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Outcomes of antiretroviral therapy in northern Alberta: The impact of Aboriginal ethnicity and injection drug use

by

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For my father

ABSTRACT

Background: Aboriginals are overrepresented in Canada's HIV epidemic and are more likely to be infected with HIV through injection drug use (IDU) than non-Aboriginals. However, little research has investigated the outcomes of combination antiretroviral therapy (cART) among Aboriginal HIV-patients or compared outcomes between Aboriginal and non-Aboriginal HIV-patients.

Objectives: The primary objectives of this research were to 1) compare all-cause and HIV-related mortality rates between Aboriginal and non-Aboriginal HIV-patients after they start cART, 2) determine if Aboriginal patients were less likely to achieve virological suppression and more likely to experience subsequent treatment failure after starting cART; 3) describe and compare the health-related quality of life (HRQL) of Aboriginal and non-Aboriginal HIV-patients; and 4) describe the life stability of Aboriginal and IDU HIV-patients treated with cART and explore associations between life stability, clinical status, and HRQL.

Methods: This research was conducted in northern Alberta, Canada using a clinical database, vital statistics data, and data collected through interview and a self-administered HRQL questionnaire. Data analyses included multivariable Cox proportional hazards models and multiple linear and logistic regression models.

Results: After starting cART, Aboriginals suffer higher rates of all-cause and HIV-related mortality than non-Aboriginals. Furthermore, Aboriginals are less likely to achieve virological suppression after starting cART and, among those who achieve

suppression, Aboriginals experience higher rates of virological failure ≥1 year after suppression. Aboriginal IDUs, Aboriginal non-IDUs, and non-Aboriginal IDUs reported similarly worse physical HRQL compared to non-Aboriginals non-IDUs. Among Aboriginals and IDUs, factors significantly associated with poor clinical status were unemployment, lower income, not completing high school, homelessness, and perceiving that one's current life was not much better compared to before starting cART. Similarly, factors significantly associated with lower HRQL in this group were unemployment, perceiving that one's current health or one's current life was not much better compared to before starting cART, and having a current CD4 cell count ≤350 cells/μL.

Conclusions: Overall, after starting cART, Aboriginal HIV-patients suffer worse outcomes than non-Aboriginal HIV-patients. Future research should investigate adherence among Aboriginals and IDUs treated with cART and explore their treatment experiences to develop interventions to improve the prognosis of these vulnerable populations.

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
cART	Combination antiretroviral therapy
CI	Confidence interval
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQL	Health-related quality of life
ICD-9, -10	International Classification of Diseases-9th, and 10th revisions
IDU	Injection drug user or injection drug use
IQR	Interquartile range
LSQ	Life Stability Questionnaire
MOS-HIV	Medical Outcomes Study (MOS)-HIV
MSM	Men who have sex with men
NAHIVP	Northern Alberta HIV Program
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OR	Odds ratio
PI	Protease inhibitor
RNA	Ribonucleic acid
SD	Standard deviation
SE	Standard error

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CHAPTER 1: INTRODUCTION

1.1 OVERVIEW

1.1.1 Objectives

The objectives of this review are to summarize the literature investigating outcomes of combination antiretroviral therapy (cART) among Aboriginals, injection drug users (IDUs), and the general HIV-infected population and to identify gaps in understanding. Since this thesis focuses on Aboriginal HIV-patients in Canada specifically, this review focuses more detailed attention on this population. However, because a large proportion of Aboriginals are infected with HIV through IDU, IDUs are examined as well to help to inform our understanding of Aboriginal patients' experiences with cART. The impact of cART on the general HIV-infected population is investigated as it likely represents the "non-Aboriginal" comparison group used in our analyses.

1.1.2 Organization

This literature review is organized to correspond with the thesis chapters. First, to provide context for the rest of the thesis, I summarize the epidemiology of HIV and AIDS, with a brief look at the history of the epidemic and a focus on current Canadian trends. Next, I discuss each of the three outcomes investigated in this thesis: mortality, clinical outcomes, and health-related quality of life (HRQL). Mortality and clinical outcomes are discussed together because of the large overlap in these two areas of research. Within each section, I divide the discussion into research on the HIV population in general, on Aboriginal HIV-patients, and on IDUs. As a closing section, I attempt to summarize the main gaps in the literature as a rationale for this thesis research.

1.1.3 Scope

This thesis research specifically focuses on how cART impacts mortality, clinical outcomes, and HRQL in northern Alberta, Canada. Since this thesis research was conducted in Canada, the literature review is limited to industrialized countries. Parallels may exist between marginalized populations in Canada, such as Aboriginals and IDUs, and populations in low-income countries. However, a discussion of these comparisons was considered to be beyond the scope of this thesis.

Indigenous populations in Canada, including First Nations, Inuit, and Métis, together can be described as Aboriginal peoples. It is difficult to know which other Indigenous populations internationally make appropriate comparison groups for Aboriginal peoples in Canada. As discussed by Waldram et al, "[t]here are three broad dimensions fundamental to understanding the Aboriginal people of Canada, with particular reference to health and health care. These are the biological, cultural, and legal dimensions." (page 4) [1]. To make comparisons with populations outside of Canada for this literature review, I have focused on the biological dimension because the cultural and legal dimensions are likely somewhat unique to Aboriginal peoples in Canada, making international comparisons more tenuous. With this reasoning, Aboriginal populations in the United States (Native Americans and Alaska Natives) and Greenland (the Inuit) appear to be appropriate comparators to Aboriginal peoples in Canada. Therefore, this literature review explores outcomes of cART for Aboriginal populations in Canada primarily, and the United States and Greenland (Denmark) as available.

In the HIV literature, injection drug use is defined in various ways. One common definition is as an exposure category for HIV. Other studies define injection drug use as an ongoing activity or as an activity that a patient has ever practiced in the past, regardless of HIV exposure category. However, exposure category is a convenient definition because it is commonly collected in HIV studies and assesses behaviour at a similar point in time during the course of an HIV infection for all

patients. This thesis research has primarily focused on injection drug use as a route of HIV transmission; therefore, this literature review follows suit.

1.2 SUMMARY OF THE EPIDEMIOLOGY OF HUMAN IMMUNODEFICIENCY VIRUS AND ACQUIRED IMMUNODEFICIENCY SYNDROME

1.2.1 Brief global history

On June 5, 1981, Acquired Immunodeficiency Syndrome (AIDS) was first described in the United States in an article in the Morbidity and Mortality Weekly Report describing *Pneumocystis carinii* (now *P. jiroveci*) pneumonia occurring among 5 homosexual men in Los Angeles, California [2]. In the years that followed, human immunodeficiency virus (HIV), a retrovirus, was isolated from an AIDS patient and identified as the cause of AIDS. Since the first report of AIDS, the disease has evolved into a pandemic, with global HIV prevalence estimated to be 33 million in 2007 [3].

1.2.2 HIV and AIDS in Canada and Alberta

In Canada, the first AIDS case was reported on March 27, 1982 in a homosexual man who had recently returned from Haiti [4]. However, a later report found that one of the first cases to experience AIDS symptoms in Canada was a patient, treated in Edmonton, who died in June 1980 after receiving a blood transfusion in Zaire in 1976; in 1983, a sample of his blood tested HIV-positive [5].

Although the number of people living with HIV in Canada represents a small proportion of cases worldwide (approximately 0.22% in 2007 according to UNAIDS estimates [3]), HIV/AIDS continues to be epidemic in this country. Since the beginning of reporting in 1985, 64,800 positive HIV tests have been reported in Canada up to December 31, 2007; and, since 1979, 20,993 AIDS cases have been reported [6]. Specifically in Alberta, 218 HIV positive tests were reported in 2007 (9.0% of the national total) and 4,786 positive tests have been reported since 1985 (7.4% of the national total) [6].

In 2007, the most common risk behaviour associated with HIV infection in Canada was men who have sex with men (MSM) (41.2% of 1,261 positive tests with exposure category reported), followed by heterosexual contact (29.3%) and IDU (22.5%, including 22 MSM/IDU cases) [6]. Routes of exposure differ by gender: in 2007, among males, most infections were due to MSM (54.2%) followed by heterosexual sex (21.2%) while among females, most were due to heterosexual sex (57.2%) followed by IDU (36.0%) [6].

1.2.3 Epidemiology of HIV and AIDS among Aboriginal peoples in Canada

Aboriginals are over-represented in Canada's HIV epidemic. Based on data from the 2006 census, approximately 3.8% of the Canadian population self-identified as Aboriginal; with 5.8% of the 3.26 million people living in Alberta self-identifying as Aboriginal [7]. Data on the ethnicity of individuals with HIV-positive tests reported to the Public Health Agency of Canada is not representative of the situation in Canada as a whole because ethnicity is not reported by all provinces and territories (provinces and territories that report ethnicity data are: British Columbia, Yukon, Alberta, Northwest Territories, Nunavut, Saskatchewan, Manitoba, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador) [6]. Furthermore, not all tests from these regions include ethnicity data. For example, between 1998 and 2007, only 29.9% (n=7,118) of HIV tests included ethnicity data [6]. Despite these low numbers, these data do give some indication of the overrepresentation of Aboriginals among HIV-positive tests reported in Canada. In 1998-2007, 1,656 (23.3%) of the HIV tests reported from these provinces and territories with ethnicity data were from Aboriginals [6]; however, only 7% of the population of these reporting provinces and territories identified as Aboriginal in the 2006 census [7]. The proportion of HIV tests attributed to Aboriginals has increased from 15.0% in 1985-1997 to a high of 26.5% in 2006, falling to 21.4% in 2007 [6]. In comparison, the proportion of tests from Whites decreased from 75.7% in 1985-1997 to 58.4% in 2007 [6].

Although limitations in reporting also exist for AIDS cases, ethnicity data are reported for a larger proportion of AIDS cases than for HIV tests in Canada. Since

reporting began in 1979, 78.6% of AIDS cases had ethnicity available (n=16,498 cases) [6]; therefore, AIDS case data may be a better representation of ethnicity trends for the country as a whole, however, these data are limited by the lag time between acquiring an HIV infection and progressing to AIDS. Overall, since reporting began in 1979, 3.9% of AIDS cases were from Aboriginals [6]. However, this proportion increased from 2.5% in 1979-1998 to 9.9% in 1999 [8] and a high of 23.4% in 2006, before falling to 14.0% in 2007 [6].

By sex, a much smaller proportion of males testing HIV positive are Aboriginal than females. In 1985-2007, among males, a large proportion (70.9%) of HIV tests reported with available sex information were from Whites whereas a smaller proportion (15.0%) were from Aboriginals; in contrast, among females in the same period, the proportion of HIV tests from Whites (39.9%) and Aboriginals (39.2%) were approximately equal [6].

Injection drug use is a major transmission route among Aboriginals testing HIV positive. Among HIV positive tests reported in 1998-2006, IDU accounted for 58.8% of exposures among Aboriginals (53.7% among males and 64.4% among females) but only 24.8% among non-Aboriginals [9]. In contrast, in the same period, MSM accounted for only 6.8% of exposures among Aboriginals but 38.9% of exposures among non-Aboriginals [9].

Therefore, although Aboriginals do not make up the largest absolute number of HIV infections or AIDS cases reported in Canada, they are substantially overrepresented in Canada's HIV epidemic and their contribution to reported HIV tests and AIDS cases has increased over time. Although the 2007 surveillance data show a decrease in these proportions, given the limitations of the data, these figures need to be interpreted with caution and additional data from 2008 and coming years will help to determine if the proportion of HIV tests and AIDS cases that are reported from Aboriginals are truly decreasing. Furthermore, the HIV epidemic is distinct among Aboriginals, with a substantial impact on Aboriginal women and injection drug use playing a much more important role [9].

1.3 BRIEF OVERVIEW OF THE HEALTH OF ABORIGINALS IN CANADA

A complete description of the social determinants of health for Aboriginal people in Canada is beyond the scope of this review; however, the following resources help to cover the topic more extensively: Waldram et al, 2006 [1], Adelson, 2005 [10], and MacMillan, 1996 [11]. For the purposes of this review, an overview of life expectancy, mortality rates, main causes of death, and socioeconomic status is provided as background to understanding the impact of HIV on this diverse population.

1.3.1 Life expectancy and mortality

Life expectancy for Aboriginals is lower than for the Canadian population. In 2000, Registered Indians had an estimated life expectancy of 68.9 years (males) and 76.6 years (females), compared to estimates for the Canadian population of 76.3 years (males) and 81.8 (females) [12]. Although this represents a difference of 7.4 and 5.2 years for each sex, respectively, the difference has decreased over time, from 10.9 and 11.0 years, respectively, in 1980 [12].

Among First Nations people in 2000, the top 5 causes of death (by deaths per 100,000 population using ICD-9 codes) were diseases of the circulatory system (105.4), injury and poisoning (104.9), neoplasms (69.5), diseases of the respiratory system (26.5), and diseases of the digestive system (25.4) [12]. For these 5 top causes of death, compared to the Canadian population in 1999, the age-standardized mortality rates (per 100,000 population) for First Nations people in 2000 were higher for injury and poisoning (125.0 vs. 41.7), diseases of the circulatory system (260.3 vs. 195.8), and diseases of the respiratory system (65.5 vs. 53.2), but lower for neoplasms (162.9 vs. 180.1) [12]. An important cause of death among Aboriginals is suicide. In 2000, among First Nations people, 22% and 16% of deaths among those aged 10-19 years and 20-44 years, respectively, were due to suicide [12].

1.3.2 Determinants of health

In general, Aboriginals in Canada fare poorly compared to the rest of the Canadian population in terms of education, income, and employment. Education

levels are lower among Aboriginals than the general Canadian population. In 2001, only 31.1% of off-reserve Canadians had less than a high school level education compared with 57.7% of Inuit and 58.9% of on-reserve Registered Indians [12]. Similarly, 18.1% of off-reserve Canadians had a university certificate, diploma, or degree compared with only 2.7% of Inuit and 3.6% of on-reserve Registered Indians [12]. In 2001, employment rates for Inuit and on-reserve Registered Indians were 48.6% and 37.3%, respectively, compared to 61.7% among Canadians living off-reserve [12]. Similarly, the unemployment rate was higher for Aboriginals, at 22.2% for Inuit and 27.7% for on-reserve Registered Indians, compared to only 7.3% for off-reserve Canadians [12]. Aboriginals also have lower levels of income than the general Canadian population. For example, median incomes in 2005 among those 15 years of age and older were $25,615 overall [13], but only $16,752 for Aboriginals [14].

Aboriginals in general have lower life expectancies, higher rates of mortality for certain conditions, and poorer socioeconomic status than the general Canadian population. In British Columbia, HIV-infected individuals of lower socioeconomic status, as measured by neighbourhood characteristic data from the Canadian Census, have been shown to have higher rates of HIV-related mortality, which was likely due to these patients being less likely to access cART [15]. Similar results were found in San Francisco: individuals diagnosed with AIDS living in neighbourhoods of higher socioeconomic status had improved survival compared to those living in neighbourhoods of lower socioeconomic status; however, this relationship was no longer statistically significant after adjusting for use of cART [16]. Another study conducted among individuals with AIDS in San Francisco showed that both race and neighbourhood socioeconomic status have independent impacts on all-cause mortality [17]. Blacks had higher all-cause mortality rates compared to whites and, independent of race, individuals living in neighbourhoods of lower socioeconomic status had higher all-cause mortality rates than those living in neighbourhoods of higher socioeconomic status; this latter relationship decreased in significance after accounting for use of cART [17]. Therefore, Aboriginals infected with HIV may be

more likely to suffer worse treatment outcomes compared to non-Aboriginals, and this may be related to their poorer health and lower socioeconomic status, but other cultural and ethnicity-related factors may also play an important, independent role in how Aboriginals patients access and succeed on cART.

1.4 OVERVIEW OF COMBINATION ANTIRETROVIRAL THERAPY[1]

1.4.1 Brief history

On March 19, 1987, the first antiretroviral drug to treat AIDS, zidovudine (also known as AZT), was approved by the FDA [18]. Over the next several years, three other nucleoside analogues (zalcitabine, didanosine, and stavudine) were also approved [19]. In time, the benefits of treating patients with combination therapy (two nucleoside analogues used together) were demonstrated in two clinical trials [20, 21]. Treatment continued to advance with the approval of drugs from two new classes: protease inhibitors (PIs) on December 6, 1995 and non-nucleoside reverse transcriptase inhibitors (NNRTIs) on June 21, 1996 [22]. With the demonstrated effectiveness of combining antiretroviral therapies and the availability of new therapies, combination antiretroviral therapy became standard practice. The term "highly active antiretroviral therapy" or HAART is used to describe treatment with at least three antiretroviral drugs in combination. Today, this therapy combination is also known as "combination antiretroviral therapy" or "cART", which is the term that will be used throughout this thesis. Although these combination therapies produced successful outcomes, they were not without disadvantages, including the often large number of pills patients needed to take and side-effects [23]. Drug therapy continues to advance, and in more recent years, drugs from three new classes have been approved: fusion inhibitors on March 15, 2003, CCR-5 co-receptor antagonists on August 6, 2007, and integrase inhibitors on October 12, 2007 [24].

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[1] This section is based in part on: Hoffmann C & Mulcahy F. ART 2007. In: HIV Medicine 2007, 15th ed. Eds Hoffmann C, Rockstroh JK, Kamps BS. Available at: http://www.hivmedicine.com/hivmedicine2007.pdf

1.4.2 Goals of therapy

"The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality" [25]. However, ART is not a cure for HIV and treatment is currently life-long, which makes adherence and long-term treatment outcomes especially important to consider.

1.4.3 Measuring treatment success

With these goals of therapy in mind, treatment success is defined using three main types of outcomes: virological, immunological, and clinical [26]. Virological success is defined as suppression of a patient's plasma HIV RNA levels (viral load) below the limits of detection [26]. As the sensitivity of tests has improved over time, this detection limit has decreased, but <500 copies/mL, <400 copies/mL, or <50 copies/mL are commonly used. Viral rebound occurs when a patient's viral load increases above a specified level. However, a "blip" is considered to be a temporary increase in a patient's viral load to a relatively low level, with the previous and subsequent viral loads suppressed, that does not necessarily indicate virological failure [26]. Viral load is considered the most significant indicator to monitor [26] because it is the most sensitive and specific indicator of treatment response. An increase in a patient's CD4 cell count, either by a certain number of cells or to a certain level, is considered immunological success and decreases in AIDS-defining illnesses and mortality are usually considered indicators of clinical success [26]. Before the introduction and widespread use of cART, viral load was shown to predict the rate of decline in a patient's CD4 cell count, as well as progression to AIDS and death; furthermore, viral load was more predictive of these latter two outcomes than a patient's CD4 cell count [27, 28].

1.4.4 Adherence to therapy

Adherence can be defined as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [29]. A high level of adherence to ARTs is associated with good treatment outcomes, including virological suppression, improved CD4 cell counts, and decreased morbidity. For example, a study by Paterson et al showed that, compared to patients with <95% adherence to PI-based ART regimens, patients with ≥95% adherence were less likely to have virological failure (22% vs. 72%, $p<0.001$), had a higher mean increase in CD4 cell count (83 ± SE 23 cells/mm^3 vs. 6 ± 20 cells/mm^3, $p=0.045$), and had fewer mean hospitalized days per 1,000 follow-up days (2.6 vs. 12.9 days, $p<0.001$) [30]. Although ≥80% adherence is commonly considered acceptable for many medications, the authors of this study concluded that cART – specifically PI-based therapies – may require adherence levels of ≥95% to be effective at suppressing viral load [30]. However, as pointed out by Hoffman and Mulcahy, this study is rather dated (published in 2000) and the drugs in currently used regimens may tolerate lower levels of adherence [31].

As a result of treatment failure, poor adherence is associated with development of drug resistant HIV infections. Poor adherence to ART allows a patient's viral load to increase, which can facilitate the development of HIV resistance. Resistance to several drug classes can develop and viruses that are resistant to one antiretroviral in a class are often resistant to other drugs within that same class, even if the virus has not been previously exposed to those drugs (this is known as cross-resistance) [32]. It becomes more challenging to suppress the viral load in patients with resistant HIV infections as fewer effective drugs remain available. Thus, achieving the goals of ART therapy requires a high level of adherence.

1.5 CLINICAL AND MORTALITY OUTCOMES AMONG HIV-PATIENTS AFTER STARTING CART

1.5.1 Clinical and mortality outcomes among HIV-patients in general after starting cART

cART is associated with dramatic improvements in HIV-patients' clinical outcomes and decreases in their mortality rates. Clinical trials have demonstrated that dual therapies are superior to monotherapies and, subsequently, that triple therapies or cART are superior to dual therapies in suppressing viral loads, corresponding improvement in immunological responses, and preventing progression to AIDS and death [20, 33-35]. Furthermore, numerous observational studies conducted among HIV-patient cohorts have shown that, as cART use became more widespread, all-cause and HIV-related mortality rates decreased [36-41] (Table 1.1). However, a Swiss study showed that, even after the introduction of cART, mortality rates were still higher for HIV-patients than for the general Swiss population, with the standardized mortality ratio (SMR) decreasing from 79.3 in 1996 (before cART was introduced) to 15.3 afterwards [42].

Furthermore, the pattern of causes of mortality has changed since the introduction of cART. For example, among HIV-patients treated in southern Alberta, before the introduction of cART (1984-1996), 90% of observed deaths were AIDS-related and only 7% were non-AIDS-related [43]. In contrast, after the introduction of cART (1997-2003), these proportions changed: only 67% of deaths were AIDS-related while 32% were non-AIDS-related [43].

1.5.2 Clinical and mortality outcomes among Aboriginals after starting cART

Limited research has been conducted on cART treatment outcomes among HIV-infected Aboriginal patients in Canada or among Indigenous populations in other countries. Furthermore, few comparisons between Aboriginal and non-Aboriginal HIV-patient populations have been made to determine if clinical treatment outcomes and rates of mortality between the two groups are similar.

However, the research conducted to date suggests that Aboriginals have similar rates of virological suppression and immunological reconstitution, but higher rates of all-cause mortality after starting cART compared to non-Aboriginals. Comparison data for HIV-related mortality were not found.

1.5.2.1 Clinical outcomes

In Canada, only two studies have examined clinical outcomes of cART among Aboriginal patients; both were conducted in British Columbia. In a study of 622 HIV-patients (14% Aboriginal), Lima et al found no significant differences between Aboriginals and non-Aboriginals in terms of time to CD4 cell increase of 100 cells above baseline or in time to first of two consecutive viral loads <500 copies/mL after starting cART in either univariable or multivariable models [44]. In a similar study, Miller et al studied 892 HIV-patients (16% Aboriginal) and found that Aboriginals had a lower rate of achieving virological suppression after starting dual or triple therapy in unadjusted analyses, but Aboriginal ethnicity was not retained in the final multivariable model after controlling for age, baseline viral load, triple vs. dual ART, transmission by MSM vs. IDU, adherence, and starting therapy before July 1997 [45]. In a sub-analysis comparing Aboriginals who achieved initial virological suppression to Aboriginals who did not, the variables positively associated with virological suppression were good levels of adherence, MSM, and lower baseline viral load [45]. The methods employed in these two studies are similar in that they use the same data source (the HIV/AIDS Drug Treatment Program of the British Columbia Centre for Excellence in HIV/AIDS) and a similar definition of virological suppression (Lima et al use the first of two and Miller et al use the second of two viral loads <500 copies/mL). However, the study by Lima et al is limited to patients starting cART, whereas the study by Miller et al also includes patients who started dual therapy.

Based on these two studies, it appears that Aboriginals have similar rates of virological suppression and similar rates of immunological reconstitution after starting cART as non-Aboriginals. However, these results are limited in that they may not be generalizable to a wider patient population outside of British Columbia and the study

by Lima et al included a relatively small number of Aboriginal patients (n=87). Furthermore, neither study examined rates of subsequent virological rebound after patients achieved suppression, which is another important outcome of ART.

1.5.2.2 Mortality outcomes

In the same study described above, Lima et al also compared rates of all-cause mortality between Aboriginals and non-Aboriginals after starting cART [44]. Although rates of virological suppression and immune reconstitution appear similar, Aboriginals had significantly higher rates of all-cause mortality after starting cART compared to non-Aboriginals in both the univariable analysis and in the adjusted analysis (HR=3.12, 95% CI=1.77-5.48) controlling for gender, age, income, baseline cART combination, adherence, history of IDU, and baseline year. Although most deaths in this study were HIV-related (67%), no analyses were conducted specifically on HIV-related mortality; therefore, it is difficult to conclude that Aboriginals suffer poorer outcomes of cART.

In addition to this Canadian study, a study conducted among a group of Native American (NA)/Alaskan Native (AN) HIV-patients treated in Phoenix, Arizona examined rates of all-cause mortality after the introduction of cART [46]. Rates of mortality for this patient population decreased by 12 deaths per 100 person-years after the introduction of cART: from 18.4 per 100 person-years before 1998 (pre-cART and early cART eras) to 6.4 per 100 person-years in 1998-2004 (cART era). Therefore, these data suggest that NA/AN patients were receiving beneficial outcomes from cART. However, these results from the southwest United States may not be representative of outcomes among Aboriginals in Canada. Although the health care system for NA/AN appears similar to that for Aboriginal peoples in Canada, in which NA/ANs from "federally recognized tribes" are eligible to receive health care through the Indian Health Service [47], the HIV-patient populations in these two countries may differ from each other in many ways. For example, in contrast to the high rate of IDU exposure to HIV observed among Aboriginal populations in Canada, few patients in this study from the United States reported MSM/IDU or IDU [46]. Therefore, given the

potential differences between Canadian Aboriginals and NA/AN HIV-positive populations, it is unclear how comparable treatment outcomes for Indigenous populations in Canada and the United States may be.

Another potentially relevant comparison to Aboriginals in Canada are the Inuit in Greenland. In an almost exclusively Inuit cohort of HIV-patients treated in Greenland in the study period January 1, 1995-March 1, 2004, after initiating cART, patients had much higher all-cause mortality rates than the general population of Greenland (111.2 vs. 10.3 per 1,000 person-years) [48]. Similar to the study from the United States, the mortality rate observed among this population decreased over time. Among patients diagnosed in 1995-1996, the mortality rate was 158/1,000 person years, which decreased to 62/1,000 person-years among those diagnosed in 1997-1999. Although cART is available free of charge in Greenland, the authors note that the country's geography and climate make it difficult to care for HIV-patients. One major limitation of this study is the small number of patients included (n=103).

