Rates of Initial Virological Suppression and Subsequent Virological Failure After Initiating Highly Active Antiretroviral Therapy: The Impact of Aboriginal Ethnicity and Injection Drug Use

L.J. Martin*,1, S. Houston1,2, Y. Yasui1, T.C. Wild3 and L.D. Saunders*1

1Department of Public Health Sciences, School of Public Health, University of Alberta, Canada; 2Division of Infectious Diseases, Department of Medicine, University of Alberta; Canada; 3Centre for Health Promotion Studies, School of Public Health, University of Alberta; Canada

Abstract: Objectives: To compare rates of initial virological suppression and subsequent virological failure by Aboriginal ethnicity after starting highly active antiretroviral therapy (HAART).

Methods: We conducted a retrospective cohort study of antiretroviral-naïve HIV-patients starting HAART in January 1999-June 2005 (baseline), followed until December 31, 2005 in Alberta, Canada. We compared the odds of achieving initial virological suppression (viral load <500 copies/mL) by Aboriginal ethnicity using logistic regression and, among those achieving suppression, rates of virological failure (the first of two consecutive viral loads >1000 copies/mL) by Aboriginal ethnicity using cumulative incidence curves and Cox proportional hazards models. Sex, injection drug use as an HIV exposure category (IDU), baseline age, CD4 cell count, viral load, calendar year, and HAART regimen were considered as potential confounders.

Results: Of 461 study patients, 37% were Aboriginal and 48% were IDUs; 71% achieved initial virological suppression and were followed for 730.4 person-years. After adjusting for confounding variables, compared to non-Aboriginals with other exposures, the odds of achieving initial virological suppression were lower for Aboriginal IDUs (OR=0.33, 95% CI=0.19-0.60, p=0.0002), non-Aboriginal IDUs (OR=0.30, 95% CI=0.15-0.60, p=0.0006), and Aboriginals with other exposures (OR=0.38, 95% CI=0.21-0.67, p=0.0009). Among those achieving suppression, Aboriginals experienced higher virological failure rates 1 year after suppression (hazard ratio=3.35, 95% CI=1.68-6.65, p=0.0006).

Conclusions: Future research should investigate adherence among Aboriginals and IDUs treated with HAART and explore their treatment experiences to assess ways to improve outcomes.

Keywords: Aboriginal populations, antiretroviral therapy, highly active, intravenous drug users, treatment outcomes.

INTRODUCTION

Despite the well documented benefits of highly active antiretroviral therapy (HAART), Aboriginal HIV-patients in Canada appear to experience less successful HAART outcomes; however, findings are inconsistent. Recent research has shown that, after starting HAART, Aboriginal HIV-patients experience higher rates of HIV-related [1] and all-cause [1, 2] mortality compared to non-Aboriginals. In contrast, rates of initial virological suppression after starting HAART do not appear to differ by Aboriginal ethnicity [2, 3]. However, to our knowledge, no research has examined the durability of virological suppression, a key goal of HAART [4], in relation to Aboriginal ethnicity. We hypothesize that the higher rates of HIV-related mortality observed among Aboriginals after starting HAART may be explained by higher rates of HAART failure, that is, failure to maintain virological suppression, which may be observed as a detectable viral load or potentially represented by a patient being lost to follow-up from treatment.

Developing a better understanding of how HAART outcomes may differ between Aboriginals and non-Aboriginals is especially important for two reasons. First, Aboriginals are overrepresented in Canada’s HIV epidemic [5], with 24% of positive HIV tests reported with available ethnicity data between 1998-2008 being from Aboriginals [6]. Therefore, poorer treatment outcomes may impact a substantial proportion of the HIV-patient population in Canada. Second, it is well recognized that, in general, Aboriginal people in Canada have poorer health and socioeconomic status compared to the general Canadian population. For example, Aboriginals have lower life expectancies, higher infant mortality rates, lower education levels, and higher unemployment rates [7]. These factors may be related to poorer HAART outcomes. Furthermore, they may facilitate progression from HAART failure to mortality.

We undertook this study to compare the odds of experiencing initial virological suppression and the rates of subsequent HAART failure between Aboriginal and non-Aboriginal HIV-patients treated with HAART in northern Alberta, Canada to help create a better understanding of the
observed higher rates of HIV-related mortality associated with Aboriginal ethnicity.

METHODS

This was a retrospective cohort study carried out in two parts: in Part 1, we investigated the odds of achieving initial virological suppression by Aboriginal ethnicity and in Part 2, we investigated rates of HAART failure by Aboriginal ethnicity among patients who achieved initial virological suppression in Part 1.

