Identifying Determinants of HIV Disease Progression in Saskatoon, Saskatchewan

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ABSTRACT

Context & Rationale: Individuals with similar CD4 cell counts and RNA levels can vary considerably with regards to clinical progression. This variation is likely the result of a complex interplay between viral, host and environmental factors. This study aimed to characterize and identify predictors associated with disease progression to AIDS or death in Saskatoon, Saskatchewan.

Methods: This is a retrospective cohort study of 343 seroprevalent HIV positive patients diagnosed from Jan 2005 to Dec 2010. Of these, 73 had an estimated seroconversion date. Data was extracted from medical charts at two clinics specialized in HIV/AIDS care. Disease progression was measured as time from HIV diagnosis (or seroconversion) to immunological AIDS and death. The Cox hazard model was used.

Results: The 3-year and 5-year immunological AIDS free probability was 53% and 33%, respectively. The 3-year and 5-year survival probability was 89% and 77%, respectively. Among the seroconversion cohort, the 3-year immunological AIDS free probability was 76%.

Due to multicollinearity, separate models were built for IDU, hepatitis C and ethnicity. A history of IDU (HR, 3.0; 95%CI, 1.2-7.1), hepatitis C coinfection (HR, 2.9; 95%CI, 1.2-6.9), baseline CD4 counts (HR, 0.95; 95%CI, 0.92-0.98, per ever 10 unit increase), ever on ART, and year of diagnosis were significant predictors of progression to immunological AIDS among the seroprevalent cohort. Age at diagnosis, sex and ethnicity

were not.

For survival, only treatment use was a significant predictor (HR, 0.34; 95%CI, 0.1-0.8). Hepatitis C coinfection was marginally significant (p=0.067), while a history of IDU, ethnicity, gender, age at diagnosis, and year of diagnosis were not.

Among the seroconversion cohort, no predictors of progression to immunological AIDS were identified. Ethnicity, hepatitis C coinfection and history of IDU could not be assessed.

Conclusion: Our study found that IDU, HCV coinfections, baseline CD4 counts, and ART use were significant predictors of disease progression. This highlights the need for increased testing and early detection and for targeted interventions for these particularly vulnerable populations to slow disease progression.

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ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
AI/AN	American Indians/Alaska Natives
ART	Antiretroviral therapy
CI	Confidence intervals
FN	First Nations
HAART	Highly active antiretroviral therapy
HC	Heterosexual contact
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IDU	Intravenous drug users
MSM	Men who have sex with men
PHAC	Public Health Agency of Canada
PLP	Positive Living Program
SHR	Saskatoon Health Region
SK	Saskatchewan
STI	Sexually transmitted infection
WCC	Westside Community Clinic

1. Introduction

1.1. Rationale of the study

The rates of new cases of HIV among adults (≥ 15 years) in Saskatchewan (SK) have risen over the past 5 years from 3.3 to 20.8 per 100,000 population, the highest HIV incidence rate in Canada and almost twice the national average.[1] Over 70% of new cases are intravenous drug users (IDU) and over 60 % of cases are of First Nation or Métis descent. Surveillance findings and clinicians report high levels of co-infection with hepatitis C. Most HIV notifications within Saskatchewan are from three urban centers, Saskatoon, Regina, and Prince Albert.[2]

Saskatchewan clinicians report rapid deterioration of HIV cases to AIDS and have observed that at diagnosis a number of cases have both high viral loads and low CD4 counts, as stated by the HIV Surveillance officer for Saskatchewan (G. Bukassa Kazadi, oral communication, March 2011). CD4 count is an important indicator of disease stage and prognosis for HIV positive individuals.[3, 4] Patients with low CD4 counts have increased susceptibility to opportunistic infections, are more likely to acquire AIDS, and have an increased risk of mortality. Moreover, it has been shown that treatment response can be suboptimal in patients with low CD4 counts, compared to patients with higher counts.[4, 5]

It is unclear whether this trend of low CD4 counts at diagnosis is the result of a late diagnosis or rapid disease progression. While late diagnosis is definitely a possibility, other studies are potentially pointing towards the latter option. Studies by one research team have suggested the

possibility of a more virulent virus than in later decades.[6-8] A recent report on Saskatoon's inner core population, provided support to these anecdotal claims by showing rapid progression in 16% of its study population, a significantly higher proportion than the 5-10% typically observed. [9] The province of Manitoba has also noted a higher proportion of rapid progressors than typically observed. The mechanisms which drive HIV disease progression are complex and not well understood.

1.2. Purpose of the study

The HIV spread has prompted the Saskatchewan HIV Strategy 2010-2014, supported by a fund of 2.5 million by the Saskatchewan Ministry of Health. Among other objectives, this strategy calls for a decrease in the number of HIV patients progressing rapidly to AIDS.[10] In accordance with these goals, this study aimed to characterize and identify individual determinants of HIV disease progression.

Identification of factors influencing disease progression is vital to effectively care for patients and to improve their survival and quality of life. The detection of clinical features and characteristics associated with a more rapid progression can help identify patients who may benefit from a closer and more frequent clinical follow-up. Moreover, this study will enable evidence-informed policy development and contribute to a more comprehensive understanding of disease progression in the Saskatchewan population. Furthermore, this study examines a unique and under-researched population, where HIV is a new emerging health concern.

1.3. Research objectives

The general research objectives of this study were as follows:

Objective 1. To characterize HIV disease progression for the study population

1.1 To estimate the time to immunological AIDS

1.2. To estimate the time to death

Objective 2. To identify risk factors associated with disease progression

2.1. To compared disease progression between HIV/Hepatitis C co-infected and HIV mono-infected patients

2.2. To compare disease progression between Aboriginal people and non-Aboriginal people

2.3. To compare disease progression between IDUs and non-IDUs

2. Literature Review

This section provides a brief introduction of HIV and AIDS. The magnitude of the problem, including the epidemiology of HIV/AIDS at a global, national and local level, are also described. The section then explores HIV disease progression and the various definitions used to measure progression. Finally, an overview of potential proximate prognostic factors influencing disease progression are also presented.

2.1 HIV/AIDS

The human immunodeficiency virus (HIV) is a retrovirus (lentivirus) that causes acquired immunodeficiency syndrome (AIDS), a condition in which the immune system begins to deteriorate, exposing infected individuals to life-threatening opportunistic infections. HIV is transmitted person to person by the transfer of bodily fluids, such as blood, semen, and vaginal fluid. The major routes of transmission include unprotected sexual intercourse, contaminated needles, and mother to child transmission.[11]

A cure or vaccine for HIV or AIDS does not currently exist. However, great strides have been made in treatment termed highly active antiretroviral therapy (HAART). HAART consists of cocktails of at least two to three different classes of antiretroviral therapies and effectively lowers the concentration of the virus in the body. In most developed countries, where these drugs are available, a large reduction in HIV-associated morbidity and mortality has occurred to the extent that HIV/AIDS is now considered a chronic condition.[11]

2.2. HIV/AIDS Epidemiology

The World Health Organization considers HIV infection a pandemic that has claimed the life of more than 25 million people worldwide. In December 2008, it was estimated that there were 33.4 million people living with HIV globally, with 2.7 million new infections that year. In 2008, there were 2.0 million deaths.[12] While the prevalence of HIV infected individuals continues to increase, due to the continued addition of new HIV cases and the decrease in deaths, the incidence of HIV is decreasing. The incidence rate peaked in the mid 1990s with roughly 3.5 million new infections per year and has since decreased by 30% in 2008.[12] In general, the global incidence of HIV has been stable in the decade of 2000-2009 (but with important regional differences in trends and modes of transmission).[13]

2.2.1. Canada

In Canada, HIV has caused over 13,500 deaths.[1] Estimates in 2008 state that there are 65,000 Canadians living with HIV, a 14% increase from 2005.[14] While the number of Canadians living with HIV continues to rise, the incidence rate appears to be stable at around 2500 new cases per year since 2002.[1] In 2008, however, the number of new cases did show a 7.0% increase from the previous year.[1]

The Surveillance Report released by the Public Health Agency of Canada (PHAC)[1] revealed more details with regards to the national trends. In 2008, older age groups (40-49 years of age and 50+) represented an increased proportion of positive HIV test reports. Female cases, while

less prevalent than male cases since 1999, have also shown to be consistently rising. When stratified by age, only in the 15-19 age group were females more numerous than males (58.3% vs. 41.7%) in 2008, a trend noted since 1999. The most frequently reported exposure categories among adults in 2008 were MSM (45.1%), heterosexual contact (30.8%), and IDU (19.1%). Trends according to ethnicity comparing the 1998-2002 period with 2008, showed a decline in whites (from 61.3% to 44.6%), and an increase in Aboriginal persons (from 23.4% to 29.4%) and black Canadians (from 7.3% to 14.5%). The overall incidence rate among Aboriginal persons was 3.6 times higher compared to non-aboriginal persons in 2008.[1]

The number of AIDS diagnosis have consistently dropped since peaking in 1993 with 1829 cases to about 255 cases in 2008. Among adults, males continue to be more prevalent among AIDS cases, representing up to three quarters of the cases. According to exposure categories, MSM similarly accounts for the largest portion of AIDS cases (45.5%) followed by heterosexual contact (30.5) and IDU (19.0%), among adults in 2008. When stratified by sex and ethnicity, key differences emerged. Among males, MSM accounted for a slightly higher percentage (56.1%) while IDU was slightly lower (9.2%). For females, IDU accounted for the majority of AIDS cases (60.9%) with the remained accounted by heterosexual contact (39.1%). Among Aboriginal adults, over 50% of AIDS diagnoses have been attributed to IDU from 1999 to 2008. MSM constitutes about 10% of AIDS diagnoses, while heterosexual contact accounted for about 30%. This is in comparison to Whites in which over 50% of AIDS diagnoses were attributed to MSM, followed by IDU (20%) and heterosexual exposure (19%). Aboriginal persons accounted for

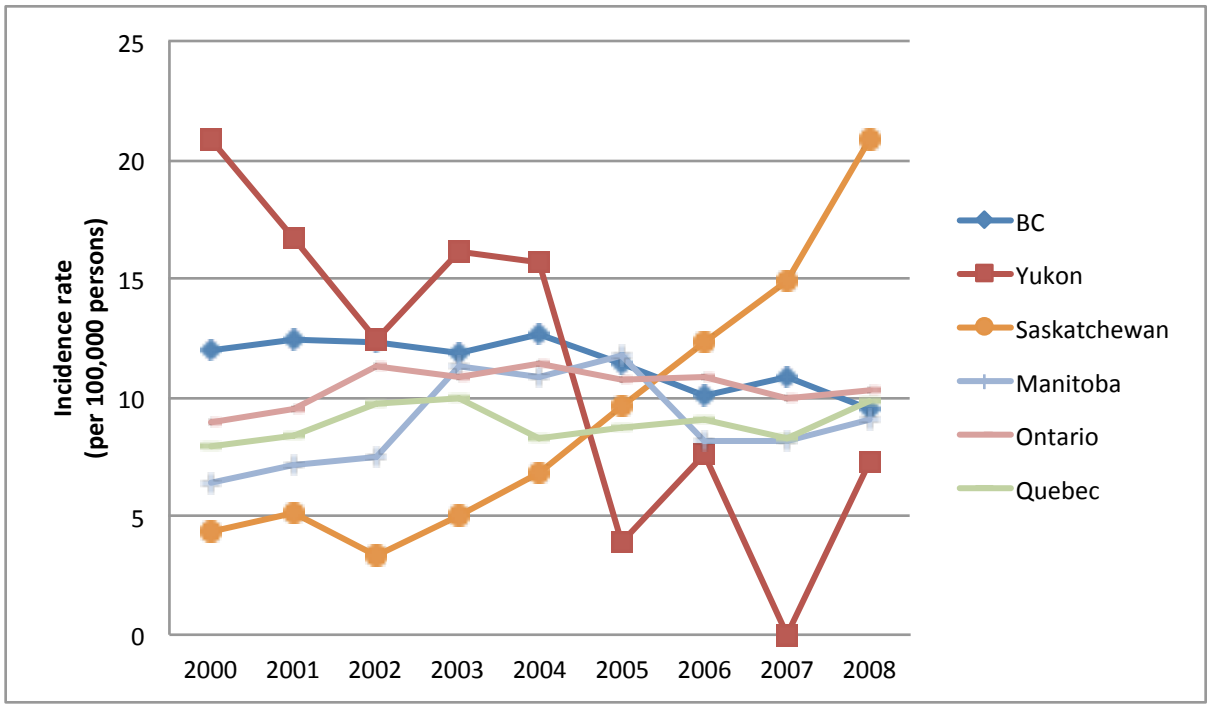
2.8% of all AIDS diagnosis from 1979 to 2008, the third highest percentage, following White (81.4%) and Blacks (9.3%).

2.2.2. Saskatchewan

Unlike the national trend, since 2003, SK has seen a consistent rise in new HIV cases. The populations growing problem is not only concerning, but also quite unique when compared to national trends. This section discusses SK's HIV epidemiology and provides a comparison to the national trends. In addition, it comments on the large problem of IDU and concludes with comments on SK's HIV epidemic.

Epidemiological statistics show the emergence of HIV in the province of SK. Since 1984, when HIV became notifiable, there were 1198 HIV cases, of which 75% were identified in the years 2000-2009.[2] Compared to 2007, this province experienced a 40% increase in the number of new cases of HIV in 2008, and an additional 15% increase in 2009. [2] This new incidence rate has situated SK above the nation's rate.[1] Annual incidence rates for the provinces most affected by HIV are presented in Figure 1.1.

Figure 1.1. Annual incidence rates for select provinces in Canada, from 2000 to 2008



Source: PHAC, Surveillance Report 2008.

From an epidemiological standpoint, SK's growing HIV situation is quite unique. The demographics of this provinces HIV population differ greatly from the national trends. SK has the lowest male to female ratio at 3:2, compared to the national ratio of 5:1 from 1985 to 2008.[1] Trends in gender have fluctuated within the last 10 years. Since 2007, male cases have surpassed female cases. When stratified by age, 2009 data shows female continued to more numerous in the lower age groups (15-29 years) while males were more numerous in the older age groups (>30 years),[2] as was the case in 2008.[1] In 2008, the mean age of female cases was 30.8 years with a range from 15-53, while male cases had a mean age of 37.8 with a range from 16-77.[1]

Aboriginal people are over represented in SK's HIV population comprising 79% of all new HIV cases in 2009, compared to the national rate of 29.4%.[1] Since 2006, they annually represent over 65% of new cases. This disparity is even more notable among females; eighty-nine percent of all female cases were Aboriginals in 2008 (70% for males).[2]

In terms of exposure categories, SK's major route of transmission continues to be injection drug use. In the early 2000s, IDU exposure accounted for nearly half of all HIV cases annually in SK. This percentage has since risen to 75% in 2008,[15] which is much higher than the national percentage of 18.9%.[1] In SK, MSM and heterosexual contact continue to stay constant with only a slight increase from 2006 to 2008. In 2008, MSM accounted for less than 5% of new cases while heterosexual contact accounted for less than 3%.[15] This trend contrasts with the nation's major route of transmission, MSM (45%).[1] Transmission via IDU has actually been decreasing in Canada.[1]

AIDS diagnosis became a reportable disease in 1984. Since then, there have been 271 AIDS cases in SK, comprising of 215 males and 56 females. In 2009, there were 14 AIDS cases. With regards to mortality among AIDS cases, there have been 199 deaths since 1984. In 2009, six newly diagnosed AIDS cases died within the same year of their diagnosis.[2]

The major mode of transmission points to the significant problem of IDU in Saskatchewan. According to estimates in 2008, there were roughly 5,000 IDUs in the province, concentrated in the three largest cities; powdered cocaine and opiates, particularly morphine, identified as the

most commonly used injection drugs.[16] These IDU are marginalized and impoverished populations, many suffering from abuse and neglect, lack of education and employment and racism.[16] While HCV co-infections appeared to be common in the early 2000s, HIV appears to be a new concern for these individuals. The I-track, an enhanced surveillance assessment among IDUs, was carried out in seven cities across Canada, including Regina, SK in 2004.[17] The study include 250 IDUs residing in Regina at the time of data collection. HIV tests found the prevalence among these IDUs to be 2.9%, roughly 10 times higher than that of the Canadian adult population (0.3%), but much lower than the average national rate of 14% among IDUs. However, the prevalence of HCV was found to be 63.7%, which closely resembled the prevalence of other cities. However, in 2007 HIV had risen to 9.0% (information from the I-track study, not yet published and obtained from the Needle Exchange Review Report[16]). In 2008, the Saskatoon Health Region (SHR) reported a prevalence of 15.0% among its active registered needle exchange clients.[16]

The rise in cases in SK is likely attributed to a continued spread of the virus and not other potentially competing causes (such as increased testing). However, it is important to note that beginning in 2005, the consistent rise in HIV cases caused changes in public health surveillance contact tracing.[18] Initiated at the SHR, additional naming of 'other individuals that you may feel are at-risk for HIV acquisition' was included in contact tracing. This enhanced surveillance investigation method helped public health workers identify other individuals who may benefit from testing. This was later adopted by the Regina Qu'Appelle Health Region and assisted further identification of HIV positive individuals. While this protocol change may have

accounted for some of the increase in HIV cases in the years that followed, it is unlikely to account for all of it. In 2005, 0.14% of all specimens tested positive. This percentage had steadily increased to 0.37% in 2008, indicating a continued spread of HIV infections.[15]

2.2.3. Saskatoon

The Saskatoon Health Region (SHR) encompasses the city of Saskatoon along with numerous surrounding communities, rural municipalities and First Nations communities. The region accounts for 5.25% of Saskatchewan's geographic area and approximately 30% of the province's population.[19] Data specific to Saskatoon is not generally available, and thus data from the SHR will be discussed, unless otherwise stated.