The HIV-patient population in Greenland appears to offer an interesting comparison to Inuit HIV-patients in Canada. The Inuit Circumpolar Council (Canada) defines the Inuit as "indigenous members of the Inuit homeland recognized by Inuit as being members of their people and … include the Inupiat, Yupik (Alaska), Inuit, Inuvialuit (Canada), Kalaallit (Greenland) and Yupik (Russia)" [49]. Furthermore, geographic challenges described in Greenland are likely similar to those experienced in northern Canada and both Greenland and Canada offer free health care and antiretrovirals to their patients. Therefore, comparisons between these two populations are likely appropriate. To take advantage of these similarities, a circumpolar collaboration could be initiated to explore HIV treatment challenges and cART outcomes among Inuit populations in countries such as Canada, Denmark (Greenland), Russia, and the United States (Alaska). This could provide an opportunity for larger sample sizes, which is likely a challenge for any study of these populations that is limited to one country. The Inuit represent a small proportion of the Canadian population (0.16% of the national population) [14]. The rates of HIV

among the Inuit are not known at a national level, since surveillance data published by the Public Health Agency of Canada combines all Aboriginal peoples into one category. As a beginning in Canada, we should determine the prevalence of HIV among Inuit peoples in the country. From there, we could begin to examine whether Inuit HIV-patients in Canada suffer similarly higher rates of mortality compared to the general Canadian population as observed in this Greenland study.

All of these studies described that examine mortality outcomes among Aboriginal HIV-patients are limited by their focus on all-cause mortality alone rather than also examining HIV-related mortality specifically. If Aboriginal or other Indigenous populations have shorter life expectancies than the general population, then one would expect higher rates of all-cause mortality among Aboriginal HIV-patient populations as well. However, all-cause mortality does not effectively describe cART treatment success. As Mocroft et al indicate, to investigate patients' responses to cART, it is important to specifically examine HIV-related mortality rates [50]. Therefore, more research is needed to investigate the impact of Aboriginal ethnicity on HIV-related mortality rates specifically, in addition to all-cause mortality rates.

1.5.3 Clinical and mortality outcomes among injection drug users after starting cART

1.5.3.1 Accessing cART

Several studies have shown that IDUs are less likely to access cART compared to patients with other exposure behaviours. For example, among 6,645 HIV-patients in the EuroSIDA study, IDUs were less likely than MSMs to be on cART at study entry (OR=0.48, 95% CI=0.37-0.62, $p<0.0001$) and, during follow-up, the relative hazard of starting cART for IDUs was 0.73 compared to MSMs (95% CI=0.64-0.82, $p<0.0001$), but no difference was observed between patients with heterosexual risk behaviour and MSMs [51]. Similarly, in a study conducted in Spain among 3,421 cART-naïve patients, after adjusting for sex, age, CD4 cell count, viral load, and previous AIDS diagnosis, IDUs were less likely to start cART than MSM (HR=0.67, 95%

CI=0.57-0.79); however, in the same model, among patients previously treated with non-cART ARTs (mono or dual therapies), there was no difference for IDUs (HR=1.07, 95% CI=0.83-1.37) [52]. Therefore, IDUs previously treated with ARTs appear to be equally likely to start cART as previously treated patients with other exposures. In a study conducted in British Columbia among IDU HIV-patients, factors associated with patients being less likely to access ARTs were female sex, not being in a drug or alcohol treatment program, younger age, and having a physician with less experience [53]. However, these studies did not consider past versus current drug use, which may help to explain these lower rates of access to ARTs. In a study in Baltimore that enrolled patients who should have been prescribed cART (i.e. they had either a nadir CD4 cell count <500 cells/μL or a peak viral load >30,000 copies/mL), active drug users were more likely to have never accessed cART compared to non-drug users (OR=4.8, 95% CI=2.8-8.3) whereas the difference between former drug users and non-drug users was less pronounced (OR=1.6, 95% CI=1.0-2.7) [54].

1.5.3.2 Clinical outcomes

All studies included in this review found that IDUs were less likely than other patients to experience virological suppression [52, 55, 56]; however, in one of these studies, this difference was explained by lower adherence to cART among IDUs [55]. One study showed that, after starting cART, IDUs were less likely to achieve virological suppression compared to MSMs (adjusting for sex, age, AIDS diagnosis, previous non-cART ART, CD4 cell count, and viral load; HR=0.86, 95% CI=0.74-0.99) [52]. However, this study did not adjust for adherence to therapy in the analysis, which would be expected to be one of the main factors explaining this difference. In a Canadian study, Wood et al found that, compared to patients with no history of IDU, those with a history of IDU had lower rates of virological suppression and higher rates of subsequent virological "rebound" (two successive viral loads ≥500 copies/mL) in unadjusted analyses [55]. However, in multivariable analyses adjusting for adherence (measured by pharmacy-refill data), sex, age, use of PIs, baseline CD4 cell count, viral load, and year of cART start, they found no significant difference in rates of

suppression (adjusted relative hazard=0.9, 95% CI=0.7-1.0) or rebound (adjusted relative hazard=1.3, 95% CI=1.0-1.6) [55]. In sub-analyses limited to patients with ≥95% adherence, IDU was not significantly associated with either suppression or rebound. The authors concluded that the lower rates of suppression and higher rates of rebound among IDUs were related to their poorer adherence to therapy [55]. However, another study conducted in British Columbia found that, even after adjusting for adherence (also measured by pharmacy-refill data), active IDU was associated with a lower odds of virological suppression after starting cART relative to having no history of IDU (adjusted OR=0.30, 95% CI=0.13-0.67) [56]. The authors suggested that assessing adherence using pharmacy-refill data was ineffective for active IDUs because the relationship between adherence and suppression was not statistically significant for this group [56].

Along with access to therapy, it is also important to consider current versus past drug use when considering the impact of IDU on treatment outcomes. Drug use behaviours can change over time and past injection drug use may not be associated with a patient's current drug use, and thus may not represent a patient's current ability to adhere to therapy. For example, among patients receiving cART, active drug users have been reported to have lower decreases in viral loads from baseline and lower increases in CD4 cell counts from baseline compared to individuals without a history of using either heroin or cocaine [54]. However, former drug users were similar to non-drug users for both of these outcomes [54].

Therefore, IDUs appear to be less likely to achieve virological suppression compared to other patients, which may be due to poorer rates of adherence among IDUs. However, current vs. past drug use and the accuracy of the method used to assess adherence are important considerations in assessing the impact of IDU on virological suppression.

1.5.3.3 Mortality outcomes

Studies have found that IDUs have higher rates of all-cause and non-HIV-related mortality and lower life expectancies compared to other patients, and that cART has not had a major influence on mortality outcomes among IDUs; however, one study found that rates of all-cause mortality did not differ by IDU after controlling for other variables (including adherence to therapy). Therefore, as with clinical outcomes, adherence to therapy is an important confounding variable to consider in research investigating mortality outcomes among IDUs after they start cART.

Results from a large, combined analysis of prospective cohort studies has shown that, compared to patients exposed to HIV through MSM, IDUs suffer higher rates of all-cause mortality as well as the combined outcome of all-cause mortality or a new AIDS diagnosis after starting cART [57, 58]. However, Mocroft et al found that, among patients treated in the EuroSIDA study, although IDUs had higher incidence rate ratios of the combined outcome of a new AIDS diagnosis or all-cause mortality, IDUs did not have significantly higher rates of HIV-related mortality or AIDS after adjusting for confounding variables [50]. However, IDUs did have significantly higher rates of non-HIV-related mortality compared to MSM patients [50]. Therefore, the authors suggest that IDUs responded similarly well to cART as MSM patients, since HIV-related mortality is a more specific indicator of treatment success [50]. In another study, limited to IDU HIV-patients, rates of natural death after seroconversion (which excluded deaths from suicide, overdose, and unintended injuries) did not significantly differ in the cART period compared to the pre-cART period (HR=0.64, 95% CI=0.36-1.17) after adjusting for age at seroconversion, sex, region, and type of care (hospital-based vs. non-hospital-based), suggesting that the impact of cART on rates of mortality from natural causes (including HIV- and non-HIV-related causes) has been minimal for IDUs [59]. Furthermore, a British Columbia study, which used positive HCV status as a proxy for a history of IDU in a subset of study patients, found that life expectancy at exact age 20 was highest for HCV-negative participants (presumably

non-IDUs) who had started cART (38.9 years); however, life expectancy was lower for IDUs taking ARTs (24.5 years), HCV-positive patients (presumably IDUs) who had started cART (23.0 years), and IDUs who had never taken ARTs or were not taking ARTs at the time of their death (19.1 years) [60]. Therefore, IDUs appeared to experience worse all-cause mortality outcomes than other HIV-patients in this study.

However, a recent study conducted in British Columbia found that, among patients starting cART, being an IDU was not significantly associated with all-cause mortality [61]. In 84 months of follow-up after initiating cART, cumulative rates of all-cause mortality did not differ between IDUs (26.5%, 95% CI=23.2%-29.8%) and non-IDUs (21.6%, 95% CI=16.9%-26.2%) (Wilcoxon test p=0.47). Using a multivariable time-updated Cox proportional hazards model, the researchers controlled for sex, physician experience, adherence (measured by pharmacy-refill data), and baseline age, AIDS diagnosis, and CD4 cell count and found that the hazard ratio of all-cause mortality did not differ between IDUs and non-IDUs (HR=1.09, 95% CI=0.92-1.29) [61]. The authors also conducted a sub-analysis considering accidental deaths as non-events and the findings were similar [61]. Therefore, this recent work suggests that IDUs in British Columbia treated with cART have similar rates of mortality as non-IDUs.

Overall, most studies appear to have found that IDUs suffer higher rates of mortality than other patients; however, as with the virological suppression outcome, adherence to therapy needs to be considered as a potential confounding variable that could help to explain these differences, especially in terms of HIV-related mortality. The differences observed among these studies may be due to differences in patient populations, variables controlled for in analyses (such as adherence), and the study period. More research is needed to investigate outcomes of cART for IDUs, especially within the context of Aboriginal HIV-patient populations, which have not been widely studied.

1.6 HEALTH-RELATED QUALITY OF LIFE OUTCOMES OF COMBINATION ANTIRETROVIRAL THERAPY

1.6.1 Overview

"Health-related quality of life (HRQL) refers to how well an individual functions in daily life and his or her perceived well-being" [62]. In the cART era, when HIV is considered a chronic disease, HRQL has become a more important outcome to examine. Patients now live longer with the disease and antiretrovirals are currently life-long therapies, with associated toxicities and side-effects that may adversely impact patients' quality of life.

Although one of the goals of cART is to improve HRQL, even with this treatment, HIV-patients may not achieve levels of HRQL similar to the general population. For example, studies conducted in the United Kingdom [63] and Canada [64, 65] have shown that HIV-patients have poorer HRQL than the general population; however, not all patients in these studies were taking cART, which may have impacted the study results. If cART does improve HRQL, the HRQL for these patients may have been more comparable to the general population if they were all on treatment. However, regardless of the impact cART may have on HRQL, marginalized HIV-patients likely experience a number of social factors, including poverty, addictions, homelessness, and mental health issues, which may impact negatively on their HRQL. Therefore, rather than comparing HIV-patients' HRQL to that of the general population, it is likely more appropriate to compare a patient's own baseline HRQL, before they started combination antiretroviral therapy, to their HRQL after they have begun therapy as a way to monitor the impact of treatment on their well-being.

1.6.2 Does cART improve HRQL?

Several longitudinal studies have examined the association between cART use and change in quality of life, but they have come to different conclusions. Some found that HRQL improved over time [66, 67], or improved over time and then stabilized

after the first year on cART [68], while others found no change in HRQL over four years [64], and one study found certain areas of HRQL remained unchanged or declined in the first 6 months after starting therapy [69]. As pointed out by Protopopescu et al, differences in the results of HRQL studies such as these may be explained by differences in HRQL instruments and small sample sizes [68], as well as differences among the patient populations [68].

1.6.3 HRQL among Aboriginal HIV-patients after starting cART

Only one study, conducted in British Columbia, has specifically examined the impact of cART on quality of life among Aboriginals in Canada, and appeared to use the HIV/AIDS-Targeted Quality of Life Instrument (HAT-QoL) to measure quality of life. The researchers studied 457 patients (33% Aboriginal) and found that, after adjusting for clinical and sociodemographic variables, among patients treated with cART, Aboriginals reported better life satisfaction, fewer financial worries, and more provider trust compared with non-Aboriginals; furthermore, Aboriginals reported better overall function (a measure of physical, role, and social functioning) [70] than non-Aboriginals, but this result was of borderline statistical significance ($p=0.07$) [71]. This study offers hope that Aboriginal HIV-patients experience successful quality of life outcomes with therapy; however, at the time of writing, this research study was not published in full as a peer-reviewed paper; therefore, details regarding methodology are lacking.

Given the importance of improving HRQL as a goal of cART and the evidence that Aboriginal HIV-patients have higher mortality rates than non-Aboriginal HIV-patients in Canada, more research is needed that compares the impact of cART on HRQL between Aboriginals and non-Aboriginals. Although this one study has begun to compare HRQL by Aboriginal ethnicity in a cross-sectional study, future studies should examine changes in HRQL over time by Aboriginal ethnicity. The study conducted in British Columbia was based on a longitudinal cohort; therefore, this research program may be able to design future studies that assess HRQL prospectively.

1.6.4 HRQL among injection drug users after starting cART

Available evidence suggests that IDUs have worse HRQL than the general population [72] and, among HIV-infected individuals, worse HRQL compared to non-IDUs [73]. However, little research has specifically investigated the impact of cART on HRQL among IDUs or compared the impact of cART between IDUs and non-IDUs. One study conducted in France among 243 HIV-infected IDUs found that, compared to those receiving no ART therapy, those receiving cART or non-cART ART therapies had a similar odds of having a normal mental or physical HRQL score (with a normal HRQL score defined relative to the general population) [74]. In this study, factors associated with worse mental HRQL were not having strong social support from a partner, being a former IDU on opioid substitution therapy (OST) (vs. being a former IDU not on OST), having a history of violent "negative life events" ("NLE"), and having a higher number of cART-related side-effects. Factors associated with worse physical HRQL were older age, lack of a stable relationship, CD4 cell count ≤500 cells/μL, history of NLE of a financial nature, current IDU or stopping injection activities for less than one year vs. having stopped injecting for at least one year, and reporting a higher number of cART-related side-effects. In terms of the injection drug use variables, the authors concluded that IDUs who had stopped injecting long enough to have completed OST had better mental HRQL than those who had stopped injecting but were still taking OST. Similarly, those who had stopped injecting for at least one year had better physical HRQL. Based on these results, it appears that cART use may not be the most influential factor impacting HRQL for IDUs; rather, other factors related to drug use, life experience, and social support may be more important areas to investigate.

1.7 SUMMARY

Overall, cART has resulted in dramatic improvements in clinical outcomes and has decreased mortality rates for HIV-patients. The impact of cART on HRQL is less clear, however, most studies appear to support either a stabilization or improvement in HRQL over time. Although a great deal of research has investigated

the impact of cART in the general HIV-patient population, very little is known about the outcomes of cART among Aboriginal HIV-patients. This gap in knowledge is especially troublesome given the well-documented overrepresentation of Aboriginal peoples in Canada's HIV epidemic. The few studies conducted in Canada appear to show no difference in clinical outcomes, but higher rates of all-cause mortality for Aboriginals, and better quality of life compared with non-Aboriginals. All Canadian studies comparing cART outcomes by Aboriginal ethnicity have been conducted in British Columbia, specifically in Vancouver. Therefore, the results may not be representative of the experiences of Aboriginal patients in other areas of the country. Although international research provides interesting comparisons for Aboriginals in Canada, more research is needed to better understand the impact of cART for Aboriginal HIV-patients in this country. Since IDU is a primary route of HIV transmission for Aboriginals in Canada, an investigation of treatment outcomes among Aboriginals requires consideration about how this risk factor may influence treatment outcomes. Research shows that IDUs experience less successful clinical outcomes of cART than non-IDUs; however, this may be explained by lower rates of adherence among IDUs. Similarly, rates of all-cause mortality are higher for IDUs, but not necessarily rates of HIV-related mortality, which is a better indication of treatment success. In addition to IDU, determinants of health including education, income, and employment status and adherence to therapy should be considered as potential confounders in studies investigating the impact of Aboriginal ethnicity on cART outcomes.

1.8 RESEARCH OBJECTIVES

The primary objectives of this thesis research, based on HIV-patients treated in northern Alberta as the patient population, are to:

1. Compare all-cause and HIV-related mortality rates between Aboriginal and non-Aboriginal HIV-patients after they start cART.
2. Determine if Aboriginal patients were less likely to achieve virological suppression and more likely to experience subsequent treatment failure after starting cART.
3. Describe the HRQL of HIV-patients treated with cART.
    a. Compare HRQL between Aboriginals and non-Aboriginals, and because of the overrepresentation of IDUs among Aboriginal HIV-patients, between IDUs and those with other HIV-exposures.
    b. Assess whether any associations between Aboriginal ethnicity or IDU with HRQL could be explained by clinical status.
4. Describe the life stability of Aboriginal and IDU HIV-patients treated with cART in northern Alberta and to explore associations between life stability, clinical status, and HRQL.

Table 1.1 Summary of decreases in all-cause and HIV-related mortality rates for HIV-infected individuals reported in the literature

Location	N	Years	All-cause mortality, per 100 person-years (95% CI)	HIV-related mortality, per 100 person-years (95% CI)	Reference
United States	1,255	1st quarter 1994 2nd quarter 1997	35.1 8.8	N/A	36
United States	1,011 1,098 1,162 1,175 1,103 (N=3,211)	1994 1995 1996 1997 1998	20.2 (17.2-23.6) 16.3 (13.8-19.2) 11.2 (9.2-13.7) 7.0 (5.4-9.1) 8.4 (6.6-10.7)	N/A	39
Europe, Argentina, Israel	3,793 3,425 2,585 (N=9,803)	1994-1995 1996-1997 ≥1998	19.0 (17.7-20.3) 9.3 (8.6-10.0) 2.6 (2.4-2.8)	14.6 (13.4-15.8) 7.4 (6.8-8.1) 1.5 (1.4-1.7)	41

Adapted in part from: Hoffmann C, Mulcahy F. ART 2007. In: HIV Medicine 2007, 15th ed. Eds Hoffmann C, Rockstroh JK, Kamps BS. Available at: http://www.hivmedicine.com/hivmedicine2007.pdf

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CHAPTER 2: ALL-CAUSE AND HIV-RELATED MORTALITY RATES AMONG HIV-INFECTED PATIENTS AFTER INITIATING COMBINATION ANTIRETROVIRAL THERAPY: THE IMPACT OF ABORIGINAL ETHNICITY AND INJECTION DRUG USE

2.1 INTRODUCTION

Combination antiretroviral therapy (cART) has dramatically reduced mortality among human immunodeficiency virus (HIV)-infected individuals [1, 2]. However, since the introduction of cART, higher rates of mortality have been observed among injection drug users (IDUs) [3, 4] and Aboriginal peoples [5] within this population.

In Canada, the HIV epidemic is distinct among Aboriginals. In 2006, 27.3% of positive HIV tests reported with available ethnicity information from submitting Canadian provinces and territories were from Aboriginals [6]; however, in the same year, Aboriginals represented only 7.0% of the population of these regions of the country [7]. In addition, IDU is more commonly reported as a route of HIV exposure among Aboriginals than non-Aboriginals. Between 1998 and 2006, among positive HIV test reports with available ethnicity data, IDU was the route of exposure for 58.8% of tests from Aboriginals and only 24.8% of tests from non-Aboriginals [8]. Although collaborative analyses of prospective cohort studies from North America and Europe have shown IDU to be associated with increased rates of mortality after starting CART [9, 10], less is known about the impact of Aboriginal ethnicity on mortality after starting cART. One recent Canadian study found Aboriginals to have significantly higher rates (hazard ratio (HR)=3.12, 95% CI=1.77-5.48) of all-cause mortality after starting cART [5]. However, this study did not investigate HIV-related mortality specifically and included only 88 Aboriginal subjects (14.1% of the study population). As Mocroft et al. illustrate, it is inappropriate to assume that higher all-cause mortality rates necessarily demonstrate a poorer response to cART; to

investigate patients' responses to cART, it is important to specifically examine HIV-related mortality rates [11].

The objectives of this study were to compare all-cause and HIV-related mortality rates between Aboriginal and non-Aboriginal HIV-patients after starting cART, adjusting for factors known to influence mortality among HIV-patients. Because Aboriginal HIV-patients have higher rates of exposure to HIV via IDU and because we observed a strong association between IDU and mortality, we also examined the relationship between IDU and these two mortality outcomes.

2.2 METHODS

2.2.1 Data sources

This was a retrospective cohort study using data collected by the Northern Alberta HIV Program (NAHIVP). 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, clinical test results (e.g. CD4 cell counts and HIV RNA measures (viral loads)), and deaths reported to the clinics are recorded in the NAHIVP database. This database has been used in other studies [12-14]; however, an investigation of mortality after starting cART has not yet been undertaken for these patients. In addition to data from NAHIVP, we linked cause and date of death data from Alberta Health and Wellness to the study database and used viral load data from the Alberta Provincial Public Health Laboratory to replace missing baseline viral loads where possible. Deaths that occurred outside Alberta and not reported to NAHIVP would be missed in our analysis. The study procedures were approved by the University of Alberta Health Research Ethics Board.

2.2.2 Study patients

We assembled a cohort of patients using the NAHIVP database who satisfied the following eligibility criteria: 1) started cART between 1 January 1999 and 30 June 2005 (baseline); 2) were previously ART-naïve; and 3) were ≥15 years of age when starting cART. Patients were excluded if they were missing ethnicity data. To limit the study to patients who started cART for the purpose of treatment, rather than to prevent vertical transmission of HIV, we excluded patients if they started cART ≤26 weeks before being recorded as delivering a baby. We assumed that starting cART earlier in pregnancy or after delivery would be for maternal indications. Patients were followed retrospectively until 31 December 2005, which allowed follow-up time of 6 months to 7 years.

2.2.3 Definitions

We defined Aboriginals as Treaty and non-Treaty Aboriginals, Métis, and Inuit. One patient was defined as Aboriginal who was identified as both Caucasian and Métis in the database. HIV exposure categories were classified using an exposure category hierarchy [6]. Patients were defined as IDUs if their HIV exposure was recorded as IDU or any other exposure combined with IDU; patients with other exposures, including unknown or missing exposures, were considered to have "other exposures". We defined cART 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 cART start date was the first date that a cART prescription was recorded in the database. We used an intention-to-treat analytic approach and therefore assumed patients continued on cART. Baseline CD4 cell counts and viral loads were defined as those measures that were taken closest to the cART start date, ≤6 months before, and not after starting cART. We classified causes of death using the ninth and tenth revisions of the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and 10) [15]. We defined

ICD-9 categories 042-044 and ICD-10 categories B20-B24 as HIV-related causes of death; all other known causes were coded as non-HIV-related causes of death. Cause of death was unavailable for 5 patients; therefore, one of the authors (SH) reviewed their charts and determined cause of death to be HIV-related for two patients and non-HIV-related for two patients. Cause of death remained undetermined for one patient (an Aboriginal female IDU), who we excluded from our analysis of HIV-related mortality.

2.2.4 Data analyses

Patient characteristics were tabulated and compared between Aboriginals and non-Aboriginals and between IDUs and patients with other exposures, using χ^2 and two-sided Fisher exact tests for categorical variables and two-sided Wilcoxon rank sum test (normal approximation) for continuous variables.

To examine unadjusted all-cause mortality risk, we compared Kaplan-Meier estimates of survival probabilities by Aboriginal ethnicity as well as by IDU grouping using the Log-Rank test. We then used Cox proportional hazards models to estimate the adjusted hazard rate ratios of mortality by Aboriginal ethnicity as well as by the IDU grouping, adjusting for potential confounding variables identified using the procedure described below. To examine HIV-related mortality risk, we estimated cumulative incidence curves, as described by Gooley et al [16], by Aboriginal ethnicity and by the IDU grouping (unadjusted analysis) and compared HIV-related mortality hazard rate ratios using Cox proportional hazards models, adjusting for potential confounding variables.

Potential confounding variables were identified as those associated with all-cause (or HIV-related) mortality in unadjusted analyses with $p<0.20$. Baseline age and baseline CD4 cell count were forced to enter the models because other studies [9, 10] have shown these variables to be prognostic in progression to mortality. We tested the interaction between Aboriginal ethnicity and IDU in the final main effects multivariable models to determine if the impact of Aboriginal ethnicity on mortality

differed by IDU status. The proportionality assumption of Cox proportional hazards models was assessed using two time varying covariates (Aboriginal by the log of survival time and IDU by the log of survival time), which were each tested separately in unadjusted models that included only the main effect and the time varying covariate. P-values were two-sided 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).

2.3 RESULTS

2.3.1 Derivation of the study population

The NAHIVP database contained 2,258 patient records. After removing duplicates and applying study eligibility criteria (Figure 2.1), 548 individuals (426 (78%) males and 122 (22%) females) remained in the study population, contributing 1,889.8 person-years of follow-up time.

We excluded 45 patients who appeared to have started cART to prevent vertical transmission of HIV, of whom 3 (6.7%) died. Compared to the 548 study patients, these 45 women were more likely to have been Aboriginal (56% (n=43) vs. 35%, p=0.0076), started cART at a younger age (median 25.8 vs. 39.4 years, p<0.0001), had a higher baseline CD4 count (median 350 (n=43) vs. 210 cells/μL, p<0.0001), had a lower baseline viral load (median 9,900 (n=45) vs. 100,000 copies/mL, p<0.0001), and were more likely to have started cART on a protease inhibitor (PI)-based regimen (47% vs. 27%, p=0.0050).

We excluded 36 patients who were missing ethnicity data, of whom 3 died (8.3%). Compared to study patients, these 36 patients were less likely to be IDU (28% vs. 47%, p=0.029), were less likely to start cART in 1999-2001 vs. 2002-2005 (17% vs. 43%, p=0.0021), were followed for a shorter time (median 1.9 vs. 3.3 years, p=0.0003), and died at an older age (62.3 (n=3) vs. 40.9 years, p=0.017).