Data Sources

Our primary data source was the Northern Alberta HIV Program (NAHIVP) clinical database. NAHIVP operates primarily out of four sites in Edmonton (University of Alberta Hospital, Royal Alexandra Hospital, Sexually Transmitted Disease Clinic, and the private practice of one infectious disease physician). Most patients are cared for by a health care team that includes infectious disease specialists, nurses, pharmacists, social workers, psychologists, and a dietician. Data related to patients seen at NAHIVP clinics, including demographics, risk behaviours, antiretroviral therapies (ARTs) prescribed, CD4 cell counts, viral loads, and deaths reported to the clinics are recorded in the NAHIVP database. In addition to data from NAHIVP, we linked cause and date of death data from the provincial vital status registry at Alberta Health and Wellness to the study database and used viral loads from the Alberta Provincial Public Health Laboratory to replace missing baseline viral load results where possible. The study procedures were approved by the University of Alberta Health Research Ethics Board.

Study Patients

We assembled a cohort of patients using the NAHIVP database and the following eligibility criteria: 1) started HAART between 1 January 1999 and 30 June 2005 (baseline); 2) previously ART-naive; and 3) ≥15 years of age when starting HAART. We defined HAART as a combination of at least three antiretrovirals, other than ritonavir, recorded as prescribed on the same date. We excluded ritonavir under the assumption that, during the study period (1999-2005), ritonavir would have been prescribed at low dosages intended to boost other protease inhibitors, rather than at clinically therapeutic levels. The HAART start date was the first date that a HAART prescription was recorded in the database and we assumed that patients remained on HAART. We excluded patients if they 1) were missing ethnicity data, 2) were missing baseline viral load data; 3) had a baseline viral load <500 copies/mL; or 4) started HAART <26 weeks before delivering a baby. We excluded the latter group of patients in an effort to limit the study to patients who started HAART for the purpose of treatment, rather than to prevent vertical transmission of HIV; we assumed that starting HAART earlier in pregnancy or after delivery would be for maternal indications. We excluded patients with baseline viral loads that were missing or <500 copies/mL because we suspected these patients were not ART-naive when starting HAART.

Explanatory Variables

Our exposure variable of interest was Aboriginal ethnicity; we defined Aboriginals as Treaty and non-Treaty Aboriginals, Métis, and Inuit, which are the main groups of Indigenous peoples in Canada. We considered several potential confounding variables: injection drug use (IDU) as an HIV exposure category, sex, and baseline age, CD4 cell count, viral load, HAART regimen prescribed, and calendar year. We classified HIV exposure categories using an exposure category hierarchy [8]. Subjects were defined as IDUs if their HIV exposure was recorded as IDU or any exposure combined with IDU; patients with other exposure categories, including unknown or missing exposures, were considered to have “other exposures”. Baseline CD4 cell count and viral load were defined as those tests taken closest to the HAART start date, which was ≤6 months before, and not after starting HAART.

Statistical Analyses

Initially, patient characteristics were tabulated and compared between Aboriginals and non-Aboriginals and between IDUs and patients with other exposures using χ² and Fisher exact tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

For Part 1, we used logistic regression to assess the odds of achieving initial virological suppression (one viral load measure <500 copies/mL ≤6 months after starting HAART) in relation to Aboriginal ethnicity, adjusting for potential confounding variables. We defined patients with no viral load tests ≤6 months after starting HAART as not achieving initial virological suppression.

For Part 2, our primary definition of HAART failure was virological failure, defined as the first of two consecutive viral load tests >1000 copies/mL. In addition, we conducted a secondary analysis investigating loss to follow-up (which we considered as a marker of possible, untested virological failure) and all-cause mortality. Patients were classified as lost to follow-up, without achieving virological failure, if they: 1) had >12 months between any two viral load tests or 2) did not have a viral load test taken >12 months before the end of the study (December 31, 2005) but were still alive 12 months after their last viral load test (i.e., they had not died before meeting our definition of being lost to follow-up). Patients who returned to the clinic after being lost to follow-up were not entered back into the analysis.

Observation time for Part 2, measured in person-years [9], started on the date of initial virological suppression and, depending on the patient’s outcome, ended on the earliest of the following events: 1) the virological failure date for those who experienced virological failure; 2) 12 months after the last recorded viral load test date for those lost to follow-up; 3) December 31, 2005 for those who were censored; or 4) the date of death for those who died.

In unadjusted analyses for Part 2, we compared rates of virological failure, loss to follow-up, and all-cause mortality by Aboriginal ethnicity using cumulative incidence curves,
as described by Gooley et al. [10]. Then, we compared hazard ratios (HRs) of virological failure using Cox proportional hazards models [11], adjusting for potential confounding variables. We assessed the proportional hazards assumption for Aboriginal ethnicity graphically and using a time-varying covariate (Aboriginal ethnicity by the logarithm of observation time), which we entered into an unadjusted model of virological failure that included only the main effect for Aboriginal ethnicity.