Within SK, the SHR has been particularly burdened by the spread of HIV. Since 2004, the rates of new HIV infections for the SHR have consistently been slightly higher than that of the provincial rate.[19] However, in more recent years, this disparity has widened, with an incidence of 31.3 per 100,000 in 2009 for SHR compared to 20.0 for the province.[19] In total, the region accounted for ~48% of the province's new cases in 2009.[20]

HCV, hepatitis C virus, causing chronic liver disease, has also been increasing in the health region. The incidence rate increased from 63.3 per 100,000 in 1996 to 82.4 in 2008. This is in contrast to the national trend where HCV infections are decreasing.[19]

Similar to provincial trends, IDU continues to be a major driver of HIV infections in SHR. It is estimated that there are roughly 2000 IDUs in Saskatoon.[16] As mentioned previously, based on the database from the needle exchange site in Saskatoon, the prevalence of HIV among active registered needle exchange clients was 15.0% in 2008. In addition to addiction problems, these individuals are of great concern due to other reasons, including high mobility and unwillingness to seek care. Based on a survey administered in 2008 to IDUs in Saskatoon, over one third (37.7%) of participants reported spending three or more consecutive days in a rural community or reserve in the last six months.[21] This was similar among those reporting a history of HIV (38.9%). The survey also found that 45.7% of participants did not go to health care centre even when they thought they should; the majority mentioned discrimination as a reason why they did not seek care. These are concerning findings given the self-reported prevalence of HIV and HCV among these survey participants was 23.8% and 79.5%, respectively. Transient behaviours, particularly travel to rural communities, is concerning as harm reduction services such as needle exchange programs are not available in many rural areas of SK and an average of 18.5 needles per person per day was reported among these study participants.[21]

2.3. Disease progression

HIV disease progression is a continuum of progressive damage to the immune system from the time of infection to the manifestation of severe immunologic damage by opportunistic infections or low CD4+ T-lymphocyte that define AIDS. CD4+ T-lymphocytes will be described below. Progression can be described to follow a rudimentary course that includes an acute infection, a clinically asymptomatic period, a symptomatic period and death. Generally, the time of infection

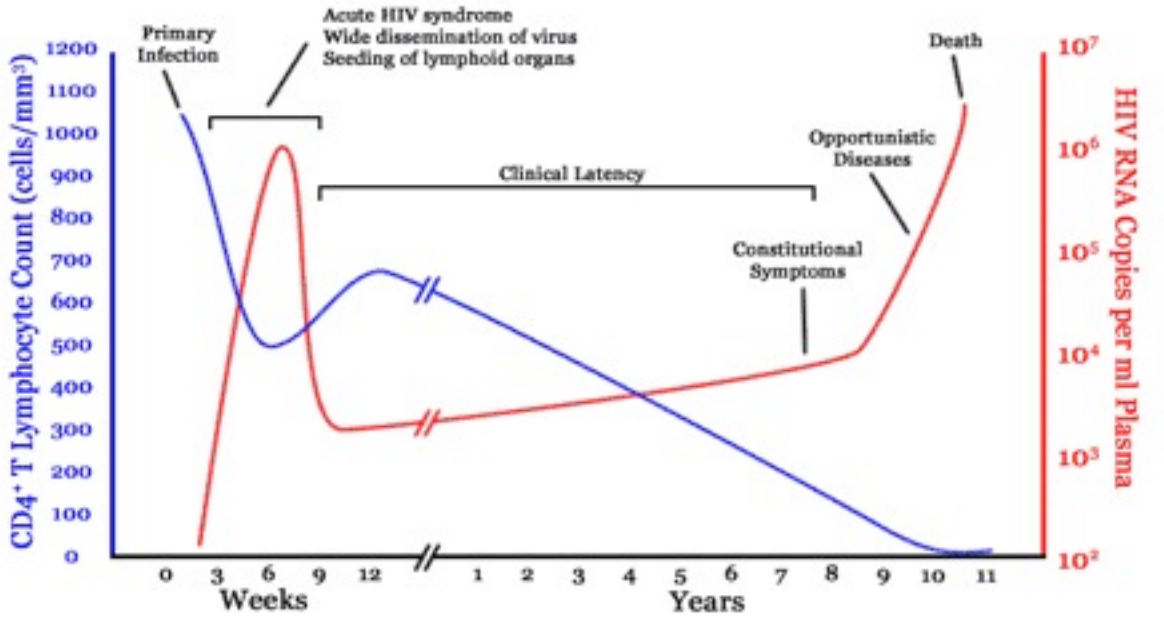
is unknown. Nevertheless, the acute infection is the initial HIV infection characterized by a period of flu-like symptoms. During this stage the body produces HIV antibodies and seroconverts to HIV-positive status. This stage is often referred to as seroconversion. Following seroconversion is the asymptomatic period, in which the virus is present in the body but does not produce significant symptoms. As the virus continues to replicate there is progressive damage to the immune system subsequently leading to clinical symptoms and opportunistic infections. A profound immune suppression is representative of a clinical diagnosis of AIDS. Without treatment, HIV infection will typically lead to death.[22]

However, considerable variability is seen in the natural history of HIV disease progression.[23] While the stages mentioned above tend to occur in sequence, it is possible to experience several stages simultaneously or to alternate among stages. To better understand the variability, two key biomarkers need to be discussed.

CD4+ T lymphocytes and viral load are considered important biomarkers of HIV disease progression. CD4+ T lymphocytes are cells of the immune system, which begin to deplete as the virus infects the body. These cells are more simply termed CD4 cells and will be referred like so from here onwards. Viral load is a term referring to the HIV RNA concentration in the body. As the virus replicates, the RNA concentration increases in the bodily fluids, including the blood. Both of these markers are measured through a blood sample and result in the count of CD4 cells per millimeter cubed and the number of viral copies per milliliter of blood.[22]

Given its direct relation to the immune system, CD4 cell counts are the primary indicator for prognostic information and a guide for antiretroviral therapy for HIV-positive individuals.[24] However, the combination of the viral RNA (i.e., viral load) and CD4 cell count more accurately predict the time to AIDS than the CD4 cell count alone. The CD4 cell count indicates the degree of immunosuppression, and a viral load correlates with more rapid progression.[24] Figure 1.2 illustrates how these two biomarkers highlight changes in disease progression.

Figure 1.2. CD4 cell counts and viral load changes during progression of the disease



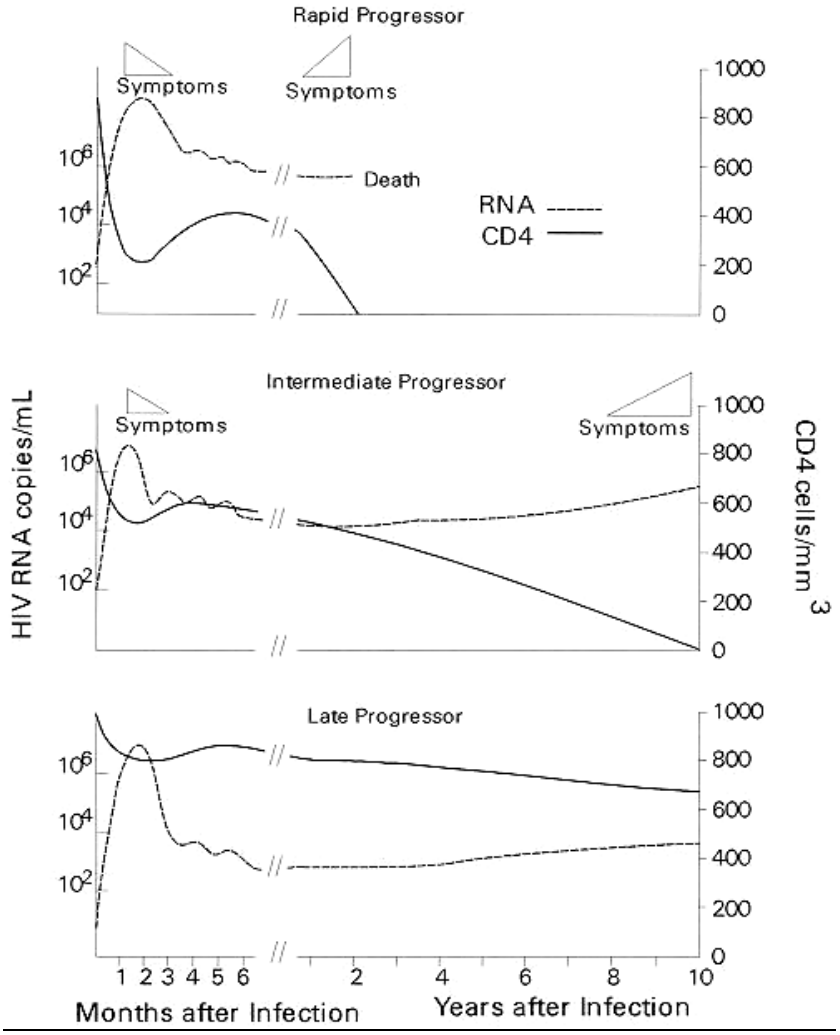
Source: Originally published as Figure 1 in Pantaleo G, et al. New concepts in the immunopathogenesis of human immunodeficiency virus infection. New England Journal of Medicine, 1993;328(5)

As can be seen in Figure 1.2, there is an initial drop in CD4 cell during the acute infection, followed by a small rebound in the following year. Subsequently, CD4 counts progressively decline over time. The decline in CD4 cells varies for each individual. Similarly, the

concentration of the virus spikes during infection, followed by a slower incline in the following years. The subsequent increase in viral load will vary for each individual.

As mentioned, this pattern in progression varies considerably. Review of progression among the HIV population has lead to three main patterns in progression rates. The key differences are highlighted by the different trends in CD4 counts and viral load. These three patterns are illustrated in Figure 1.3.

Figure 1.3. HIV-RNA levels and CD4 counts at three rates of disease progression



Source: Langford et al. Predictors of disease progression in HIV infection: a review. AIDS Research and Therapy. 2007;4(11).

Patients following the various rates have been termed typical progressors or intermediate progressors, long-term nonprogressors, and rapid progressors.[22] Typical progressors represent roughly 50-70% of HIV infected individuals. For the majority of the population, disease progresses over 8-10 years from infection to AIDS. Long-term nonprogressors experience delayed progression as indicated by measures such as CD4 cell loss, viral load, and time to

death. Long-term nonprogressors carry on without AIDS for 10 or more years, comprising about 5% of the population. Rapid progressors, on the other hand, develop AIDS in 2-3 years from seroconversion and comprise 5-10% of all HIV infected individuals. These individuals have a rapid decline in CD4 cells and increase in viral load.[22]

2.3.1. Measures of disease progression

Various measures with differing endpoints have been used to define disease progression. No one definition is more prominent or important than the other; instead, each definition contributes to the overall understanding of disease progression. Below is a brief description of the various measure used to define disease progression, what information each contributes, and their limitations.

Observed AIDS-free Interval

One commonly used measure is referred to as an observed AIDS-free interval, which measures time from HIV diagnosis to AIDS. Its popularity is likely due to the availability of these two data points. Within this definition, AIDS diagnosis has be classified in one of two ways. Clinical AIDS refers to a diagnosis due to the development of an AIDS defining disease, as per the corresponding guidelines. Immunological AIDS refers to the development of severe CD4 lymphocytopenia (i.e. CD4 count < 200 cells/μL). Both clinical AIDS or immunological AIDS are representative definitions for advanced HIV disease.[25]

The observed AIDS-free interval provides important information about disease progression following diagnosis. However, an observed AIDS-free interval is shaped by the timing of HIV diagnosis and therefore does not allow a differentiation between late diagnosis and rapid progression. Nevertheless, by controlling for CD4 counts at diagnosis, comparisons between groups can be performed. Cohorts that deliver information from HIV diagnosis are referred to as seroprevalent cohorts.

HIV to Death

Mortality is an alternate endpoint used to define the progression of the disease. Death can be specific to the diagnosis (i.e. HIV-related mortality) or non-specific (i.e. all cause mortality). Both provide important information about the causes of death specific to HIV positive populations, given this population increased susceptibility to other chronic conditions. This measure of progression, time from HIV diagnosis to death, provides important information about survival following HIV diagnosis, valueable data for health care planning. Nevertheless, measures relying on date of diagnosis as the starting point can not provide "true" data on disease progression.

HIV seroconversion to AIDS and Death

A more accurate measure of disease progression defines time from HIV seroconversion to AIDS or death. These two measures provide data unbiased by the delay in diagnosis. Occasionally these measures are limited to data prior to treatment initiation, providing information on the natural course of HIV disease progression. However, it is sometimes more informative to

include data following treatment. This latter measure provides information on the real progression of the disease within the context of the resources that are available, such as treatment.

Unlike HIV diagnosis, the date of seroconversion is generally unknown, and difficult to obtain. Occasionally, when an HIV test result is indeterminate, the specimen is further tested for a p24 antigen, which is present in the blood only during the initial phase of HIV infection. This, along with recent prior negative HIV tests, are appropriate methods available for obtaining an estimated seroconversion date when dealing with retrospective data.[26, 27]

Overcoming the initial obstacle of determining the initial infection has its advantages. As mentioned previously, working with HIV seroconversion allows disease progression to be evaluated in its truest form and allows for equal comparisons. This measure is not biased by delays in diagnosis. A cohort containing this information is referred to as a seroincident (or seroconversion) cohort.

CD4 cell decline

The final measure that is commonly employed takes advantage of an important biomarker in disease progression, CD4 counts. While slightly variable during the initial phase of infection, CD4 counts slowly decrease through the chronic phase of infection. During this specific stage, CD4 counts have been shown to decrease in a linear association with time. When looking to

compare groups, this measure has a strong advantage. Unlike time-to-event analysis, which all the previous measures would generally require, this measure uses longitudinal analysis resulting in a difference of CD4 counts per specified time between the groups of interest. This difference is easy to understand and interpret. A time-to-event analysis, provides a hazard ratio (HR), which is less easy to understand. However, this analysis is more difficult to apply due to the variability seen at the beginning and later stages of disease progression. Identifying when an individual is at the chronic phase of infection can be difficult to assess. In addition, this measure requires a long follow-up time with multiple data points for each patient to provide accurate results.[28] Moreover, factors such as other infections, stress and drugs can highly affect absolute CD4 counts, which could introduce further noise.

2.4. Potential prognostic factors influencing disease progression

There is a large volume of literature that has been published on the topic of HIV disease progression. This literature review focuses solely on demographic variables, behavioural factors and clinical variables, covariates that were available to be studied in this research. Please refer to the methods section for further details on those variables. This review does not attempt to include all papers written on the subject, but rather provides an overview of the topic.

2.4.1. Demographics

Research in the field of HIV disease progression commonly assesses the effects of demographic variables. These variables are repeatedly studied due to the disparities seen in the number of HIV and AIDS cases across the various demographics. As mentioned previously, males,

Aboriginal persons, and those aged 30-39 at diagnosis are more prevalent than females, non-Aboriginal persons and those of other age groups in Canada's HIV & AIDS diagnosed population.[1] A review of these demographic variables is written below. Due to the limited research in disease progression within Canada, most of the literature focuses on other countries.

Age

Age, typically defined as age at HIV diagnosis (or seroconversion), is well acknowledged to effect disease progression. Older age has repeatedly been found to be associated with poorer survival and faster progression.[23, 29-35] For example, a Canadian study found men aged 30 and over experienced a mortality risk about 50% higher than men under 30 years of age,[33] while another study found an increased risk of death at a rate of 2% per year of age.[30] Age has been shown to be a significant predictor of survival and disease progression independent of gender, exposure category, ethnicity, prior treatment and CD4 counts.[29, 30]

While not fully understood, several biological factors associated with age are believed to contribute to this more rapid course. Aging is associated with an increase in co-morbidities, which are believed to impact disease progression and survival.[36] Similarly, age is correlated with diminishing immune function, another factor likely to effect progression.[31] A study by Geskus et al[37] highlighted this by showing that at similar times from seroconversion older age was associated with lower CD4 counts.

Due to the importance of age at diagnosis, it would be beneficial to quantify the influence of age on HIV disease progression in this study's population. Furthermore, it would be necessary to control for this potential confounder in the analysis.

Gender

Mostly sex, and sometimes gender, are terms applied to the study of the variables 'male' and 'female' in HIV disease progression analysis. However, before commenting on the findings of these studies, it is important to define these two distinct but inextricably interconnected constructs and explain why it is important to acknowledge these differences.

As defined by Johnson et al,[38] sex is "a multidimensional biological construct that encompasses anatomy, physiology, genes, and hormones, which together affect how we are labelled and treated in the world." The researchers contrast gender as "a multidimensional social construct that is culturally based and historically specific, and thus constantly changing. Gender refers to the social prescribed and experienced dimensions of femaleness or maleness in a society, and is manifested at many levels." In essence, it is a distinction between biological sex and the social conventions, roles and behaviours regarding that biological sex. For instance, once exposed to HIV through heterosexual contact, women are more likely to acquire the virus than men, due to the biological physiologies. Moreover, in cultures where gender inequities are present, varying powers to negotiate around sex may also increase the risk of transmission for women. In these two examples, the risk of exposure is gender-linked while the risk of acquisition is sex-linked. It

is in the understanding and applying of these two constructs to health research that will yield more comprehensive science which in turn informs policy and effective programs.[38]

It is thought that the 'male' and 'female' dichotomy routinely collected in questionnaires provides both the sex and gender of individuals, given the interconnectedness of these two structures.[38] Prins et al thus suggests that, "there is no difference in the use of the binary variables of sex and gender. The distinction between the two terms is usually relevant only when the mechanisms of influence are being studied."[39] The variables available for this study do not provide for an analysis of the mechanisms that may influence potential differences between men and women. Furthermore, sex or gender based analysis is currently lacking in the field of HIV disease progression. Sex and gender are incorrectly interchanged in much of the research, with sex being the more dominate term in this literature. When differences are noted, researchers tend to relate to social constructs as possible suggestions for the inequities. Give the greater support for the latter option, as is touched upon in the literature review, gender was chosen as the term to use for this study. However, it is entirely possible that biological factors may be the cause or could contribute to the potential differences observed.