2.3.2 Description of the study patients

At baseline, the median age was 39.4 (interquartile range (IQR)=32.9-45.0) years, median CD4 cell count was 210 cells/μL (IQR=100-320 cells/μL, n=505), and median viral load was 100,000 copies/mL (IQR=18,000-350,000, n=529); 68 (12%) patients had baseline viral loads <500 copies/mL. The single most common HIV exposure category was IDU (227, 41%) followed by heterosexual contact (137, 25%), men who have sex with men (MSM) (124, 23%), MSM/IDU (28, 5.1%), and other (8, 1.5%); the exposure category was missing or unknown for 24 (4.4%) patients. Most patients initiated cART on a non-PI-based regimen (400, 73%).

2.3.2.1 Aboriginal ethnicity

Of the 548 study patients, 194 (35%) were Aboriginal. Compared to non-Aboriginals, Aboriginal patients were significantly more likely to be female, be infected with HIV through IDU, start cART at a younger age, start cART on a non-PI-based regimen, have a lower baseline CD4 count, and die (Table 2.1).

2.3.2.2 Injection drug use

Almost half of the patients (255, 47%) were IDU. Compared to patients with other exposures, IDUs were significantly more likely to be Aboriginal, start cART in 1999-2001, have a longer duration of follow-up, and die (Table 2.1).

2.3.3 Mortality

2.3.3.1 Causes of death

Overall, 55 patients (10%) died, an incidence rate of 2.91 deaths per 100 person-years. Most deaths occurred among Aboriginals (31, 56%) and IDUs (40, 73%). The single most common cause of death was HIV disease (26, 47%), followed by external causes of morbidity and mortality (16, 29%), which included accidents (8, 50%), intentional self-harm (4, 25%), and events of undetermined intent (4, 25%). All 8 accidental deaths occurred among IDUs and three of the four deaths caused by intentional self-harm occurred among non-Aboriginal patients.

2.3.3.2 All-cause mortality

Compared to non-Aboriginals, Aboriginal patients had a lower all-cause survival probability (p=0.0015) (Figure 2.2) and a higher crude all-cause mortality rate (HR=2.31, 95% CI=1.36-3.94, p=0.0021) (Table 2.2). Controlling for IDU, baseline CD4 cell count, and baseline age, Aboriginals had an all-cause mortality hazard rate 1.85 (95% CI=1.05-3.26, p=0.034) times higher than non-Aboriginals (Table 2.2). Similarly, compared to patients with other exposures, IDUs had a lower survival probability (p=0.0003) (Figure 2.2) and a higher crude all-cause mortality rate (HR=2.82, 95% CI=1.56-5.11, p=0.0006) (Table 2.2). Controlling for Aboriginal ethnicity, baseline CD4 cell count, and baseline age, IDUs had an all-cause mortality rate 2.45 (95% CI=1.31-4.57, p=0.0050) times higher than patients with other exposures (Table 2.2). The interaction between Aboriginal ethnicity and IDU was not statistically significant (p=0.55) and was not retained in the final model.

2.3.3.3 HIV-related mortalities

Compared to non-Aboriginals, Aboriginal patients had a higher cumulative incidence rate of HIV-related mortality (p=0.0001) (Figure 2.3a) and a higher crude HIV-related mortality rate (HR=4.76, 95% CI=2.00-11.33, p=0.0004) (Table 2.3); among patients who died, Aboriginals were more likely to die from an HIV-related cause (63% vs. 29%, Table 1). Until approximately 4 years after starting cART, Aboriginals also appeared to experience a higher cumulative incidence of non-HIV-related mortality compared to non-Aboriginals; however, overall, the incidence of non-HIV-related mortality did not differ by Aboriginal ethnicity (p=0.75) (Figure 2.3b). Adjusting for IDU, sex and baseline CD4 cell count, viral load, age, and calendar year, the HIV-related mortality hazard rate was 3.47 times higher for Aboriginals compared to non-Aboriginals (95% CI=1.36-8.83, p=0.0091) (Table 2.3). Compared to patients with other exposures, IDUs had higher cumulative incidence rates of HIV-related (p=0.039) and non-HIV-related (p=0.006) mortality (Figure 2.3c, d), and a higher crude HIV-related mortality rate (HR=2.42, 95% CI=1.05-5.57, p=0.038) (Table 2.3); among patients who died, IDUs were not more likely to die from

an HIV-related cause (46% vs. 53%, Table 1). Adjusting for Aboriginal ethnicity, sex, and baseline CD4 cell count, viral load, age, and calendar year, the HIV-related mortality hazard rate was higher among IDUs than patients with other exposures, but this result was not statistically significant (HR=1.65, 95% CI=0.67-4.04, p=0.27) (Table 2.3). The interaction between Aboriginal ethnicity and IDU was not statistically significant (p=0.14) and was not retained in the final model.

2.4 DISCUSSION

Aboriginal HIV-patients suffer higher rates of all-cause and HIV-related mortality compared to non-Aboriginal HIV-patients after starting cART, even after controlling for IDU as an exposure category. This suggests that Aboriginal HIV-patients experience inferior responses to cART compared to non-Aboriginals. This finding may be explained by confounding variables we were unable to control for in this analysis, such as poor adherence to therapy, which may be caused by ongoing injection drug and other substance abuse behaviours, as opposed to injection drug use only as a route of HIV exposure. Intermittent use of cART has been associated with increased rates of mortality [17]. In addition, active drug use has been associated with poor adherence [18] and intermittent and persistent drug users have been shown to have higher mortality rates than non-users [19]. The higher rates of HIV-related mortality observed among Aboriginals may also be explained by lower socioeconomic conditions, including factors such as lower income, lower education levels, and unstable housing. In general, Aboriginals have lower education levels and higher unemployment rates compared to the general Canadian population [20] and these differences were likely represented in our study population. More research is needed to understand the reasons for the higher rates of HIV-related mortality observed among Aboriginal HIV-patients; adherence, active substance use, and socioeconomic factors should be measured in future studies.

In addition to poor adherence, another hypothesized explanation for the higher rates of HIV-related mortality observed among Aboriginals are potential differences in the prevalence of certain genetic polymorphisms among Aboriginal

peoples, which may lead to differences in ART action and, therefore, potential differences in cART outcomes. For example, the hepatic cytochrome P450 enzyme (CYP)2B6 metabolizes efavirenz [21]; the homozygous T/T genotype at position 516 of CYP2B6 is more common among African-Americans compared to European-Americans and this genotype is associated with higher plasma exposure to efavirenz [22]. However, this polymorphism has not been associated with time to virological failure or toxicity-related failure [23]. Although no research has examined the prevalence of polymorphisms such as this among Aboriginals, one could hypothesize that similar differences might exist. If polymorphisms such as this occur at higher prevalence rates among Aboriginals and these polymorphisms are associated with poorer responses to cART, leading to increased risk of HIV-related mortality, then this explanation may help to explain the differences in HIV-related mortality observed in our study. However, much more research is required to test this hypothesis.

IDU appears to be the strongest predictor of higher all-cause mortality rates after starting cART. Although HIV was the most common cause of death among IDUs, after controlling for Aboriginal ethnicity and other confounders, IDU was not a significant predictor of higher HIV-related mortality rates. These results are consistent with findings from the EuroSIDA study, which shows that, compared to patients with other exposures, IDUs have higher rates of non-HIV-related mortality after starting cART, but similar rates of HIV-related mortality [11]. The EuroSIDA authors, therefore, concluded that IDUs in their study responded to cART as well as patients with other exposures.

However, other research suggests that IDUs may receive less benefit from cART due to delayed treatment initiation [24]; treatment interruptions [25]; and continued drug use [19], which may also be associated with lower levels of adherence [18]. In addition, hepatitis C virus (HCV) co-infection, which is far more common among IDUs than those infected with HIV via other transmission routes [26], has been shown to be an independent predictor of mortality among HIV-infected patients [27]. Our

results show that IDUs did not have significantly lower CD4 cell counts or higher viral loads at baseline compared to patients with other exposures. This suggests that IDUs were provided cART at similar clinical periods during their illnesses and did not experience a relative delay in treatment. However, interruptions in treatment may have occurred more commonly among IDUs, which could have adversely impacted their health. In our study, all 8 deaths due to accidents, primarily accidental poisonings, occurred among IDUs. This is not surprising, as drug overdoses are a common cause of death among IDUs [28], and it demonstrates that at least some individuals infected with HIV through IDU continue substance abuse behaviours after starting cART. This study did not assess adherence to therapy, continued drug use, HCV co-infection, or socioeconomic status, all of which may have contributed to higher mortality rates among IDUs after starting cART.

To our knowledge this is the first study to investigate the relationship between Aboriginal ethnicity and mortality after starting cART that has included such a large number of Aboriginal HIV-patients, has investigated HIV-related mortality as an outcome, rather than all-cause mortality alone, and has attempted to exclude women who started cART to prevent vertical transmission of HIV. We consider this latter exclusion criterion to be important when investigating outcomes of cART, especially among Aboriginal populations. This is illustrated by the fact that, in our study, the 45 women excluded for this reason were significantly more likely to have been Aboriginal, have had less severe baseline clinical characteristics, and have started cART on a PI-based regimen.

2.4.1 Limitations

This study has several limitations. First, ethnicity and HIV exposure categories used in this analysis were self- or physician-reported and misclassifications may have occurred. In particular, as pointed out by Wood et al, the stigma associated with injection drug use might cause it to go unreported [29] and we may have misclassified patients 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, the number of deaths that occurred in this study was low; therefore, small changes in numbers may have relatively large impacts on results. In our study, the sample size was limited to a time period cross-referenced with provincial vital statistics data and to patients with known ethnicity. Because only a small number of HIV-related deaths occur after starting cART, it would be beneficial to conduct multi-provincial studies investigating the association between Aboriginal ethnicity and HIV-related cause of death across Canada.

Lastly, 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. Using these data, we could not be certain that patients were ART-naïve when starting cART. In particular, for the 68 (12%) patients with baseline viral loads <500 copies/mL, the cART start date was likely earlier than the date entered into the database. In addition, certain variables such as socioeconomic status measures, adherence to therapy, HCV co-infection, presence of other co-morbid conditions, and ongoing behaviours such as smoking and substance abuse were not collected, or were not available in formats appropriate for this analysis. These variables may have impacted mortality rates. Most importantly, data assessing patients' adherence to cART were not available in our study dataset. However, because this is the most probable reason for the difference in HIV-related mortality rates we observed between Aboriginals and non-Aboriginals, adherence needs to be investigated further. Although there is no agreed upon gold standard for measuring adherence [30], other researchers comparing ART outcomes between Aboriginals and non-Aboriginals have used prescription-refill data as an indirect measure of adherence and found conflicting results. One study defined adherence to cART as a dichotomous variable (<95% vs. ≥95%) and found no significant difference by Aboriginal ethnicity [5]. However, another study 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 [31]. These equivocal findings may be related to different methods of measuring adherence (i.e. as a dichotomous vs. continuous variable), to differences in adherence to cART vs. dual therapies, or to measurement error associated with this indicator of adherence. Pharmacy-refill data are considered to be a useful measure of adherence in retrospective, population-based studies when more accurate measures are not feasible [32]. In HIV research, they have been shown to correlate with virological suppression [33] and mortality [17]. However, one disadvantage of this method is that patients who refill their prescriptions may not take their pills as prescribed. Prospective studies are needed to compare adherence rates between Aboriginals and non-Aboriginals; existing evidence from pharmacy-refill data should be corroborated with more sensitive methods, such as electronic monitoring, pill counts, directly observed therapy, or a composite measure, which is an approach explored by Liu et al [34] and recommended by others [35].

2.4.2 Conclusions and future research

Aboriginal ethnicity is associated with higher rates of all-cause mortality after starting cART; this seems to be largely explained by a significantly higher rate of death from HIV-related causes among Aboriginals. IDU appears to be the strongest and most significant predictor of higher all-cause mortality rates. Future research should examine reasons for the high mortality rates we observed among Aboriginals from HIV-related causes of death. Specifically, we recommend four areas of research. First, the relationship between Aboriginal ethnicity, IDU, and clinical outcomes of cART, including virological treatment success and failure, should be examined to determine if the relationship we observed for mortality extends to these clinical outcomes. Second, adherence to cART should be prospectively measured using sensitive methods to determine if Aboriginal ethnicity is associated with poorer adherence to treatment. Third, qualitative studies should explore how Aboriginal HIV-patients experience cART treatment to understand if they encounter challenges that have not yet been well-documented. Finally, studies should compare the

frequencies of genetic polymorphisms associated with the activity of cART drugs between Aboriginal and non-Aboriginal HIV-patients.

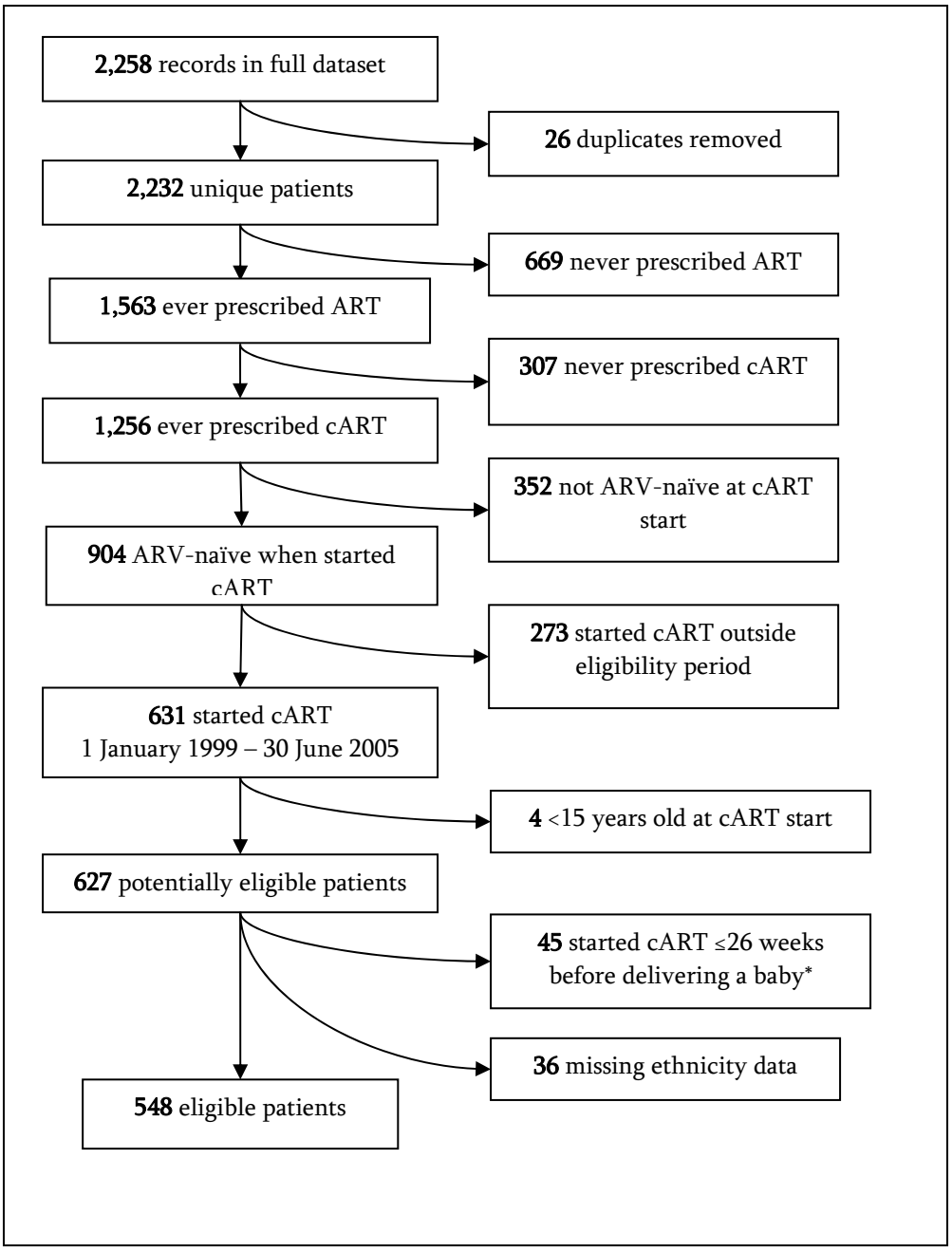
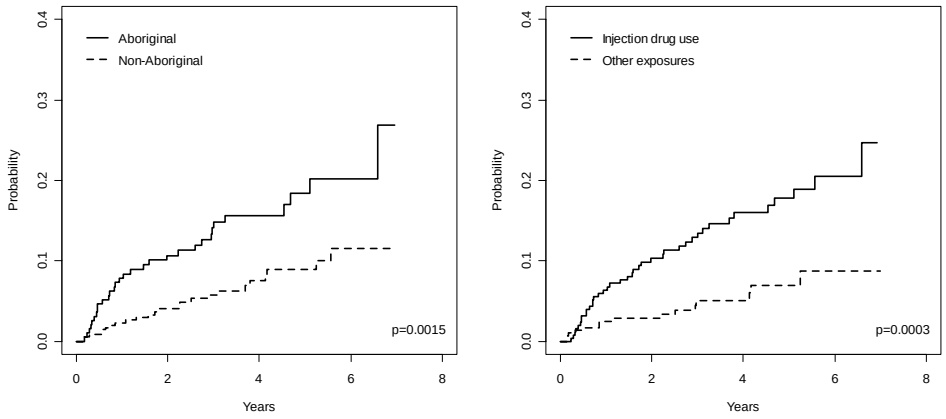


Figure 2.1 Derivation of the study population (N=548)

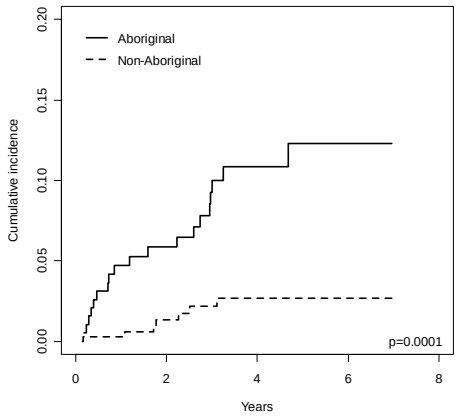
Notes: ART = antiretroviral therapy, cART = combination antiretroviral therapy

*Of these 45 patients, 2 were also missing ethnicity data

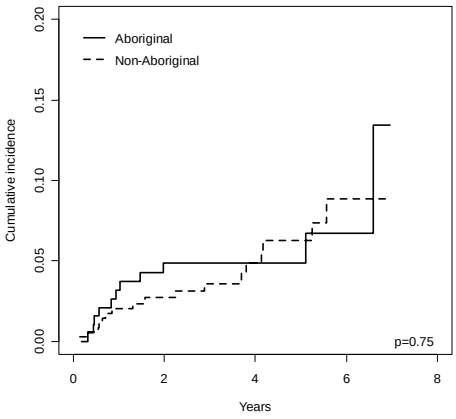


(a) Aboriginal ethnicity (b) Injection drug use exposure category

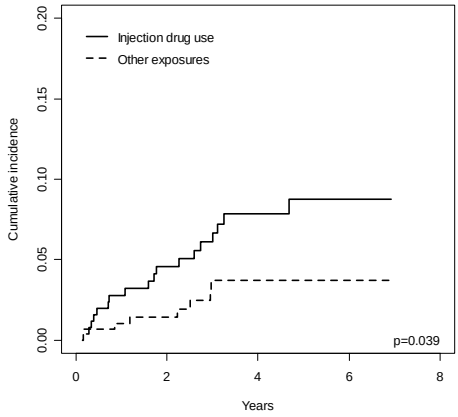
Figure 2.2 Probability of all-cause mortality by years since starting cART, comparing patients by (a) Aboriginal ethnicity and (b) injection drug use exposure category (N=548)



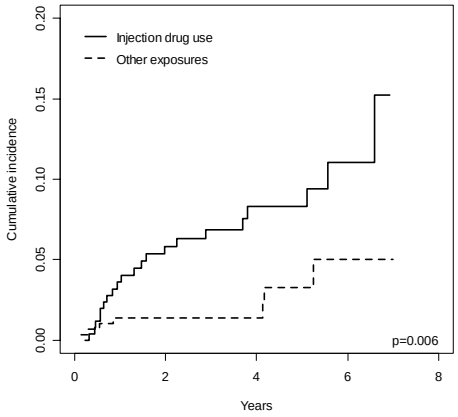
(a) HIV-related mortality by Aboriginal ethnicity



(b) Non-HIV-related mortality by Aboriginal ethnicity



(c) HIV-related mortality by IDU



(d) Non-HIV-related mortality by IDU

Figure 2.3 Cumulative incidence of mortality by years since cART initiation, comparing patients by (a, b) Aboriginal ethnicity and (c, d) injection drug use exposure category for HIV-related mortality (left side) and non-HIV-related mortality (right side) (N=547)

*Note: We excluded one individual who died of an unknown cause from these analyses

Table 2.1 Patient characteristics by ethnicity (N=548)

Characteristic	Aboriginal (n=194, 35%)	Non-Aboriginal (n=354, 65%)	p-value
Years of follow-up time, median (IQR), total	3.4 (2.2-5.1), 682.0	3.3 (1.6-5.1), 1213.0	0.55
Sex, no (%)			<0.0001
Female	71 (37)	51 (14)	
Male	123 (63)	303 (86)	
HIV exposure category, no (%)			<0.0001
Injection drug use	131 (68)	124 (35)	
Other exposures	63 (32)	230 (65)	
CD4 cells/μL at baseline, median (IQR)	195 (85-295), (n=180)	220 (110-340), (n=325)	0.037
CD4 cells/μL at baseline, no (%)			0.23
≤50	30 (15)	50 (14)	
>50-200	63 (32)	101 (29)	
>200-350	61 (31)	99 (28)	
>350	26 (13.4)	75 (21)	
Missing	14 (7.2)	29 (8.2)	
HIV RNA copies/mL at baseline, median (IQR)	100,000 (22,000-390,000) (n=187)	100,000 (16,000-335,000) (n=342)	0.46
HIV RNA copies/mL at baseline, no (%)			0.41
<10,000	32 (16)	77 (22)	
10,000-<100,000	59 (30)	90 (25)	
≥100,000	96 (49)	175 (49)	
Missing	7 (3.6)	12 (3.4)	
Initial cART regimen, no (%)			0.013
PI-based	40 (21)	108 (31)	
Not PI-based	154 (79)	246 (69)	
Year starting cART, no (%)			0.45
1999-2001	87 (45)	147 (42)	
2002-2005	107 (55)	207 (58)	
Age at baseline, median (IQR)	37.4 (31.7-42.7)	40.1 (33.6-45.7)	0.0020
Age at baseline, no (%)			0.024
15-<30	32 (16)	59 (17)	
30-<40	84 (43)	114 (32)	
40-<50	64 (33)	133 (38)	
≥50	14 (7.2)	48 (14)	
Mortalities, no (%)			0.0006
Died	31 (16)	24 (6.8)	
Alive	163 (84)	330 (93)	
Cause of death, no (%) (n=54)*			0.013
HIV-related causes	19 (63)	7 (29)	
Non-HIV-related causes	11 (37)	17 (71)	
Age at death, median (IQR) (n=55)	40.6 (33.7-46.1)	40.9 (37.7-50.4)	0.43

*Note: One death of unknown cause was excluded from this calculation

Table 2.2 Patient characteristics by injection drug use exposure category (n=548)

Characteristic	Injection drug use (n=255, 47%)	Other exposures (n=293, 53%)	p-value
Years of follow-up time, median (IQR), total	3.6 (2.1-5.3), 929.9	3.2 (1.6-4.7), 965.1	0.034
Sex, no (%)			0.090
Female	65 (25)	57 (19)	
Male	190 (75)	236 (81)	
Ethnicity			
Aboriginal	131 (51)	63 (22)	<0.0001
Non-Aboriginal	124 (49)	230 (79)	
CD4 cells/μL at baseline, median (IQR)	220 (100-320), (n=230)	210 (110-330), (n=275)	0.91
CD4 cells/μL at baseline, no (%)			0.26
≤50	38 (15)	42 (14)	
>50-200	71 (28)	93 (32)	
>200-350	80 (31)	80 (27)	
>350	41 (16)	60 (20)	
Missing	25 (9.8)	18 (6.1)	
HIV RNA copies/mL at baseline, median (IQR)	99,000 (25,000-350,000) (n=242)	100,000 (11,000-360,000) (n=287)	0.58
HIV RNA copies/mL at baseline, no (%)			0.0025
<10,000	39 (15)	70 (24)	
10,000-<100,000	83 (33)	66 (23)	
≥100,000	120 (47)	151 (52)	
Missing	13 (5.1)	6 (2.1)	
Initial cART regimen, no (%)			0.32
PI-based	74 (29)	74 (25)	
Not PI-based	181 (71)	219 (75)	
Year starting cART, no (%)			0.0017
1999-2001	127 (50)	107 (37)	
2002-2005	128 (50)	186 (63)	
Age at baseline, median (IQR)	39.3 (33.0-45.0)	39.5 (32.8-45.0)	0.83
Age at baseline, no (%)			0.038
15-<30	37 (15)	54 (18)	
30-<40	98 (38)	100 (34)	
40-<50	100 (39)	97 (33)	
≥50	20 (7.8)	42 (14)	
Mortalities, no (%)			<0.0001
Died	40 (16)	15 (5.1)	
Alive	215 (84)	278 (95)	
Cause of death, no (%) (n=54)*			0.64
HIV-related causes	18 (46)	8 (53)	
Non-HIV-related causes	21 (54)	7 (47)	
Age at death, median (IQR) (n=55)	40.4 (35.0-45.2)	42.4 (33.7-53.8)	0.22

*Note: One death of unknown cause was excluded from this calculation

Table 2.3 Univariable and multivariable Cox proportional hazards models assessing all-cause mortality after starting cART (N=548)