In adjusted analyses for Parts 1 and 2, we controlled for potential confounding variables that were associated with initial virological suppression (or virological failure) in unadjusted analyses at p<0.20. We a priori planned and tested the interaction between Aboriginal ethnicity and IDU in models that included both terms as main effects to determine if the impact of Aboriginal ethnicity on initial suppression (or virological failure) differed by IDU status. P-values were two-tailed and those <0.05 were considered statistically significant. Analyses were conducted with SAS® (version 9.1; SAS Institute Inc., Cary, NC) and R (version 2.6.2).

**Sensitivity Analyses**

To supplement our primary analyses in Parts 1 and 2, we conducted four sensitivity analyses to assess our findings. For Part 1, we re-ran the final logistic regression model after excluding patients with no viral load tests in the 6 months following baseline. We did this because Aboriginals were less likely to have at least one viral load test after baseline and, in our primary analysis, these patients were defined as not achieving initial virological suppression. For Part 2, we conducted three sensitivity analyses using the final multivariable Cox proportional hazards model. First, we redefined HAART failure as exhibiting one viral load test result >1000 copies/mL instead of two consecutive tests >1000 copies/mL. We did this because some patients had <2 viral load tests after initial virological suppression and, therefore, could not be defined as experiencing virological failure in the primary analysis. Second, for patients who were lost to follow-up, censored, or who died, we ended observation time on the date of their last viral load test but maintained the same HAART failure definition as in the primary analysis. We did this because our primary analysis may have overestimated the time that patients were assumed to be virologically suppressed before reaching one of these three outcomes. For example, we assumed that patients lost to follow-up were virologically suppressed for 12 months after their last viral load test; however, we can only be certain that they were suppressed until their last viral load test. Third, we combined the first and second sensitivity analyses: we redefined HAART failure as exhibiting one viral load >1000 copies/mL and, for patients who were lost...
to follow-up, censored, or who died, we ended observation time on the date of the last viral load test. This combined analysis was meant to assess the maximum amount our primary results would change if we adopted all the alternate assumptions of our sensitivity analyses.

RESULTS

The study sample for Part 1 (initial virological suppression analysis) included 461 patients (Fig. 1). We excluded 87 patients for having a baseline viral load that was missing (n=19) or <500 copies/mL (n=68). Compared to the study patients, these 87 patients were less likely to be Aboriginal (25% vs 37%, p=0.032), were more likely to start HAART on a protease inhibitor (PI)-based regimen (43% vs 24%, p=0.0004), and had a higher baseline CD4 cell count (median 370 (n=69) vs 190 cells/μL, p<0.0001).

Of the 461 study patients, 172 (37%) were Aboriginal; most non-Aboriginals were Caucasian (226, 78%). Almost half the patients were defined as IDU (220, 48%); other exposures were primarily heterosexual contact (126, 52%) and men who have sex with men (MSM) (90, 37%). Compared to non-Aboriginals, Aboriginal patients were significantly more likely to be female (39% vs 14%, p<0.0001), have IDU as an HIV exposure category (66% vs 34%), and had a lower baseline CD4 cell count (median 370 vs 410 cells/μL, p<0.0001), have HIV RNA copies/mL at baseline (median 130,000 vs 105,000 copies/mL, p=0.042), and start HAART later (median 2002 vs 1999, p=0.001).

Table 1.  Patient Characteristics by Ethnicity for Part 1 (Initial Virological Suppression) (N=461)

| Characteristic                        | Aboriginal (n=172, 37%) | Non-Aboriginal (n=289, 63%) | p-Value |
|---------------------------------------|-------------------------|-----------------------------|---------|
| Number of viral load tests in the 6 months after baseline, no. (%) |                        |                             |         |
| 0                                     | 28 (16)                 | 23 (8.0)                    | 0.0059  |
| ≥1                                    | 144 (84)                | 266 (92)                    |         |
| Sex, no (%)                           |                         |                             | <0.0001 |
| Female                                | 67 (39)                 | 41 (14)                     |         |
| Male                                  | 105 (61)                | 248 (86)                    |         |
| HIV exposure category, no (%)         |                         |                             | <0.0001 |
| Injection drug use                    | 113 (66)                | 107 (37)                    |         |
| Other exposures                       | 59 (34)                 | 182 (63)                    |         |
| CD4 cells/μL at baseline, median (IQR)| 180 (80-280) (n=165)    | 200 (110-290) (n=271)       | 0.31    |
| CD4 cells/μL at baseline, no. (%)     |                         |                             | 0.55    |
| 0-50                                  | 29 (17)                 | 49 (17)                     |         |
| 51-200                                | 61 (35)                 | 94 (33)                     |         |
| 201-350                               | 55 (32)                 | 82 (28)                     |         |
| >350                                  | 20 (12)                 | 46 (16)                     |         |
| Missing                               | 7 (4.1)                 | 18 (6.2)                    |         |
| HIV RNA copies/mL at baseline, median (IQR)| 105,000 (38,000-405,000) | 130,000 (46,000-410,000) | 0.42    |
| HIV RNA copies/mL at baseline, no. (%) |                         |                             | 0.59    |
| 0-9,999                               | 17 (9.9)                | 24 (8.3)                    |         |
| 10,000-99,999                         | 59 (34)                 | 90 (31)                     |         |
| ≥100,000                              | 96 (56)                 | 175 (61)                    |         |
| Age at baseline, median (IQR)         | 36.5 (31.6-42.5)        | 40.2 (33.7-45.6)            | 0.0008  |
| Age at baseline, no. (%)              |                         |                             | 0.020   |
| 15-<30                                | 30 (17)                 | 46 (16)                     |         |
| 30-<40                                | 77 (45)                 | 93 (32)                     |         |
| 40-<50                                | 52 (30)                 | 113 (39)                    |         |
| ≥50                                   | 13 (7.6)                | 37 (13)                     |         |
| Initial HAART regimen, no. (%)        |                         |                             | 0.095   |
| PI-based                              | 34 (20)                 | 77 (27)                     |         |
| Not PI-based                          | 138 (80)                | 212 (73)                    |         |
| Year starting HAART, no. (%)          |                         |                             | 0.47    |
| 1999-2001                             | 75 (44)                 | 116 (40)                    |         |
| 2002-2005                             | 97 (56)                 | 173 (60)                    |         |