The binary variable of 'male' and 'female' is commonly collected and included in HIV disease progression analysis. However, the effects of this variable are highly variable and inconclusive. The literature review is presented in two parts, studies pertaining to the pre-HAART era and those pertaining to the post-HAART. This was done given the large impact treatment has had on HIV disease progression. These two lines of studies tend to also provide different information.

Pre-HAART studies inform on the natural course of HIV disease progression, while post-HAART studies tend to relate to beneficiary outcomes of treatment. Of course, post-HAART studies can choose to focus on treatment naive cohorts, and thus would also obtain information on the natural history of progression.

Since early on, studies were examining the effects of gender on disease progression. A total of 20 studies were found to have assessed gender in the pre-HAART era. While the majority of studies found no significant effects,[30, 32, 40-53] a few studies did find an association.[35, 54-56] All but one of these studies[54] were prospective cohorts from the United States, and they found that men had a lower risk of progression from HIV or AIDS diagnosis. The remaining study, by Prins and colleagues,[54] was one of seven seroconversion cohorts. While Prins et al. combined 8 European IDU cohorts, its sample size was comparable to other seroconversion cohorts. In contrast to the three US studies, this study found women were at lower risk of progression to AIDS, but no differences were observed for mortality. In general, while some studies did show differences in progression rates, when adjustments were made for factors such as socioeconomic status and health care utilization these differences disappeared, similar to what others have concluded.[57]

An additional six studies were identified that assessed this particular topic in the post-HAART era. Again, a minority of the studies found a significant association[58, 59] while the rest did not.[60-63] The two former studies were based on US surveillance data, which did not contain information on treatment use or adherence and thus represented more crude statistics. Interestingly, Grigoryan et al[58] focused on IDUs from 33 states and found women were at a lowers risk of

AIDS and death, which was in contrast to Hall et al[59] findings. For the entire population (i.e. not only IDUs), Hall et al found men appeared to have better outcomes.

Eight additional studies examined gender extending across both eras. All but one study, by Poundstone et al,[64] were based on a seroconversion cohort. Four of these were larger studies composed of up to 38 different cohorts from Europe, Australia and North America. This expanding cohort has been termed Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE). The first, in 2000, consisted of 5893 seroconverters from European countries and Australia and found no differences in survival on the basis of gender.[65] The second CASCADE based study in 2000, included additional cohorts resulting in a sample size of 13 030 patients, did find a lower risk of death and AIDS progression for women compared to men. However, this was no longer the case when analysis was restricted to IDU and HC.[66] In 2003, analysis was restricted to IDUs, and they observed a lower risk of death for women in 1999-2001 compared to men.[67] This was not noted in the period prior to 1999. Again, in 2008, including all cases, researchers noted women had slower progression to AIDS & death in the post-HAART era, something not noted in the pre-HAART era. They found a 24% lower risk of AIDS and 32% lower risk of death in women compared to men from 1997 onward. This study highlights that while the possibility for a biological factor accounting for these differences is possible, changes over time are more likely attributable to external changes, such as the environment.

Two other studies were from a Spanish cohort, termed Spanish Multicentre Study Group of Seroconverters (GEMES). The first study was published in 2003, and it noted women IDU had a

slower progression to AIDS and death than men IDUs. Attempting to further explore these results, the second study in 2004 further controlled for educational level.[68] Results became marginally significant. Finally, the remaining two studies were US based. Sterling et al noted no differences in their seroconversion cohort.[69] Poundstone et al did find men to have a lower risk of opportunistic infections or death than women in a seroprevalent cohort.[64] In total, half of the studies found significant differences.

Although these disparities have been shown to exist, there tends to be a general consensus that gender is a function of a social construct and not biological. Therefore, while crude data may show differences in progression, after adjusting for confounders these differences tend to disappear. This is highlighted in the latest literature review conducted in 2005. Prins, Meyer, and Hessol[70] concluded that there was little evidence for sex differences in the rate of disease progression in both the pre- and post-HAART eras indicating there were no differences in the natural course of HIV or in the benefits of antiretroviral therapy. In reviewing settings with acceptable gender equity in access to care, women have been reported to be healthier, more likely to exercise health-seeking patterns, and have higher rates of adherence compared to men, which could potential explain the differences observed.[70-73]

In Canada we tend to find an over representation of males in our HIV population (5:1 ratio). However, Saskatchewan has the lowest male to female ratio (3:2) compared to the other provinces.[1] In acknowledging this province's unique characteristics, it is important to identify how gender may be impacting progression of the disease.

Ethnicity

Similar to gender, ethnicity has always been of interest due to the disparities seen in prevalence and clinical outcomes in the various ethnic groups since the beginning of the epidemic. Historically, HIV and AIDS disproportionately affected minority groups in North America, and these minorities had consistently shown less favorable clinical outcomes.[74, 75] Currently, this trend continues to exist and a review of the crude national statistics in America clearly highlights this point.[43, 58, 59, 76] The magnitude of these ethnic disparities also appear to be increasing. While survival has dramatically increased largely due to the widespread use of HAART, these beneficial effects have not been uniformally distributed. American data found hazard ratios for survival for AIDS-diagnosed non-Hispanic blacks compared to whites increased from 1.18 in 1993-1995 to 1.51 in 1996-2001, a 33% increase.[77] This increased risk was not due to a faster progression in non-Hispanic blacks, but as a result of the decreased progression rate in the whites due to treatment.[77] These growing disparities have consequently led to researching the association of ethnicity and disease progression.

Studies in both the pre-HAART and post-HAART era have found inconsistent results. Unadjusted results for some studies found ethnicity to influence disease progression,[45, 60, 62, 78-81] but not all.[5, 35, 40, 50, 63, 64] The vast majority of these studies were from the US. In general, minority groups, such as blacks and Hispanics were shown to have unfavorable outcomes compared to whites. However, when adjusting for potential confounders such as treatment, age, and clinical status at baseline, however, these differences disappeared.

It is difficult to draw conclusion given the inherent limitations of these studies. All of the studies were based on seroprevalent cohorts, with varying study designs and definitions of ethnicity/ race. One of the more rigorous studies was a multi-centre randomized control trial composed of 1357 treatment naive patients initiating HAART.[60] This study found that at enrollment, African Americans had lower CD4 count, more likely to have history of AIDS and hepatitis C compared to whites. Adherence scores were also lower in African Americans than whites. When adjusting for all these differences, ethnicity was no longer a predictor of AIDS diagnosis or death. These studies seem to suggest that disparities in HIV disease progression are more likely the result of social and not biological factors. Differences observed could be reflective of differences in access and use of health care for minority groups compared to whites, particularly when these studies are based in a setting without universal health care.

It is important to note a Switzerland study that found contrasting results.[82] This study compared follow-up data of 586 treatment naive HIV residents. African descent was associated with a slower decline in CD4 cell counts compared to European descent (+26.6 cells/yr., $p<0.001$). The decline in CD4 cell count was not found to be dependent on baseline VL for those of African descent. The authors state that these results could point to a potential tolerance of high virus levels in patients of African descent. Two American studies have also found this association,[55] one within a subgroup population.[35] With this findings in mind, it is quite possible that both social and biological factors may play into ethnic disparities. Teasing apart the effects of these two factors, however, is a definite challenge.

Aboriginal Ethnicity

In Canada, the ethnic group of Aboriginal people experience wide disparities in health compared to their non-Aboriginal counterparts. Mortality and morbidity rates of Aboriginal people are higher than in the general Canadian population.[83, 84] Aboriginal people also tend to have lower family income, lower education attainment, and inadequate housing,[85, 86] indicators of a lower socio-economic status, which have been linked directly to health.[87] These disparities in the health status of Aboriginal people have been traced back to Aboriginal-specific historical contextual factors such as colonization and racism,[88] which have been linked directly and indirectly to adverse health outcomes for Aboriginal people.[87, 89]

These health disparities are also very evident in the field of HIV. As mentioned previously, Aboriginals are disproportionately burdened by HIV/AIDS in Canada. While Aboriginal people account for only 3.8% of Canada's population, they constitute 16.2% of all HIV cases in Canada from 1984 to 2008.[1] Aboriginal people make up a unique segment with different characteristics. In comparison to non-Aboriginal people, HIV positive Aboriginal people tend to be younger and have a higher proportion of women, with IDU being the dominate driver of transmission. These characteristics raise further issues such as pregnancy and mother to child transmission.[90] Due to these unique characteristics and the vulnerabilities linked to the social determinants of health, it is important to examine the effects of Aboriginal ethnicity on disease progression.

A review of the literature yielded one study focused on Aboriginal people and disease progression. This study, from British Columbia, Canada, was based on a longitudinal cohort. The findings showed that Aboriginals persons had all-cause mortality rates 3.12 times higher than non-Aboriginals.[80] This study was able to control for many potential confounders including treatment and adherence, in addition to equal health care access. The all-cause mortality rate was associated mainly with HIV-related causes. Co-morbidities, however, were not controlled for in the study. One additional US study should be noted. This study by Diamond et al[79] compared American Indians/Alaska Natives (AI/AN) to non-AI/AN from three western metropolitan cities in the US. AI/AN ethnicity was found to be predictive of a slower progression to clinical AIDS compared to non-AI/AN but not for immunological AIDS (i.e. CD4 counts below 200). In the adjusted model, however, no differences were seen between the two groups. This study, however, is limited chiefly by its inability to compare between the various ethnic groups, but rather pooled 54% Whites, 20% Blacks, 22% Latinos and 2% Asian and Pacific Islanders into one category and compared it to the 1% AI/AN, which likely diluted any potential differences. No studies incorporating Aboriginal ethnicity were found to examine time to AIDS.

There is reasonable conjecture to believe that Aboriginal people may have a more rapid progression that non-Aboriginal people. In efforts to understand why there is a high proportion of Aboriginal people, much research has focused on the antecedent risk factors of HIV acquisition. Aboriginals people appear to have an increase of antecedent risk factors for HIV infections, such as sexual abuse, history of IDU, poverty, poor mental health and involvement in the sex trade.[91-93] Unfortunately, HIV infected Aboriginals are also more like to suffer from other

morbidities, including Hepatitis C co-infections, and depression.[80] Aboriginal ethnicity has also been shown to be associated with a lower likelihood of HIV treatment.[94] All of these factors have been linked to poor outcomes in disease progression.

In summary, there is limited research on this topic providing a lack of understanding on the influences of Aboriginal ethnicity on disease progression.

While examing Aboriginal ethnicity, the author acknowldegdes that precautions need to be undertaken when dealing with ethnic data. While aiming to better characterize the natural history of HIV positive patients researchers must be aware that differences in ethnicity may be simply due to differences in socioeconomic factors, which may be a much better predictor of differences. Also, it must be noted that differences observed could lead to increased discrimination or stigmatization of particular ethnic groups. On the other hand, failure to address ethnic difference may have severe consequences. Ignoring ethnicity would prevent the acquisition of knowledge of disparities in health among ethnic groups. It would weaken the efforts of public health to properly respond. Furthermore, inadequate knowledge would give false reassurance, and most importantly could lead to further marginalization of vulnerable groups.

2.4.2. Behavioural factors

More recently the effects of poor health behaviours, such as substance abuse (e.g. injection drug use) and smoking, have began to be examined. There is great interest in looking at these factors,

because while other cofactors, such as age or genetic composition, are not alterable, lifestyle factors are modifiable. It must be noted that there are other variables that are showing potentially important associations with HIV disease progression, such as alcohol use.[95] However, this literature review will only focus on those variables which are available to be assessed in this study. Presented below is a review on the effects of drug use and smoking on disease progression.

Drug use

Drug use is associated with many harmful consequences including health problems. It is not surprising that the potential impacts of drug use have been of interest with regards to disease progression. Raw data, as expected, shows IDU is association with a higher risk of mortality. For instance, US national data showed that male IDUs were at a greater risk for death than men who have sex with men (MSM).[59] More recent analysis of 33 US states from 1996 to 2004, found three year survival after HIV diagnosis was lower for IDU males than males exposed through male-to-male sexual contact or high-risk heterosexual contact. Survival was also lower for IDU females compared to high-risk heterosexual contact females. The analysis controlled for race, age, CD4 cell count at diagnosis, concurrent diagnosis of HIV and AIDS, metropolitan residence and diagnosis year.[58]

Strong support from the harmful effects from drug use come from studies based in basic science. In vitro research has highlighted that drugs including morphine, cocaine, and marijuana up-

regulates the growth of HIV.[96, 97] Cocaine has also been shown to cause immune alterations and interfere with the body's defenses suggesting that it may directly affect the pathology of HIV.[98, 99]

However, epidemiological research on this topic has yielded inconsistent results. Most rigorous prospective studies with seroconversion cohorts have found no differences in progression to AIDS or death.[29, 53, 65, 66, 100] Two of these studies, published in 2000, were based on the expanding CASCADE cohort. Interestingly, a third study based on the CASCADE cohort was published 3 years later with contrasting results.[67] In the pre-HAART era, IDU had a lower adjusted hazard ratio for AIDS than MSM (HR: 0.74; 95%CI: 0.64-0.86). This reversed in 1999-2001 with an adjusted HR of 2.76 (95%CI: 1.87-4.06). Similar results were seen for survival analysis. While these studies have large sample sizes and are based on seroconversion cohorts, they do have a few key limitations. First, they have utilized the transmission mode of IDU as a proxy for drug use. This results in a possible misclassification bias as it excludes drug users who do not inject. Second, the comparison group of MSM may be inappropriate as we know that they tend to have different characteristics (see below). And finally, there is a lack of control for important confounders such as access to and adherence to treatment. What most studies do consistently report is that IDU exposure category is associated with a lower reduction in risk to AIDS and death compared to the other exposure categories (MSM and HC) in the post-HAART era compared to the pre-HAART era.[67, 72, 101] Additional prospective cohort studies focused on IDUs have noted substantial pre-AIDS morbidity and mortality compared to other transmission categories.[102, 103]

In effort to further explore drug use, other measures have been used. For instance, three seroprevalent studies have tested the association between frequency of drug use or current versus former drug use. Similarly, no differences were seen between these measures.[52, 104-106] Other studies have focused on the type of drugs. In a large US longitudinal multi-center cohort of 1686 women, crack cocaine use was shown to be an independent predictor for AIDS-related mortality, immunologic and virologic markers of HIV-1 disease progression and the development of AIDS-defining illnesses.[107] Specifically, they found persistent crack users had an adjusted HR of 1.65 ($p<0.05$) and intermittent crack users had an adjusted HR of 1.57 ($p<0.01$) for AIDS compared to nonusers. The hazard ratio for mortality was 3.61 ($p<0.001$) for persistent crack users than non-users, but no difference for intermittent users. This study was able to control for many important confounders including treatment adherence and socioeconomic status. Two other studies have similarly found crack-cocaine to be associated with AIDS.[46, 108] Hallucinogen use has also been significantly associated with both AIDS diagnosis and death in another US study. [109] In this study, cocaine use was only associated with a higher risk of death. A combination of crack cocaine and marijuana has also been shown to increase the rate of progression to CD4 count <200 cells/ml to 2.42 times higher, when controlling for ART and alcohol.[108]

A critical review by Kapdia et al[110] in 2005 attempted to reconcile difference between laboratory and epidemiological investigations with regards to the role of substance abuse in HIV disease progression. The authors note that epidemiological studies have key methodological issues. As mentioned previously, comparing IDU to MSM is problematic in that MSM tend to have different characteristics, such as higher socioeconomic status than IDUs. Furthermore, IDU are

more likely to experience non-AIDS-related mortality due to overdose, violence and accidents potentially masking differences between IDU and non-IDUs. Lastly, IDUs enrolled in cohorts may be healthier and better able to manage their drug use, thus progressing to AIDS or death less rapidly. The authors concluded that findings from both of these fields indicate that the relationship between drug use and HIV disease progression may be "mediated by several key factors, including immunological and virological conditions affecting host susceptibility, underlying co-morbidities among drug users, use of antiretroviral therapy, and viral strain, as well as pharmacodynamic aspects of drug use, such as the pattern and type of drug administration and the route of administration."[110]

In summary, while laboratory studies do seem to provide reasonable support for IDU potentially adverse effects on progression, epidemiological studies provide mixed results. Studies focused on IDU found minimal differences, while studies focused on other routes of administration found more significant results. Certain methodological limitations may account for differences seen between these two lines of research.

Smoking

Similarly to drug use, smoking is another life-style factor that is more common among those with HIV compared with the general population.[111] In parts of Canada, smoking prevalence was three times higher for HIV positive individuals than that of the general population.[112] As such, it is important to examine its potential effects on disease progression, and few studies have done so.