Variable	Unadjusted Hazard Ratio (95% CI)		p-value	Adjusted Hazard Ratio (95% CI)		p-value
Ethnicity (Aboriginal vs. non-Aboriginal)	2.31	(1.36-3.94)	0.0021	1.85	(1.05-3.26)	0.034
Sex (Female vs. male)	1.39	(0.78-2.48)	0.27	-*	-	-
HIV exposure category (Injection drug use vs. other exposures)	2.82	(1.56-5.11)	0.0006	2.45	(1.31-4.57)	0.0050
CD4 cells/μL at baseline			Class p=0.16			
≤50 (ref)	1.00	-	-	1.00	-	-
>50-200	0.58	(0.28-1.20)	0.14	0.60	(0.29-1.26)	0.18
>200-350	0.42	(0.19-0.92)	0.030	0.40	(0.18-0.87)	0.022
>350	0.39	(0.16-0.91)	0.029	0.44	(0.19-1.05)	0.065
Missing baseline CD4 count	0.55	(0.19-1.54)	0.25	0.53	(0.19-1.51)	0.23
HIV RNA copies/mL at baseline			Class p=0.51			
<10,000	0.55	(0.24-1.27)	0.16	-	-	-
10,000-<100,000	0.98	(0.53-1.79)	0.94	-	-	-
≥100,000 (ref)	1.00	-	-	-	-	-
Missing baseline viral load measure	1.23	(0.37-4.06)	0.73	-	-	-
Age at baseline			Class p=0.75			
15-<30 (ref)	1.00	-	-	1.00	-	-
30-<40	1.49	(0.66-3.36)	0.33	1.26	(0.55-2.87)	0.58
40-<50	1.37	(0.60-3.13)	0.46	1.24	(0.53-2.88)	0.62
≥50	1.71	(0.59-4.97)	0.33	2.02	(0.68-6.01)	0.21
Initial cART regimen (PI vs. non-PI based)	0.98	(0.55-1.76)	0.95	-	-	-
Baseline calendar year (1999-2001 vs. 2002-2005)	0.79	(0.44-1.43)	0.44	-	-	-

*Note: Other than baseline age and baseline CD4 count, variables with p-values ≥0.20 were not included in the multivariate model

Table 2.4 Univariable and multivariable Cox proportional hazards models assessing HIV-related mortality after starting cART (N=547)

Variable	Unadjusted Hazard ratio (95% CI)		p-value	Adjusted Hazard ratio (95% CI)		p-value
Ethnicity (Aboriginal vs. non-Aboriginal)	4.76	(2.00-11.33)	0.0004	3.47	(1.36-8.83)	0.0091
Sex (Female vs. male)	1.79	(0.80-4.02)	0.16	1.18	(0.50-2.77)	0.70
HIV exposure category (Injection drug use vs. other exposures)	2.42	(1.05-5.57)	0.038	1.65	(0.67-4.04)	0.27
CD4 cells/μL at baseline			Class p=0.014			
≤50 (ref)	1.00	-	-	1.00	-	-
>50-200	0.53	(0.22-1.31)	0.17	0.56	(0.22-1.42)	0.22
>200-350	0.15	(0.04-0.57)	0.0049	0.17	(0.041-0.68)	0.012
>350	0.07	(0.01-0.54)	0.011	0.14	(0.016-1.21)	0.074
Missing baseline CD4 count	0.49	(0.13-1.81)	0.29	0.24	(0.034-1.62)	0.14
HIV RNA copies/mL at baseline			Class p=0.11			
<10,000	0.30	(0.07-1.30)	0.11	0.68	(0.14-3.19)	0.62
10,000-<100,000	0.67	(0.26-1.73)	0.41	1.19	(0.43-3.31)	0.74
≥100,000 (ref)	1.00	-	-	1.00	-	-
Missing baseline viral load measure	2.42	(0.70-8.38)	0.16	6.47	(0.99-42.27)	0.051
Age at baseline			Class p=0.29			
15-<30 (ref)	1.00	-	-	1.00	-	-
30-<40	3.59	(0.82-15.79)	0.091	1.77	(0.37-8.42)	0.47
40-<50	2.14	(0.45-10.07)	0.34	1.14	(0.22-5.91)	0.88
≥50	2.00	(0.28-14.24)	0.49	1.17	(0.15-9.41)	0.88
Initial cART regimen (PI vs. non-PI based)	0.74	(0.30-1.85)	0.52	-*	-	-
Baseline calendar year (1999-2001 vs. 2002-2005)	0.26	(0.10-0.66)	0.0048	0.29	(0.11-0.79)	0.016

*Note: Other than baseline age and baseline CD4 count, variables with p-values ≥0.20 were not included in the multivariate model

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CHAPTER 3: LOWER RATES OF INITIAL VIROLOGICAL SUPPRESSION AFTER STARTING COMBINATION ANTIRETROVIRAL THERAPY AND HIGHER RATES OF SUBSEQUENT VIROLOGICAL FAILURE AMONG ABORIGINALS

3.1 INTRODUCTION

Despite the well documented benefits of combination antiretroviral therapy (cART), Aboriginal HIV-patients in Canada appear to experience less successful cART outcomes; however, findings are inconsistent. Recent research has shown that, after starting cART, 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 cART 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 cART [4], in relation to Aboriginal ethnicity. We hypothesize that the higher rates of HIV-related mortality observed among Aboriginals after starting cART may be explained by higher rates of cART 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 cART outcomes may differ between Aboriginals and non-Aboriginals is especially important for two reasons. First, Aboriginals are overrepresented in Canada's HIV epidemic. In 2006, 27.3% of positive HIV tests reported with available ethnicity information were from Aboriginals [5]; however, in the same year, Aboriginals represented only 7.0% of the population of the reporting provinces and territories [6]. Therefore, poorer treatment outcomes may impact a substantial proportion of the HIV-patient population in Canada.

Second, it is well recognized that 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 cART outcomes. Furthermore, they may facilitate progression from cART failure to mortality.

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

3.2 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 cART failure by Aboriginal ethnicity among patients who achieved initial virological suppression in Part 1.

3.2.1 Data sources

Our primary data source was the Northern Alberta HIV Program (NAHIVP) clinical database. Detailed methods have been described elsewhere (see Chapter 2). 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 HIV RNA test results (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.

3.2.2 Study patients

We assembled a cohort of patients using the NAHIVP database and the following eligibility criteria: 1) started cART between 1 January 1999 and 30 June 2005 (baseline); 2) previously antiretroviral therapy (ART)-naïve; and 3) ≥15 years of age when starting cART. We defined cART as a combination of at least three antiretrovirals, other than ritonavir, recorded as prescribed on the same date. The

cART start date was the first date that a cART prescription was recorded in the database and we assumed that patients remained on cART. 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 cART ≤26 weeks before delivering a baby. We excluded the latter group of patients in an effort to limit the study to patients who started cART for the purpose of treatment, rather than to prevent vertical transmission of HIV; we assumed that starting cART 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-naïve when starting cART.

3.2.3 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, cART regimen prescribed, and calendar year. We classified HIV exposure categories using an exposure category hierarchy [5]. 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 cART start date, which was ≤6 months before, and not after starting cART.

3.2.4 Statistical Analyses

Initially, patient characteristics were tabulated and compared between Aboriginals and non-Aboriginals and between IDUs and patients with other exposures using χ^2 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 cART) in relation to Aboriginal ethnicity, adjusting for potential confounding variables. We defined patients with no viral load tests ≤6 months after starting cART as not achieving initial virological suppression.

For Part 2, our primary definition of cART 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 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 [8]. Then, we compared hazard ratios (HRs) of virological failure using Cox proportional hazards models, 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).

3.2.5 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 cART 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 cART 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 cART 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.

3.3 RESULTS

3.3.1 Derivation of the study sample

The NAHIVP database contained 2,258 patient records. After removing duplicate records and applying patient eligibility criteria, 461 patients (353, 77% males and 108, 23% females) remained to create the study sample for Part 1 (initial virological suppression analysis) (Figure 3.1).

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 cART 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).

3.3.2 Description of study patients

Among the 461 study patients, at baseline, the median subject age was 39.4 (interquartile range (IQR)=32.8-44.9) years, median CD4 cell count was 190 (IQR=90-285) cells/μL, and median viral load was 120,000 (IQR=43,000-410,000) copies/mL. The single most common HIV exposure category was IDU (200, 43%) followed by heterosexual contact (126, 27%), men who have sex with men (MSM) (90, 20%), MSM/IDU (20, 4.3%), transfusion (5, 1.1%), and other (1, 0.22%); the exposure category was missing or unknown for 19 (4.1%) patients. Therefore, 220 (48%) patients were defined as IDU and 241 (52%) were defined as having other exposures. Most patients initiated cART in 2002-2005 (270, 59%) and most patients (350, 76%) were prescribed non-PI-based regimens at baseline (343, 74% non-nucleoside reverse

transcriptase inhibitor [NNRTI]-based regimens and 7, 1.5% triple nucleoside reverse transcriptase inhibitor [NRTI]-based regimens).

Of the 461 study patients, 226 (49%) were Caucasian, 172 (37%) were Aboriginal, 46 (10%) were Black, and 17 (3.7%) were Hispanic or Asian. 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. 37%, $p<0.0001$), start cART 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 cART (16% vs. 8.0%, $p=0.0059$) (Table 3.1).

3.3.3 Part 1 – Initial virological suppression

Within 6 months of starting cART, 328 patients (71%) achieved initial virological suppression. Of the 133 patients who did not achieve initial virological suppression, 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 of starting cART, 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, cART regimen, and calendar year, compared to non-Aboriginals with other exposures, the odds of achieving initial virological suppression were significantly 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, $p=0.0009$) (Table 3.2). The other factor inversely and significantly associated with achieving initial suppression was baseline PI-based regimen; in addition, baseline CD4 cell count >350 vs. ≤50 cells/μL also tended to be inversely related to initial suppression (Table 3.2). In our sensitivity analysis for Part 1, which excluded patients who had no viral load tests in the first 6 months after starting cART, the odds of achieving initial virological suppression remained similar to the primary analysis for non-Aboriginal IDUs and Aboriginals with other exposures; however, for Aboriginal

IDUs, this relationship weakened and became of borderline statistical significance (Table 3.2).

3.3.4 Part 2 – cART 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 (8.0, IQR=2.0-10 vs. 6.0, IQR=3.0-12, 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) (Figure 3.2).

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 3.3). 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 3.3). In addition, other variables positively and significantly associated with a higher rate of virological failure were having a baseline viral load of <10,000 copies/mL vs. >100,000 copies/mL and starting cART in 1999-2001 vs. 2002-2005 (Table 3.3). In our sensitivity analyses, our estimated HRs for Aboriginal patients remained similar to our primary model (Table 3.4).

3.4 DISCUSSION

Among HIV-patients starting cART, 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 cART 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, 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 6 months of starting cART. 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 cART 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 [9]. 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 [10]. 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.

Although adherence is the most likely explanation for the difference in rates of initial virological suppression we observed in our study, another potential explanation is possible differences in the prevalence of genetic polymorphisms among Aboriginals compared to non-Aboriginals. For example, the TT genotype of cytochrome P-450 (CYP) 2B6, the hepatic enzyme that metabolizes efavirenz [11], has been shown to have a higher prevalence rate among African Americans compared to European Americans, and this polymorphism is associated with higher plasma exposure to efavirenz and central nervous system symptoms one week after starting

efavirenz [12]. However, CYP2B6 has not been associated with treatment failure [13] and no studies have investigated the prevalence of this polymorphism among Aboriginals; therefore, it is difficult to conclude that this polymorphism is likely to explain the differences in rates of initial virological suppression we observed in our study. Furthermore, sub-analyses we conducted within the Aboriginal patients and within the non-Aboriginal patients showed that, for both groups, those initiating cART on an efavirenz-containing regimen were significantly more likely to achieve initial virological suppression compared to those who started on other types of regimens. In addition, genetic polymorphisms are unlikely to explain the differences we observed in rates of virological failure because failure rates were similar by Aboriginal ethnicity within the first year, and one might expect that differences in drug action would have a more immediate impact. Therefore, a genetic polymorphism associated with the activity of efavirenz does not appear to explain the differences we observed in our study.

The other variable significantly inversely associated with achieving initial virological suppression in our primary analysis was PI-based vs. non-PI-based initial cART regimen; in addition, baseline CD4 cell count >350 vs. ≤50 cells/μL tended to be inversely associated with achieving initial virological suppression. Patients who started cART on a PI-based regimen were less likely to achieve initial virological suppression than those starting on a non-PI-based regimen; a similar relationship was observed by Palepu et al and Wood et al [9, 14]. However, Wood et al reported substantial differences in baseline characteristics between the patients prescribed PI-based vs. NNRTI-based regimens, representing potential bias by physicians prescribing these regimens [14]. Given the potential for such biases, we cannot conclude from this study that PI-based regimens are associated with inferior virological responses compared to non-PI-based regimens. Our finding that having a baseline CD4 cell count >350 cells/μL tended to be associated with not achieving initial virological suppression is less easily understood, but appears to be partly explained by lack of virological monitoring among these patients. Within 6 months

of starting cART, patients with baseline CD4 cell counts >350 cells/μL were less likely to receive a viral load test compared to other patients (79% vs. 91%, p=0.0045); this would have caused them to be defined as unsuppressed in our primary analysis of initial virological suppression. Patients with higher baseline CD4 cell counts may not have had their viral loads monitored as frequency after starting cART because the treating clinician may have considered them at lower risk of clinical progression. In our sensitivity analysis, the relationship between baseline CD4 cell count >350 cells/μL and virological suppression became non-significant (p=0.12), however, the direction remained protective (0.48); therefore, this relationship does not appear to be explained entirely by a lack of virological monitoring. These patients may not have been ART-naïve at baseline, evidenced by their higher CD4 cell counts, and perhaps were less likely to achieve virological suppression due to virological resistance; however, we are uncertain of the true reason for this relationship.

To our knowledge, the present study is the first to compare virological failure between Aboriginals and non-Aboriginals after starting cART. 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 cART [1]. Rates of virological failure did not differ by Aboriginal ethnicity in the first year after achieving initial virological suppression; therefore, it appears that 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 [15], 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 [16, 17]. Poor adherence to therapy has been associated with poor socioeconomic status and social instability, including factors such as low income, unstable housing, and unemployment [18-20] as well as active substance abuse [21]. 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 cART 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 cART 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 to compared to non-Aboriginals [3]. These differences in results may be due to the different definitions of adherence or to differences in adherence to cART 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 [22].

In addition to Aboriginal ethnicity, the other variables significantly and positively associated with a higher rate of virological failure were having a baseline

viral load <10,000 vs. ≥100,000 copies/mL and starting cART in 1999-2001 vs. 2002-2005. The association between having a lower baseline viral load and experiencing virological failure is similar to our finding that patients with higher baseline CD4 cell counts were less likely to achieve initial virological suppression. Similarly, patients with baseline viral loads <10,000 copies/mL may not have been ART-naïve at baseline; however, it seems less likely that these patients' infections were resistant at baseline because they achieved initial virological suppression. Therefore, we are uncertain of the true reason for this relationship. Patients initiating cART in 1999-2001 vs. 2002-2005 also had a higher rate of virological failure. The decreased rates of virological failure observed over time may be explained by improvements in adherence and clinical knowledge. For example, between these two time periods, research has shown that patient adherence and physician experience both increased, with an associated decreased risk of mortality [23].

The present study has several potential limitations. First, ethnicity and HIV exposure categories were self- or physician-reported and misclassifications may have occurred. In particular, as pointed out by Wood et al, the stigma associated with injection drug use might cause it to go unreported [10] and we may have misclassified patients 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-naïve when starting cART 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 show that, among HIV-patients treated in northern Alberta, Aboriginals are less likely than non-Aboriginals to achieve initial virological suppression after initiating cART; 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 cART, examine strategies to improve their adherence, and explore their cART treatment experiences to assess ways to improve treatment outcomes. Socioeconomic factors and cultural barriers should be investigated.

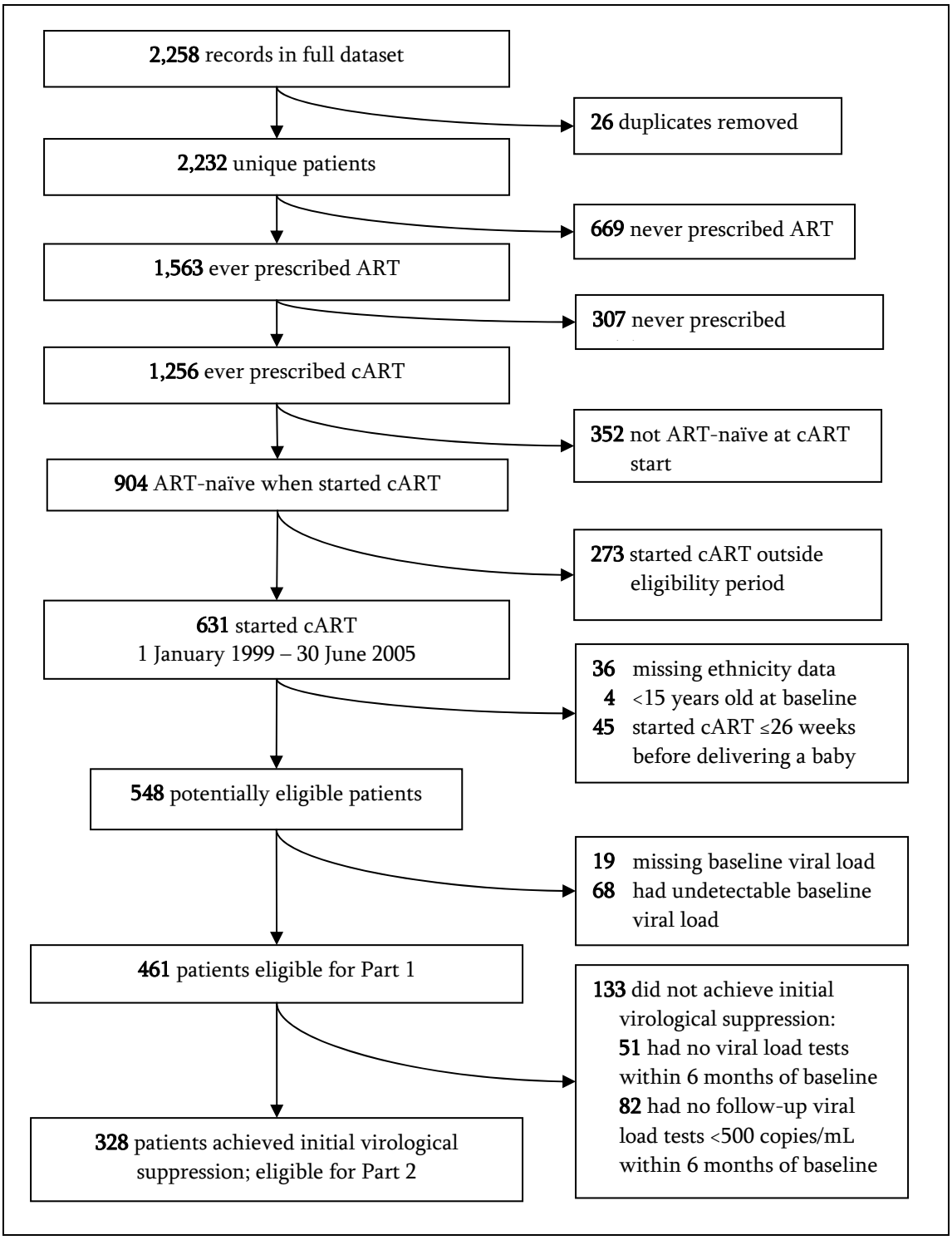
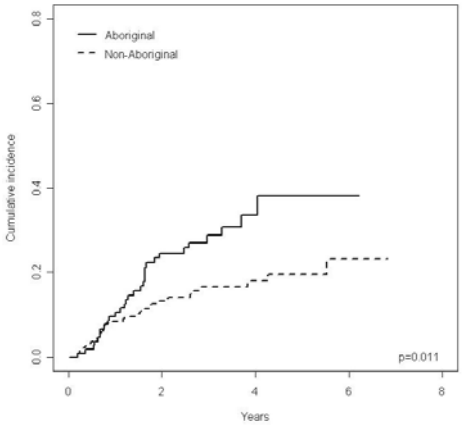
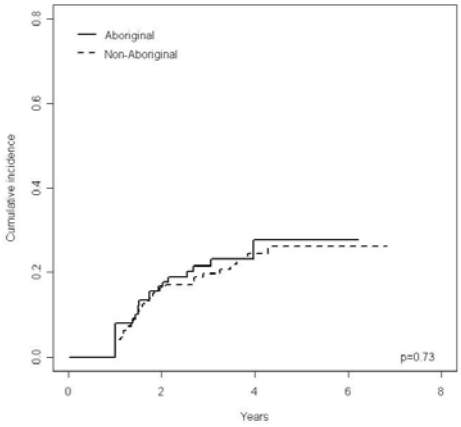


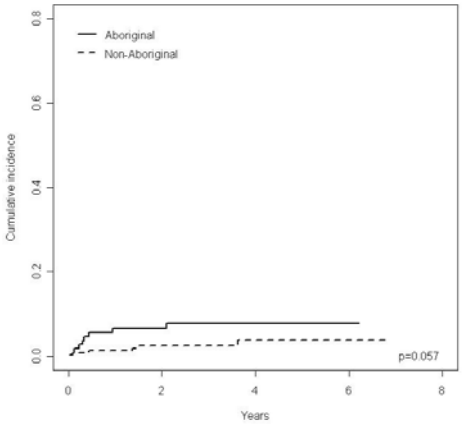
Figure 3.1 Derivation of the study population for Parts 1 (initial virological suppression) and 2 (cART failure)



(a) Virological failure



(b) Loss to follow-up



(c) All-cause mortality

Figure 3.2 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)

Table 3.1 Patient characteristics by ethnicity for Part 1 (initial virological suppression) (N=461)

Characteristic	Aboriginal (n=172, 37%)	Non-Aboriginal (n=289, 63%)	p-value
No. viral load tests in the 6 months after baseline, no. (%)			0.0059
0	28 (16)	23 (8.0)	
≥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 cART regimen, no. (%)			0.095
PI-based	34 (20)	77 (27)	
Not PI-based	138 (80)	212 (73)	
Year starting cART, no. (%)			0.47
1999-2001	75 (44)	116 (40)	
2002-2005	97 (56)	173 (60)	

Table 3.2 Unadjusted and adjusted logistic regression models, including primary analysis and sensitivity analysis assessing initial virological suppression after starting cART

Variable	Unadjusted analyses (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	0.0 003	-	-	-	-	-	-
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			Class p=0.079						
≤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	-	-	-	-	-	-	-	-
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 cART 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

*Note: Variables with p-values ≥0.20 were not included in the multivariate model

Table 3.3 Unadjusted and adjusted Cox proportional hazards models assessing virological failure after achieving initial virological suppression (N=328)

Variable	Unadjusted Hazard Ratio (95% CI)		p-value	Adjusted Hazard Ratio (95% CI)		p-value
Ethnicity (Aboriginal vs. non-Aboriginal)	2.09	1.27-3.43	0.0038	-	-	-
<1 year after initial virological suppression	1.16	0.53-2.51	0.71	1.06	0.48-2.31	0.89
≥1 year after initial virological suppression	3.34	1.70-6.59	0.0005	3.35	1.68-6.65	0.0006
Sex (Female vs. male)	1.47	0.84-2.56	0.18	1.25	0.71-2.22	0.44
HIV exposure category (Injection drug use vs. other exposures)	1.37	0.83-2.24	0.22	-*	-	-
CD4 cells/μL at baseline			Class p=0.24			
≤50 (ref)	1.00	-	-	-	-	-
>50-200	0.98	0.45-2.10	0.95	-	-	-
>200-350	1.04	0.48-2.25	0.92	-	-	-
>350	2.04	0.90-4.70	0.087	-	-	-
Missing	0.88	0.24-3.19	0.84	-	-	-
HIV RNA copies/mL at baseline			Class p=0.015			
<10,000	2.69	1.35-5.32	0.0047	2.62	1.32-5.20	0.0059
10,000-<100,000	1.07	0.61-1.87	0.83	0.98	0.56-1.73	0.94
≥100,000 (ref)	1.00	-	-	1.00	-	-
Age at cART start			Class p=0.67			
15-<30 (ref)	1.00	-	-	-	-	-
30-<40	1.29	0.61-2.74	0.51	-	-	-
40-<50	0.97	0.45-2.11	0.94	-	-	-
≥50	0.82	0.27-2.43	0.71	-	-	-
Initial cART regimen (PI vs. non-PI based)	1.10	0.61-1.98	0.75	-	-	-
Baseline calendar year (1999-2001 vs. 2002-2005)	1.72	1.02-2.89	0.042	1.82	1.08-3.07	0.024

*Note: Variables with p-values ≥0.20 were not included in the multivariate model

Table 3.4 Comparing the outcomes of four adjusted Cox proportional hazards models assessing the impact of Aboriginal ethnicity on virological failure after achieving initial virological suppression

Model	Ethnicity (Aboriginal vs. non-Aboriginal)						Outcome, no. (%)				N (%)
	<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 analysis 1†	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 analysis 2	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 analysis 3	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 cART 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, on December 31, 2005 for those who were censored, and on the date of death for those who died

†Sensitivity analyses:

1. Defined cART failure as one viral load >1000 copies/ml
2. Observation time ended at the last viral load date for patients who were lost to follow-up, censored, or died
3. Defined cART failure as one viral load >1000 copies/ml and observation time ended at the last viral load date for patients who were lost to follow-up, censored, or died

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CHAPTER 4: RELATIONSHIPS BETWEEN HEALTH-RELATED QUALITY OF LIFE, ABORIGINAL ETHNICITY, AND INJECTION DRUG USE AMONG HIV-PATIENTS TREATED WITH COMBINATION ANTIRETROVIRAL THERAPY IN NORTHERN ALBERTA

4.1 INTRODUCTION

Aboriginals and non-Aboriginals do not appear to receive equal benefit from combination antiretroviral therapy (cART). After starting cART, Aboriginals have been shown to experience lower rates of initial virological suppression, higher rates of virological failure [1], and higher rates of all-cause [2, 3] and HIV-related [2] mortality compared to non-Aboriginals. Although these outcomes are all important indictors of treatment success, they do not provide a complete picture. Improved quality of life (QOL) is another important goal of cART [4]. Health-related quality of life (HRQL) is of particular interest in a clinical setting and "refers to how health impacts an individual's ability to function and his or her perceived well-being in physical, mental and social domains of life" [5].