IQR=interquartile range, HAART=highly active antiretroviral therapy, PI=protease inhibitor.
37%, \( p<0.0001 \), start HAART at a younger age (median 36.5 vs 40.2 years, \( p=0.0008 \)), and have no viral load tests in the 6 months after starting HAART (16% vs 8.0%, \( p=0.0059 \)) (Table 1).

### Part 1 – Initial Virological Suppression

Within 6 months of starting HAART, 328 patients (71%) achieved initial virological suppression. Of the 133 patients who did not achieve initial virological suppression (65, 49% were Aboriginal), 51 (38%) had no viral load tests after baseline and 82 (62%) had no follow-up viral load tests <500 copies/mL 6 months after baseline. Five of these 133 patients (3.8%) died 6 months after starting HAART, 4 of whom were Aboriginal. Aboriginals were less likely than non-Aboriginals to experience initial virological suppression (62% vs 76%, \( p=0.0011 \)) in the unadjusted analysis. After controlling for the effects of sex and baseline CD4 cell count, HAART regimen, and calendar year, compared to non-Aboriginals with other exposures, the odds of achieving initial virological suppression were significantly lower for Aboriginal IDUs (odds ratio (OR)=0.33, 95% CI=0.19-0.60, \( p=0.0002 \)), non-Aboriginal IDUs (OR=0.30, 95% CI=0.15-0.60, \( p=0.0006 \)), and Aboriginals with other exposures (OR=0.38, 95% CI=0.21-0.67, \( p=0.0009 \)) (Table 2). In our sensitivity analysis for Part 1, which excluded patients who had no viral load tests in the first 6 months after starting HAART, the odds of achieving initial virological suppression remained similar to the primary analysis for non-Aboriginal IDUs and Aboriginals with other exposures;

### Table 2. Unadjusted and Adjusted Logistic Regression Models, Including Primary Analysis and Sensitivity Analysis Assessing Initial Virological Suppression After Starting HAART