In 2006 a systematic literature review was conducted on this topic by Furber et al.[113] Included were 10 studies using progression to AIDS as an endpoint, in which nine found no relation with tobacco smoking. The authors did note that most of the studies were done in the pre-HAART ear and were conducted over a short follow-up period. With the increased life expectancy due to HAART, it is possible that the smoking may now cause inter-current illness, which could contribute to general debilitation and progression to AIDS. More recent research has shown that inter-current illnesses are more frequent in smokers compared to non-smokers among those HIV positive.[112]

Additional studies were since published. Three of these studies focused on the incidence of respiratory-related infections (tuberculosis, bacterial pneumonia, and pneumocystis carinii pneumonia), some of which are considered AIDS-defining illnesses.[114-116] All three found an increased relative risk of getting these respiratory infections ranging from 1.56 to 2.55 higher for smokers compared to non-smokers. The final study examined declines in CD4 cells and found an increased risk of developing AIDS (HR, 1.36; 95%CI, 1.07-1.72) among smokers compared to non-smokers.[117] Three studies also assessed the effects of cigarette smoking on mortality. All found an increased hazard ratio for all-cause mortality (ranging from 1.53-1.99) when comparing current smokers to never smokers.[115, 117, 118]

In summary, owing to the increased life expectancy in the post-highly active antiretroviral therapy ear, smoking is likely an increasingly important contributor to morbidity and mortality in HIV infected populations.[119] Furthermore, the high prevalence of smoking in Saskatoon's HIV

positive population makes it even more important to examine this life-style factor influence on disease progression.

2.4.3. Clinical factors

Co-morbidities not only reduce the quality of life for HIV infected persons, but may also be influencing disease progression. Numerous studies have shown certain co-morbidities were associated with HIV disease progression.[120-123]

Hepatitis C Co-infection

Due to the shared modes of transmission, Hepatitis C virus (HCV) co-infections are high among HIV positive IDUs, with a prevalence of 50-80% in Western Canada.[124, 125] A high proportion of Saskatchewan's HIV population are IDUs,[15] and consequently HCV co-infections are a significant problem for this province. Thus, this potential risk factor is important to address.

HIV infection has been associated with faster progression of HCV-related liver disease,[126] however, the effect of HCV infection on the progression of HIV are less clear. While numerous studies have found an association[127-131] other have not.[132-135]

A recent meta-analysis examining the effect of HCV infection on HIV disease progression and overall mortality was conducted. Based on 27 studies in HAART era, the authors calculated that HCV co-infection was associated with a 35% increased risk of mortality, but not the risk of AIDS

defining events.[136] The adverse effect of HCV co-infection was more apparent with longer follow-up and among patients who were receiving HAART than those not receiving HAART. Two of these studies adjusted for IDU, a common confounder in HIV and HCV co-infected cohorts, and found the negative effects of HCV infection on mortality were independent of IDU. One key limitation of these studies is that all ascertained HCV infection status through antibody level, and could not control for HCV viral load or patients who experienced a spontaneous clearance of HCV without treatment, common among 25% of adults infected with HCV.[137]

In attempts to address the inconsistent findings, one detailed study in 2010 examined the effects of viremic load and immune activation.[138] It is hypothesized that immune activation, induced by an infection, leads to lengthened HIV replication period and consequently an accelerated disease progression, as has been seen with other co-morbidities.[139, 140] This study, focused on a US prospective cohort of women, found that HCV viremia was associated with AIDS outcome, independent of injection drug use, HIV RNA level, CD4 count and ART. Furthermore, the authors found HCV viremia was associated with CD4 and CD8 activation, independent of HIV RNA level. Finally they also showed that high levels of CD8 activation were associated with AIDS in HCV-positive viremic women but not in HCV negative women.

In summary, the literature overall does appear to suggest that HCV has adverse effects on HIV and HCV co-infected patients compared to those HIV mono-infected. However, while limited research does show influences on HIV disease progression to AIDS, a more substantial effect on

overall mortality is seen. Given the high prevalence on HCV among Saskatchewan's HIV population, this is an important risk factor to consider.

3. Methodology

3.1. Theoretical perspective & conceptual framework

This section provides a brief introduction into the theoretical perspective and conceptual model that framed this study. The theoretical perspective provides information as to the ideologies and philosophical ideas that explain health, while the conceptual model provides the operationalization of the theory for this study.

Numerous theoretical perspectives of disease or health exist to explain or predict a certain phenomena. Within the field of HIV, two commonly competing theories are present. Social production of disease is an epidemiological theory that "conceptualizes determinants of disease distribution as economic and social relationships forged by a society's political and economic structure."[141] The structure of the society results in a variety of social groups that are differentially aided or hindered by their position relative to others.

Within the realm of HIV research, this theory has been utilized to explain the distribution of HIV and AIDS. For instance, risk of acquisition of HIV is characterized by economic deprivation and racial discrimination.[142-144] Thus, "hypothesis emerging from this theory proposed explanations of HIV transmission in relation to social class, access to health-related resources, work place conditions, and discrimination based on gender, ethnicity, sexual orientation/identity or other attributes." [141]

A common competing theory in the field of HIV is the life-style theory. This theory postulates that determinants of disease occur as a result of behavior clusters or cultural factors that are shared among individuals.[141] For instance, homosexual men were believed to have a life-style conducive to HIV acquisition.[145] In essence, it suggests that an aggregate of individuals make choices, and that these choices thus determine the distribution of disease at a population level. A key component of this theory is that if these are individual choices, these choices are also amendable to change, which is the foundation for many HIV prevention programs.[146]

The two theories presented are at opposite ends of the spectrum, and positioned within is where this research lies. This researcher acknowledges that both the social and economic factor and individual factors affect the distribution of health. In fact, these two views are seen as mutually inclusive. Individuals are not self-contained units, but are highly influenced by their social structures. Similarly, political and economic structures do not solely determine individual choice. In other words, neither influence health in isolation, but it is the interplay between these two factors that determine health.

Conceptual framework

The Etches Pyramid is a paradigm for health research, developed in 2006.[147] This paradigm, like many others, acknowledges that many interconnected aspects of society, the environment and individuals all contribute to the status of health. Integrated in the framework are macro- or upstream factors that affect the health of the population and individual, such as political and social influences. Also included are the meso- and micro-levels of causal analysis, which include

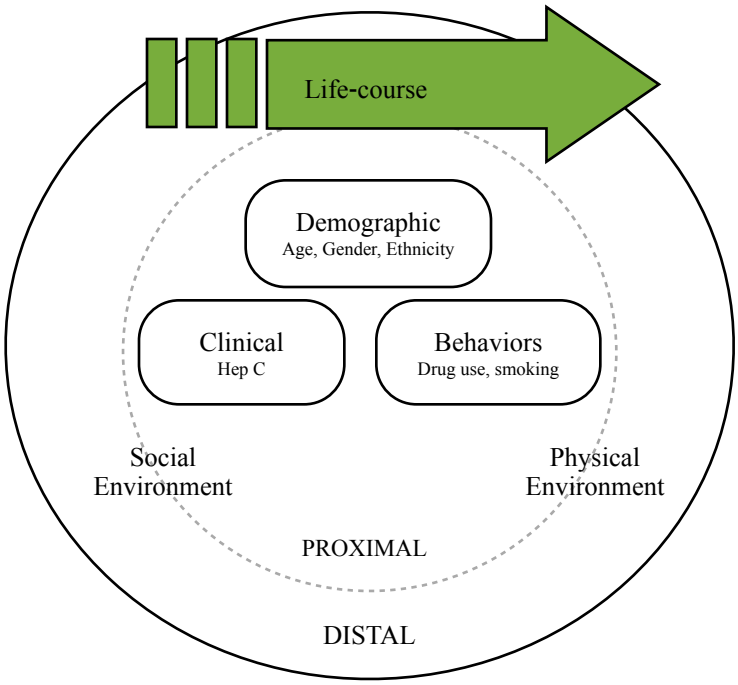
biological factors and more proximal causes of health such as genetic predispositions and lifestyle factors.

The life-course process is another key concept incorporated in the Etches Pyramid. This life-course perspective is an approach used to analyze people's lives within structural, social and cultural contexts. This approach accounts for an individual's history and examines how these earlier events influence various outcomes – in this case, health. A life course perspective is thought to contain both a 'critical period' and an 'accumulation of risk' perspective. The critical period refers to exposures acting during a specific period that have subsequent long-lasting effects on the future health of the individual. Accumulation of risk refers to an additive effect of continuous adverse exposures through-out life. Risk can also be thought to be chained together, such that one adverse exposure tends to lead to another in a sequential manner. For instance, poverty tends to be followed by poor education and unemployment. Life course is not limited to the individual, but can reach across generational effects.[148]

My proposed research relies on this integrated framework in which health is considered within both a temporal and hierarchical framework in a mutually inclusive manner. Presented below is a conceptual model that addresses specific determinants that were examined in this study of HIV disease progression (Figure 3.1). This conceptual model acknowledges that risk factors are operating concurrently at various hierarchical levels from the macroeconomic to the molecular. However, this conceptual model is simplified into proximal and distal influences on health. Biological factors and health behaviours are considered to be proximate level risk factors. The distal factors would include the wider upstream factors that would also directly and indirectly

impact the health of the individual. Bridging these two spheres are the social and physical environment. In this schema, proximal factors are not considered equivalent to individual factors, as individuals are recognized as social and contextualized persons and therefore their characteristics and behavioural choices are considered in-light of their surroundings.[149, 150] As above, these factors, do not exist in isolation, but rather continuously interact to create complex levels of health status.

Figure 3.1. HIV disease progression conceptual model



Embedded within this multi-level framework is the life-course perspective. In examining ethnicity and gender, it is important to acknowledge historical and possibly intergenerational influences. Furthermore, there is an understanding that behavioral factors and clinical outcomes

are shaped by experiences early in life and throughout the life-stages.[151] Risk acquisition evolves over time through a cumulative and interactive process.

While this study can only focus on certain proximate risk factors, their biological mediators and more distal factors are recognized as important influential domains. For instance, many viral, host and environmental factors have been identified to influence disease progression. Viral factors encompass the genetic variability of HIV, including viral subtypes[152] and viral phenotypes.[153, 154] Genetic variability of the host, such as the CCR5 Δ32 mutation, and immune function can also come into play. Lastly, all of these factors are found to interact with the environment which can include variables such as availability of adequate medical treatment[11] and the coexistence of TB.[155] All of these factors interact to create a complex and multifaceted environment that determines the rate of disease progression.

In summary, although this research was undertaken with an understanding of the complex multi-level model, examining the effects of all potential factors is not feasible. Thus, while all components play important roles, host factors, particularly demographic variables, behavioural factors, and clinical variables are more readily identified. As such, they could potentially contribute more information. Due to the availability of these factors such as demographics this research will focus on these proximal variables.

3.2. Study design

The research is a retrospective longitudinal cases-based study. Data collection comprised of data extraction from medical charts of the most recently diagnosed HIV positive patients at the Positive Living Program (PLP) and West Side Community Clinic (WCC) in Sasaktoon, Saskatchewan, Canada.

3.3. Setting and population

Saskatoon is the most populous urban center in the province, located in central Saskatchewan, Canada. Saskatoon's population is composed of 10% Aboriginals, and 7% other visible minorities.[85] In Saskatoon, the PLP and the WCC are the only sites specialized in HIV/AIDS care.

The PLP, located at the Royal University Hospital, serves adults and children with HIV and/or Hep C who reside in central and northern Saskatchewan, with the exception of one other site in Prince Albert. A distribution of patients from the PLP in 2007 showed that 59% of patients were from Saskatoon, 13% from Prince Albert, and the remaining 28% from other areas. Individuals are referred to the PLP by Public Health, private physicians, or through self-referrals. This study focused only on HIV positive patients at the PLP.

The WCC serves the core residents of Saskatoon, primarily marginalized populations such as Aboriginals, the elderly and the economically disadvantaged.[156] The WCC therefore does not

solely function as an HIV/AIDS clinic but rather as a community clinic, which is highly burdened by HIV, as exemplified in the case load. Given that HIV has disproportionately affected marginalized populations, as of March 2010, the clinic had a case load of 204 clients, a 105% increase from the previous year.[157] Again, this study focused solely on HIV positive patients at the WCC.

3.4. Operational and ethics approvals

Approval to collect data from the WCC occurred early in 2010 by a separate individual working on a related project. Operational and ethics approval documents were drafted, submitted and approved during the summer of 2010 for data collection at the PLP site. Following both approval processes, an amendment was submitted requesting approval to combine and use both datasets, which was granted.

3.5. Data collection

The WCC data was collected from May to July 2010. Data collection at this site began with the most recently diagnosed HIV patients and moved backwards to earlier cases up to 2007, which represented the majority of HIV cases attending the clinic. The data collected at this site was directly recorded into a password protected excel dataset. Data items included information on demographics (age, sex and ethnicity/race), HIV diagnosis data (date of HIV diagnosis), HIV risk factor (IDU, MSM, HC, etc.), past medical history, co-morbidities, HIV treatment, and laboratory data (CD4 cell counts, CD4% and VL, along with other diagnostic laboratory results).

For the PLP, data extraction was conducted from August to December 2010. Data collection began with the most recently diagnosed HIV patients and moved backwards to earlier cases up to 2005. Data collection was directly recorded into a password protected excel dataset. Data items included information on demographics (age, sex and ethnicity/race), HIV and AIDS diagnosis data (date of HIV and AIDS diagnosis), HIV risk factor (IDU, MSM, HC, etc.), past medical history, co-morbidities, HIV treatment, and laboratory data (CD4 cell counts, CD4% and VL, along with other diagnostic laboratory results).

Data extraction at the PLP was modeled after data extraction tools at the WCC. There were a few additional variables that were collected for the PLP site and not the WCC. These include, AIDS diagnosis (date and AIDS defining illness), date of initiation and termination of ART treatment, and smoking status.

Two standardized medical forms were central in extracting specific data. The first was an 'HIV Case Reporting Form,' a standardized provincial report form. This form includes patient information (i.e ethnicity, date of birth, and gender), HIV risk factors and clinical/laboratory data. All risk factors that apply are checked off. For a copy of this form, please refer to Appendix 2. The form is filled out by the physician or nurse with the assistance of the patient. The other form was the Saskatoon Health Region 'HIV Initial Assessment' form. Similar to the form, it includes patient information (i.e. ethnicity, date of birth, and gender) and risk factors. In addition,

this form records the previous HIV negative serology. Please see Appendix 2 for a copy of this form. Again, this form is completed by the physician or nurse with the assistance of the patient.

Specific details as to the variables collected are described below:

HIV diagnosis date (month & year) - was extracted from either the HIV Case Reporting Form, HIV Initial Assessment Form, or laboratory result.

AIDS diagnosis date (month & year) and AIDS defining illness - was extracted from the HIV/ AIDS Case Report by PHAC (see Appendix 2).

Date of death (month & year) and cause of death - was extracted from the HIV/AIDS Case Report by PHAC (see Appendix 2) or from any notations indicating this event within the medical chart.

Last negative HIV serology - was collected when the previous negative HIV serology test was present in the medical chart. The initial assessment form was recorded this information. This information was only used if a month and year was recorded.

Age at HIV diagnosis - was calculated from the month and year of DOB recorded in either the HIV Case Reporting Form, HIV Initial Assessment Form, any laboratory results, or other such reliable documents.

Gender - was obtained from either the HIV Case Report or HIV Initial Assessment Form, which included 'male' or 'female' options.

Ethnicity - was collected from either the HIV Case Report or HIV Initial Assessment Form, which included: White, Black (e.g. African, Haitian, Jamaican, Somali, etc.), First Nations, Métis, Inuit, Asian (e.g. Chinese, Japanese, Vietnamese, Cambodian, Indonesian, Filipino, etc.), South Asian (e.g. East Indian, Pakistani, Sri Lankan, Punjabi, Bangladeshi, etc.), Arab/ West Asian (e.g., Armenian, Egyptian, Iranian, Moroccan, etc.), Latin-American (e.g. Mexican Central/South American, etc.), or other / mixed ethnicity (ethnicity is known but is not included in one of the above categories, or case has dual ethnicity).

HIV risk factors - were obtained from the HIV case report or the HIV Initial Assesment Form. For a complete list of all risk factors, please refer to Appedix 3.

Hepatitis C antibody - testing was done during the initial 'entry visit'. If an indeterminate or positive antibody test resulted, PCR testing was ordered to determine if the patient was actively infected with hepatitis C. These two data points were collected from the laboratory results. However, an earlier HCV test reported by the patient was also collected.

VL, CD4 counts, and CD4% - were ordered at the first visit and at various follow up visits as deemed appropriate by the physician. All VL, CD4 count, CD4% results were recorded as well as the corresponding date of collection of the specimen.

Comorbidity information - was generally collected in the HIV Initial Assessment Form. However, this data was collected if it was recorded at any point during follow-up.

Treatment information - was collected from physician's visit notes or prescription copies keep in the file. This information was updated at every visit within its specified area in the follow-up forms. Adherence, however, was difficult to assess as there was no standardized measure or a section to record this.

Smoking status - was commonly written on follow-up forms, while there was no formal section for this information.

History of IDU - a significant number of cases did not mark IDU as a risk factor for HIV transmission, however indications of IDU were recorded elsewhere in the medical charts. These were combined with those reporting IDU risk factor, to create the history of IDU variable.

Incarceration - was collected whenever there were indications the individual was incarcerated during follow-up.

Social Assistance - was collected when copies of supplementary social assistance forms signed by the attending physician were present in the medical chart. Any additional information stating the individual was on social assistance was also used.

3.6. Inclusion/exclusion criteria

All HIV positive individuals who were clients of the PLP or the WCC were eligible to be included in the study. However, cases were limited to those diagnosed in or following the year 2005. This was done to obtain a manageable number for data collection and also to reduce the amount of missing data. Those diagnosed more recently tended to have more complete records in their medical charts. In addition it would reduce bias introduced by temporal changes, such as new treatment. Individuals under the age of 18 at HIV diagnosis were excluded in this study, as rates in progression have been shown to differ between children and adults.[70] The inclusion and exclusion criteria are summarized below.