Despite the poorer outcomes of cART experienced by Aboriginals and the importance of QOL, to our knowledge, only one study, conducted in British Columbia, has specifically examined the impact of cART on QOL among Aboriginals in Canada. The researchers appeared to use the HIV/AIDS-Targeted Quality of Life Instrument (HAT-QoL) to measure quality of life. They found that, among patients treated with cART, Aboriginals reported better life satisfaction, fewer financial worries, and more provider trust compared to non-Aboriginals; furthermore, Aboriginals reported better overall function (a measure of physical, role, and social functioning) [6] than non-Aboriginals, but this result was only of borderline statistical significance ($p=0.07$) [7]. This study offers hope that Aboriginal HIV-patients experience successful quality of life outcomes with therapy; however, at the time of writing, this research study was not published in full as a peer-reviewed paper; therefore, details regarding methodology are lacking.

Despite the results of this recent research, the poorer virological outcomes experienced by Aboriginals suggests they may be at risk of experiencing poor physical HRQL. Some research has found worse physical HRQL to be associated with higher viral loads and lower CD4 cell counts [8]; however other studies have found no such associations [9, 10]. In addition, Aboriginal HIV-patients may also be at increased risk of worse HRQL due to injection drug use (IDU). In northern Alberta, Aboriginal HIV-patients are more likely to be infected with HIV through IDU compared to non-Aboriginals (see Chapter 2). Studies have shown that IDUs have worse HRQL than the general population [11] and than non-IDUs among HIV-infected individuals [12]. Therefore, both clinical status and IDU are important covariates to consider in the relationship between Aboriginal ethnicity and HRQL

Given the limited evidence available, more research is needed to compare the HRQL of Aboriginal vs. non-Aboriginal HIV-patients receiving cART to help improve our understanding of treatment outcomes for Aboriginals. Therefore, we conducted this study to 1) describe the HRQL of HIV-patients treated with cART in northern Alberta, Canada; 2) compare HRQL between Aboriginals and non-Aboriginals, and because of the overrepresentation of IDUs among Aboriginal HIV-patients, between IDUs and those with other HIV-exposures; and 3) assess whether any associations between Aboriginal ethnicity or IDU with HRQL could be explained by clinical status.

4.2 METHODS

4.2.1 Data sources

Our primary source of patient data was the Northern Alberta HIV Program (NAHIVP) database, which has been described previously (see Chapter 2). In addition to data from NAHIVP, we used viral load data from the Alberta Provincial Public Health Laboratory to replace missing baseline viral loads where possible.

We used the Medical Outcomes Study (MOS)-HIV questionnaire to measure HRQL. This instrument consists of 35 items that measure health transition (1 item)

and 11 other health dimensions: general health perceptions (5 items), physical functioning (6 items), role functioning (2 items), pain (2 items), social functioning (1 item), cognitive functioning (4 items), mental health (5 items), energy/fatigue (4 items), health distress (4 items), and quality of life (1 item). Scores range from 0 (worst) to 100 (best). In addition to these 12 areas, we generated mental (MHS) and physical (PHS) health summary scores. The PHS score is weighted most strongly on physical function, pain, role function, and social function and the MHS score is weighted most strongly on mental health, health distress, and quality of life. These summary scores were developed using data from 1,022 HIV-patients enrolled in a multi-centre clinical trial; they had a mean age of 38.7 (SD=8.4) years, were >18 years of age, and most were male (93%), Caucasian (75%), and had at least high school level education (93%) [13]. They are standardized with mean 50 (SD 10) [13]; therefore, patients with scores above or below 50 have better or worse physical or mental HRQL compared to this standard population.

4.2.2 Study patients

We assembled a cohort of patients using the NAHIVP database and the following eligibility criteria: 1) started cART between 1 January 1997 and 31 December 2005 (baseline); 2) previously antiretroviral therapy (ART)-naïve; 3) ≥18 years of age (as of September 1, 2006), 4) had ever visited the University of Alberta Hospital (UAH) or Royal Alexandra Hospital (RAH) clinics during their time at NAHIVP, 5) visited a NAHIVP clinic within the two calendar years before the study (2004-2006), and 6) were alive according to information available in the database at the time of extraction.. We excluded patients if they started cART ≤26 weeks before delivering a baby in an effort to limit the study to patients who started cART for the purpose of treatment, rather than to prevent vertical transmission of HIV; we assumed that starting cART earlier in pregnancy or after delivery would be for maternal indications. In addition, we excluded patients who did not have current CD4 cell count or viral load test results.

4.2.3 Definitions

We defined Aboriginals as Treaty and non-Treaty Aboriginals, Métis, and Inuit. HIV exposure categories were classified using an exposure category hierarchy [14]. Subjects were defined as injection drug users (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". We defined cART as a combination of at least three antiretrovirals, other than ritonavir, recorded as prescribed on the same date. The cART start date was the first date that a cART prescription was recorded in the database. Baseline CD4 cell count and viral load were defined as those measures taken closest to the cART start date, which was ≤6 months before, and not after starting cART. Clinical status at interview (current clinical status) was assessed using a patient's most recent viral load and CD4 cell count in the 6 months before the interview date.

4.2.4 Study management

We generated a list of eligible patients using the NAHIVP database and labelled their charts to identify them to the clinic staff. Between September 2006 and June 2007, clinic staff approached eligible patients about the study; interested patients spoke with the research assistant to learn more about the study, provided written consent to participate, and were interviewed at that time. Patients self-administered the MOS-HIV questionnaire, however, the research assistant was available to help patients and administer the questionnaire if needed. The present study was conducted in conjunction with a more in-depth interview for Aboriginals and IDUs; these patients were administered the MOS-HIV first and were given $10 for their participation because of the longer duration of the second interview. The study procedures were approved by the University of Alberta Health Research Ethics Board.

4.2.5 Data management and statistical analyses

We double entered the MOS-HIV questionnaires using EpiData 3.1 and linked patients' MOS-HIV results with their NAHIVP record and current CD4 cell

counts and viral load results. We used the "MOS-HIV SAS Scoring Program from JHU" to calculate MOS-HIV scores; missing values were imputed using the average score for multi-item (≥4 items) questions if at least half the items were completed [15]. Patient characteristics were tabulated and compared between Aboriginals and non-Aboriginals and between IDUs and those with other exposures using χ^2 and Fisher exact tests for categorical variables and Wilcoxon rank sum test for continuous variables. In unadjusted analyses, we compared Aboriginals vs. non-Aboriginals and IDUs vs. patients with other exposures on each dimension of the MOS-HIV and the summary scores using linear regression.

We developed two multivariable regression models for each outcome (PHS and MHS). In the first, we controlled for Aboriginal ethnicity, IDU, age at interview, sex, years of follow-up since baseline, and the interaction between Aboriginal ethnicity and IDU. In the second, we additionally adjusted for the patient's current clinical condition by adding their current viral load (>400 copies/mL vs. ≤400 copies/mL) and CD4 cell count (>350 cells/μL vs. ≤350 cells/μL) into the model. The first models show the difference in HRQL between Aboriginals and non-Aboriginals and between IDUs and patients with other exposures without accounting for their current clinical status. The second models show any additional differences that may remain after adjusting for differences in clinical status. We assessed model assumptions (homoscedasticity, normality of residuals, and the linearity of relationships between the outcomes and continuous predictors) and explored unusual and influential observations by examining residuals, leverage values, and DFBeta values for the Aboriginal ethnicity and IDU variables. Data were analyzed using SAS® (version 9.1; SAS Institute Inc., Cary, NC) and STATA SE 9.2 (College Station, TX).

4.3 RESULTS

4.3.1 Derivation of the study population

The NAHIVP database contained 2,258 patient records. After removing duplicates, 480 patients were potentially eligible for this study, of whom we excluded 56 (12%) who started cART during pregnancy (n=36) or were missing ethnicity information (n=21). Of the remaining 424 patients, 119 (28%) were approached by the clinic staff to participate in the study. These 119 patients were not significantly different from the 305 patients who were not approached with respect to Aboriginal ethnicity, IDU, sex, or baseline age; however, approached patients were more likely to have started cART recently (in 2003-2005) compared to those not approached (50% vs. 37%, p=0.018). Of the 119 patients approached to participate, 103 (87%) were interviewed. One patient was interviewed twice, the second interview was excluded; two patients were excluded for missing current CD4 cell counts; and four patients were excluded for missing current viral load test results. The remaining 96 patients created the study sample. Compared to patients who declined to participate or were ineligible, study patients had a higher median baseline viral load (160,000 vs. 28,000 (n=18) copies/mL, p=0.028) and tended to have a lower median baseline CD4 cell count (170 vs. 220 (n=15) copies/mL, p=0.066). Despite the incentive to participate, the study patients were not more likely to be Aboriginal or IDU, nor did they differ with respect to gender, age, or baseline calendar year.

4.3.2 Description of study patients

Of the 96 (72, 75% male and 24, 25% female) study patients, most were Caucasian (52, 54%), followed by Aboriginal (34, 35%), black (9, 9.4%; at least 7 of whom were from HIV-endemic countries), and Asian (1, 1.0%). Most patients were exposed to HIV through IDU (35, 36%) or heterosexual contact (34, 35%), followed by MSM (19, 20%) and MSM/IDU (5, 5.2%); three patients had no identified risk. Therefore, 40 (42%) patients were IDU and 56 (58%) had other exposures. At interview, the mean age was 45.4 (SD=8.5) years, 81 patients (84%) had a viral load

≤400 copies/mL, 42 (44%) had a CD4 cell count >350 cells/μL, and median time since starting cART was 4.2 (IQR=2.3-7.7) years.

Compared to non-Aboriginals, Aboriginals were more likely to be female (38% vs. 18%, p=0.027), were more likely to be IDU (62% vs. 31%, p=0.003), were less likely to have a CD4 cell count >350 cells/μL (29% vs. 52%, p=0.036), and tended to be less likely to have a viral load ≤400 copies/mL (74% vs. 90%, p=0.041) (Table 4.1).

Compared to those with other exposures, IDUs were more likely to be Aboriginal (53% vs. 23%, p=0.003), were less likely to have a CD4 cell count >350 cells/μL (28% vs. 55%, p=0.007), and tended to be less likely to have a viral load ≤400 copies/mL (75% vs. 91%, p=0.046) (Table 4.1).

4.3.3 Health-related quality of life

The internal consistency within each multi-item domain of the MOS-HIV ranged from 0.77 to 0.92 overall (Table 4.2), 0.65 to 0.92 among Aboriginals, 0.81 to 0.92 among non-Aboriginals (Table 4.3), 0.63 to 0.94 among IDUs, and 0.79 to 0.91 among patients with other exposures (Table 4.4). Four of the 96 study patients were missing 6 items. Overall, the 96 study patients had a mean MHS score of 49.6 (SD=11.6) and mean PHS score of 46.6 (SD=11.9). The median scores for each dimension ranged from 50.0 (role function and health transition) to 100.0 (social function) (Table 4.2). Compared to non-Aboriginals, Aboriginals had significantly lower physical function, role function, and PHS scores; Aboriginals also had lower MHS scores, but this difference was not statistically significant (Table 4.3). Compared to those with other exposures, IDUs had significantly lower physical function, role function, cognitive function, pain, energy/fatigue, quality of life, MHS, and PHS scores (Table 4.4).

4.3.3.1 Physical health

Lower PHS scores were associated with being Aboriginal (p=0.027), being IDU (p=0.013), having a current CD4 cell count ≤350 cells/μL (p<0.0001), and having a current viral load >400 copies/mL (p=0.017) (Table 4.5). Among patients with other

exposures, Aboriginals had significantly lower PHS scores than non-Aboriginals (p=0.0007), but among IDUs, Aboriginals and non-Aboriginals had similar PHS scores (p=0.49) (Figure 4.2). In our first model, adjusting for age, sex, and follow-up years, compared to non-Aboriginals with other exposures, the PHS score was lower for Aboriginal IDUs (β=-8.22, 95% CI=-14.27, -2.17, p=0.008), Aboriginals with other exposures (β=-11.37, 95% CI=-18.51, -4.24, p=0.002), and non-Aboriginal IDUs (β=-10.19, 95% CI=-16.47, -3.90, p=0.002) (Table 4.5). In our second model, which additionally adjusted for current CD4 cell count and viral load, compared to non-Aboriginals with other exposures, the PHS score was significantly lower for Aboriginals with other exposures (β=-7.90, 95% CI=-14.87, -0.92, p=0.027) and non-Aboriginal IDUs (β=-6.35, 95% CI=-12.64, -0.063, p=0.048); however, the PHS scores were no longer statistically significantly lower for Aboriginal IDUs (β=-4.72, 95% CI=-10.74, 1.31, p=0.12) (Table 4.5).

4.3.3.2 Mental health

Lower MHS scores were associated with being IDU (p=0.034), a longer duration since starting cART (p=0.031), and having a CD4 cell count ≤350 cells/μL (p=0.030); having a current viral load ≤400 copies/mL also tended to be associated with higher MHS scores (p=0.056) (Table 4.6). Among patients with other exposures, Aboriginals had significantly lower PHS scores than non-Aboriginals (p=0.0007), but among IDUs, Aboriginals and non-Aboriginals had similar PHS scores (p=0.49) (Figure 4.2). Aboriginal ethnicity was associated with a lower MHS score, but this was not statistically significant (β=-3.11, p=0.21) (Table 4.6). After adjusting for age, sex, and follow-up years, compared to non-Aboriginals with other exposures, Aboriginal IDUs tended to have lower MHS scores (β=-5.59, 95% CI=-11.74, 0.57, p=0.075) as did non-Aboriginal IDUs (β=-6.27, 95% CI=-12.67, 0.12, p=0.054); however, no variables reached statistical significance in this model (Table 4.6). After additionally adjusting for current clinical status, both of these relationships lost strength and significance. Similarly, in our second model, which additionally adjusted for current clinical status, no variables met statistical significance; however,

duration of follow-up was of borderline significance, with an increase in time since starting cART of one year associated with a decrease in MHS score of 0.78 points (95% CI= -1.61, 0.059, p=0.068; Table 4.6).

4.4 DISCUSSION

Aboriginal IDUs, Aboriginals with other exposures, and non-Aboriginal IDUs reported similarly worse PHS scores compared to non-Aboriginals with other exposures. These differences appear to be partly explained by clinical status. Current CD4 cell count was the most significant predictor of PHS in this study. Once clinical status was adjusted, older age tended to become more statistically significantly associated with worse PHS. Regarding mental health, compared to non-Aboriginals with other exposures, Aboriginal IDUs and non-Aboriginal IDUs tended to have worse MHS, but these relationships weakened after adjusting for current clinical status, especially for Aboriginal IDUs; Aboriginals with other exposures did not report statistically significantly worse MHS scores. Overall, the variables assessed in our study were not as strongly associated with MHS as they were with PHS.

Several factors likely underlie the differences in PHS scores observed by Aboriginal ethnicity and IDU. First, the worse clinical status (lower CD4 cell counts and higher viral loads) of Aboriginals and IDUs appears to be partially responsible for the observed worse PHS scores, especially for IDUs (Aboriginal and non-Aboriginal). This is demonstrated by our second model that controlled for CD4 cell count and viral load: the difference in PHS for these two groups weakened and became statistically non-significant. Although the lack of statistical significance may be due to a lack of power in our study because of the small sample size, clinical status seems to represent an important confounder of these associations and this suggests that these observed inequalities in physical HRQL may be diminished by helping to improve patients' clinical status through improved adherence to cART.

Second, whether patients identified as IDUs or not, they may have used illicit drugs at the time of the study and this may have contributed to worse PHS scores.

Among IDUs, the duration of time free from drugs has been shown to positively correlate with better HRQL [16].

Third, higher rates of unemployment may help to explain the lower PHS scores we observed in our study. Compared to the general Canadian population, Aboriginals have lower rates of employment [17]; this difference may be represented in our study sample. Studies have shown a positive association between employment and HRQL. For example, Worthington and Krentz conducted a study among HIV-patients in southern Alberta and found that being employed was strongly and positively associated with scores on five MOS-HIV subscales (general health, energy/fatigue, mental health, health distress, and cognitive functioning) [10]. However, these subscales have a greater influence on MHS scores than on PHS scores; therefore, these findings do not provide a complete understanding of our results. Additional research has been conducted among HIV-infected IDUs by Préau et al who found employment to be associated with both better physical and better mental HRQL in univariable statistics, but employment was not included in the study's multivariable models [18]. However, more research is needed to help better understand the relationship between employment and physical HRQL among Aboriginal HIV-patients.

Lastly, other aspects of socioeconomic status such as lower income and lower levels of education may also help to explain the lower PHS scores we observed. Worthington and Krentz found income to be positively associated with the MOS-HIV health distress and mental health subscales (i.e. lower income was associated with more health distress and poorer mental health), but these relationships were much weaker than the association they reported for employment status [10]. They also reported a significant positive relationship between mental health and having a university degree, compared to high school level education [10]. However, another study found no association between education and HRQL [18].

In addition to Aboriginal ethnicity and IDU, other variables that appeared to be important independent predictors of PHS were clinical status (especially CD4 cell

count >350 cells/μL) and age. Research reports discrepant results with respect to the impact of clinical status on HRQL. Some studies have found no significant relationship [9, 19], while others have found higher CD4 cell count associated with better physical HRQL [8, 18]. In our study, patients may have been aware of their clinical status before completing the MOS-HIV and this knowledge may have influenced patients' perceptions about their HRQL: patients with high CD4 cell counts or low viral loads may perceive their HRQL more positively because they feel they are succeeding on therapy. This may help to explain the associations we observed. Older age tended to be associated with poorer PHS in both multivariable models. Poorer physical health in older age is not an unexpected finding, and some research has found older age to be associated with worse physical HRQL [18] and better mental health [20]. However, several studies have found no association between age and HRQL [8, 10, 19].

In contrast to our results for PHS, MHS scores did not differ significantly by Aboriginal ethnicity. Aboriginals and non-Aboriginals did not report significantly different scores for any of the domains most influential in making up the MHS score. These results appear to differ from the one study comparing QOL between Aboriginal and non-Aboriginal HIV-patients, which found that Aboriginals reported better life satisfaction, fewer financial worries, and more trust in their care providers [7]. This apparent difference is likely due to the different areas of mental health we assessed, using different instruments; but it could also be explained by differences between the patient populations in British Columbia vs. northern Alberta. Given the dearth of research in this area and the overrepresentation of Aboriginals in Canada's HIV epidemic [21], more research in this area is necessary.

For IDUs, MHS differed significantly in univariable statistics; however, after adjusting for clinical status, this relationship became non-significant. This could be due to a lack of statistical power caused by our small sample size. In addition to clinical status, other variables that may account for the poorer mental HRQL we

observed among IDUs may be similar to the variables that may help to explain physical HRQL, including current drug use, socioeconomic status, and employment.

Overall, the variables assessed in our study were not as strongly associated with MHS as they were with PHS. The only variable that tended to be associated with worse MHS, after adjusting for clinical status, was longer time since starting cART. The longer a patient receives cART, the longer he or she lives with HIV and the impacts of these parallel experiences are not easy to disentangle. Worthington and Krentz also examined duration of HIV-infection and found it to be associated with poorer cognitive functioning and poorer overall health in unadjusted statistics, but these relationships were not significant in multivariable models [10]. However, given that cART is currently a life-long therapy, a worsening in HRQL over time should be investigated further.

4.4.1 Limitations

This study had several limitations. First, ethnicity and HIV exposure categories were self- or physician-reported and misclassifications may have occurred. In particular, as pointed out by Wood et al, the stigma associated with injection drug use might cause it to go unreported [22] and we may have misclassified patients 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, who have the opportunity to know the patients well, and who are strongly motivated to obtain accurate information on these important characteristics, which gives us more confidence in its accuracy. Second, this study had a small sample size; therefore, to assess the power in our study, we ran post-hoc power analyses for the two multivariable linear regression models of MHS using PASS 2008 software and an alpha value of 0.05. In our first model (excluding clinical variables), our power was 0.50 and in our second model (including clinical variables), our power was 0.22. Therefore, we lacked sufficient power in these two models to detect statistically significant differences in HRQL for our main variables of interest (Aboriginal ethnicity and IDU). However, these results provide an initial description of the

relationship between Aboriginal ethnicity, IDU, and other important predictors of HRQL as a basis for future research. Third, a clinical database was used to identify eligible patients and determine clinical status, which has inherent limitations. Data quality can be affected by data entry errors and omissions. Using these data, we could not be certain of the date patients first started cART or whether they were ART-naïve when starting cART. Fourth, we did not randomly select patients for interview from the list of eligible patients. In approaching patients for interview, the clinic staff may have selected patients they thought would make better subjects; however, clinic staff were asked to approach every eligible patient possible in the time available to them. Fifth, we lacked data on potentially important confounders, including use of and adherence to cART at the time of the interview, education, income, employment, comorbid conditions, ongoing substance use, and social support which may influence HRQL. Future studies should assess how these variables might help to explain the relationships investigated. Lastly, the validity and reliability of the MOS-HIV has not been determined for this patient population and the instrument showed some psychometric weaknesses. Many of the domains had substantial ceiling effects, with >20% of patients scoring the maximum value on all domains except overall health, mental health, and energy/fatigue. And, among Aboriginals and IDUs, several domains showed Cronbach alpha scores <0.70 (role functioning, mental health, and pain), which suggests that, for these two groups, the internal consistency reliability for these domains was less than satisfactory. Comparing different cultural groups to each other does pose some difficulties. For example, Aboriginals and non-Aboriginals may perceive QOL differently; therefore, these two groups may have responded to the MOS-HIV questions differently. This may be a possible explanation for the differences we observed in HRQL between Aboriginals and non-Aboriginals.

In summary, Aboriginals reported lower physical HRQL than non-Aboriginals and IDUs reported lower physical HRQL than those with other exposures, but no significant differences in mental HRQL were observed after adjusting for confounding variables. Poor physical

functioning in particular, have been identified as prognostic of mortality among HIV-infected individuals [23]. Furthermore, in our own research, we found that, after starting cART, Aboriginals and IDUs suffer higher rates of all-cause mortality than non-Aboriginals and patients with other exposures, respectively [2] (see Chapter 2). The evidence consistently demonstrates that Aboriginals and IDUs, who are often socially and economically marginalized, suffer worse outcomes after starting cART. Although more evidence describing these disparities is becoming available, we need to carefully examine the reasons underlying these disparities to help us develop effective intervention strategies aimed at improving cART outcomes for these vulnerable HIV-patients. Future research should be conducted that describes the HRQL of Aboriginal and IDU HIV-patients in more depth. In particular, studies should investigate reasons for the poorer physical HRQL reported by Aboriginals with other exposures.