| Variable                                      | Unadjusted Analysis (n=461) | Primary Analysis (n=461) | Sensitivity Analysis (n=410) |
|-----------------------------------------------|-----------------------------|--------------------------|-----------------------------|
|                                               | Unadjusted Odds Ratio       | 95% CI                   | p-Value                     | Adjusted Odds Ratio       | 95% CI                   | p-Value                     | Adjusted Odds Ratio       | 95% CI                   | p-Value                     |
| Ethnicity (Aboriginal vs non-Aboriginal)       | 0.51                        | 0.34-0.76                | 0.0012                      | -                          | -                        | -                          | -                          | -                        | -                          |
| HIV exposure category (Injection drug use vs other exposures) | 0.47                        | 0.31-0.71                | 0.0003                      | -                          | -                        | -                          | -                          | -                        | -                          |
| Aboriginal, injection drug use exposure       | -                           | -                        | -                           | 0.33                       | 0.19-0.60                | 0.0002                      | 0.50                       | 0.25-1.01                | 0.053                      |
| Non-Aboriginal, injection drug use exposure   | -                           | -                        | -                           | 0.30                       | 0.15-0.60                | 0.0006                      | 0.30                       | 0.14-0.64                | 0.0019                      |
| Aboriginal, other exposures                  | -                           | -                        | -                           | 0.38                       | 0.21-0.67                | 0.0009                      | 0.41                       | 0.21-0.80                | 0.0090                      |
| Non-Aboriginal, other exposures (ref)         | -                           | -                        | -                           | 1.00                       | -                        | -                          | 1.00                       | -                        | -                          |
| Sex (Female vs male)                          | 0.61                        | 0.39-0.96                | 0.033                       | 0.72                       | 0.44-1.18                | 0.19                       | 0.61                       | 0.35-1.09                | 0.098                      |
| CD4 cells/μL at baseline                     | 1.00                        | -                        | -                           | 1.00                       | -                        | -                          | 1.00                       | -                        | -                          |
| ≤50 (ref)                                     | 1.00                        | -                        | -                           | 1.00                       | -                        | -                          | 1.00                       | -                        | -                          |
| >50-200                                       | 0.99                        | 0.53-1.85                | 0.98                        | 1.01                       | 0.53-1.93                | 0.98                       | 0.95                       | 0.44-2.06                | 0.91                       |
| >200-350                                      | 0.93                        | 0.50-1.76                | 0.83                        | 1.00                       | 0.52-1.95                | 0.98                       | 0.96                       | 0.44-2.12                | 0.92                       |
| >350                                          | 0.44                        | 0.22-0.89                | 0.022                       | 0.47                       | 0.22-1.01                | 0.052                      | 0.52                       | 0.21-1.30                | 0.16                       |
| Missing baseline CD4 count                   | 0.89                        | 0.32-2.44                | 0.82                        | 0.99                       | 0.35-2.82                | 0.98                       | 0.90                       | 0.27-3.05                | 0.86                       |
| HIV RNA copies/mL at baseline                | Class p=0.80                |                          |                             |                            |                          |                             |                            |                          |                             |
| <10,000                                       | 1.30                        | 0.61-2.77                | 0.50                        | -*                        | -                        | -                          | -                          | -                        | -                          |
| 10,000–<100,000                               | 1.03                        | 0.67-1.60                | 0.89                        | -                          | -                        | -                          | -                          | -                        | -                          |
| ≥100,000 (ref)                                | 1.00                        | -                        | -                           | 1.00                       | -                        | -                          | 1.00                       | -                        | -                          |
| Baseline age, years                           | Class p=0.60                |                          |                             |                            |                          |                             |                            |                          |                             |
| 15–<30 (ref)                                  | 1.00                        | -                        | -                           | -                          | -                        | -                          | -                          | -                        | -                          |
| 30–<40                                       | 1.25                        | 0.70-2.22                | 0.45                        | -                          | -                        | -                          | -                          | -                        | -                          |
| 40–<50                                       | 1.39                        | 0.77-2.49                | 0.27                        | -                          | -                        | -                          | -                          | -                        | -                          |
| ≥50                                          | 1.65                        | 0.74-3.68                | 0.22                        | -                          | -                        | -                          | -                          | -                        | -                          |
| Baseline HAART regimen (PI vs non-PI based)   | 0.49                        | 0.31-0.77                | 0.0020                      | 0.50                       | 0.31-0.82                | 0.0054                      | 0.51                       | 0.29-0.92                | 0.024                      |
| Baseline calendar year (1999-2001 vs 2002-2005) | 0.63                        | 0.42-0.94                | 0.024                       | 0.87                       | 0.55-1.37                | 0.54                       | 1.17                       | 0.68-2.02                | 0.57                       |

Ref=referent group, PI=protease inhibitor.

*Variables with p-values ≥0.20 were not included in the multivariate model.
however, for Aboriginal IDUs, this relationship weakened and became of borderline statistical significance (Table 2).

**Part 2 – HAART Failure**

Of the 461 patients eligible for Part 1, the 328 patients who achieved virological suppression were eligible for Part 2 and were followed for a total of 730.4 person-years; 63 (19%) experienced virological failure, 60 (18%) were lost to follow-up, 191 (58%) were censored, and 14 (4.3%) died before experiencing any other event. In addition, 4 patients (6.4%) who experienced virological failure died and 3 patients (5.0%) who were lost to follow-up died. One third of the patients (107, 33%) in Part 2 were Aboriginal. Overall, after initial virological suppression, Aboriginals and non-Aboriginals had a similar median number of viral load tests (8, interquartile range (IQR)=2-10 vs 6, IQR=3-12 tests, p=0.29) and median follow-up time (1.6, IQR=1.0-2.9 vs 1.8, IQR=1.1-3.3 years, p=0.29). However, Aboriginals were more likely than non-Aboriginals to have no viral load tests after achieving initial suppression (15, 14% vs 14, 6.3%, p=0.022). Aboriginal patients were significantly more likely than non-Aboriginals to experience virological failure (30, 28% vs 33, 15%, p=0.0047) but were not more likely than other patients to be lost to follow-up (22, 21% vs 38, 17%, p=0.46). Furthermore, compared to non-Aboriginals, Aboriginal patients experienced significantly higher cumulative incidence rates of virological failure (p=0.011) but similar cumulative incidence rates of loss to follow-up (p=0.73) (Fig. 2).