Inclusion criteria:

a) HIV positive individuals from the PLP or the WCC

Exclusion criteria:

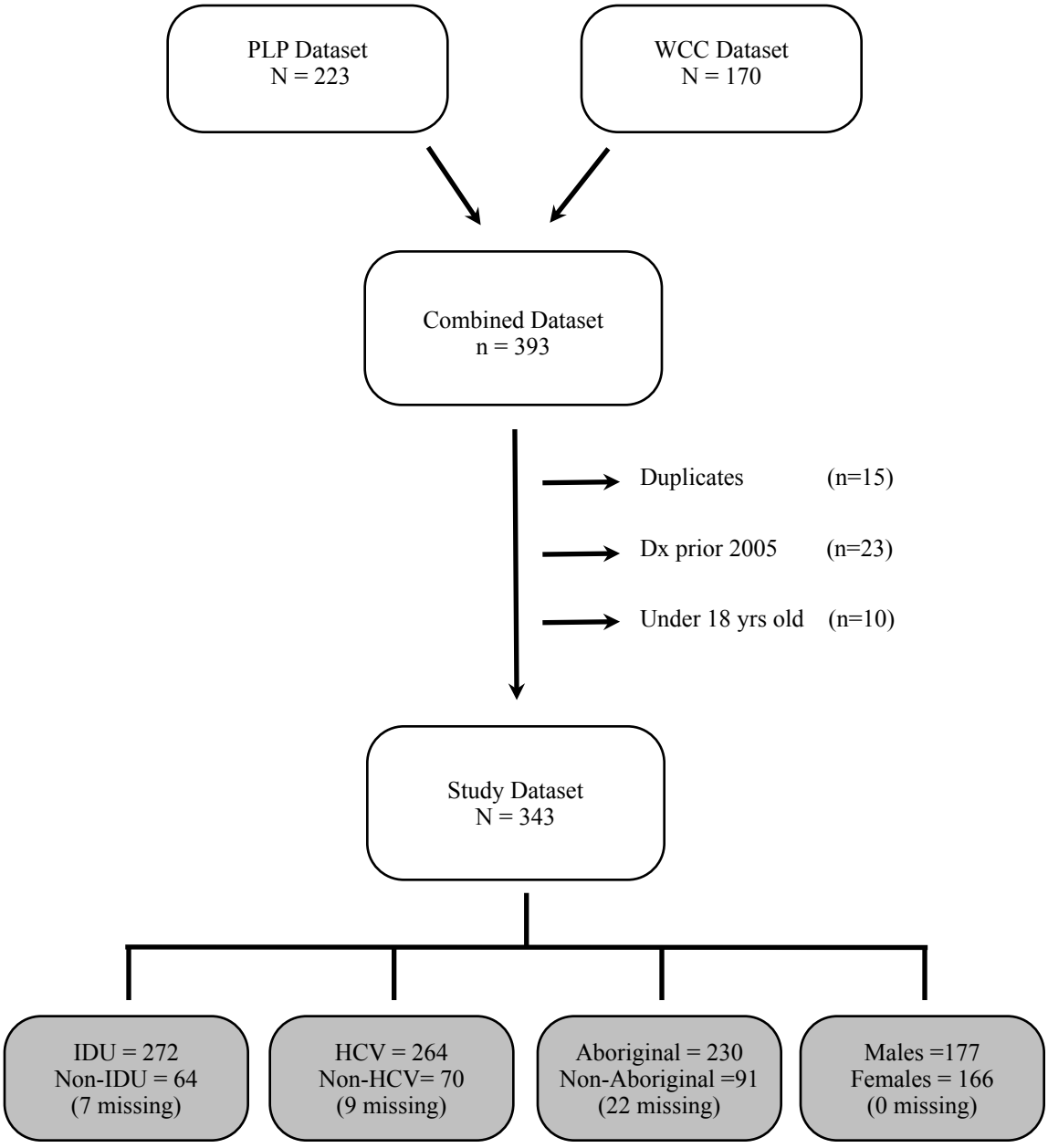
a) HIV diagnosis prior to 2005

b) Children and youth (<18 years of age at HIV diagnosis)

Due to the exclusion criteria, a number of cases were removed from the final dataset. First, a total of 15 duplicates were identified and removed. Twenty two cases had a diagnosis date prior

to 2005 and were thus also removed. An additional 3 cases had no year of diagnosis and were also excluded. Finally, an additional 10 cases were under the age of 18 years at diagnosis leaving a total of 343 cases. Figure 3.2 details the merging of the two datasets and the exclusion of cases.

Figure 3.2. Summary of inclusion process into study dataset



3.7. Variable selection

The independent variables that were available for analysis are summarized in Table 3.1. Some of these variables were not included in the study analysis for a number of reasons. Residency was not included as this variable was poorly defined. Serological antibody tests, including Hep A, Hep B, TB, and varicella, were not included as they may only indicate immunity due to immunizations and not prior infections. The frequency of active TB (confirmed by chest x-rays) were too small to be included. The frequency of the other antibody tests were to numerous to allow for comparisons between those infected and those uninfected. Active IDU was difficult to assess, as active IDU was not commonly recorded. In addition, issues with social desirability response bias made this a weak variable and was therefore not included. The types of drugs reported were generally in multiples and were not included in the analyse. Incarceration was difficult to assess from medical charts, but was collected whenever reported. Methadone treatment was believed to not have analytical value for the study of disease progression as it did not include the duration of time on methadone and adherence to methadone.

Table 3.1. Independent variables available in the database

Category	Variable	Description	Type
Demographics	Sex	Female, Male, or Unknown	Categorical
	Age	At diagnosis	Continuous
	Ethnicity	Caucasian, First Nations, Metis, Inuit, African, Asian, Other	Categorical
	Primary Residence	First 3 digits of postal code	Categorical
	Secondary Residence	First 3 digits of postal code	Categorical
Exposure category	Exposure categories	Sex with a male, sex with a female, bisexual contact, sex with high risk partner, needle stick, immigrant from endemic area, IV drug use, other (acupuncture, tattoo, body piercing), commercial sex trade worker	Categorical
Medical History	Co-morbidities	List and date of onset/diagnosis if available	Categorical
	Family History	List	Categorical
	TB mantoux test	Date and result (most recent)	Categorical
	Active TB	Yes, No, Unknown	Categorical
	Hep B Ab	Yes, No	Categorical
	Hep C Ab	Yes, No	Categorical
	Date of Hep C Test	First Hep C test recorded	Categorical
	Hep C Positive PCR Test	Date	
	Hep C Genotype	1, 1a, 1b, 2b, 3a	Categorical
	CMV Ab	Yes, No; first records at clinic entry	Categorical
	Toxoplasma Ab	Yes, No; first records at clinic entry	Categorical
	HSV Ab	Yes, No; first records at clinic entry	Categorical
	Varicella Ab	Yes, No; first records at clinic entry	Categorical
	Syphilis Ab	Yes, No; first records at clinic entry	Categorical
	Chlamydia Ab	Yes, No; first records at clinic entry	Categorical
	Gonorrhea Ab	Yes, No; first records at clinic entry	Categorical
Opportunistic Infections	PCP Date	Laboratory confirmed	Continuous
	MAC Date	Laboratory confirmed	Continuous
	OHL Date	Physician diagnosis, or laboratory confirmed	Continuous
	Candida Date	Physician diagnosis, or laboratory confirmed	Continuous
	MRSA	Yes, No (and date if available)	
	Other Infections	List and date of diagnosis	
Social	Active IDU	Yes, No; within last 6 mo of follow-up	Categorical
	History of IDU	Yes, No; ever IDU	Categorical
	Methadone Treatment	Yes, No, Referred; ever	Categorical
	Substance Abuse	List of types of drugs used	
	History of Incarceration	Yes, No	Categorical
	Smoking Status	Current, Former and Ex-smoker	Categorical
ART Treatment	History of ART	Yes, No; ever	Categorical
	ART	Type, date of initiation and termination	Categorical

The independent variables used in this analysis are summarized in Table 3.2. These variables were chosen because of their potential influence in disease progression as identified by the literature review.

Table 3.2. Independent variables used in data analysis

Category	Variable	Description	Type
Demographics	Sex	Female, Male, or Unknown	Categorical
	Age	At diagnosis	Continuous
	Ethnicity	Caucasian, First Nations, Metis, African, Asian, Inuit, Other	Categorical
Exposure category	Exposure categories	Sex with a male, sex with a female, bisexual contact, sex with high risk partner, needle stick, immigrant from endemic area, IV drug use, other (acupuncture, tattoo, body piercing), commercial sex trade worker	Categorical
Medical History	Co-morbidities	List and date of onset/diagnosis if available	Categorical
	Date of Hep C Antibody Test	First Hep C test recorded	Categorical
	Hep C Positive PCR Test	Date	
Social	History of IDU	Yes, No; ever IDU	Categorical
	Smoking Status	Current, Former and Ex-smoker	Categorical
	Incarceration	Record of during follow-up, Yes or No	Categorical
	Social Assistance	Record of during follow-up, Yes or No	Categorical
ART Treatment	History of ART	Yes, No; ever	Categorical
	ART	Type, date of initiation and termination	Categorical

Risk factors were categorized according to PHAC's exposure category hierarchy. Individuals having a positive HIV test may report more than one exposure category for acquiring the infection. These individuals are assigned to the exposure category with the highest probability of transmission. See Appendix 3 for the hierarchy list of risk factors. Baseline CD4 count was defined as the first CD4 cell count within 6 months of diagnosis.

3.8. Dependent variables

For this project, disease progression was defined as the time to an event of interest. Those events of interest where immunological AIDS and death. For a subgroup analysis of cases with estimated seroconversion dates, disease progression was adjusted to include a definition from seroconversion to immunological AIDS and death. While it would have been preferred, clinical AIDS was not chosen as a outcome, as this data was only collected at the PLP site. Due to the relatively short follow-up time within the dataset, and other limitations of a CD4 cell decline measure (see section 2.3), this outcome was not used. Opportunistic infections were recorded as yes/no for the WCC, and date of opportunisitc infection for the PLP; for this reason, opportunistics infections could not be considered an outcome.

There were two outcome variables (i.e. event) as follow:

(1) Time to immunological AIDS(CD4 count <200 cells/μl)

(2) Time to death

3.9. Statistical analysis

The data was cleaned by checking the distribution of variables. Potentially incorrect values were identified in this process.

Descriptive statistics were then used to summarize the data. To compare dichotomous variables, chi-square or Fishers exact test were used. For continuous variables, t-test were used.

Time-to-event was the statistical method used to analyze HIV disease progression.[158] The events of interest were immunological AIDS and death. Time to immunological AIDS was defined as the length of time (in months) from HIV diagnosis to the first CD4 count to drop below 200 cells/μl. If the individual did not reach a CD4 count of less than 200 cells/μl, that individual was censored at his last CD4 count. Individuals with a CD4 count below 200 cells/μl within one month of HIV diagnosis were excluded from this analysis.

Time to death was defined as the length of time (months) from HIV diagnosis to death. An individual who did not have the event of interest was censored at his last clinic visit.

Censoring is a common practice in survival analysis. While it would be ideal to follow all patients until the event of interest occurs, that is not always possible. It is not practical or economic to follow-up patients for long periods of time. Also, there will usually be patients who are lost to follow-up for some reason or another. Therefore, the at-risk time that each patient contributes ends when the study ends, they are lost to follow-up, or leave the study. In this study, censoring was assumed to be random (non-informative).

The Kaplan-Meier method[159] was used to estimate the survival function of time to immunological AIDS and death. The log-rank test was used to compare survival time distributions among all variables of interest. Cox proportional hazards model[160] was used to determine independent predictors of disease progression and death. The β-coefficients were

estimated based on the method of maximum likelihood. Ties were analyzed based on Breslow method.[161]

Cox proportional hazards regression models were constructed using the following steps: 1) Variables were added one at a time and compared to the null –2log likelihood value. Those that significantly reduced the –2log likelihood value were considered for step two. A p-value of less than 0.25 also assisted in the identification of potentially important covariates. 2) Variables identified from step one were added together into the model. Those variables not significant were discarded and the –2log likelihood values were compared. 3) Variables previously excluded were again added to see if they became significant in the presence of other variables. The aim was to identify the model with the smallest –2 log likelihood value. All 2-way interactions were also tested. Adding time-dependent variables one at a time tested the proportional hazards assumption.

Only fixed covariates were included in the model. The fixed covariates were the baseline demographics, exposure categories (i.e. IDU), Hep C coinfection, and treatment use. Based on the literature, potential confounders that were tested included in the multivariate models were age, gender, calendar time, and treatment use. Goodness of fit test based on Cox-Snell and Martingale residuals were run to assess the model.

As a subgroup analysis, a cohort of patients with estimated seroconversion (infection) dates was selected and the analysis was rerun. The time (in months) from the last negative HIV serology to

the first positive HIV test was calculated for all patients. Those with a time of 12 months or less were selected. The estimated time of seroconversion date was calculated as the midpoint between the last negative and first positive HIV serology.[65] Additional patients with a positive p24 antigen test, indicating a recent HIV infection, were also included. Seroconversion dates for these individuals was the date of their p24 antigen test, indicative of a recent infection.[26, 27]

A significance level of 0.05 was used. All data analyses were performed using SAS version 9.2.

In review, the analysis addressed the following objectives. First, it characterized HIV disease progression in terms of time to immunological AIDS and time to death. Second, it identified risk factors associated with disease progression to AIDS and death.

4. Results

4.1. Data manipulations

Viral load was log transformed in order to normalize its distribution.

4.2. Study population characteristics

Demographics

There was a total of 343 HIV positive patients. One-hundred and eighty-seven patients (55%) were from the PLP, 84 (25%) patients from the WCC and an additional 72 (21%) attended both clinics. Among these were 177 males (52%). Ethnic data was unknown for 22 cases, but of the remaining 322 patients, 230 (72%) were of self-reported Aboriginal descent. These individuals represented First Nations (89%) and Metis (11%), and not Inuit. The remaining non-aboriginals comprised of 79 (25%) Caucasians, 10 (3%) African and 2 (1%) other ethnicities.

The mean age of the population was 35 years (SE = 0.6) at diagnosis. Thirteen patients did not have recorded HIV risk factors. A hierarchal composition of the reported risk factors (see appendix 3 for details) showed that 252 (76%) of cases were attributed to IDU, followed by 45 (14%) for HC, 21 (6%) for MSM and 12 (4%) for MSM/IDU.

Behavioral Characteristics

A total of 272 (81%) reported a history of IDU. Smoking was only recorded at the PLP site; 132 (75%) were current-smokers, 22 (13%) ex-smokers and 22 (13%) non-smokers (not shown in

table).

Social Characteristics

During follow-up, there was a record of social assistance for 109 (32%) of patients. One-hundred and two (30%) had a record of incarceration.

Clinical Characteristics

Nine patients did not have a hepatitis C antibody test. Of the 334 patients with an antibody test, hepatitis C antibodies were present in 264 (79%) patients, of which 248 (94%) had an RNA confirmatory test (i.e. PCR test). This revealed 27 (11%) of those with HCV antibodies, did not have the virus present in the blood, and thus were not actively infected by HCV. In total, we found 22% were HCV antibody negative, 9% were HCV antibody positive, but RNA negative, and the remaining 70% were HCV antibody and RNA positive.

Two-hundred and fifty-three (74%) of patients had a CD4 count measure within 6 months of diagnosis. Of these, 53 (20%) had a CD4 count of less than 200, 74 (29%) had a CD4 count between 200 and 350, and 54 (29%) had a CD4 count between 350 and 500, and 72 (29%) had a CD4 count above 500. The mean CD4 count was 382 cells/μl (SE=14). The mean log viral load was 4.38 (SE=0.07).

Antiretroviral therapy information was unknown for 53 cases. Of the remaining 290, 167 (58%) patients were on HIV treatment at some point following diagnosis. Excluding the 19 cases with

no CD4 count measures, 242 (75%) were eligible for treatment based on a CD4 count of less than 350 at some point during follow-up. Of those that were eligible for treatment, 154 (71%) were on treatment at some point. All of these results are summarized in Table 4.1.

Table 4.1. Study population characteristics (N=343)

Characteristics	N	%	Characteristics	N	%
DEMOGRAPHICS			SOCIAL CHARACTERISTICS		
Gender			Record of Social Assistance		
Males	177	51.6	Yes	109	31.8
Females	166	48.4	No	234	68.2
Ethnicity			History of IDU		
Aboriginal	230	71.7	Yes	272	81.0
Caucasian	79	24.6	No	64	19.0
Other	12	3.7	CLINICAL CHARACTERISTICS		
Missing (22)			Hepatitis C Antibodies		
Age at Diagnosis			Present	264	79.0
Under 20	15	4.4	Absent	70	21.0
20-29	108	31.5	Missing (9)		
30-39	108	31.5	Hepatitis C Status		
40-49	80	23.3	HCV antibody negative	70	22.0
50 or over	32	9.3	HCV antibody positive, RNA negative	27	8.5
Mean Age at Diagnosis (±s.e.)	35.1	0.6	HCV antibody positive, RNA positive	221	69.5
Exposure Category[a]			Missing (25)		
MSM	21	6.4	Ever on ART		
MSM/IDU	12	3.6	Yes	167	57.6
IDU	252	76.4	No	123	42.4
HC	45	13.6	Missing (53)		
Missing (13)			Eligible for ART[b]		
Year of Diagnosis			Yes	242	74.5
2005	54	15.7	No	82	25.5
2006	41	12.0	Missing (19)		
2007	55	16.0	Of those Eligible for ART[b]		
2008	74	21.6	On ART	154	71.0
2009	88	25.7	Not on ART	63	29.0
2010	31	9.0	Missing (25)		
Site			CD4 Counts at Diagnosis		
Positive Living Program	187	54.5	<50	14	5.5
Westside Community Clinic	84	24.5	50-199	39	15.4
Both	72	21.0	200-349	74	29.3
SOCIAL CHARACTERISTICS			350-499	54	21.3
Record of Incarceration			≥500	72	28.5
Yes	102	29.7	Missing (90)		
No	241	70.3	Mean CD4 Count at Diagnosis (±s.e.)	382.1	14.4
			Mean Log_{10}VL at Diagnosis (±s.e.)	4.38	0.07

[a]MSM, men who have sex with men; IDU, injection drug use; HC, heterosexual contact

[b]Eligible for antiretroviral therapy (ART) based on CD4 < 350 cells/μl at some point during follow-up

4.2.1. Differences by gender

These patient characteristics were stratified by gender and a few key differences were observed for Aboriginal ethnicity, age at diagnosis, year of diagnosis, HIV risk factors, smoking status, record of social assistance, HCV co-infection and CD4 count and VL at diagnosis. These significant results are summarized in Table 4.2.