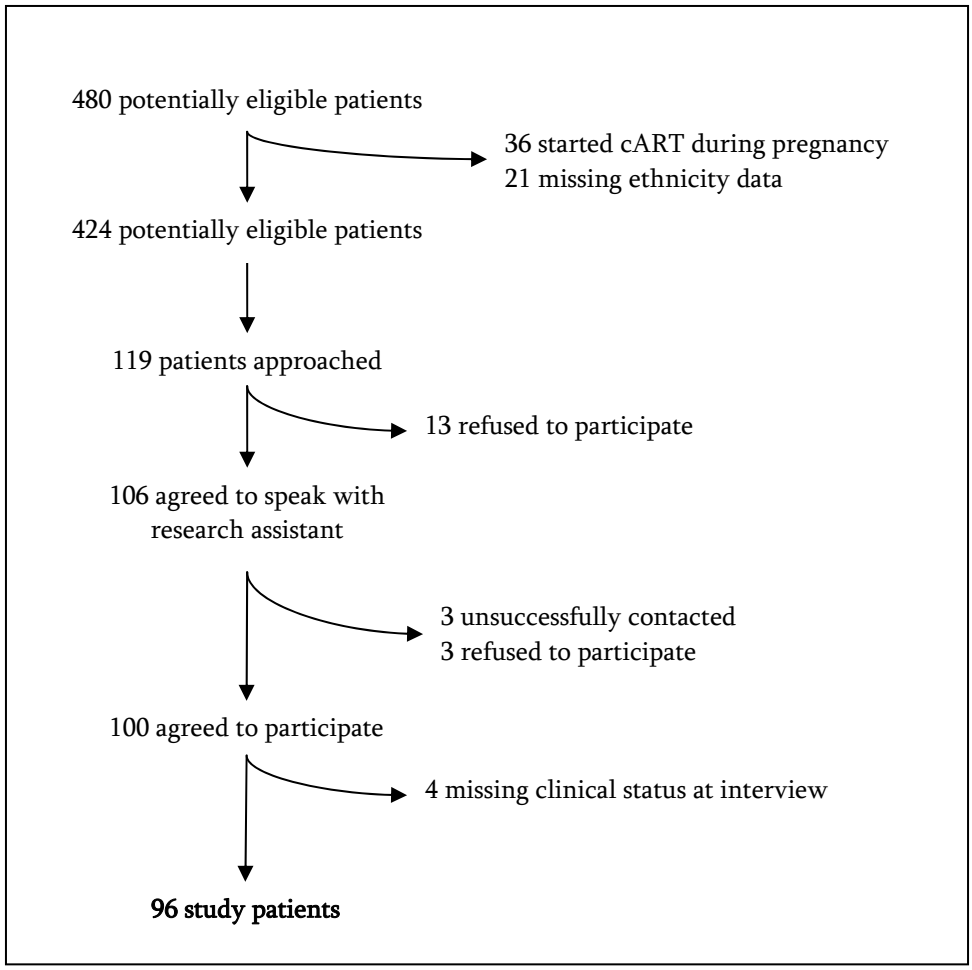

Figure 4.1 Derivation of the study sample

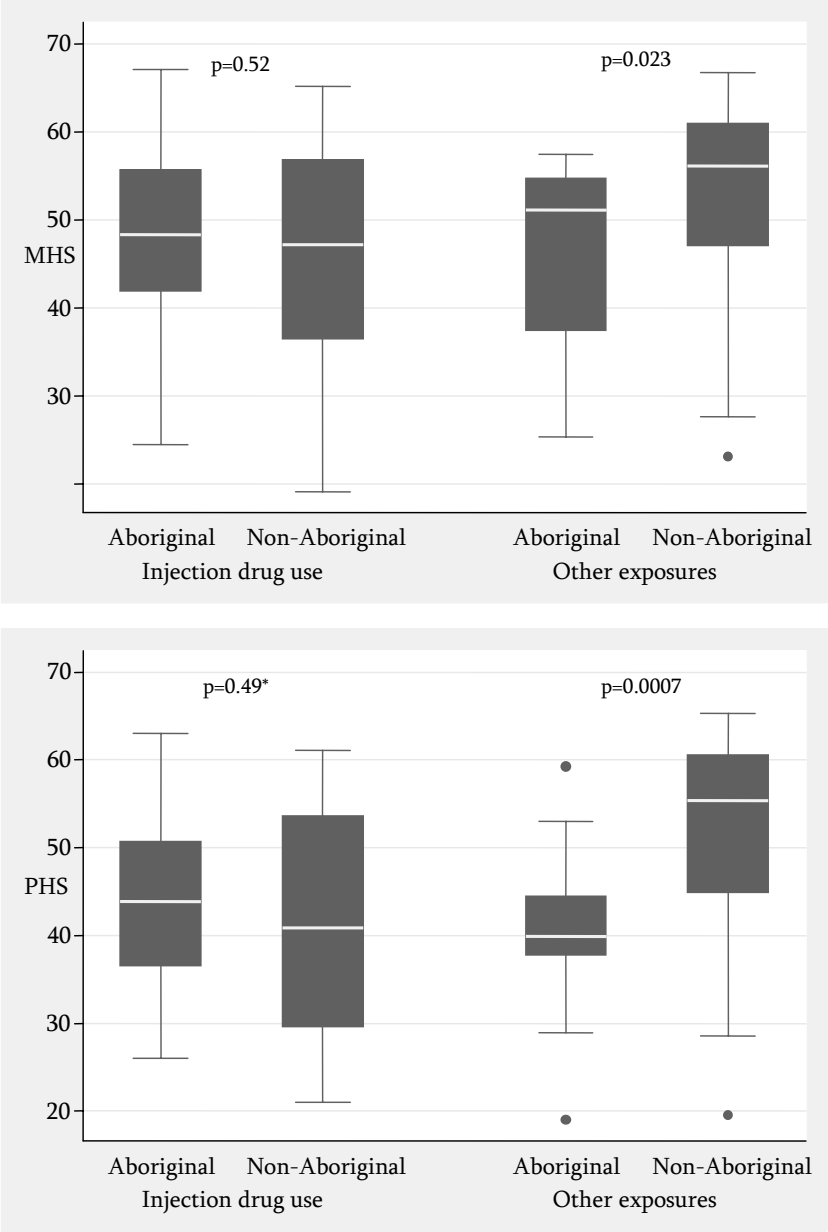

Figure 4.2 Box plots of physical health (PHS) (top) and mental health (MHS) (bottom) summary scores for Aboriginals and non-Aboriginals by injection drug use as an HIV exposure

Table 4.1 Patient characteristics by ethnicity and injection drug use exposure (N=96)

Characteristic	Aboriginal (n=34, 35%)	Non-Aboriginal (n=62, 65%)	p-value	IDU (40, 42%)	Other exposures (56, 58%)	p-value
Sex, no (%)						
Male	21 (62)	51 (82)	0.027	28 (70)	44 (79)	0.34
Female	13 (38)	11 (18)		12 (30)	12 (21)	
HIV exposure category, no (%)						
IDU	21 (62)	19 (31)	0.003	-	-	
Other exposures	13 (38)	43 (69)		-	-	
Ethnicity, no (%)						
Aboriginal	-	-		21 (53)	13 (23)	0.003
Non-Aboriginal	-	-		19 (48)	43 (77)	
Age at interview, median (IQR)	41.3 (39.0-50.3)	46.2 (40.8-51.9)	0.11	44.7 (39.0-49.7)	45.8 (40.3-52.2)	0.27
HIV RNA level at interview, copies/mL, median (IQR)	50 (50-5000)	50 (50-50)	0.012	50 (50-2660)	50 (50-50)	0.011
>400	9 (26)	6 (9.7)	0.041**	5 (8.9)	10 (25)	0.046**
≤400	25 (74)	56 (90)		51 (91)	30 (75)	
CD4 cell count at interview, cells/μL, median (IQR)	275 (170-390)	380 (250-550)	0.028	255 (165-375)	395 (265-555)	0.0018
>350	10 (29)	32 (52)	0.036	11 (28)	31 (55)	0.007
≤350	24 (71)	30 (48)		29 (73)	25 (45)	
Years since starting cART, median (IQR), total	4.2 (2.1-7.5), 170.3	4.2 (2.3-8.4), 307.5	0.62	5.2 (2.1-8.3), 215.6	3.8 (2.3-6.8), 262.2	0.51

**Fischer's exact test

Table 4.2 MOS-HIV results for all study patients (N=96)

MOS-HIV scale	Mean score (SD)	95% CI	Median score	IQR	% of subjects with		α*
					Minimum score	Maximum score	
Overall health	56.5 (28.4)	51.2-62.7	60.0	32.5-80.0	0.0	8.3	0.88
Physical function	74.9 (26.3)	69.5-80.2	83.3	58.3-100.0	0.0	32.0	0.88
Role function	51.6 (46.1)	42.2-60.9	50.0	0.0-100.0	41.0	44.0	0.81
Social function	76.7 (28.7)	70.9-82.5	100.0	60.0-100.0	1.0	51.0	-
Cognitive function	74.0 (25.3)	68.8-79.1	80.0	60.0-100.0	1.0	26.0	0.92
Pain	69.1 (26.6)	63.7-74.5	77.8	55.6-94.4	0.0	25.0	0.82
Mental health	72.5 (19.3)	68.6-76.4	72.0	60.0-88.0	0.0	9.4	0.77
Energy/fatigue	57.1 (22.9)	52.4-61.7	60.0	40.0-75.0	1.0	3.1	0.86
Health distress	74.8 (27.4)	69.2-80.3	80.0	60.0-100.0	2.1	26.0	0.92
Quality of life	70.6 (22.7)	66.0-75.2	75.0	50.0-75.0	1.0	23.0	-
Health transition	59.6 (24.4)	54.7-64.6	50.0	50.0-75.0	3.1	21.0	-
MHS	49.6 (11.6)	47.3-52.0	53.3	42.2-57.6	-	-	-
PHS	46.6 (11.9)	44.1-49.0	46.3	37.7-58.1	-	-	-

*Internal consistency measured by standardized Cronbach's α

Table 4.3 MOS-HIV domain scores by Aboriginal ethnicity (N=96)

MOS-HIV scale	Aboriginal (n=34)				Non-Aboriginal (n=62)				Difference in Means	Difference in Medians	p-value**
	Mean score (SD)	95% CI	Median score (IQR)	α*	Mean score (SD)	95% CI	Median score (IQR)	α*			
Overall health	56.0 (27.6)	46.4-65.7	60.0 (35.0-75.0)	0.87	57.4 (29.0)	50.0-64.8	60.0 (30.0-80.0)	0.89	-1.4	0.0	0.82
Physical function	64.2 (26.5)	55.0-73.5	62.5 (50.0-91.7)	0.85	80.7 (24.5)	74.5-86.9	91.7 (66.7-100.0)	0.88	-16.5	-29.2	0.0013
Role function	35.3 (41.8)	20.7-49.9	0.0 (0.0-50.0)	0.65	60.5 (46.3)	48.7-72.2	100.0 (0.0-100.0)	0.87	-25.2	-100.0	0.010
Social function	71.2 (31.2)	60.3-82.1	80.0 (40.0-100.0)	-	79.7 (27.0)	72.8-86.5	100.0 (60.0-100.0)	-	-8.5	-20.0	0.20
Cognitive function	69.3 (22.7)	61.3-77.2	75.0 (50.0-85.0)	0.91	76.5 (26.4)	69.8-83.2	85.0 (60.0-100.0)	0.93	-7.2	-10.0	0.059
Pain	64.7 (24.8)	56.0-73.4	66.7 (44.4-88.9)	0.75	71.5 (27.4)	64.5-78.5	77.8 (55.6-100.0)	0.86	-6.8	-11.1	0.16
Mental health	69.4 (18.8)	62.9-76.0	72.0 (56.0-84.0)	0.71	74.2 (19.6)	69.2-79.2	76.0 (60.0-88.0)	0.81	-4.8	-4.0	0.20
Energy/fatigue	54.6 (21.1)	47.2-61.9	55.0 (35.0-70.0)	0.84	58.5 (23.9)	52.4-64.5	60.0 (40.0-75.0)	0.87	-3.9	-5.0	0.47
Health distress	69.7 (29.9)	59.3-80.2	80.0 (55.0-95.0)	0.92	77.6 (25.7)	71.1-84.1	82.5 (65.0-100.0)	0.92	-7.9	-2.5	0.14
Quality of life	66.2 (21.2)	58.8-73.6	75.0 (50.0-75.0)	-	73.0 (23.2)	67.1-78.9	75.0 (50.0-100.0)	-	-6.8	0.0	0.095
Health transition	56.6 (27.0)	47.2-66.1	50.0 (50.0-75.0)	-	61.3 (22.9)	55.5-67.1	50.0 (50.0-75.0)	-	-4.7	0.0	0.34
MHS	47.6 (10.3)	44.0-51.2	51.1 (39.1-55.7)	-	50.7 (12.2)	47.6-53.8	54.7 (42.5-59.5)	-	-3.1	-3.6	0.082
PHS	42.9 (10.3)	39.3-46.5	42.8 (36.8-48.1)	-	48.5 (12.4)	45.4-51.7	50.6 (40.9-59.6)	-	-5.6	-7.8	0.015

*Internal consistency measured by standardized Cronbach's α, **Wilcoxon rank-sum test

Table 4.4 MOS-HIV domain scores by injection drug use exposure (N=96)

MOS-HIV scale	Injection drug use (n=40)				Other exposures (n=56)				Difference in Means	Difference in Medians	p-value**
	Mean score (SD)	95% CI	Median score (IQR)	α*	Mean score (SD)	95% CI	Median score (IQR)	α*			
Overall health	51.1 (28.9)	41.9-60.4	50.0 (27.5-75.0)	0.91	61.0 (27.5)	53.7-68.4	65.0 (37.5-82.5)	0.86	-9.9	-10.0	0.092
Physical function	70.1 (24.0)	62.4-77.8	75.0 (58.3-91.7)	0.82	78.3 (27.6)	70.9-85.7	91.7 (58.3-100.0)	0.91	-8.2	-16.7	0.028
Role function	35.0 (41.1)	21.8-48.2	0.0 (0.0-50.0)	0.63	63.4 (46.2)	51.0-75.8	100.0 (0.0-100.0)	0.89	-28.4	-100.0	0.0027
Social function	72.5 (27.4)	63.7-81.3	80.0 (50.0-100.0)	-	79.6 (29.4)	71.8-87.5	100.0 (60.0-100.0)	-	-7.1	-20.0	0.12
Cognitive function	66.6 (25.8)	58.4-74.9	70.0 (52.5-85.0)	0.92	79.2 (23.8)	72.8-85.6	87.5 (65.0-100.0)	0.91	-12.6	-17.5	0.011
Pain	62.5 (26.1)	54.1-70.9	66.7 (38.9-83.3)	0.82	73.8 (26.2)	66.8-80.8	77.8 (55.6-100.0)	0.82	-11.3	-11.1	0.032
Mental health	69.7 (18.8)	63.7-75.7	72.0 (54.0-84.0)	0.73	74.5 (19.7)	69.2-79.8	76.0 (60.0-94.0)	0.79	-4.8	-4.0	0.21
Energy/fatigue	51.1 (22.0)	44.1-58.2	55.0 (35.0-67.5)	0.85	61.3 (22.8)	55.2-67.4	60.0 (45.0-77.5)	0.87	-10.2	-5.0	0.047
Health distress	70.8 (30.7)	60.9-80.6	80.0 (57.5-95.0)	0.94	77.7 (24.6)	71.1-84.3	85.0 (65.0-100.0)	0.89	-6.9	-5.0	0.26
Quality of life	63.1 (22.6)	55.9-70.4	62.5 (50.0-75.0)	-	75.9 (21.3)	70.2-81.6	75.0 (75.0-100.0)	-	-12.8	-12.5	0.0030
Health transition	58.8 (25.7)	50.5-67.0	50.0 (50.0-75.0)	-	60.3 (23.7)	53.9-66.6	50.0 (50.0-75.0)	-	-1.5	0	0.88
MHS	46.7 (11.6)	43.0-50.4	47.7 (38.6-56.2)	-	51.7 (11.2)	48.7-54.7	54.8 (47.0-59.3)	-	-5.0	-7.1	0.023
PHS	43.0 (11.4)	39.4-46.7	43.5 (33.5-52.1)	-	49.1 (11.7)	45.9-52.2	50.7 (41.6-59.4)	-	-6.1	-7.2	0.013

*Internal consistency measured by standardized Cronbach's α, **Wilcoxon rank-sum test

Table 4.5 Unadjusted and adjusted models describing physical health (PHS) summary scores (N=96)

Variable	Unadjusted models			Multivariable model (excluding clinical variables)			Multivariable model (including clinical variables)		
	Parameter estimate	95% CI	P-value	Parameter estimate	95% CI	P-value	Parameter estimate	95% CI	P-value
Ethnicity (Aboriginal vs. non-Aboriginal)	-5.60	-10.55 – -0.65	0.027	-	-	-	-	-	-
HIV exposure category (injection drug use vs. other exposures)	-6.06	-10.83 – -1.29	0.013	-	-	-	-	-	-
Aboriginal IDUs	-	-	-	-8.22	-14.27 - -2.17	0.008	-4.72	-10.74-1.31	0.12
Aboriginals with other exposures	-	-	-	-11.37	-18.51 – -4.24	0.002	-7.90	-14.87 – -0.92	0.027
Non-Aboriginal IDUs	-	-	-	-10.19	-16.47 – -3.90	0.002	-6.35	-12.64 – -0.063	0.048
Non-Aboriginals with other exposures (ref)	-	-	-	0.00	-	-	0.00	-	-
Age at interview (years)*	-0.17	-0.45 – 0.12	0.25	-0.24	-0.52 – 0.032	0.082	-0.25	-0.51 – 0.0072	0.057
Sex (Female vs. male)	-1.18	-6.79 – 4.43	0.68	0.090	-5.31 – 5.49	0.97	0.60	-4.56 – 5.76	0.82
Follow-up years*	-0.53	-1.38 – 0.32	0.22	-0.17	-1.00 – 0.66	0.68	-0.30	-1.09 – 0.48	0.44
CD4 cell count >350 vs. ≤350 cells/μL	10.19	5.75 – 14.62	<0.0001	-	-	-	7.19	2.44 –11.95	0.003
Viral load ≤400 vs. >400 copies/mL	7.92	1.43 – 14.42	0.017	-	-	-	5.21	-1.01 – 11.42	0.099

*Centred variables at 18 years for age at interview and 1 year for follow-up years

Table 4.6 Unadjusted and adjusted models describing mental health (MHS) summary scores (N=96)

Variable	Unadjusted			Multivariable model (excluding clinical variables)			Multivariable model (including clinical variables)		
	Parameter estimate	95% CI	P-value	Parameter estimate	95% CI	P-value	Parameter estimate	95% CI	P-value
Ethnicity (Aboriginal vs. non-Aboriginal)	-3.11	-8.00 – 1.78	0.21	-	-	-	-	-	-
HIV transmission category (Injection drug use vs. other exposures)	-5.06	-9.73 - -0.39	0.034	-	-	-	-	-	-
Aboriginal IDUs	-	-	-	-5.59	-11.74-0.57	0.075	-3.37	-9.81-3.08	0.30
Aboriginals with other exposures	-	-	-	-4.74	-12.00 – 2.52	0.20	-3.07	-10.53 – 4.40	0.42
Non-Aboriginal IDUs	-	-	-	-6.27	-12.67 – 0.12	0.054	-4.48	-11.20 – 2.25	0.19
Non-Aboriginals with other exposures (ref)	-	-	-	0.00	-	-	0.00	-	-
Age at interview (years)*	-0.060	-0.34 – 0.22	0.67	-0.11	-0.39 – 0.17	0.44	-0.12	-0.40 – 0.16	0.39
Sex (Female vs. male)	-2.00	-7.43 – 3.43	0.47	-0.94	-6.43 – 4.56	0.74	-1.05	-6.57 – 4.47	0.71
Follow-up years*	-0.90	-1.71 - -0.084	0.031	-0.70	-1.54 – 0.14	0.10	-0.78	-1.61 – 0.059	0.068
CD4 cell count >350 vs. ≤350 cells/μL	5.15	0.52 – 9.79	0.030	-	-	-	2.72	-2.37 – 7.81	0.29
Viral load ≤400 vs. >400 copies/mL	6.21	-0.16 – 12.58	0.056	-	-	-	5.24	-1.41 – 11.89	0.12

*Centred variables at 18 years for age at interview and 1 year for follow-up years

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CHAPTER 5: LIFE STABILITY OF ABORIGINALS AND INJECTION DRUG USERS TREATED WITH COMBINATION ANTIRETROVIRAL THERAPY IN NORTHERN ALBERTA

5.1 INTRODUCTION

Among HIV-patients treated with combination antiretroviral therapy (cART) in northern Alberta, Aboriginals and injection drug users (IDUs) suffer worse outcomes. Compared to non-Aboriginals, Aboriginals achieve lower rates of initial virological suppression, experience higher rates of subsequent virological failure [1], and suffer higher rates of HIV-related [2] and all-cause mortality [2, 3]. Furthermore, Aboriginal IDUs, Aboriginal non-IDUs, and non-Aboriginal IDUs report worse physical health-related quality of life (HRQL) compared to non-Aboriginal non-IDUs [4].

High levels of adherence to cART are the primary determinant of treatment response assuming an appropriate choice of regimen [5, 6]. Therefore, it is likely that the poorer treatment outcomes observed among Aboriginals and IDUs are substantially attributable to poorer adherence to cART. Adherence to therapy can be difficult for patients who lead unstable lifestyles, which may be the case for many Aboriginal and IDU patients. Previous research investigating social instability and adherence among individuals infected with HIV though IDU combined several factors to create an indicator of social instability: living on welfare, unemployment, no stable relationship, past incarceration, and unstable housing [7]. The authors found that, among ex-IDUs, high social instability was associated with non-adherence, whereas among current opiate users, injecting behaviour was the only variable significantly associated with non-adherence. Therefore, similar social instability factors may underlie the differences in treatment outcomes we have observed by Aboriginal ethnicity and IDU. Although HIV-clinicians in northern Alberta are experienced treating patients who have life stability issues, such as housing instability, addictions, and poverty, to date, we have a limited systematic understanding of the life stability

of patients treated with cART in northern Alberta and we have not investigated how their life stability issues may be associated with treatment outcomes. Therefore, we conducted this study to describe the life stability of Aboriginal and IDU HIV-patients treated with cART in northern Alberta and to explore associations between life stability, clinical status, and HRQL. In addition, as a secondary objective, we sought to describe the HIV-risk behaviours of this patient population in terms of injection practices and condom use.

5.2 METHODS

5.2.1 Study patients

We assembled a cohort of patients using the Northern Alberta HIV Program (NAHIVP) database, which has been described previously (see previous Chapters), and the following eligibility criteria: 1) started cART between 1 January 1997 and 31 December 2005 (baseline); 2) previously antiretroviral therapy (ART)-naïve; 3) ≥18 years of age (as of September 1, 2006), 4) Aboriginal patients or those who reported their HIV-exposure as injection drug use (IDU) or any exposure combined with IDU, 5) had ever visited the University of Alberta Hospital (UAH) or Royal Alexandra Hospital (RAH) clinics during their time at NAHIVP, 6) were recently active patients, that is, they visited a NAHIVP clinic within the two calendar years before the study (2004-2006), and 7) were alive according to information available in the database at the time of extraction. We excluded patients if they started cART ≤26 weeks before delivering a baby in an effort to limit the study to patients who started cART for the purpose of treatment, rather than to prevent vertical transmission of HIV; we assumed that starting cART earlier in pregnancy or after delivery would be for maternal indications.

We defined Aboriginals as Treaty and non-Treaty Aboriginals, Métis, and Inuit. HIV exposure categories were classified using an exposure category hierarchy [8]. We defined cART as a combination of at least three antiretrovirals, other than ritonavir, recorded as prescribed on the same date. The cART start date was the first

date that a cART prescription was recorded in the database. Clinical status at interview (current clinical status) was assessed using a patient's last viral load and CD4 cell count ≤6 months before the interview date.

5.2.2 Study management

Between September 2006 and June 2007, clinic staff approached eligible patients who attended the clinic for their appointments; interested patients spoke with the research assistant to learn more about the study, provided written consent to participate, and were interviewed at that time. Patients were remunerated $10 for their participation. The study procedures were approved by the University of Alberta Health Research Ethics Board.

5.2.3 MOS-HIV

We used the Medical Outcomes Study (MOS)-HIV questionnaire to measure HRQL. Patients self-administered the questionnaire, however, the research assistant was available to help patients and administer the questionnaire if needed. The MOS-HIV consists of 35 items that measure health transition (1 item) and 11 other health dimensions: general health perceptions (5 items), physical functioning (6 items), role functioning (2 items), pain (2 items), social functioning (1 item), cognitive functioning (4 items), mental health (5 items), energy/fatigue (4 items), health distress (4 items), and quality of life (1 item). Scores range from 0 (worst) to 100 (best). In addition to these 12 areas, we generated mental health (MHS) and physical health (PHS) summary scores. These summary scores were developed using data from 1,022 HIV-patients enrolled in a multi-centre clinical trial; they had a mean age of 38.7 (SD=8.4) years, were >18 years of age, and most were male (93%), Caucasian (75%), and had at least high school level education (93%) and standardized with mean 50 (SD 10) [9]. Therefore, patients with scores above or below 50 have better or worse physical or mental HRQL compared to this standard population.

5.2.4 Life Stability Questionnaire

We developed the Life Stability Questionnaire (LSQ) after conducting 5 focus groups with n=25 participants similar to the proposed target population for the present study (they were recruited from a Directly Observed Therapy (DOT) for cART treatment program and an HIV agency in Edmonton). Questions were designed to describe patients' sociodemographics, life stability factors (including housing, employment, substance use, and criminal justice involvement), sexual behaviour, and perceptions of their overall health and life since before they started cART. Our questions regarding homelessness asked patients "In the past 12 months, have you been homeless?" and "Do you currently consider yourself to be homeless?". We intentionally determined patients' own perceptions about their housing status, rather than imposing an external definition of homelessness upon them. We adapted relevant questions from the OPICAN baseline survey, from Statistics Canada questionnaires, and from the Addiction Severity Index – 5th edition [10]. The LSQ was reviewed by the study authors, a physician who treats inner-city patients, and a nurse who manages an inner-city needle-exchange program. The first 12 interviews were conducted by one of the study authors (LJM) using a pilot version of the questionnaire; the questionnaire was minimally edited for the remaining interviews, which were conducted by a trained research assistant. Interviews were audio recorded to allow for accurate recording of responses unless the subject refused.

5.2.5 Data management and statistical analyses

We double entered the LSQ and MOS-HIV responses using EpiData 3.1 and linked patients' interview data with their NAHIVP record and current CD4 cell counts and viral load results. We used the "MOS-HIV SAS Scoring Program from JHU" to calculate MOS-HIV scores; missing values were imputed using the average score for multi-item (≥4 items) questions if at least half the items were completed [11].

Associations among patient characteristics, life stability characteristics, HRQL, and clinical status were assessed using the Fisher's exact test (categorical variables), Wilcoxon rank sum test (continuous variables), and unadjusted linear

regression. Specifically, we compared life stability characteristics between Aboriginals and non-Aboriginals, and examined the relationship between life stability characteristics and two main treatment outcomes: HRQL (PHS and MHS) and clinical status (CD4 cell count and viral load).

5.3 RESULTS

5.3.1 Derivation of the study patients

Of the 238 patients potentially eligible to participate, 64 (27%) were approached by the clinic staff. Of these 64 patients, 56 (88%) were interviewed and included as study patients; one patient was interviewed twice, and the second interview was excluded. Interviews lasted for a median of 15 (range = 10-55) minutes and were conducted at either the UAH (33, 59%) or RAH (23, 41%). Study patients did not differ from those not approached by the clinic staff with respect to Aboriginal ethnicity, sex, IDU, or baseline age, viral load, or calendar year (1997-2001 vs. 2002-2005). However, study patients tended to have lower baseline CD4 cell counts (median 160.0 (n=53) vs. 218.5 (n=164) cells/μL, p=0.10) than patients not approached, but this difference was not statistically significant.

5.3.2 Demographics

The 56 study patients (39, 70% males and 17, 30% females) had a median age of 44.7 (interquartile range (IQR)=39.0-50.1) years at interview. The median time since starting cART was 5.2 (IQR=2.3-8.1) years. All patients were born in Canada. Most (36, 64%) were Aboriginal, of whom 24 (67%) were treaty Indians, 7 (19%) were unclassified Aboriginal, and 5 (14%) were Métis. All non-Aboriginals were Caucasian. Almost half the patients were single and never married (27, 48%); the others were separated or divorced (13, 23%), not married but in a common-law relationship (10, 18%), married (4, 7.1%), or widowed (2, 3.8%).

5.3.3 HIV transmission risks

Non-Aboriginal patients were infected with HIV through IDU (17, 85%) or MSM/IDU (3, 15%). Aboriginal patients were most commonly infected through IDU (20, 56%), followed by heterosexual contact (12, 33%), MSM/IDU (2, 5.6%), or MSM (1, 3.8%); one Aboriginal patient (2.8%) had no identified risk.

5.3.4 Housing

Many patients (21, 38%) reported being homeless in the previous 12 months and 10 (18%) currently considered themselves to be homeless. Rates of homelessness in the previous 12 months and current homelessness did not differ by Aboriginal ethnicity (p=0.57 and p=1.0, respectively) (Table 5.1). Most subjects were currently living in their own place (32, 57%) or staying with a friend or family member (13, 23%). Most subjects lived with at least one other person (40, 71%). Nine (16%) patients, all Aboriginal, were currently living on a First Nations reserve or Métis settlement.