![Graphs](image)

**Fig. (2).** Cumulative incidence of (a) virological failure, (b) loss to follow-up, and (c) all-cause mortality after initial virological suppression by Aboriginal ethnicity (N=328).
In Cox proportional hazards models, Aboriginal patients experienced significantly higher crude virological failure rates compared to non-Aboriginals ($HR=2.09$, 95% CI=1.27-3.43, $p=0.0038$; Table 3). In checking the proportional hazards assumption, the continuous time-varying Aboriginal ethnicity covariate was statistically significant ($p=0.042$). To better characterize this relationship, we categorized time into four categories: <1 year and <2 years, 2 years and <3 years, and >3 years, all compared to <1 year. At 1 year, the rate of virological failure was significantly higher for Aboriginals compared to non-Aboriginals, but at 2 years and 3 years, this association appeared to remain similarly high. Therefore, we felt that one dichotomous time-varying covariate (>1 year vs <1 year) best represented this relationship and included this variable in the final model (Table 3). Adjusting for sex and baseline viral load and calendar year, Aboriginals appear to have similar rates of virological failure less than one year after achieving initial virological suppression; however, at one year and beyond, Aboriginals have a significantly higher rate of virological failure compared to non-Aboriginals ($HR=3.35$, 95% CI=1.68-6.65, $p=0.0006$; Table 3). In our sensitivity analyses, our estimated HRs for Aboriginal patients remained similar to our primary model (Table 4).

### DISCUSSION

Among HIV-patients starting HAART, Aboriginal IDUs, non-Aboriginal IDUs, and Aboriginals with other exposures were all similarly less likely to achieve initial virological suppression compared to non-Aboriginals with other exposures. Among patients who achieved initial virological suppression, rates of virological failure did not differ by Aboriginal ethnicity <1 year after suppression; however, ≥1 year after suppression, Aboriginals experienced a significantly higher rate of virological failure compared to non-Aboriginals. In contrast, loss to follow-up rates did not differ by Aboriginal ethnicity and rates of virological failure did not differ by IDU.

Two studies conducted in British Columbia (BC), Canada have compared rates of initial virological suppression by Aboriginal ethnicity and observed different results from the present study. Lima et al. and Miller et al., respectively, defined virological suppression as time to the first of two consecutive viral loads <500 copies/mL after...
starting HAART and the second of two consecutive viral loads <500 copies/mL after starting dual or triple ART [2, 3]. Lima et al. and, after adjusting for confounding variables, Miller et al. observed no significant difference in rates of virological suppression by Aboriginal ethnicity. Both studies controlled for adherence to treatment, which may help to explain why Aboriginals may have been less likely to achieve initial virological suppression in our study. In addition, both studies excluded patients with <2 viral load tests, which is more methodologically similar to our sensitivity analysis in Part 1 when we excluded patients who had no viral load tests within the 6 months after starting HAART. Our sensitivity analysis of initial virological suppression showed a weaker difference of borderline statistical significance between Aboriginal IDUs and non-Aboriginals with other exposures because these excluded patients were more likely to be Aboriginal IDUs. Therefore, these two BC studies may have selected a subset of patients who were more likely to achieve suppression, which may be another reason they found no difference by Aboriginal ethnicity.

Two other studies conducted in BC report a similar relationship between virological suppression and IDU as we found in our study. Palepu et al. found that active injection drug users were less likely to achieve virological suppression after starting HAART compared to patients with no history of IDU, even after adjusting for adherence measured by pharmacy-refill data; however, they suggest that this measure does not effectively assess adherence among active injection drug users because it was not significantly associated with virological suppression [12]. Wood et al. also found that patients with a history of injection drug use were less likely to achieve virological suppression, but this relationship was not statistically significant after adjusting for adherence measured by pharmacy-refill data [13]. Therefore, in BC, IDU is also associated with lower rates of virological suppression, and this relationship appears to be explained by lower rates of adherence.

To our knowledge, the present study is the first to compare virological failure between Aboriginals and non-Aboriginals after starting HAART. Results of our sensitivity analyses suggest that the relationship we observed between Aboriginal ethnicity and higher rates of virological failure are robust to different analytic methods. This relationship appears to be consistent with our previous research, which demonstrates that Aboriginal HIV-patients have significantly higher rates of HIV-related mortality compared to non-Aboriginals after starting HAART [1]. Rates of virological failure did not differ by Aboriginal ethnicity in the first year after achieving initial virological suppression; therefore, it appears that, among those who initially achieve suppression, these two patient groups are initially equally likely to adhere to therapy. However, after this time, Aboriginals may have more difficulty adhering to treatment. We found no differences in rates of loss to follow-up by Aboriginal ethnicity; however, this was defined as not receiving a viral load test in >12 months, and may not represent missed clinic appointments, which has been associated with virological failure [14], and does not describe adherence over this 12 month period.