Of the 151 females, 130 (80%) were of Aboriginal descent, while among the 170 males, 100 (59%) were of Aboriginal descent ($p<0.001$). Females were significantly younger, with a mean age of 31(SE=0.7) compared to males who were roughly 7 years older (39; SE=0.8). A temporal trend was also seen with females accounting for a decreasing proportion of the cases from 59% in 2005 to 32% in 2010. Among males, 115 (68%) patients were attributed to IDU, 21 (12%) to MSM, 21 (12%) to HC, and 12 (7%) to MSM/IDU. Among females, 137 (85%) were attributed to IDU and 124 (15%) to HC.

Among those at the PLP, differences in smoking status were noted between females and males ($p=0.06$). Among females, 65 (82%) were current smokers, 5 (6%) ex-smokers and 9(11%) were non-smokers, compared to 67 (69%) current smokers, 17 (18%) ex-smokers and 13 (13%) non-smokers among males. Females were more likely to have a record of social assistance (40%) compared to males (25%; $p=0.003$).

Females were also more likely to have a positive HCV antibody test (84% vs. 74% for males; p=0.024). Baseline CD4 counts were significantly higher among females than males (425 vs. 344, p=0.005). The logVL was significantly lower among females than males (4.10 vs. 4.62, p<0.001).

Table 4.2. Study characteristics stratified by gender (n=343)

Characteristics	Male		Female		p-value
	N	%	N	%	
Ethnicity					
Aboriginal	100	58.8	130	86.1	<0.0001
Non-Aboriginal	70	41.2	21	13.9	
Missing (22)					
Mean Age at Diagnosis (s.e.)	38.9	0.8	31.1	0.7	0.093
Exposure Categories					
MSM	21	12.4	0	0.0	<0.0001
MSM/IDU	12	7.1	0	0.0	
IDU	115	68.1	137	85.1	
HC	21	12.4	24	14.9	
Missing (13)					
Year of diagnosis					
2005	22	14.4	32	19.3	0.030
2006	14	7.9	27	16.3	
2007	32	18.1	23	13.9	
2008	39	22.0	35	21.1	
2009	49	27.7	39	23.5	
2010	21	11.9	10	6.0	
History of IDU					
Yes	132	76.7	140	85.4	0.044
No	40	23.3	24	14.6	
Missing (7)					
Smoking Status					
Current Smoker	67	69.1	65	82.3	0.063
Ex-smoker	17	17.5	5	6.3	
Non-smoker	13	13.4	9	11.4	
Missing (167)					
Record of Incarceration					
Yes	56	31.5	46	27.7	0.447
No	122	68.5	120	72.3	
Record of Social Assistance					
Yes	44	24.7	66	39.8	0.003
No	134	75.3	100	60.2	
Hepatitis C Antibodies					
Present	126	74.1	138	84.2	0.024
Absent	44	25.9	26	15.9	
Missing (9)					
Mean CD4 Count at Diagnosis (±s.e.)	343.7	18.7	425.4	21.8	0.005
Mean Log_{10}VL at Diagnosis (±s.e.)	4.62	0.08	4.10	0.11	<0.0001

* MSM, men who have sex with men; IDU, injection drug use; HC, heterosexual contact

4.2.2. Differences by ethnicity

Ethnicity was known for 321 study patients. Study characteristics were stratified by Aboriginal ethnicity with key differences to note on gender, age at diagnosis, HIV risk factors, site of care, smoking status, record of social assistance and incarceration and HCV coinfection. These stratified results are summarized in Table 4.3.

Among Aboriginals (n=230), females were more prevalent than males (130 57% vs. 44%, respectively). Among non-Aboriginals (n=91), males were much more prevalent at 77%. Aboriginals were younger at diagnosis (mean age of 33 vs. 41 for non-Aboriginals) and reported different risk factors. HIV acquisition was attributed to IDU for 198 (90%) patients, HC for 16 (7%) patients, MSM/IDU for 5 (2%) patients, and MSM for 1 (1%) patient. In contrast, HIV acquisition was attributed to IDU for 36 (40%) patients among non-Aboriginals. An additional 28 (31%) were likely due to HC, 20 (22%) to MSM, and 6 (7%) to MSM/IDU. More Aboriginals were noted to be seeking care at the WCC (31%) or both sites (23%) than non-Aboriginals (4% for WCC, 13% for both sites). The remaining 106 (46%) Aboriginals and 75 (82%) non-Aboriginals were seeking care at the PLP.

Among those at the PLP, differences in smoking status were noted between these two groups ($p<0.001$). Among Aboriginals, 95 (91%) were current smokers, 6 (6%) were ex-smokers and 4 (4%) were non-smokers, compared to 34 (51%) current smokers, 15 (22%) ex-smokers and 18 (27%) non-smokers for non-Aboriginals. Compared to non-Aboriginals, Aboriginals were more

likely to have a record of social assistance (37% vs. 20%; p=0.002) and incarceration (34% vs. 22%; p=0.031).

Positive hepatitis C antibody tests were more common among Aboriginals than non-Aboriginal (90% vs. 48, p<0.001). For Aboriginals, of those with an RNA test (n=190), 12% had a negative RNA result. Among non-Aboriginals with an RNA test (n=42), 10% had a negative RNA result (results not in table).

Table 4.3. Study characteristics stratified by ethnicity (n=321)

Characteristics	Aboriginal		Non-Aboriginal		
	N	%	N	%	p-value
Gender					
Male	100	43.5	70	76.9	<0.0001
Female	130	56.5	21	23.1	
Mean Age at Diagnosis (±s.e.)	33.0	0.6	41.4	1.2	<0.0001
Exposure Categories					
MSM	1	0.5	20	22.2	<0.0001
MSM/IDU	5	2.3	6	6.7	
IDU	198	90.0	36	40.0	
HC	16	7.3	28	31.1	
Missing (11)					
Site					
Positive Living Program	106	46.1	75	82.4	<0.0001
Westside Community Clinic	71	30.9	4	4.4	
Both	53	23.0	12	13.2	
History of IDU					
Yes	209	93.7	42	46.2	<0.0001
No	14	6.3	49	53.9	
Missing (7)					
Smoking Status					
Current Smoker	95	90.5	34	50.8	<0.0001
Ex-smoker	6	5.7	15	22.4	
Non-smoker	4	3.8	18	26.9	
Missing (149)					
Record of Incarceration					
Yes	79	34.4	20	22.0	0.031
No	151	65.7	71	78.0	
Record of Social Assistance					
Yes	86	37.4	18	19.8	0.002
No	144	62.6	73	80.2	
Hepatitis C Antibodies					
Present	203	90.2	43	48.3	<0.0001
Absent	22	9.8	46	51.7	
Missing (7)					

* MSM, men who have sex with men; IDU, injection drug use; HC, heterosexual contact

4.2.3. Differences by history of IDU

A history of IDU was unknown for 7 patients. When descriptive analysis was stratified by IDU, key differences were noted for gender, ethnicity, age at diagnosis, site of care, smoking status, record of incarceration and social assistance, and HCV coinfection. These stratified results are summarized in Table 4.4.

There were an equal proportion of females and males among IDUs (n=172), but close to a 2:1 ratio for non-IDUs (n=64). Among IDUs, 209 (83%) were of self-reported Aboriginal descent, while among non-IDUs, only 14 (22%) were of Aboriginal descent ($p<0.001$). IDUs were younger at diagnosis with a mean age of 34 (SE=0.6) compared to 40 (SE=1.6) for non-IDUs ($p=0.003$). While 60 (94%) non-IDUs received care at PLP, only 127 (47%) IDUs did as well ($p=0.001$).

Among IDUs that attended the PLP, 108 (87%) patients were recorded as current smokers, 10 (8%) as ex-smokers and 6 (5%) as non-smokers. This is in contrast to non-IDUs in which 24 (46%) patients were current smokers, 12 (23%) were ex-smokers and 16 (31%) were non-smokers. Compared to non-IDUs, IDUs were more likely to have a record of social assistance (36% vs. 5%; $p<0.001$) and incarceration (37% vs. 11%; $p<0.001$).

HCV coinfection was much more common among IDUs. An antibody positive test was recorded for 253 (95%) IDUs and 5 (8%) non-IDUs ($p<0.001$). For IDUs, of those with a PCR test

(n=238), 10% had a negative PCR result. Among non-IDUs with a PCR test (n=4), 75% had a negative PCR result (results not in table).

Table 4.4. Study characteristics stratified by IDU (n=336)

Characteristics	IDU		Non-IDU		p-value
	N	%	N	%	
Gender					
Male	132	48.5	40	62.5	0.044
Female	140	51.5	24	37.5	
Aboriginal Ethnicity					
Aboriginal	209	83.3	14	22.2	<0.0001
Non-Aboriginal	42	16.7	49	77.8	
Missing (22)					
Mean Age at Diagnosis, s.e.	33.8	0.6	40.0	1.6	<0.0001
Site					
Positive Living Program	127	46.7	60	93.8	<0.0001
Westside Community Clinic	78	28.7	1	1.6	
Both	67	24.6	3	4.7	
Smoking Status					
Current Smoker	108	87.1	24	46.2	<0.0001
Ex-smoker	10	8.1	12	23.1	
Non-smoker	6	4.8	16	30.8	
Missing (160)					
Record of Incarceration					
Yes	97	35.7	3	4.7	<0.0001
No	175	64.3	61	95.3	
Record of Social Assistance					
Yes	100	36.8	7	10.9	<0.0001
No	172	63.2	57	89.1	
Hepatitis C Antibodies					
Present	253	95.1	5	8.1	<0.0001
Absent	13	4.9	57	91.9	
Missing (8)					

4.2.4. Differences by HCV coinfection

Hepatitis C antibody status was unknown for 9 patients. Given the high overlap between IDUs and those HCV coinfected, differences among this latter group closely resembles the differences between IDUs and non-IDUs. With minor differences in percentages and p-values, differences were similarly noted for gender, ethnicity, age at diagnosis, HIV risk factors, site of care,

smoking status, record of incarceration and social assistance, and history of IDU. Please refer to Table 4.5 for more detailed information.

Table 4.5. Study characteristics stratified by hepatitis C antibody status, present or absent (n=334)

Characteristics	Hepatitis C+		Hepatitis C-		p-value
	N	%	N	%	
Gender					
Male	126	47.7	44	62.9	0.024
Female	138	52.3	26	37.1	
Aboriginal Ethnicity					
Aboriginal	203	82.5	22	32.4	<0.0001
Non-Aboriginal	43	17.5	46	67.7	
Missing (20)					
Mean Age at Diagnosis (±s.e.)	34.2	0.6	38.0	1.5	0.008
Exposure Categories					
MSM	1	0.4	20	29.0	<0.0001
MSM/IDU	9	3.5	3	4.4	
IDU	240	93.8	9	13.0	
HC	6	2.3	37	52.2	
Missing (9)					
Site					
Positive Living Program	128	48.5	58	82.9	<0.0001
Westside Community Clinic	67	25.4	10	14.3	
Both	69	26.1	2	2.9	
History of IDU					
Yes	253	98.1	13	18.6	
No	5	1.9	57	81.4	<0.0001
Missing (6)					
Smoking Status					
Current Smoker	106	85.5	26	51.0	<0.0001
Ex-smoker	10	8.1	11	21.6	
Non-smoker	8	6.5	14	27.5	
Missing (159)					
Record of Incarceration					
Yes	95	36.0	7	10.0	<0.0001
No	169	64.0	63	90.0	
Record of Social Assistance					
Yes	99	37.5	9	12.9	<0.0001
No	165	62.5	61	87.1	

* MSM, men who have sex with men; IDU, injection drug use; HC, heterosexual contact

Correlations

As becomes evident through the descriptive statistics, there was high correlation between various variables. A pearson's correlation highlights this (see Table 4.6). In particular, there was high correlation between IDU and HCV (Pearson's coefficient 0.832, $p<0.001$).

Table 4.6. Pearson's correlation of select variables

Coefficient *p-value* *frequency*	***IDU***	***HCV***	***Aboriginal***	***Gender***	***Site***	***Incarc-eration***	***Soc. Assistance***
IDU	**1**	**0.832**	**0.539**	**-0.110**	**0.328**	**0.266**	**0.218**
		<.001	<.001	0.044	<.001	<.001	<.001
	336	328	314	336	336	336	336
HCV	**0.832**	**1**	**0.459**	**-0.123**	**0.291**	**0.230**	**0.214**
	<.001		<.001	0.024	<.001	<.001	<.001
	328	334	314	334	334	334	334
Aboriginal	**0.539**	**0.459**	**1**	**-0.302**	**0.261**	**0.121**	**0.170**
	<.001	<.001		<.001	<.001	0.031	0.002
	314	314	321	321	321	321	321
Gender	**-0.110**	**-0.123**	**-0.302**	**1**	**-0.114**	**0.043**	**-0.166**
	0.044	0.024	<.001		0.035	0.428	0.002
	336	334	321	343	343	343	343
Site	**0.328**	**0.291**	**0.261**	**-0.114**	**1**	**0.081**	**0.028**
	<.001	<.001	<.001	0.035		0.134	0.609
	336	334	321	343	343	343	343
Incarceration	**0.266**	**0.230**	**0.121**	**0.043**	**0.081**	**1**	**0.090**
	<.001	<.001	0.031	0.428	0.134		0.095
	336	334	321	343	343	343	343
Social Assistance	**0.218**	**0.214**	**0.170**	**-0.166**	**0.028**	**0.090**	**1**
	<.001	<.001	0.002	0.002	0.609	0.095	
	336	334	321	343	343	343	343

In examining the three variables of interest (i.e. Aboriginal ethnicity, IDU, and HCV coinfection) we excluded all patients with unknown aboriginal ethnicity, history of IDU and hepatitis C

antibody test result. This resulted in 308 study patients. Of these 308 study patients, 44 (14%) did not belong to any of these categories. The break down of the remaining 264 patients is presented in Figure 4.1.

Figure 4.1. Illustration of overlap between Aboriginal ethnicity, history of IDU, and HCV coinfection (n=264)

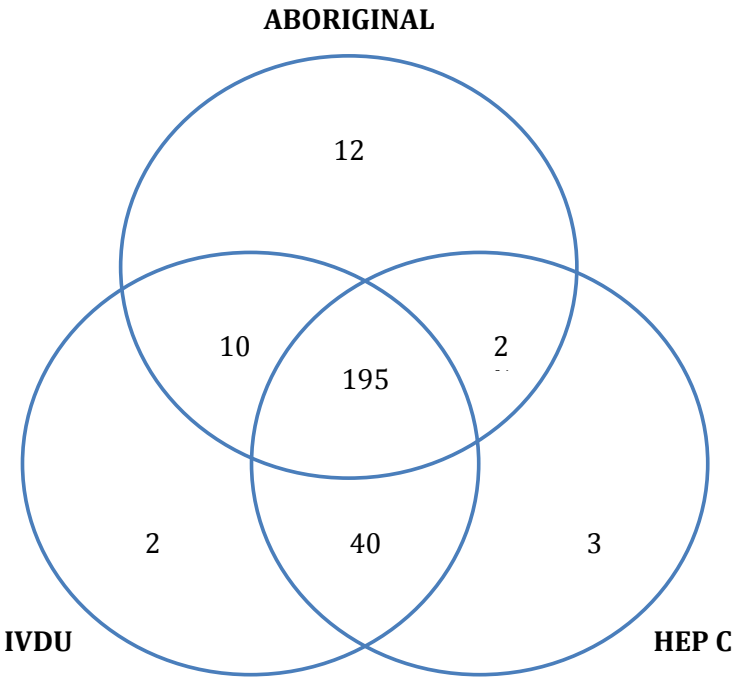


Figure 4.1 represents the overlap between the three variables of interest for this study, and does not imply that Aboriginal ethnicity is a risk factor. This high collinearity is what is seen in our study, and does not necessarily reflect all aboriginal communities.