5.3.5 Education, employment, and income

Most patients did not complete high school (38, 68%); rates of non-completion were higher for Aboriginals than for non-Aboriginals (78% vs. 50%, p=0.042) (Table 5.1). Two (3.6%) patients had technical or commercial training and 8 (14%) patients had some university or college education.

Although most patients (40, 71%) were unemployed, 14 (25%) reported full-time, part-time, or temporary work, including self-employment. Of the 10 currently homeless patients, one (10%) was employed and 9 (90%) were unemployed; however, these proportions did not differ significantly from patients who were not currently homeless (p=0.42). Among patients who reported homelessness in the previous 12 months, 2 (9.5%) were employed, compared to 12 (25%) patients who did not report homelessness in the previous 12 months (p=0.054). Employment rates did not differ by Aboriginal ethnicity (9, 25% vs. 5, 25%, p=1.0) or completion of high school (9, 24% vs. 5, 28%, p=0.75).

Of the 54 patients who reported their personal incomes during the previous year, most (38, 70%) earned <$15,000: 22 (41%) earned $10,000-<$15,000 and 16 (30%) earned <$10,000. A larger proportion of Aboriginals (26, 76% vs. 12, 60%, p=0.23) and patients living on reserve (7, 88% vs. 31, 67%, p=0.41) earned <$15,000 compared to non-Aboriginals and those not living on reserve, respectively, but these differences were not statistically significant (Table 5.1).

5.3.6 Substance use

The 56 subjects drank a median of 1.05 (IQR=0.0-12.6) alcoholic drinks per week. Thirty-six (64%) patients reported any alcohol use in the previous month. Most of these 36 patients reported drinking to the point of intoxication either never (13, 36%) or less than half the time (11, 31%); however, some patients, who were significantly more likely to be Aboriginal (33% vs. 0%, p=0.005) reported intoxication occurring half the time (3, 8.3%), more than half the time (4, 11%), or always (5, 14%) (Table 5.1). The 36 patients who drank reported spending a median of $30 (IQR = $0-70, range = $0-500) on alcohol in the previous 30 days.

Thirty-six (64%) patients reported using drugs not prescribed to them by a health professional in the previous 30 days. The most commonly reported drugs used were marijuana (21, 58%) and crack (21, 58%) followed by cocaine (9, 25%) and codeine (4, 11%). Eight patients (22%) reported using only marijuana. Patients reported using between one and five drugs, with most reporting one (20, 56%) or two (10, 28%). These 36 patients reported spending a median of $100 (range = $0-2500) on drugs in the previous 30 days.

Of the 35 patients who reported drug use with available information, 6 (17%) reported injecting drugs in the previous 30 days. In the previous 30 days, of these 6 patients, one (17%) reported using a needle that was not brand new but none reported using injection equipment with someone else. Of the 41 subjects exposed to HIV through IDU, only 5 (12%) reported injecting drugs in the previous 30 days.

Of the 52 patients with available information, 3 (5.8%) reported experiencing a drug overdose in the previous 12 months, which we defined as an experience in which one loses consciousness and cannot be aroused or an ambulance is called.

5.3.7 Encounters with the criminal justice system

In the previous 12 months, a total of 8 patients had been arrested (8, 14%) or confined to a detention centre, prison, or jail (7, 13%) for a duration of 1-135 (median 5, IQR=1-90) days. Aboriginals tended to be more likely than non-Aboriginals to report encounters with the justice system (p=0.092) (Table 5.1).

5.3.8 Steady sexual partnerships

We defined a steady sexual partner as someone with whom the patient has a committed, ongoing sexual relationship. Twenty patients (36%) reported having a current steady sexual partner; the median duration of the relationship was 11.5 (IQR=3.5-19.5) years. Half of these 20 patients (10, 50%) were in common-law relationships, 3 (15%) were married, 3 (15%) were separated, 3 (15%) were single and never married, and one (5.0%) was widowed. Of note, one patient not included among these 20 patients was married but did not report his marital relationship as a steady sexual partnership. Half (10, 50%) the patients reported that their steady sexual partners were HIV-positive, 6 (30%) reported they were HIV-negative, and 4 (20%) patients were unsure of their partner's status. All 20 of the partners knew about the patient's HIV-positive status according to the patients' report. Aboriginals tended to be more likely than non-Aboriginals to have a steady sexual partner (p=0.086) (Table 5.1).

Of the 20 subjects with steady sexual partners, condom use varied. Overall, only 6 (30%) reported always using a condom with their steady sexual partners. Among the 10 patients with HIV-positive partners, over half (6, 60%) reported rarely or never using condoms, 3 (30%) reported sometimes using condoms, and only 1 (10%) reported always using condoms. The patients said they never or rarely used

condoms because they were not having sex, they were married or in a long-term relationship, both partners were infected, or it was the partner's preference.

Of the 6 subjects with HIV-negative partners, 3 (50%) patients always used condoms, 1 (17%) almost always used condoms, and 2 (33%) never used condoms. Those who always or almost always used condoms did so to prevent disease transmission and pregnancy. The two subjects who never used condoms were both women in heterosexual relationships; one did not know why she never used condoms and the other said her partner preferred not to.

Of the 4 subjects who were unsure of their partner's HIV status, 2 (50%) always used condoms and 2 (50%) used them almost always or sometimes. Again, the reason patients always used condoms was to prevent disease transmission and pregnancy; the reason for almost always using condoms was the patient's preference; and the reason for only sometimes using condoms was their availability.

5.3.9 Casual sexual partnerships

We defined a casual sexual partner as someone with whom the patient had sex with at least once, without paying or being paid with money or drugs, but with whom they did not have a committed relationship. Twelve subjects (21%) reported having at least one casual sexual partner in the previous 6 months. Seven patients (6 male, one female) reported having one casual partner and 5 patients (four male, one female) reported having multiple casual partners (two reported having two partners and three reported having four partners). Aboriginals and non-Aboriginals were equally likely to have casual sexual partnerships (p=0.57) (Table 5.1).

Patients' knowledge of their casual partners' HIV status at the time of the sexual encounter varied. Of the 7 patients with one casual partner, two patients' partners were HIV-positive, three were HIV-negative, and two patients were unsure of their partner's status. All 5 patients with multiple casual sexual partners were unsure of their partners' HIV status. Most patients (8, 67%) informed their casual

partners about their own HIV-positive status; however, three (25%) patients did not and one (8.3%) patient did for some partners but not for others.

Of the two patients with HIV-positive casual partners, one never used a condom because she did not think it was necessary and the other always used a condom to prevent his situation from becoming "worse than it [was]".

All three patients with HIV-negative casual partners always used condoms. The reasons for doing so were to prevent disease transmission and pregnancy, and because the patient did not have sex without a condom.

Of the 7 patients who did not know their casual partners' HIV status, 6 (86%) always used condoms and one (14%) sometimes used condoms. Patients who always used condoms did so to prevent disease transmission, prevent pregnancy, because the partner preferred to, and because the patient's personal policy was not to have sex without a condom. The patient who used a condom only sometimes did so when sober.

5.3.10 Paid sex

In the previous 6 months, one male patient reported paying for sex once, using a condom, and two patients (one male and one female) reported being paid for sex three times and 20 times, respectively; both said they always used a condom. The primary reason for always using a condom when paying for, or being paid for, sex was to prevent disease transmission.

5.3.11 Sexual partner concurrency

It is difficult to determine the concurrency of sexual relationships from our data. However, as a rough indication of concurrency, we investigated the overlap among casual and steady sexual partnerships and paid sex, and the marital status of patients reporting casual partnerships and paid sex. Two patients who were currently in steady sexual relationships reported casual sexual partners in the previous 6 months. Their steady partnerships were 2 months and 8 months long; therefore, the

latter patient may have had a concurrent casual partner. Of the 12 patients with casual sexual partners, one (8.3%) was separated and 11 (92%) were single and never married. The one patient who reported paying for sex was single and never married. Of the two patients who were paid for sex, the male was single and the female was in a common-law relationship. Therefore, overall it appears that two patients out of the 31 who reported any sexual partnerships (steady, casual, or paid sex) may have had concurrent sexual partnerships.

5.3.12 Overall health and life situation

Compared to before starting combination HIV therapy, most patients reported that their health at the time of the interview was much better (29, 53%); lower proportions reported being somewhat better (10, 18%), no different (10, 18%), or worse or much worse (6, 11%). Similarly, many patients reported that their life at the time of the interview was much better (20, 36%) than before they started combination HIV therapy. Lower proportions reported their life was somewhat better (15, 27%) or no different (14, 25%) and 6 (11%) patients reported their lives were worse. None reported that their lives were much worse. Aboriginals and non-Aboriginals were no different in their perceptions of their current health and life situation since before starting cART (p=0.42 and p=1.0, respectively) (Table 5.1).

5.3.13 Clinical status

At the time of the interview, the median viral load was 50 (IQR=50-180) copies/mL and median CD4 cell count was 260 (IQR=160-370) cells/μL. Fifteen patients (27%) had a CD4 cell count >350 cells/μL and 41 (73%) had a viral load <400 copies/mL. Aboriginals and non-Aboriginals were no different with respect to rates of current virological suppression (p=0.50) or immune status (p=0.54) (Table 5.2).

Patients with CD4 cell counts >350 cells/μL were more likely to be employed (p=0.012), more likely to have completed high school (p=0.045), and more likely to have an income ≥$15,000 (p=0.017); furthermore, they tended to be less likely to have been homeless in the previous 12 months (p=0.057) (Table 5.2).

Patients with a viral load <400 copies/mL were significantly less likely to have been homeless in the previous 12 months; they also tended to be more likely to be married or in a common-law relationship, more likely to report an income ≥$15,000, more likely to be employed, and less likely to have been arrested or jailed in the previous 12 months (Table 5.2).

5.3.14 Health-related quality of life

The median MHS score was 49.3 (IQR = 37.7-55.2) and median PHS score was 41.8 (IQR = 35.0-49.0). In univariable statistics, employment was associated with significantly higher PHS ($p<0.0001$) and MHS ($p=0.0061$) (Table 5.3). Patients with a CD4 cell count >350 cells/μL had significantly higher PHS scores ($p=0.0001$) and also tended to have higher MHS scores ($p=0.10$). Similarly, patients with viral loads <400 copies/mL had significantly higher PHS scores ($p=0.043$) and also tended to have higher MHS scores ($p=0.060$). Compared to patients who reported their current health was much better than before starting cART, those whose current health was better, the same, worse, or much worse had significantly lower PHS ($p=0.037$) and MHS ($p=0.028$) scores (Table 5.2). Compared to patients who reported that their current life was much better than before starting cART, those whose life was better, the same, or worse had significantly lower PHS scores ($p=0.0057$); however, no corresponding significant differences were observed for MHS ($p=0.77$) (Table 5.2). Other variables that tended to be associated with lower PHS were criminal activity (being arrested or jailed) in the previous 12 months ($p=0.097$) and homelessness in the previous 12 months ($p=0.14$) (Table 5.2). In addition, patients who were separated, divorced, or widowed tended to report worse MHS scores ($p=0.11$) compared to patients who were married or in common-law relationships (Table 5.2).

5.4 DISCUSSION

This study found significant associations between better life stability, better HRQL, and successful clinical outcomes of cART among Aboriginal and IDU HIV-patients treated with cART in northern Alberta.

5.4.1 Employment, education, income

Current employment was the factor most strongly and significantly associated with better physical and mental HRQL. The direction of causality in these relationships is uncertain, since we collected the data for these variables at the same point in time. Research conducted in southern Alberta reports a similar finding, that employment was strongly and positively associated with scores on five MOS-HIV subscales (general health, energy/fatigue, mental health, health distress, and cognitive functioning) [12]. Similarly, a study conducted among 702 HIV-positive men in Australia found that, in a multivariable analysis, being unemployed was associated with poorer self-rated physical and mental health [13].

Patients with a lower education level, those with a low income, and those who were unemployed were less likely to have a CD4 cell count >350 cells/μL; similarly, patients with a low income and those who were unemployed tended to be less likely to have a suppressed viral load. This poorer clinical status may be related to poorer adherence to therapy. However, a recent review of the literature found inconclusive support for the association between socioeconomic status (income, education level, and employment) and adherence to therapy among HIV-infected individuals, with several studies finding a significant association and several others finding none [14].

If poorer socioeconomic status is related to worse clinical status, then this may help to explain the poorer treatment outcomes we observed among Aboriginal patients in our previous research. In the present study, Aboriginals were less likely to have completed high school, and this relationship is supported by Canadian statistics, which show that, in 2001, only 31.1% of off-reserve Canadians had less than a high school level education compared with 57.7% of Inuit and 58.9% of on-reserve Registered Indians [15].

5.4.2 Homelessness

Patients reporting homelessness in the previous 12 months were less likely to have suppressed viral loads and also tended to have worse immune status and worse physical HRQL. A recent review of the literature supports these findings, showing that unstable housing has been associated with poorer adherence to cART and worse physical functioning among HIV-infected individuals [16].

5.4.3 Self-perceived health and life

Patients' perceptions about their current health compared to before starting cART were related to their physical and mental HRQL scores. Similarly, patients' perceptions about their current lives compared to before starting cART were related to their physical HRQL scores and their CD4 cell counts. Therefore, helping patients to improve their clinical status and physical HRQL may help to improve how patients perceive the overall quality of their lives. However, since we are uncertain of the direction of this relationship, it may be that patients who perceive their lives to be better may be better able to achieve successful clinical outcomes.

5.4.4 Marital status

All of the patients who were married or in common-law relationships had suppressed viral loads at the time of the interview. Since most (62%) of the partners of these patients were also HIV positive, this marital relationship may have provided patients with support to adhere to cART, especially if both partners were receiving therapy. Patients who were married or in common-law relationships also tended to have better mental health than those who were separated, divorced, or widowed. The direction of this relationship is unclear, but suggests marital status may be important to consider in assessing patients' treatment success and well-being.

5.4.5 Encounters with the criminal justice system

Aboriginals tended to be more likely to report contact with the criminal justice system, which is supported by data from Statistics Canada, showing that,

although Aboriginals comprised only approximately 3.8% of Canada's population in 2006, they made up 18% of adults in remand, 20% in custody in provincial or territorial custody, and 18% in federal custody in 2006-2007 [17].

Patients who were arrested or jailed in the previous year tended to be less likely to have virological suppression and tended to have worse physical health at the time of the interview. Among HIV-infected individuals released from prison who are re-incarcerated, research has shown that the mean increase in viral load and decrease in CD4 cell count during release is significantly greater than these respective measures while incarcerated [18]. In our study, the association between criminal activities and poorer outcomes may be caused by other life stability issues associated with criminal involvement, which may impede adherence, thus making it difficult to achieve treatment success. Since we did not interview patients currently in prison, we cannot determine if remaining in jail may be associated with improved treatment success.

These results suggest that life stability plays an important role in patients' clinical success with cART. Stable partnerships, a satisfactory income and education level, and employment appear to be positively related to clinical success whereas involvement with the criminal justice system and homelessness appear to be negatively related to clinical success. These variables may create difficulties for patients in adhering to their therapies, decreasing their chances of treatment success and increasing the potential to develop resistant infections.

These life stability factors may underlie the associations we observed in our previous research, in which we found that Aboriginals were more likely to experience worse cART treatment outcomes and worse physical HRQL compared to non-Aboriginals [2, 19] (see Chapter 2). However, in the present study, for most of these factors, except education level, we observed no significant differences by Aboriginal ethnicity. This may be due to the low sample size in our study rather than to a true lack of association. Furthermore, it may be because in this study, our comparison

group was non-Aboriginals who were all IDUs, rather than all non-Aboriginals, including non-IDUs.

5.4.6 Limitations

This study has several potential limitations. First, the small sample size prevented us from effectively evaluating the data in multivariable analyses. Second, we did not randomly select patients for interview from the list of eligible patients. In approaching patients for interview, the clinic staff may have selected patients they thought would make better subjects; however, clinic staff were asked to approach every eligible patient possible in the time available to them. Third, interviewing vulnerable patients about sensitive issues in a busy clinic setting was challenging for a number of reasons and this may have negatively impacted the accuracy of our results. For example, some patients may have been under the influence of drugs or alcohol, others fell asleep during the interview, seemed nervous, anxious, or distressed. This made it difficult to ensure that the patients understood each question and answered accurately. As well, several patients were interviewed in the presence of their partner, children, or sibling, which may have influenced their responses. In addition, interruptions by the clinic staff occurred during some interviews and may have encouraged the research assistant to hurry through interviews, causing patients to provide less in-depth responses. Fourth, as with any self-reported data, patients may not have been completely honest in their answers; this is of concern especially when dealing with the sensitive issues we explored in this study. For example, social desirability bias may have influenced answers to questions regarding condom use and patients' disclosure of their HIV status. However, rather than subjectively assessing the honesty of patients' responses, we took the information at face value and did not exclude patients from the analysis due to suspicions regarding the internal validity of their interviews.

5.4.7 Recommendations

Despite the small sample size, we observed significant relationships between life stability factors and important cART treatment outcomes. These factors should be examined in future studies to clarify the causal pathways involved and help develop effective intervention strategies aimed at improving treatment outcomes and overall health for vulnerable HIV patient populations.

Future research investigating the impact of Aboriginal ethnicity on treatment outcomes should control for these life stability factors in a larger study to examine whether they help to explain any differences in outcomes observed between Aboriginals and non-Aboriginals.

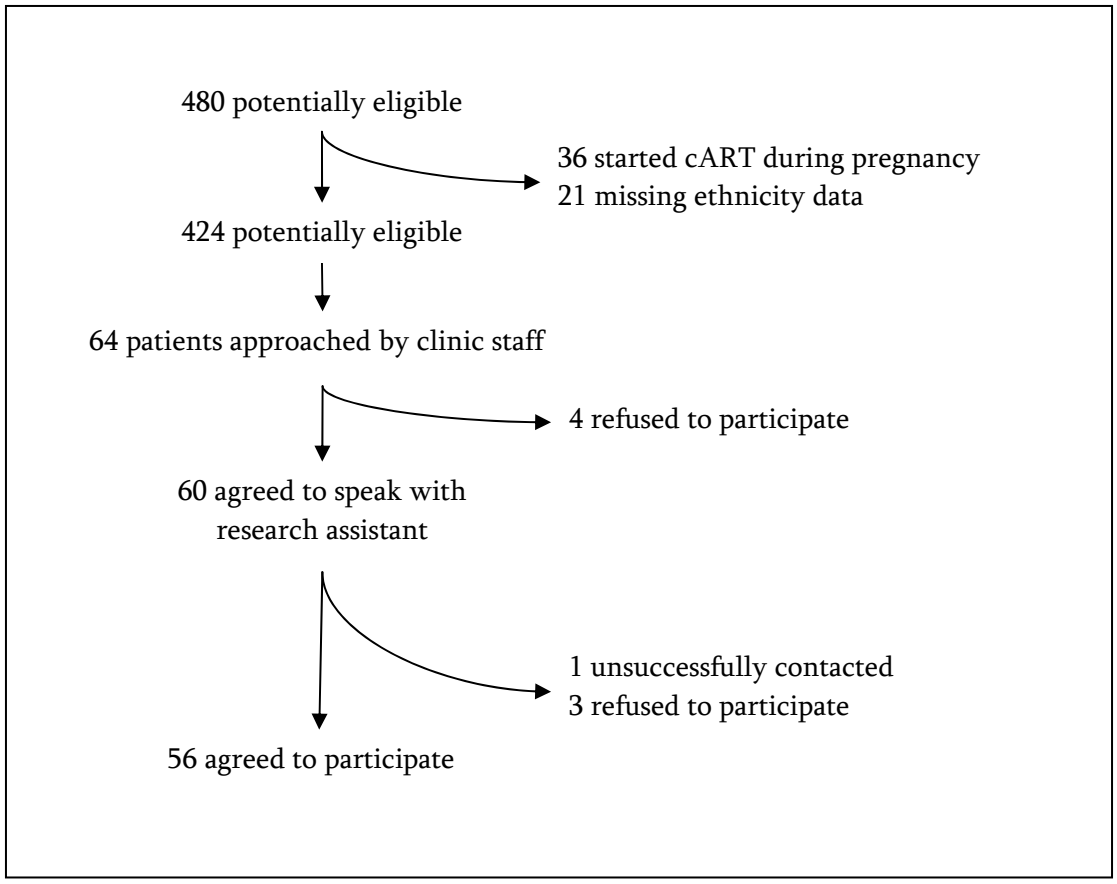

Figure 5.1 Derivation of the study sample

Table 5.1 Patient characteristics by ethnicity

Variable	Aboriginal (n=36, 64%)	Non-Aboriginal (n=20, 36%)	p-value
Age, median (years)	41.4	47.0	0.39
Sex			0.24
Female	13 (76)	4 (24)	
Male	23 (59)	16 (41)	
Marital status			0.59
Married or common-law	10 (28)	4 (20)	
Separated, divorced, widowed	8 (22)	7 (35)	
Single and never married	18 (50)	9 (45)	
Current steady sexual partnership			0.086
Steady sexual partner	16 (44)	4 (20)	
No current steady sexual partner	20 (56)	16 (80)	
Casual sexual partners in past 6 months			0.57
Casual sexual partners	8 (22)	4 (20)	
No casual sexual partners	28 (78)	16 (80)	
Employment			1.0
Employed	9 (25)	5 (25)	
Not employed	27 (75)	15 (75)	
Education			0.042
Completed high school	8 (22)	10 (50)	
Did not complete high school	28 (78)	10 (50)	
Income			0.23
<$15,000	26 (76)	12 (60)	
≥$15,000	8 (24)	8 (40)	
Criminal activity in previous 12 months			0.092
Arrested or jailed	8 (22)	1 (5)	
Not arrested or jailed	28 (78)	19 (95)	
Homelessness in previous 12 months			0.57
Homeless	12 (34)	9 (45)	
Not homeless	23 (66)	11 (55)	
Drinking to intoxication			0.005
At least half the time	12 (33)	0 (0)	
Less than half the time	24 (67)	23 (100)	
Drug use in previous 30 days			1.0
Yes	23 (64)	13 (65)	
No	13 (36)	7 (35)	
Injected drugs in previous 30 days			1.0
Injected	4 (11)	2 (11)	
Did not report injecting	32(89)	17 (89)	

Table 5.1 Patient characteristics by ethnicity, continued

Variable	Aboriginal (n=36, 64%)	Non-Aboriginal (n=20, 36%)	p-value
Current health compared to before starting cART			0.42
Much better	20 (57)	9 (45)	
Better, same, worse, much worse	15 (43)	11 (55)	
Current life compared to before starting cART			1.0
Much better	13 (37)	7 (35)	
Better, same, worse	22 (63)	13 (65)	

Table 5.2 Comparing current clinical status by patient and life stability characteristics

Variable	Viral load <400 copies/mL, no. (%) (n=53)	p-value*	CD4 cell count >350 cells/μL, no. (%) (n=55)	p-value*
Sex		0.73		0.18
Male	27 (75)		12 (32)	
Female	14 (82)		2 (12)	
Ethnicity		0.50		0.54
Aboriginal	25 (74)		4 (20)	
Non-Aboriginal	16 (84)		10 (29)	
Marital status		0.067		0.48
Married or common-law	13 (100)		4 (31)	
Separated, divorced, widowed	11 (73)		2 (13)	
Single and never married	17 (68)		8 (30)	
Current steady sexual partnership		0.31		1.0
Yes	13 (68)		5 (26)	
No	28 (82)		9 (25)	
Currently employed		0.15		0.012
Yes	13 (93)		8 (53)	
No	28 (72)		6 (15)	
Completed high school		0.73		0.045
Yes	15 (83)		8 (44)	
No	26 (74)		6 (16)	
Income		0.083		0.017
<$15,000	25 (69)		6 (16)	
≥$15,000	14 (93)		8 (50)	
Arrested or jailed in previous 12 months		0.067		0.42
Yes	4 (50)		1 (11)	
No	37 (82)		13 (28)	
Homeless in previous 12 months		0.004		0.057
Yes	10 (53)		2 (9.5)	
No	30 (91)		11 (33)	
Currently living on reserve		0.41		0.42
Yes	6 (67)		1 (11)	
No	35 (80)		13 (28)	
Drinking to intoxication		0.24		0.16
At least half the time	7 (64)		1 (7.1)	
Less than half the time	34 (81)		13 (93)	
Drug use in previous 30 days		1.00		1.0
Yes	26 (76)		9 (25)	
No	15 (79)		5 (26)	
Injected drugs in previous 30 days		0.19		1.0
Yes	2 (50)		1 (17)	
No	39 (81)		13 (27)	

Table 5.2 Comparing current clinical status by patient and life stability characteristics, continued

Variable	Viral load <400 copies/mL, no. (%) (n=53)	p-value*	CD4 cell count >350 cells/μL, no. (%) (n=55)	p-value*
Current health compared to before starting cART		0.19		0.21
Much better	23 (85)		9 (32)	
Better, same, worse, or much worse	17 (68)		4 (15)	
Current life compared to before starting cART		0.33		0.009
Much better	17 (85)		9 (45)	
Better, same, or worse	23 (72)		4 (12)	

*Fisher exact p-values

Table 5.3 Comparing mean PHS and MHS scores by patient and life stability characteristics

Variable	Difference in mean PHS scores	p-value**	Difference in mean MHS scores	p-value
Age, years	-0.35*	0.064	0.01*	0.97
Sex (female vs. male)	-0.19	0.97	-2.04	0.55
Marital status (ref=married or common-law)				
Separated, divorced, widowed	-3.37*	0.40	-6.53*	0.11
Single and never married	1.62*	0.65	2.14*	0.55
Current steady sexual partnership	-1.86	0.66	1.51	0.89
Currently employed	14.42	<0.0001	9.39	0.0061
Completed high school vs. < high school	-2.81	0.39	-0.60	0.96
Income <$15,000 vs. ≥$15,000	-3.99	0.33	-2.46	0.42
Criminal activity in previous 12 months	-5.82	0.097	-3.29	0.35
Homeless in previous 12 months	-4.72	0.14	-2.64	0.43
Currently living on reserve	-3.52	0.44	4.57	0.29
Drinking to intoxication		0.94		0.90
Used drugs in previous 30 days	2.75	0.48	0.23	0.78
Injected drugs in previous 30 days	1.28	1.00	-0.52	0.98
Current health compared to before starting cART (much better vs. better, same, worse, much worse)	6.06	0.037	6.72	0.028
Current life compared to before starting cART (much better vs. better, same, worse)	8.68	0.0057	0.69	0.77
CD4 cell count >350 cells/μL (n=55)	14.35	<0.0001	7.36	0.066
Viral load <400 copies/mL (n=53)	7.41	0.051	6.97	0.097

*Linear regression beta values

**p-values are based on two-sample Wilcoxon rank-sum tests except for those derived from linear regression

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CHAPTER 6: GENERAL DISCUSSION AND CONCLUSIONS

6.1 OVERALL SUMMARY

Overall, these four studies show that, Aboriginal HIV-patients suffer worse outcomes than non-Aboriginal HIV patients after starting cART. Aboriginals are less likely to achieve virological suppression after starting cART and, among those who achieve suppression, they suffer higher rates of virological failure ≥1 year after suppression. Furthermore, Aboriginals suffer higher rates of all-cause and HIV-related mortality than non-Aboriginals after starting cART. However, in our research, IDU was the strongest and most significant predictor of higher all-cause mortality rates. Aboriginal IDUs, Aboriginals with non-IDU exposures, and non-Aboriginal IDUs reported similarly worse physical HRQL compared to non-Aboriginals with non-IDU exposures. Among Aboriginals and IDUs, life stability factors associated with poor clinical status were unemployment, lower income, not completing high school, homelessness, and perceiving one's current life to be not much better than before starting cART. Similarly, factors associated with lower physical HRQL in this group were unemployment, perceiving one's current health or one's current life to be not much better than before starting cART, and having a current CD4 cell count ≤350 cells/μL.

