the expansion of illicit drug treatment will be required to improve access to antiretrovirals and HIV/AIDS care among populations with poor access.

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