4.3. Primary outcomes

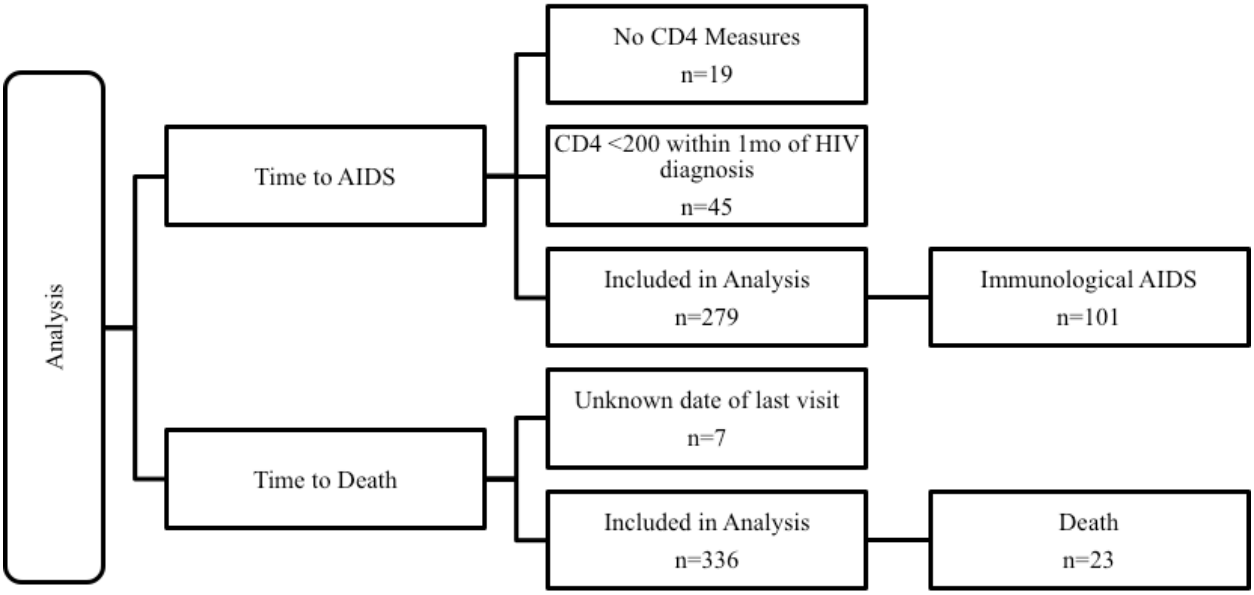
Immunological AIDS

Of the 343 patients, 19 had no CD4 measures taken during follow-up and were thus excluded. An additional 45 patients had a CD4 count <200cells/µl within one month of HIV diagnosis and were also excluded. Thus, 279 patients were considered for the survival analysis. Of these, 101 (36%) dropped below a CD4 count <200cells/µl at some point during follow-up and 178 (64%) patients were censored at the date of their last CD4 count serological test.

Death

Out of the 343 patients, 7 had an unknown date of last visit, and were thus not included in the survival analysis. Twenty-three (7%) patients died during follow-up. The remaining 313 (93%) were censored at their last clinic visit. Cause of death was unknown for 8 (35%) patients, non-HIV related for 8 (35%) patients and HIV-related for 6 (26%) patients. This study did not have access to vital statistics, due to privacy and confidentiality policies. Therefore, this data is only representative of the information held within the patients' medical charts. Given the large percentage of patients with unknown cause of death, all cause mortality was the outcome assessed. Figure 4.2 summarizes the study patients included in both sets of analysis and the outcome of interest for each analysis.

Figure 4.2. Summary of type of analysis and the frequency of the outcome of interest

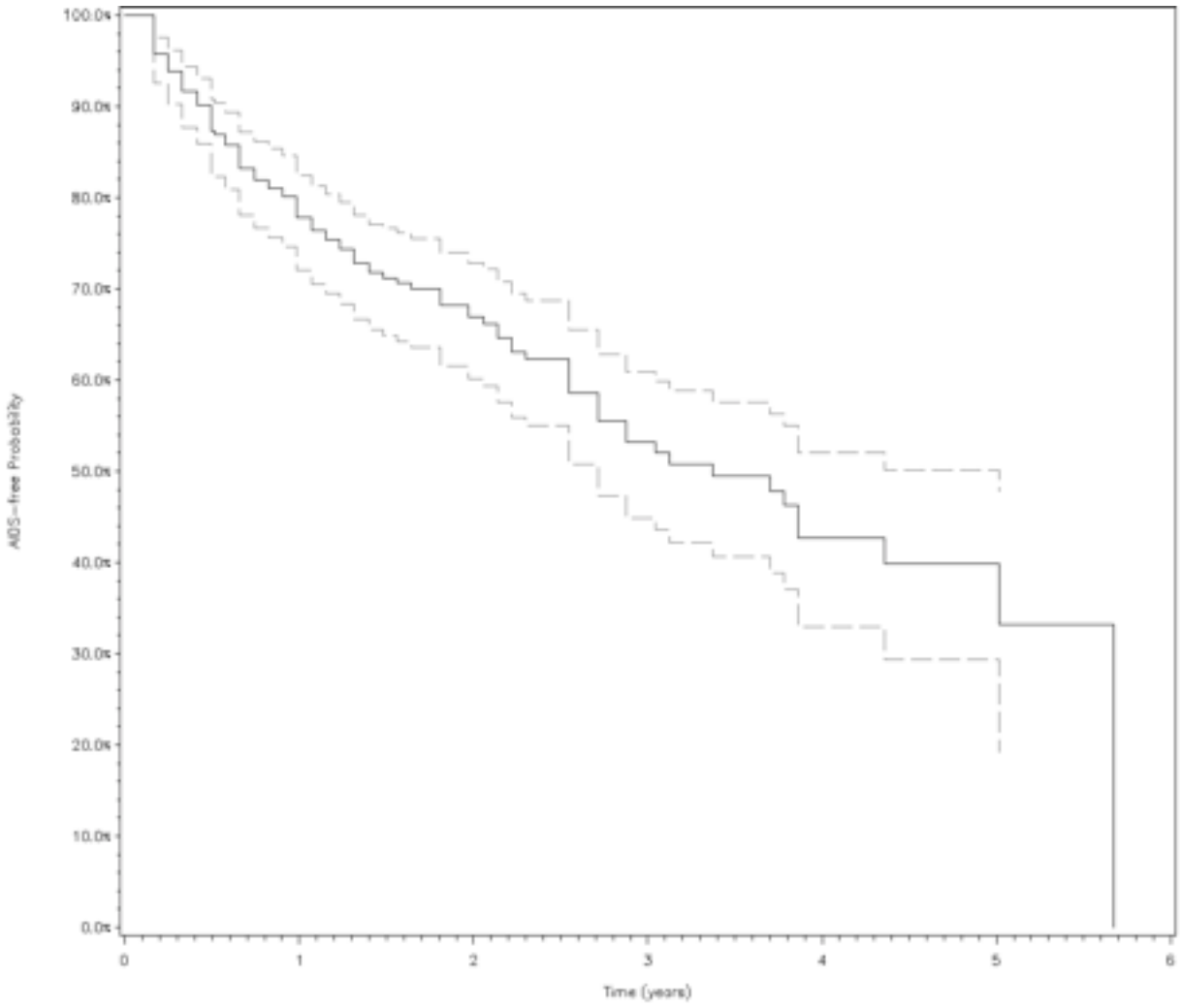


4.4. Survival analysis

4.4.1. Time to CD4 count <200cells/µl

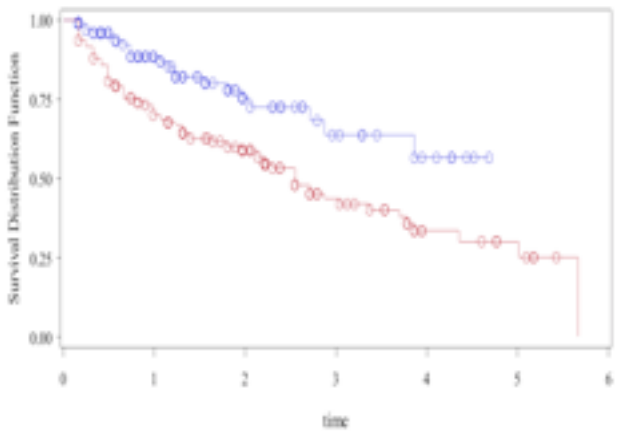
The mean and median follow-up time was 1.7 years and 1.3 years, respectively (see Figure 4.3). The median time to immunological AIDS was 3.3 years (95%CI: 2.7-5.0 years) from HIV diagnosis. There was a 25% probability of progression to immunological AIDS in 1.2 years (95%CI: 0.9-1.8 years) and 75% probability in 5.7 years (95%CI: 5.0-5.7 years).

Figure 4.3. Survival function of immunological AIDS from HIV diagnosis



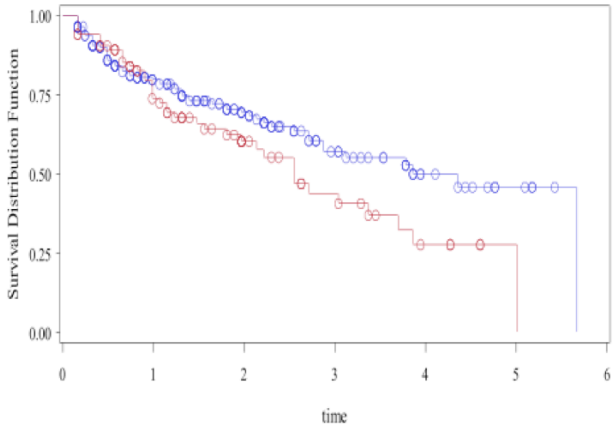
Kaplan Meier analysis showed significant differences in survival function for ever recipient of ART (log rank test, p=0.001) and year of diagnosis categorized into 2005-2008 and 2009-2010 (log rank test, p=0.001). Having a record of incarceration was shown to be marginally significant (log rank test, p=0.053). See Figure 4.4. There was no difference among gender, IDU, Aboriginal ethnicity, HCV coinfection, and record of social assistance.

Figure 4.4. Survival distribution functions of immunological AIDS, stratified by (a) treatment status, (b) record of incarceration, and (c) HIV diagnosis year



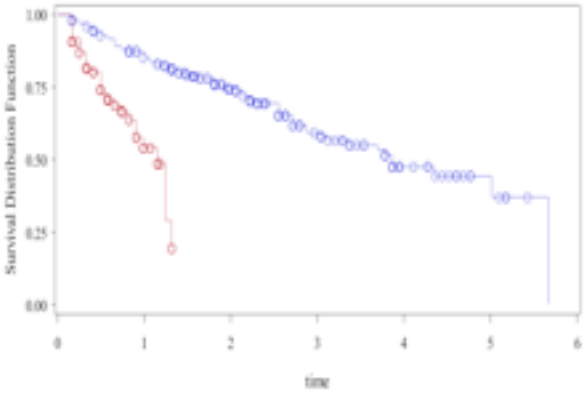
(a) —— No ART

—— ART



(b) —— No record of incarceration

—— Incarceration record



c) —— Diagnosis year 2005 to 2008

—— Diagnosis year 2009 to 2010

4.4.1.1. Univariable analysis for immunological AIDS

These results of univariable Cox regression analysis show that year of diagnosis, site of care, and ever recipient of ART were significant predictors (Table 4.7). Only 2009 and 2010 were statistically significant when compared to 2005, while the remaining years were not. Thus, again, the decision was made combine the two periods, 2005-2008 and 2009-2010. Any further mention of year of diagnosis will refer to this dichotomous variable. Univariable analysis was rerun for Aboriginals, IDUs and HCV co-infected patients, separately. A few key differences were note. Sex and age at diagnosis became significant for Aboriginals. Among those HCV coinfected, age of diagnosis also became significant. Site of care was not significant for IDUs or HCV coinfected patients.

Table 4.7. Univariable Cox regression analysis for immunological AIDS progression

Covariates	HR	95% CI	p-value
Gender			
Female	1.00		
Male	1.30	0.87-1.92	0.191
Ethnicity			
Non-Aboriginal	1.00		
Aboriginal	1.38	0.87-2.19	0.177
Age at Diagnosis	1.02	1.00-1.04	0.113
Year of Diagnosis			
2005	1.00		
2006	1.45	0.76-2.81	0.274
2007	1.26	0.62-2.58	0.521
2008	1.72	0.85-3.48	0.132
2009	5.57	2.76-11.25	<0.0001
2010	12.25	4.07-36.86	<0.0001
Year of Diagnosis			
2005-2008	1.00		
2009-2010	4.35	2.61-7.25	0.000
Site			
Positive Living Program	1.00		
Westside Community Clinic	1.83	1.11-3.02	0.019
Both	1.02	0.61-1.70	0.935
IDU Risk Factor			
No	1.00		
Yes	1.18	0.71-1.97	0.527
History of IDU			
Absent	1.00		
Present	1.27	0.75-2.15	0.370
Hepatitis C Antibodies			
No	1.00		
Yes	1.54	0.91-2.60	0.107
Hepatitis C Categories			
HCV-	1.00		
HCV+, RNA-	0.69	0.40-1.18	0.179
HCV+, RNA+	1.18	0.62-2.24	0.613
Ever on Antiretroviral therapy			
No	1.00		
Yes	2.15	1.32-3.51	0.002
Among those eligible for ART			
Not on ART	1.00		
On ART	1.23	0.76-2.00	0.407
Record of Incarceration			
No	1.00		
Yes	1.46	0.98-2.19	0.063
Record of Social Assistance			
No	1.00		
Yes	1.40	0.94-2.07	0.095
CD4 Counts at Diagnosis[a]	0.92	0.90-0.96	<0.0001

[a]Per every 10 unit increase in CD4 counts/µl

4.4.1.2. Multivariable analysis for immunological AIDS

From univariable survival analysis it was determined that sex, ethnicity, age at diagnosis, year of diagnosis, site, HCV coinfection, antiretroviral therapy, and record of incarceration and social assistance could be potentially important covariate, based on a p-value of less than 0.25. With the addition of history of IDU, multivariable model was initiated with these potential covariates.

Due to the high multi-collinearity between the three groups of interest, three separate models were constructed. No effect modifiers or interactions were noted in the creation of any of the models.

Model 1: Aboriginal Ethnicity

For this model Aboriginal ethnicity, age, treatment, and year of diagnosis remained as significant predictors of time to immunological AIDS. Gender was not found to significantly contribute to the model, nor did it significantly alter the other variables and was thus not included in the model. Thus, when controlling for the other variables in the model, the analysis showed an elevated risk of developing immunological AIDS was associated with older age (HR, 1.03; 95%CI, 1.01-1.06, per 1-year increase), ever being on treatment (HR, 2.86; 95%CI 1.72-4.75) and an HIV diagnosis in 2009-2010, when compared to 2005-2008 (HR, 5.14; 95%CI, 2.93-9.00). Compared to non-Aboriginals, Aboriginal ethnicity was also associated with an increased risk of developing immunological AIDS (HR, 1.86; 1.10-3.16).

Table 4.8. Multivariable Cox regression analysis for Aboriginal ethnicity (Model 1)

Covariates	HR_{adj}	95% CI	p-value
Age at Diagnosis	1.03	1.01-1.06	0.005
Ever on ART			
No	1.00		
Yes	2.86	1.72-4.75	<0.0001
Year of Diagnosis			
2005-2008	1.00		
2009-2010	5.14	2.93-9.00	<0.0001
Ethnicity			
Non-Aboriginal	1.00		
Aboriginal	1.86	1.10-3.16	0.021

Model 2: HCV coinfection

When controlling for the other variables in Model 2, the analysis showed an elevated risk of developing immunological AIDS was associated with older age (HR, 1.02; 95%CI, 1.00-1.05, per 1-year increase), ever being on treatment (HR, 3.09; 95%CI 1.86-5.15) and an HIV diagnosis in 2009-2010, when compared to 2005-2008 (HR, 5.66; 95%CI, 3.25-9.4). Finally, compared to mono-infected patients, HCV coinfected patients were also associated with an increased risk of developing immunological AIDS (HR, 2.11; 95%CI 1.20-3.70).

Table 4.9. Multivariable Cox regression analysis for HCV coinfection (Model 2)

Covariates	HR_{adj}	95% CI	p-value
Age at Diagnosis	1.02	1.00-1.05	0.018
Ever on ART			
No	1.00		
Yes	3.09	1.86-5.15	<0.0001
Year of Diagnosis			
2005-2008	1.00		
2009-2010	5.66	3.25-9.84	<0.0001
Hepatitis C Antibodies			
Absent	1.00		
Present	2.11	1.20-3.70	0.010

Model 3: IDU

When controlling for the other variables in Model 3, the analysis showed an elevated risk of developing immunological AIDS was associated with older age (HR, 1.02; 95%CI, 1.00-1.04, per 1-year increase), ever being on treatment (HR, 3.32; 95%CI 1.94-5.66) and an HIV diagnosis in 2009-2010, when compared to 2005-2008 (HR, 5.76; 95%CI, 3.30-10.06). Finally, compared to non-IDU, IDU were marginally associated with an increased risk of developing immunological AIDS (HR, 1.69; 95%CI 0.97-2.93).

Table 4.10. Multivariable Cox regression analysis for injection drug use (Model 3)

Covariates	HR_{adj}	95% CI	p-value
Age at Diagnosis	1.02	1.00-1.04	0.030
Ever on ART			
No	1.00		
Yes	3.32	1.94-5.66	<0.0001
Year of Diagnosis			
2005-2008	1.00		
2009-2010	5.76	3.30-10.06	<0.0001
History of IDU			
No	1.00		
Yes	1.69	0.97-2.93	0.062

4.4.1.3. Multivariate analysis with baseline CD4 counts

Given the importance of baseline CD4 counts as an indicator of disease progression, all three models were adjusted for CD4 counts at or within 6 months of HIV diagnosis, a standard practice in seroprevalent cohort studies.[162] CD4 counts were calculated as to reflect 10 unit increases in CD4 cells/μl.

For Model 1, neither age at diagnosis and Aboriginal ethnicity remained independent predictors of disease progression. Those that remained significant were year of diagnosis, treatment and baseline CD4 counts.

Table 4.11. Adjusted multivariable model with baseline CD4 counts (Model 1)

Covariates	HR_{adj}	95% CI	p-value
Age at Diagnosis	1.01	0.98-1.03	0.452
Ever on ART			
No	1.00		
Yes	4.11	1.21-13.90	0.023
Year of Diagnosis			
2005-2008	1.00		
2009-2010	3.13	1.20-8.21	0.020
Ethnicity			
Non-Aboriginal	1.00		
Aboriginal	1.94	0.83-4.56	0.128
CD4 count at Diagnosis	0.95	0.92-0.98	0.004

For Model 2, HCV coinfection remained a significant predictor of disease progression, along with year of diagnosis, ART use, and baseline CD4 counts. Age at diagnosis was not longer significant.