6.2 RECOMMENDATIONS

The following are recommendations regarding potential directions to take with future research studies investigating HIV treatment outcomes among Aboriginals and suggestions for methods to improve the NAHIVP database to help create a source of rich, high quality data for these future studies. Although by no means comprehensive, this is meant to provide a beginning to discussions about how to proceed from the research studies presented in this thesis.

6.2.1 Future Research

More research is needed to investigate outcomes of cART among Aboriginal HIV-patients treated in Canada. This research should include three types of studies:

multi-provincial and/or multi-national studies around HIV treatment outcomes in Aboriginal populations, prospective studies of HRQL and life stability of Aboriginal and IDU patients on cART, and qualitative studies of how Aboriginal HIV-patients experience cART treatment, Furthermore, future research should incorporate a more comprehensive list of variables than were included in this thesis research to allow testing for additional potential confounders.

Although the studies described in this thesis and studies conducted in British Columbia [1-3] represent a beginning in this area of research, they do not provide a complete understanding of the challenges facing HIV-positive Aboriginals in Canada. These studies represent the situation in only two provinces in western Canada (British Columbia and Alberta). Although Aboriginals make up a relatively large proportion of the population of these provinces (5.8% in Alberta and 4.8% in British Columbia), most Aboriginals in Canada (67% of a total of 1,172,785) live elsewhere in the country [4]. Although the results of this existing research may be generalizable to Aboriginals in other areas of Canada, multi-provincial studies should be conducted to better understand treatment outcomes for Aboriginal HIV-patients across the country. Multi-provincial studies would also enable enrolment of larger and more diverse patient populations. For example, it would allow inclusion of a more representative sample of the diverse Aboriginal populations that live across Canada, which may allow stratified analyses to be conducted by, for example, First Nations, Métis, and Inuit groups. Important differences may exist amongst the distinct Aboriginal groups in Canada, and this possibility should be further investigated. Furthermore, as suggested in Chapter 1, future multi-national studies could be relevant to this area of investigation. For example, the possibility of conducting circumpolar research initiatives on HIV treatment outcomes among Inuit populations in Canada, Greenland, Alaska, and Russia could be explored. However, it should be noted that only one Inuit patient was included in the analyses presented in this thesis. Therefore, these results may not be representative of treatment outcomes for Inuit

populations. More research is needed to better understand treatment outcomes among the distinct Aboriginal peoples in Canada.

In addition to multi-provincial and multi-national initiatives, future research should include prospective studies that assess treatment outcomes over time. For example, a prospective study of HRQL should be conducted to measure HRQL at baseline, before patients start cART, and then during follow-up at predetermined time points (e.g. at 6 months, 12 months, 24 months). This will help to assess whether HRQL improves after patients start cART and whether Aboriginal ethnicity and IDU are associated with changes in HRQL over time. Prospective studies could also be conducted to assess changes in patients' life stability issues (e.g. drug and alcohol use, homelessness, employment) and how these relate to clinical status and HRQL. For example, a prospective study could be designed to better understand the temporal relationship between patients' employment status and HRQL, that is, to help determine if poor HRQL is more likely to lead to a loss of employment or a loss of employment is more likely to lead to a decrease in HRQL.

Although prospective studies will help to assess changes over time, they may not provide the depth of information that qualitative studies could produce. Throughout this thesis, Aboriginal peoples are combined into a variable "Aboriginal" and compared to "non-Aboriginal" people. However, as discussed by Waldram et al, this method of generalizing is not without concerns and "[h]ow Aboriginality, broadly conceived, affects health in a contemporary sense remains poorly understood" (page 10) [5]. These studies provide an epidemiological perspective on the outcomes of cART between Aboriginals and non-Aboriginals. To some extent, they also try to better understand what factors are involved with being Aboriginal by exploring the impact that controlling for potential confounding variables has on the relationship between Aboriginal ethnicity and the outcome. However, more in-depth qualitative studies will be better positioned to more fully understand what "Aboriginality" means and how it is related to cART outcomes. Qualitative studies could be conducted to create a better understanding of how Aboriginal HIV-patients experience cART

treatment, for example, their perspectives on their medications, their challenges to adherence, and their thoughts about the care received from their physicians. This information could be used to help inform the design of future research studies and interpretation of the results.

In addition to these suggested study designs, future research should collect information on potential confounding variables that were not consistently available in this thesis. For example, adherence to therapy, income, education level, employment status, co-morbidities such as hepatitis C virus status, ongoing drug and alcohol use, and homelessness should be considered. Qualitative studies may also help to identify other important factors to consider. These variables may help to explain the differences in treatment outcomes we observed between Aboriginals and non-Aboriginals and between IDUs and patients with non-IDU exposures. A better understanding of the reasons for these differences will help to improve our ability to develop and target interventions and future research toward improving patient care and treatment outcomes.

Overall, these recommendations are intended to help provide a starting point for future research that may be undertaken after this thesis. Given the scarcity of literature published in this area to date, additional studies are necessary to more fully understand the reasons for the poor treatment outcomes observed among Aboriginal and IDU HIV-patients.

6.2.2 Northern Alberta HIV Program database

The research studies within this thesis would not have been possible without access to the Northern Alberta HIV Program (NAHIVP) database. Similarly, future studies on HIV conducted in northern Alberta will likely rely on this resource in some way. Therefore, a more in depth description of the database, an overview of our data cleaning methods, an explanation regarding some limitations to important variables in our analyses, and recommendations for future improvements will likely be helpful.

The NAHIVP database was designed to include information on all HIV patients treated at four HIV clinics in Edmonton: the University of Alberta Hospital, the Royal Alexandra Hospital, the Sexually Transmitted Diseases Clinic, and the office of one private physician who treats HIV-patients. This should represent all HIV-patients treated in Edmonton, who likely represent all HIV-patients residing in the northern Alberta area; as well, it likely includes some patients living in the northern territories, as Edmonton might be the closest site from which they could receive specialized HIV care. Data were entered into the database by data entry clerks or other staff members at the clinics primarily from the patients' paper charts. In addition, electronic sources were used to access laboratory data, and occasionally, personal communications were used to report information such as a patient dying or moving away. Included in the database are patient demographics, clinical variables (e.g. test results for diseases such as hepatitis, syphilis, and tuberculosis, as well as vaccination dates for several infectious diseases), fields describing ongoing conditions and new events experienced by patients (e.g. substance abuse, pregnancy), HIV-risk behaviours, prescriptions (including ARTs and other drugs), and information from patient visits (including visit dates and clinical data such as height, weight, and test results such as CD4 cell count and viral load). In the database, patients were defined as Aboriginals if they: 1) had treaty status or 2) self-identified as Aboriginal. Self-identification was intentionally chosen as a method of defining Aboriginal ethnicity because being Aboriginal primarily relates to culture and self-perception (Dr. Stan Houston, personal communication). The database was primarily designed to serve clinicians and support patient care. For this reason, the data were not necessarily entered using methods that would facilitate data analysis, and many of the fields were open-text comments. For our analyses, we ignored information in open-text comment fields because it was not systematically collected for all patients and was difficult to code into variables. In addition, we excluded variables that had a large amount of missing data.

In cleaning the data, two of the main tasks we undertook were to check for duplicate patients and to determine if the ARTs a patient was prescribed could be defined as cART. Duplicate patients appeared to be included in the database for two reasons: 1) to preserve patients' aliases, so that they could be searched easily under different names and 2) if the patient had not attended the clinic for some time, a new record may have been mistakenly created. To check for duplicates, we looked for duplicated patient identifiers, including PHNs, birthdates, names, and clinic/hospital identification numbers, as well as comments that stated the patient had another name or were a duplicate. We discussed possible duplicates with the clinic staff members. Patients who were identified as duplicates had their records merged into one. Using our methods, we cannot be sure that we caught all duplicate patients or that all excluded patients were truly duplicates. In determining if the ARTs a patient was prescribed could be categorized as cART, we standardized the names of all ARTs in the database to correct spelling mistakes and group the generic and brand names of drugs together. We then categorized ARTs by drug class and determined which ARTs a patient was prescribed together in one visit. The first visit in which the drugs a patient was prescribed in one visit fit our definition of cART was defined as the patient's cART start date. However, given the limitations of the data available, patients may have started cART or ARTs before the dates we identified using the database.

The studies described in this thesis, especially in Chapters 2 and 3, rely substantially on the NAHIVP database; therefore, limitations of variables included in the database, in particular the death data and calculating the time patients were treated with cART, may have affected our study results. The NAHIVP database did not have reliable cause or date of death data; therefore, we linked the database with provincial vital statistics data. In the vital statistics data, all deaths that occurred in Alberta during our study period should have been captured, but deaths that occurred out of province would have been missed. However, we may have captured some out of province deaths using information in the NAHIVP database that was collected

through personal communications with the patients' family, friends, or through community organizations. Similar to the death data, the time patients spent on cART was difficult to ascertain using the NAHIVP database. In our studies, we assessed the time patients' spent on cART using an intention-to-treat approach. However, we cannot be certain that patients remained on therapy. Treatment interruptions may have occurred for a variety of reasons, but these interruptions were not identified in the database in a way that was easily incorporated into our data analyses; therefore, we did not consider treatment interruptions. These limitations may have impacted our study results; however, we consider our methods to be the most appropriate given the data available. Nevertheless, these limitations should be considered in future studies that use the NAHIVP database.

A number of improvements could be made to the database that would help enable high quality research studies such as those suggested above to be conducted in the future. The suggestions for improvements that follow are based on my experience using the database for this thesis; they are not based on a review of the literature on the principles of creating or managing a clinic database nor are they guided by a clinician's perspective. Furthermore, these suggestions assume that the database has two main purposes: first, and most importantly, to help clinicians monitor their patients' health care and second, to provide researchers with a valid, reliable, and comprehensive source of data to conduct studies relevant to the HIV-patients treated by NAHIVP.

First, to help develop the NAHIVP database into a more effective resource for future research, it should be designed to collect data more consistently across patients and within data fields. Currently, a number of variables that would be valuable for future studies are not collected, or not collected as systematically or accurately as possible. For example, in the study described in Chapter 2, ethnicity data were missing for 36 (6.6%) patients who were therefore excluded from the analyses. In comparison, a previous study conducted in 2002 reported a slightly lower proportion (4.9%) of patients missing ethnicity data [6]; therefore, it appears that the collection of

ethnic status has not improved over time. Since the studies described in this thesis demonstrate the importance of considering Aboriginal ethnicity when assessing treatment outcomes, ethnicity should be considered a necessary element in a patient's file. In addition to ethnicity, as recommended by a previous study using this database [7], socioeconomic status measures, such as income, employment status, and homelessness should be routinely collected. These variables are currently not collected or are available for only a limited number of patients. For example, although education level is included as a variable in the database, it is missing for the vast majority of patients (81% of the 548 patients included in Chapter 2) and is therefore not a useful element in an analysis. In addition to including additional fields, existing fields that are collected as free-text should be changed to categorized variables to create consistency throughout the database and to enable researchers to more easily use these data in analyses; a previous study using this database also suggested this modification [6]. However, free-text fields could remain as a supplement to categorical data for clinical purposes or additional explanation. Another field that could be improved in the database is duration of patients' ART prescriptions. This information could help identify gaps in a patient's receipt of medications between clinic visits, which may be a marker of non-adherence or treatment interruptions. Overall, improving the collection of data in these ways will help to create a cleaner, more comprehensive and more useful database for future research studies.

One way to help ensure consistent collection of information in the database would be to have patients complete a questionnaire at the beginning of their care (ideally at their first clinic visit) and then complete routinely administered questionnaires throughout their treatment. These questionnaires could be developed in consultation with NAHIVP clinicians and relevant researchers (i.e. those who have used these data in the past and those who plan to make use of it in the future); in addition, patients could also be consulted. At the first visit (baseline), the questionnaire could include basic demographic information (e.g. ethnicity, sex, date of birth) and HIV transmission risk behaviours, as well as variables that may change

with time and are therefore best collected at the same time point for everyone (e.g. education level, employment status, income, history of injection drug use, current housing situation, and previous and current ART). Follow-up questionnaires could include information regarding changes in variables assessed at baseline (e.g. drug and alcohol use, housing status). Given the high response rate among patients approached to participate in the studies described in Chapters 3 and 4, patients appear to be interested in assisting clinicians and researchers; therefore, these questionnaires could be an effective method of improving the database for ongoing research purposes.

Second, linking data from other sources, including pharmacy-refill data and vital statistics data, could help transform the NAHIVP database into a richer data source for use in research and patient monitoring. Adherence to ARTs should be considered an essential data element in future studies. Although pharmacy-refill data may not be an ideal method to measure adherence, it could be useful as an indicator in the absence of better measures or to corroborate other adherence assessments implemented at the clinic, such as patient self-report. If possible, historic refill data for all ART prescriptions in the database could be acquired to allow retrospective studies to be conducted. These data would not only be useful in research studies, but they could provide clinicians with a valuable tool to track their patients' prescription refill behaviour. However, given the limitations of pharmacy-refill data as a measure of adherence, other methods of assessment could also be employed at the clinic and entered into the database as well. To date, the clinic has agreed that routine assessment of ART adherence should be incorporated into patient care; however, discussions are currently ongoing regarding which measurement to use. In addition to adherence data, ongoing linkage with data from vital statistics, including date and cause of death, would be a valuable addition to the database. Although date of death is captured to some extent in the database, cause of death is not well recorded. Mortality — especially HIV-related vs. non-HIV-related mortality — are key outcomes that could be examined to assess changes in trends over time. Exploration

of additional external data sources could further improve the database and allow the exploration of additional research questions.

Third, methods should be implemented to improve data entry, both to prevent data entry errors and to keep the database up-to-date. Electronic transmission of records is one method that could be used to meet both these objectives. For example, currently, laboratory reports of patients' viral loads and CD4 cell counts are transmitted to the clinic electronically, printed, and then manually entered into the database by the clinic staff. Enabling automatic uploading of lab reports into the database would eliminate the need for manual data entry of this information, thus preventing data entry errors and would also help to ensure timeliness of data availability in the database. This idea could be taken further by utilizing electronic patient records, in which clinicians would enter patient information electronically, instead of recording it by hand in paper files for entry by clerks. Another method to prevent data entry errors would be to use uneditable drop-down menus for fields in the database that have a limited number of possible entries. For example, numerous discrepancies in medication names currently occur in the database because they can now be entered as free-text. A standard list of drug names would help to prevent spelling mistakes and misinterpreted entries, thus reducing the need for data cleaning. Furthermore, if not already done so, data entry clerks employed across all clinic sites should receive standard training in data entry methods to ensure consistency across sites, across patients, and over time. These methods should help to ensure the database contains accurate, timely data.

Fourth, current duplicate patient records that exist in the database should be merged and future duplications should be prevented. The identification, cross-referencing, and verification of patients with multiple records was a time consuming and difficult step in data cleaning for this thesis. It required the use of personal identifiers, discussion with clinic staff, and checking of patients' charts. Many of these duplicates were due to patient aliases and name changes. In order to keep track of the multiple names a patient may use, a separate field for "aliases" should be

created; these aliases should be searchable so that patients' records can be found using either their legal names or their aliases. Unfortunately, at the last data extraction, duplicates discovered in this thesis still remained in the database. These duplicate records may create repeated errors in statistics reported from the database and should be corrected.

Fifth, to assess the accuracy of the database on an ongoing basis and to enable identification of systematic errors, the database should be periodically validated. This process will likely identify missing data, which could be completed using patients' charts or external data sources. For example, viral load test results could be cross-referenced to check for errors and missing data and entries could be corrected or completed using data from the Provincial Public Health Laboratory. Ongoing validation of the database will enable continual database improvements and help to improve the quality of associated research studies.

Finally, the overarching purpose and specific objectives of the database should be explicitly articulated to everyone who participates in collecting, entering, and using the data. The purpose and objectives should serve as a guide for future database development and for researchers considering the use of this database in their own work. Improving the quality of the database will help to improve the quality of resulting research studies and provide clinicians with the most accurate historic information on their patients. These outcomes will help to improve our understanding of the health and well-being of HIV-patients treated in northern Alberta and thus provide an opportunity to improve patient care.

6.3 CONCLUSIONS

Among HIV-patients treated with cART in northern Alberta, Aboriginals suffer worse treatment outcomes than non-Aboriginals. However, more research is needed to better understand the reasons underlying these differences; poor adherence to therapy is likely a key factor. If adherence is found to be as important as we hypothesize, clinicians and researchers should work with patients to develop

culturally appropriate interventions to help improve their adherence. Other underlying causes, including socioeconomic status, drug and alcohol use, and co-morbidities, should also be explored. Multi-provincial and multi-national studies should be considered to enable larger sample sizes and more generalizable results and prospective and qualitative studies should be considered to further our understanding of treatment outcomes for HIV-infected Aboriginal patients. The NAHIVP database should be improved to enable it to be as effective a resource as possible for future research studies.

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APPENDIX 1: LIMITATIONS, CHALLENGES, AND ADVANTAGES OF CONDUCTING RESEARCH WITHIN THE UNIVERSITY OF ALBERTA AND ROYAL ALEXANDRA HOSPITAL NAHIVP CLINIC SETTINGS

Conducting the retrospective cohort study, described in Chapters 4 and 5, at the UAH and RAH clinic settings presented a number of challenges that created study limitations, but also demonstrated the advantages of using these clinics to conduct research. We chose to conduct the study at these clinic sites because part of the enrolment process required a clinic staff member to approach eligible patients to ask if they would be interested in speaking with the research assistant about the study. This was most conveniently accomplished during a patient's scheduled clinic visit. The research assistant conducted interviews after the patients had been approached by the clinic staff to take advantage of the patient's presence at the clinic. This prevented the need to arrange separate interview times and locations and provided a private interview room that minimized distractions and created a familiar environment for the patients. The main challenges in conducting this study at the clinics were planning and managing the study in a way that was well-integrated into the clinic setting. Limitations that arose due to these challenges were low rates of patient enrolment and difficulty scheduling interviews in advance. Despite these challenges, the UAH and RAH clinics should be considered as sites for future research studies due to the convenience of patient recruitment and the access to safe and private interview locations. However, some potential improvements could be made to prevent these limitations, for example, research nurses could be hired to carry out patient enrolment, consent, and interviews.

One of the limitations of our retrospective cohort study was the low rate of patient recruitment. Although the study had an excellent response rate, with 89% of patients approached by the clinic staff agreeing to speak with the research assistant and 94% of those individuals participating, within the study period of approximately 11 months, only 28% of potentially eligible patients were approached by the clinic staff. Possible reasons for this low rate are: 1) few eligible patients were scheduled for

visits during this time period, 2) clinic staff were unaware of patients' eligibility during their visits, 3) the busy clinic environment made patient enrolment a challenge, for example, the clinic staff may have forgotten to introduce patients to the research assistant after their appointment, 4) the research assistant was not able to attend the clinic frequently enough and missed interviewing eligible patients, and 5) the research assistant was only able to conduct a limited number of interviews per day; therefore, additional patients were not approached by the clinic staff when the research assistant was already conducting one interview. In an effort to increase the number of patients enrolled in the study, we displayed signs in the clinic to ask patients who had already been approached about the study to remind the clinic staff that they should see the research assistant. However, we did not evaluate the effectiveness of this strategy. Future research studies conducted at the clinic that require involved consent procedures and interviews should be carefully planned and designed in collaboration with the clinic staff to ensure that they are well-integrated with clinic activities. This may help to improve patient enrolment rates in future studies.

In an ideal research study, interviews would be scheduled in advance so that both the patient and interviewer could plan for the time required. However, in this study, we were not able to arrange an interview schedule because we did not have access to patients' names or contact information before they agreed to speak with the research assistant about the study. Our solution to this challenge was to arrange for the research assistant to contact the clinic administrative staff each week to check the times of eligible patients' visits, without receiving any patient identifiers; then the research assistant would arrive at the clinic at those scheduled times. This maintained patient confidentiality but provided the research assistant with a schedule of potential interviews. For the most part this appeared to be a successful strategy. However, patients did not always arrive for their clinic appointments, or did not arrive on time, which caused the research assistant to wait at the clinic without achieving a patient interview. This may be a common challenge when conducting research with patients

who lead chaotic lifestyles, regardless of the plans in place. Therefore, these compromises likely provided the most effective solution to our interview scheduling challenges. Future studies that are conducted at the clinics need to carefully consider patient recruitment methods in order to balance effective use of time and resources with concerns about patient confidentiality. Creativity and the support of administrative and clinic staff members who are willing to provide their time are likely essential for study success.

Despite these challenges and limitations, future research studies should take advantage of the UAH and RAH clinics as sites to interview patients. Using the clinic as a patient enrolment and interview site was more convenient than attempting to arrange separate interview times and locations. Although it was possible to schedule interviews after a patient's clinic appointment, in the few instances when this was arranged, the research assistant and patient never succeeded in meeting. Therefore, conducting interviews in conjunction with patients' clinic appointments likely prevented losses to follow-up after patients agreed to speak with the research assistant and allowed for the highest possible recruitment rates.

In addition to the convenience that the clinics provided, they also offered safe and private areas to conduct interviews. The examination rooms were familiar to both the patients and the interviewer, which likely created a comfortable atmosphere. Furthermore, they allowed the interviews to be conducted behind a closed door without the clinic staff or other patients overhearing. However, given that the clinic staff were close by, the research assistant likely felt safe and secure knowing she could reach them in the event that a patient became aggressive or unstable. In contrast, conducting an interview outside the clinic may have created potentially unsafe or uncomfortable situations for the research assistant or may have risked confidentiality for the patients. For example, other sites considered for interviews were coffee shops and patients' homes. Coffee shops may have provided neutral locations in which the research assistant and patient may have both felt safe; however, given their public nature, it may have been difficult to prevent other patrons from overhearing the

interview, which may have made the patient uncomfortable and unwilling to discuss their situations openly. Similarly, although a patient's home may have been a comfortable location for the patient that offered privacy, the research assistant may have felt unsafe and uncomfortable conducting an interview there. Therefore, neither of these locations were likely suitable choices; the clinics provided the best interview site for both the research assistant and the patient.

In future studies, one method that may help to improve enrolment rates and prevent some of the challenges we faced in our research would be to hire a research nurse (or nurses) to enrol patients, obtain informed consent, and conduct interviews. As members of the clinic staff, these research nurses would have permission to access patient records; therefore, they would know in advance which patients were eligible for the study and their next appointment dates. The nurses could potentially contact patients in advance to let them know about the study and plan for additional time for the interview if they were possibly interested in participating. In addition, these nurses could spend dedicated time on the research study, which would minimize or completely eliminate the time required of the other clinic staff to work on the research study. Having a dedicated staff member in charge of the research study at the clinic may help to increase enrolment rates, and also reduce the burden on the clinic staff.

In summary, we faced several challenges conducting the retrospective cohort study at the UAH and RAH NAHIVP clinic sites which created study limitations. However, future studies should take advantage of these sites to conduct research. For studies to be successful, researchers should ensure their research is designed to be well-integrated into the clinic environment and has the support of the clinic and administrative staff. This should help to minimize challenges and encourage cooperative solutions to issues that arise.

APPENDIX 2: ANTIRETROVIRAL THERAPY DRUGS BY CLASS AND WEIGHT GIVEN IN ANALYSES

Drug name	Drug Class*	Weight
Atazanavir/ritonavir	PI	1
Lopinavir/ritonavir	PI	1
Amprenavir	PI	1
Atazanavir	PI	1
Indinavir	PI	1
Lopinavir	PI	1
Nelfinavir	PI	1
Saquinavir	PI	1
Tipranavir	PI	1
Fosamprenavir	PI	1
Abacavir	NRTI	1
Didanosine	NRTI	1
Didanosine EC	NRTI	1
Lamivudine	NRTI	1
Stavudine	NRTI	1
Tenofovir	NRTI	1
Zalcitabine	NRTI	1
Zidovudine	NRTI	1
Zidovudine/lamivudine	NRTI	2
AZT/3TC/ABC	NRTI	3
Delavirdine	NNRTI	1
DMP**	NNRTI	1
Efavirenz	NNRTI	1
Nevirapine	NNRTI	1
Enfuvirtide	FI	1

*Note: Drug class abbreviations:
PI = Protease Inhibitor
FI = Fusion Inhibitor
NRTI = Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor

**Note: DMP was an investigational NNRTI that was never licensed (Dr. S Houston, personal communication)