Aboriginals may be less likely to achieve initial virological suppression and more likely to experience virological failure due to poor adherence to treatment, which may be associated with lower socioeconomic status and ongoing substance use not captured by the variable assessing IDU as route of exposure to HIV. Adherence is a key determinant of successful virological outcomes [15, 16]. Poor adherence to therapy has been associated with poor socioeconomic status and social instability, including factors such as low income, unstable housing, and unemployment.

| Model                  | Ethnicity (Aboriginal vs Non-Aboriginal) | Outcome, no. (%) |
|------------------------|----------------------------------------|------------------|
|                        | <1 Year After Initial Virological Suppression | ≥1 Year After Initial Virological Suppression |
|                        | Failed | Died | Lost to Follow-Up | Censored |
| Adjusted* HR | 95% CI | p-Value | Adjusted* HR | 95% CI | p-Value |
|-----------------------|--------|--------|-----------------|--------|--------|
| Primary analysis**    | 1.06   | 0.48-2.31 | 0.89 | 3.35 | 1.68-6.65 | 0.0006 | 63 (19) | 14 (4.3) | 60 (18) | 191 (58) | 328 (100) |
| Sensitivity analysis1 | 1.32   | 0.77-2.29 | 0.31 | 3.81 | 2.05-7.11 | <0.0001 | 99 (30) | 10 (3.0) | 47 (14) | 172 (52) | 328 (100) |
| Sensitivity analysis2 | 1.14   | 0.52-2.49 | 0.75 | 3.39 | 1.70-6.74 | 0.0005 | 63 (21) | 7 (2.3) | 44 (15) | 185 (62) | 299 (100) |
| Sensitivity analysis3 | 1.39   | 0.80-2.40 | 0.24 | 3.70 | 1.98-6.92 | <0.0001 | 99 (33) | 3 (1.0) | 31 (10) | 166 (56) | 299 (100) |

*Adjusted for sex, baseline viral load, and baseline calendar year.
**Primary analysis:
a) Defined HAART failure as the first of two viral loads >1000 copies/ml.
b) Observation time ended 12 months after the last viral load date for patients who were lost to follow-up, censored, or died.

Sensitivity analyses:
†Defined HAART failure as one viral load >1000 copies/ml.
2Observation time ended 12 months after the last viral load date for patients who were lost to follow-up, censored, or died.
3Defined HAART failure as one viral load <500 copies/ml and observation time ended at the last viral load date for patients who were lost to follow-up, censored, or died.

Table 4. Comparing the Outcomes of Four Adjusted Cox Proportional Hazards Models Assessing the Impact of Aboriginal Ethnicity on Virological Failure After Achieving Initial Virological Suppression.
[17-19] as well as active substance abuse [20]. In Canada, Aboriginals have higher unemployment rates [7] and studies have shown Aboriginal HIV-patients to be more likely to have unstable housing [3] and income levels <$10,000 [2, 3]. However, limited data are available describing adherence to HAART among Aboriginals. The studies conducted by Lima et al. and Miller et al. compared adherence rates by Aboriginal ethnicity using pharmacy-refill data, but they report contradictory findings. The first defined adherence to HAART as a dichotomous variable (<95% vs ≥95%) and found no significant difference by Aboriginal ethnicity [2], however, the second defined adherence to dual or triple ART as a continuous variable and found that Aboriginals have a significantly lower median rate of adherence compared to non-Aboriginals [3]. These differences in results may be due to the different definitions of adherence or to differences in adherence to HAART vs the dual therapies included in the second study. However, neither study assessed adherence beyond the first year of therapy. Since our study demonstrates that rates of virological failure begin to differ by Aboriginal ethnicity ≥1 year after achieving initial virological suppression, future research should assess adherence rates for a longer duration than 1 year after starting therapy. Furthermore, future studies should attempt to corroborate the findings of these previous studies and compare adherence rates between Aboriginals and non-Aboriginals using other methods, such as pill counts, electronic monitoring, or a combined measure, as investigated by Liu et al. [21].

The present study has several potential limitations. First, ethnicity and HIV exposure categories were self- or physician-reported and misclassifications may have occurred, for example, by categorizing individuals with unknown or missing exposure categories as non-IDUs. However, this information is collected by clinicians providing ongoing care to these patients, which gives us confidence in its accuracy. Second, a clinical database was used as the primary data source in this study, which has inherent limitations. Data quality can be affected by data entry errors and omissions. Certain variables such as socioeconomic status measures, adherence to therapy, and ongoing substance abuse were not systematically collected. These variables may have impacted treatment outcomes. In addition, we could not be certain that patients were ART-naive when starting HAART using these data. To try to limit this effect, we excluded patients with baseline viral loads <500 copies/mL because previous ART may be the reason for these low baseline results.

In summary, our results suggest that, among HIV-patients treated in northern Alberta, Aboriginals are less likely than non-Aboriginals to achieve initial virological suppression after initiating HAART; and, among those achieving initial virological suppression Aboriginals have higher rates of virological failure than non-Aboriginals in spite of similar rates of loss to follow-up. Future research should investigate adherence among Aboriginal HIV-patients treated with HAART, examine strategies to improve their adherence, and explore their HAART treatment experiences to assess ways to improve treatment outcomes. Socioeconomic factors and cultural barriers should be investigated.

ACKNOWLEDGEMENTS

This study was funded by the Alberta Heritage Foundation for Medical Research (AHFMR) Health Research Fund. LJ Martin was supported by an AHFMR full-time studentship and a Canadian Institutes of Health Research Doctoral Research Award. We thank the Northern Alberta Program staff for their assistance with the database and BE Lee from the Provincial Public Health Laboratory for providing viral load data.

PREVIOUS PRESENTATIONS

This work was presented in part at the: 1) XVII International AIDS Conference, Mexico City, Mexico, August 3-8, 2008; 2) 18th Annual Canadian Conference on HIV/AIDS Research, Vancouver, British Columbia, Canada, April 23-26, 2009 (published abstract: Can J Infect Dis Med Microbiol 2009; 20(Suppl B): 40B-41B); and 3) Canadian Society for Epidemiology and Biostatistics and APHEO 2009 Joint Conference, Ottawa, Ontario, Canada, May 25-28, 2009. It was also included as a chapter in LJ Martin’s PhD thesis (2009).

REFERENCES

[1] Martin LJ, Houston S, Yasui Y, Wild TC, Saunders LD. All-cause and HIV-related mortality rates among HIV-infected patients after initiating highly active antiretroviral therapy: The impact of Aboriginal ethnicity and injection drug use. Can J Public Health (accepted).
[2] Lima VD, Kretz P, Palepu A, et al. Aboriginal status is a prognostic factor for mortality among antiretroviral naïve HIV-positive individuals first initiating HAART. AIDS Res Ther 2006; 3: 14.
[3] Miller CL, Spittal PM, Wood E, et al. Inadequacies in antiretroviral therapy use among Aboriginal and other Canadian populations. AIDS Care 2006; 18(8): 968-76.
[4] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents November 3, 2008 [cited 12 Mar 2009]. Available from: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf
[5] Public Health Agency of Canada. HIV/AIDS Epi Updates, November 2007. Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, 2007.
[6] Public Health Agency of Canada. HIV and AIDS in Canada. Surveillance Report to December 31, 2008. Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada.
[7] Public Health Canada. A Statistical Profile on the Health of First Nations in Canada for the Year 2000 = Profil Statistique de la Santé des Premières Nations au Canada pour l’an 2000. Her Majesty the Queen in Right of Canada; c2005. 123 p. Report No.: Cat. H35-4/30-2000, English, French.
[8] Public Health Agency of Canada. HIV and AIDS in Canada. Surveillance Report to December 31, 2006. Surveillance and Risk Assessment Division, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada, 2007.
[9] Porta M, Ed. A Dictionary of Epidemiology. 5th ed. New York: Oxford University Press 2008; pp. 183.
[10] Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: New representations of old estimators. Stat Med 1999; 18(6): 695-706.
[11] Dohoo I, Martin W, Stryhn H. Veterinary epidemiologic research. 2nd ed. Charlottetown, PEI: VER Inc. 2009.
[12] Palepu A, Tyndall M, Yip B, O’Shaughnessy MV, Hogg RS, Montaner JSG. Impaired virologic response to highly active antiretroviral therapy associated with ongoing injection drug use. J Acquir Immune Defic Syndr 2003; 32(5): 522-6.
Wood E, Montaner JS, Yip B, et al. Adherence and plasma HIV RNA responses to highly active antiretroviral therapy among HIV-1 infected injection drug users. CMAJ 2003; 169(7): 656-61.

Lucas GM, Chaisson RE, Moore RD. Highly active antiretroviral therapy in a large urban clinic: Risk factors for virologic failure and adverse drug reactions. Ann Intern Med 1999; 131(2): 81-7.

Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000; 133(1): 21-30. Erratum in: Ann Intern Med 2002; 136(3): 253.

Bangsberg DR, Hecht FM, Charlebois ED, et al. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. AIDS 2000; 14(4): 357-66.

Bouhnik AD, Chesney M, Carrieri P, et al. Nonadherence among HIV-infected injecting drug users: The impact of social instability. J Acquir Immune Defic Syndr 2002; 31(Suppl 3): S149-53.

Kleeberger CA, Phair JP, Strathdee SA, Detels R, Kingsley L, Jacobson LP. Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr 2001; 26(1): 82-92.

Spire B, Duran S, Souville M, et al. Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach. Soc Sci Med 2002; 54(10): 1481-96.

Lucas GM, Cheever LW, Chaisson RE, Moore RD. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. J Acquir Immune Defic Syndr 2001; 27(3): 251-9.

Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001; 134(10): 968-77. Erratum in: Ann Intern Med 2002; 136(2): 175.

Received: April 15, 2010 Revised: November 20, 2010 Accepted: November 22, 2010