Table 4.12. Adjusted multivariable model with baseline CD4 counts (Model 2)

Covariates	HR_{adj}	95% CI	p-value
Age at Diagnosis	1.01	0.98-1.03	0.459
Ever on ART			
No	1.00		
Yes	4.89	1.45-16.46	0.010
Year of Diagnosis			
2005-2008	1.00		
2009-2010	3.36	1.26-8.97	0.016
HCV Ab			
No	1.00		
Yes	2.91	1.22-6.95	0.016
CD4 count at Diagnosis	0.95	0.92-0.98	0.0001

Finally, Model 3 found IDU became a significant as a predictor of disease progression (p=0.02). Year of diagnosis, ART use, and baseline CD4 counts were significant predictors in this model. Age at diagnosis was not longer significant.

Table 4.13. Adjusted multivariable model with baseline CD4 counts (Model 3)

Covariates	HR_{adj}	95% CI	p-value
Age at Diagnosis	1.01	0.98-1.05	0.481
Ever on ART			
No	1.00		
Yes	5.00	1.48-16.92	0.010
Year of Diagnosis			
2005-2008	1.00		
2009-2010	3.08	1.13-8.40	0.016
History of IDU			
No	1.00		
Yes	2.95	1.22-7.13	0.016
CD4 count at Diagnosis	0.95	0.92-0.98	<0.0001

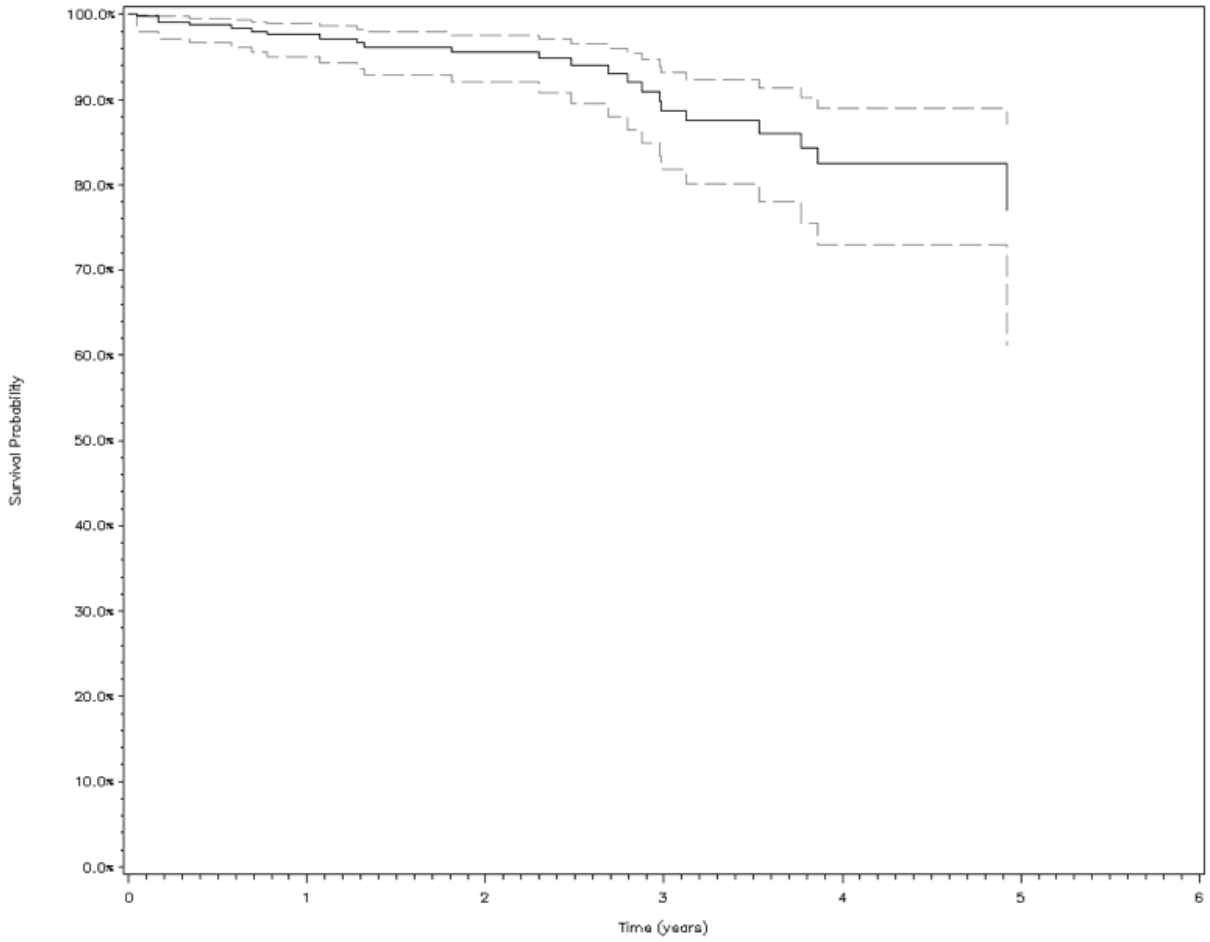
The assumptions of proportional hazards was tested by adding time-dependent covariates with the three covariate of interest, Aboriginal ethnicity, HCV coinfection and IDU. The assumption of proportional hazards was met in all models. Goodness of fit was tested using Cox-Snell residuals. All models were found to have a satisfactory fit.

4.4.2. Time to death

The mean and median follow-up time was 2.0 years and 1.72 years, respectively. The median survival time and its standard error could not be determined due to the small number of events (93% censored). However, the 3 year and 5 year overall survival probability were 88% (95%CI:

82-93%) and 77% (95%CI: 61-87%), respectively. Figure 4.5 shows the survival distribution function.

Figure 4.5. Survival curve for all-cause mortality from HIV diagnosis



Kaplan Meier graphs showed significant differences in survival function for ever recipient of ART (log rank test, p=0.012) and HCV coinfection (log rank test, p=0.035). A history of IDU was shown to be marginally significant (log rank test, p=0.056).

4.4.2.1. Univariable analysis for survival

Univariable Cox regression analysis is summarized in Table 4.14. These results show that ever recipient of ART was the only significant predictor of survival.

Table 4.14. Univariable Cox regression analysis for all cause mortality

Covariates	HR	95%CI	p-value
Sex			
Female	1.00		
Male	0.99	0.43-2.29	0.989
Ethnicity			
Non-Aboriginal	1.00		
Aboriginal	0.90	0.36-2.24	0.819
Age at Diagnosis	1.03	0.99-1.07	0.162
Year of Diagnosis			
2005-2008	1.00		
2009-2010	3.26	0.83-17.80	0.090
Site			
Positive Living Program	1.00		
Westside Community Clinic	0.68	0.15-3.04	0.618
Both	0.33	0.08-1.41	0.133
IDU Risk Factor			
No	1.00		
Yes	5.37	0.72-40.09	0.101
History of IDU			
No	1.00		
Yes	5.67	0.76-42.24	0.090
Hepatitis C Antibodies			
Absent	1.00		
Present	6.51	0.88-48.39	0.067
Hepatitis C Categories			
HCV Ab-	1.00		
HCV Ab+, RNA-	0.18	0.02-1.39	0.101
HCV Ab+, RNA+	1.73	0.57-5.22	0.334
Ever on Antiretroviral Therapy			
No	1.00		
Yes	0.34	0.14-0.82	0.017
CD4 Counts at Diagnosis[a]	1.00	0.98-1.03	0.800

[a]Per every 10 unit increase in CD4 counts/µl

Univariable analysis was rerun for Aboriginals, IDU and HCV co-infected patients, separately. Only minor differences were noted. For Aboriginals, use of antiretroviral was not a significant predictor (p=0.425). This was also noted for IDUs (p=0.070).

4.4.2.2. Multivariable analysis for survival

From univariable survival analysis it was determined that age at diagnosis, year of diagnosis, site, HCV coinfection, IDU, and antiretroviral therapy could be potentially important covariate, based on a p-value of less than 0.25. With the addition of Aboriginal ethnicity, multivariable model was initiated with these potential covariates. Due to the high multi-collinearity between the three groups of interest, three separate models were constructed. No effect modifiers or interactions were noted in the creation of any of the models.

Model 1: Aboriginal Ethnicity

For this model treatment was the only significant predictors of survival. Ever being on treatment was associated with an increased risk of death (HR, 0.273; 95%CI: 0.12, 0.76).

Table 4.15. Multivariable Cox regression analysis for ethnicity (model 1)

Covariates	HR_{adj}	95% CI	P-value
Ever on ART			
No	1.00		
Yes	0.30	0.12-0.76	0.011
Ethnicity			
Non-Aboriginal	1.00		
Aboriginal	0.88	0.35-2.21	0.778

Model 2: HCV coinfection

For this model, treatment was the only significant predictors of survival. Ever being on treatment was associated with an increase risk of death (HR, 0.36; 95%CI: 0.15, 0.88).

Table 4.16. Multivariable Cox regression analysis for HCV coinfection (model 2)

Covariates	HR_{adj}	95% CI	p-value
Ever on ART			
No	1.00		
Yes	0.36	0.15-0.88	0.026
Hepatitis C Antibodies			
Absent	1.00		
Present	5.98	0.80-44.87	0.082

Model 3: IDU

For this model treatment, was the only significant predictors of survival. Ever being on treatment was associated with an increase risk of death (HR, 0.40; 95%CI: 0.16, 0.99).

Table 4.17. Multivariable Cox regression analysis for IDU (model 3)

Covariates	HR_{adj}	95% CI	p-value
Ever on ART			
No	1.00		
Yes	0.40	0.16-0.99	0.049
History of IDU			
No	1.00		
Yes	5.09	0.68-38.27	0.114

Baseline CD4 counts were also added to the models, but this variable did not significantly improve the models and was thus eliminated. The assumptions of proportional hazards was tested by adding time-dependent covariates with the three covariate of interest, Aboriginal

ethnicity, HCV coinfection and IDU. The assumption of proportional hazards was met in all models. Goodness of fit was tested using Cox-Snell residuals. All models were found to have a satisfactory fit.

4.5. Subgroup analysis (Seroconversion Cohort)

A total of 73 patients had a negative HIV serology within 12 months of their first positive HIV test or a positive p24 antigen test indicating a recent HIV infection. The seroconversion interval (i.e. the time difference between a first antibody positive and last antibody negative HIV tests) was within one calendar month for one patient, 1-3 months for six patients, 3-6 months for 31 patients, 6-9 months for 20 patients, and 9-12 months for 7 patients, and over 12 months for 2 patients. For 277 patients, there was missing date for either the positive or negative tests. An additional 6 patients had a positive p24 antigen test.

4.5.1. Study population characteristics

While in most cases, the characteristics of this group does not differ greatly from the larger cohort, there are a few important differences. A greater proportion of Aboriginals (81% vs. 71%), IDUs (93% vs. 81%) and hepatitis C coinfected patients (92% vs. 79%) were present in this cohort, in comparison to the seroprevalent cohort. This seroconversion cohort also contained a greater proportion of those with a record of incarceration (41% vs. 30%) and social assistance (37% vs 32%). The characteristics of the 73 patients with a seroconversion date are outline in Table 4.18.

Table 4.18. Study characteristics of seroconversion cohort (n=73)

Characteristics	N	%	Characteristics	N	%
DEMOGRAPHICS			SOCIAL CHARACTERISTICS		
Gender			Record of Social Assistance		
Male	37	50.7	Yes	27	37.0
Female	36	49.3	No	46	63.0
Ethnicity			History of IDU		
Aboriginal	56	81.2	Yes	65	92.9
Non-Aboriginal	13	18.8	No	5	7.1
Missing (4)			Missing (3)		
Age at Seroconversion			Hepatitis C Antibodies		
Under 20	4	5.5	Present	66	91.7
20-29	28	38.4	Absent	6	8.3
30-39	27	37.0	Missing (1)		
40-49	12	16.4	Hepatitis C Status		
50 or over	2	2.7	HCV Ab negative	6	8.6
Mean Age at Seroconversion,(±s.e.)	34.2	1.0	HCV Ab positive, RNA negative	5	7.1
Exposure Categories			HCV Ab positive, RNA positive	59	84.3
MSM	1	1.4	Missing (3)		
MSM/IDU	2	2.8	Ever on Antiretroviral Therapy		
IDU	64	88.9	Yes	30	41.1
HC	5	6.9	No	27	37.0
Missing (1)			Missing (16)		
Year of Seroconversion			Eligible for ART (based on CD4 < 350)		
2005	10	13.7	Yes	41	56.2
2006	14	19.2	No	27	37.0
2007	10	13.7	Missing (5)		
2008	15	20.6	Of those Eligible for ART		
2009	18	24.7	On ART	25	71.4
2010	6	8.2	Not on ART	10	28.6
Site			Missing (6)		
Positive Living Program	42	57.5	CD4 Counts at Seroconversion		
Westside Community Clinic	11	15.1	<50	3	6.3
Both	20	27.4	50-199	5	10.4
SOCIAL CHARACTERISTICS			200-349	11	22.9
Smoking Status			350-499	10	20.8
Current Smoker	36	85.7	≥500	19	39.6
Ex-smoker	4	9.5	Missing (25)		
Non-smoker	2	4.8	Mean CD4 Count at Seroconversion (±s.e.)	443.7	38.9
Missing (31)			Mean Log_{10}VL at Seroconversion, (±s.e.)	4.36	0.15
Record of Incarceration					
Yes	30	41.1			
No	43	58.9			

For comparison, a similar figure was created to highlight the overlap in the three variables of interest (i.e. Aboriginal ethnicity, IDU, and HCV coinfection). Again, we excluded all patients with unknown Aboriginal ethnicity, history of IDU or hepatitis C antibody test result. This resulted in 65 study patients. Of these 65 study patients, 2 (3.1%) did not belong to any of these categories. The break down of the remaining 63 patients is presented in Figure 4.6.

Figure 4.6. Illustration of overlap between Aboriginal ethnicity, history of IDU, and HCV coinfection for seroconversion cohort (n=63)

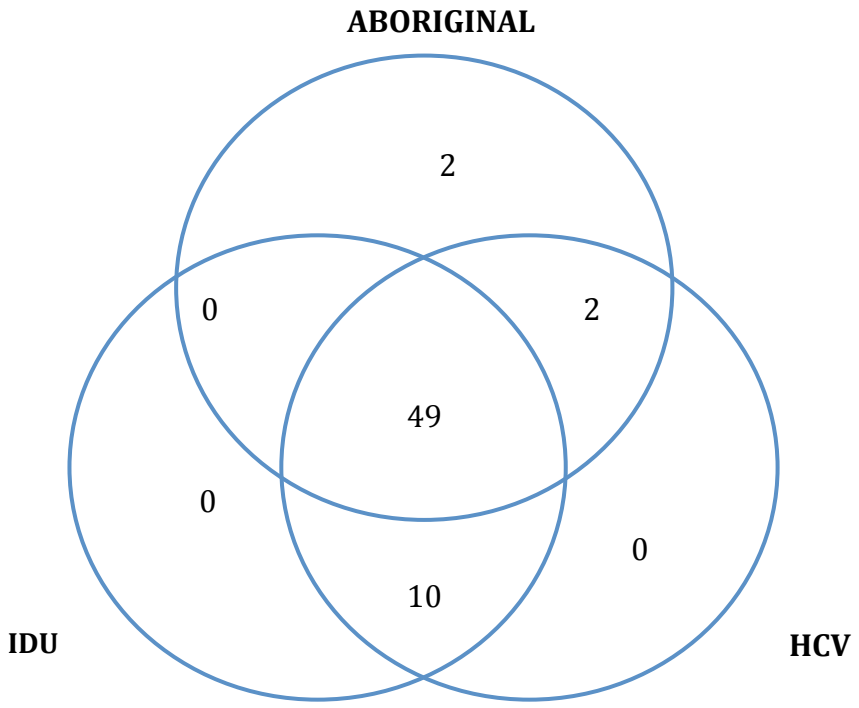


Figure 4.6 represents the overlap between the three variables of interest for this study, and does not imply that Aboriginal ethnicity is a risk factor. This high collinearity is what is seen in our study, and does not necessarily reflect all aboriginal communities.

4.5.2. Primary outcomes

Immunological AIDS

Within this cohort, 5 patients had no CD4 measures during their follow-up and were thus excluded. Therefore, out of the remaining 68 patients, 17 (25.0%) had a CD4 count <200 cells/µl while the remaining 75% did not.

CD4 cell counts can temporarily drop below 200 cells/µl during the acute infection, and thus to distinguish between a temporary drop and severe immunological damage indicative of AIDS those 17 patients were assessed in more detail. Of those 17 patients, 8 dipped within 6 months of the estimated seroconversion date. Of the eight, one patient had only one CD4 count measure and distinguishing between a temporary drop or a consistent drop in CD4 counts was not possible; this patient was thus excluded. Four patients did not recover to a CD4 count above 200 for the remainder of their treatment naïve follow-up, which was at least 6 months long, and thus the date of the event of interest remained that first drop. The remaining three patients did have a recovery of their CD4 counts above 200 cells/µl. Thus, given that two did not have a drop to 200 cells/µl, they were recorded as not having the event of interest and censored at their last CD4 count measure. One patient did drop below 200 cells/µl again, and that second drop was recorded as the date of the event of interest. Therefore, overall there were 14 who had a CD4 count <200 cells/µl, while the remaining 53 patients were censored.

Death

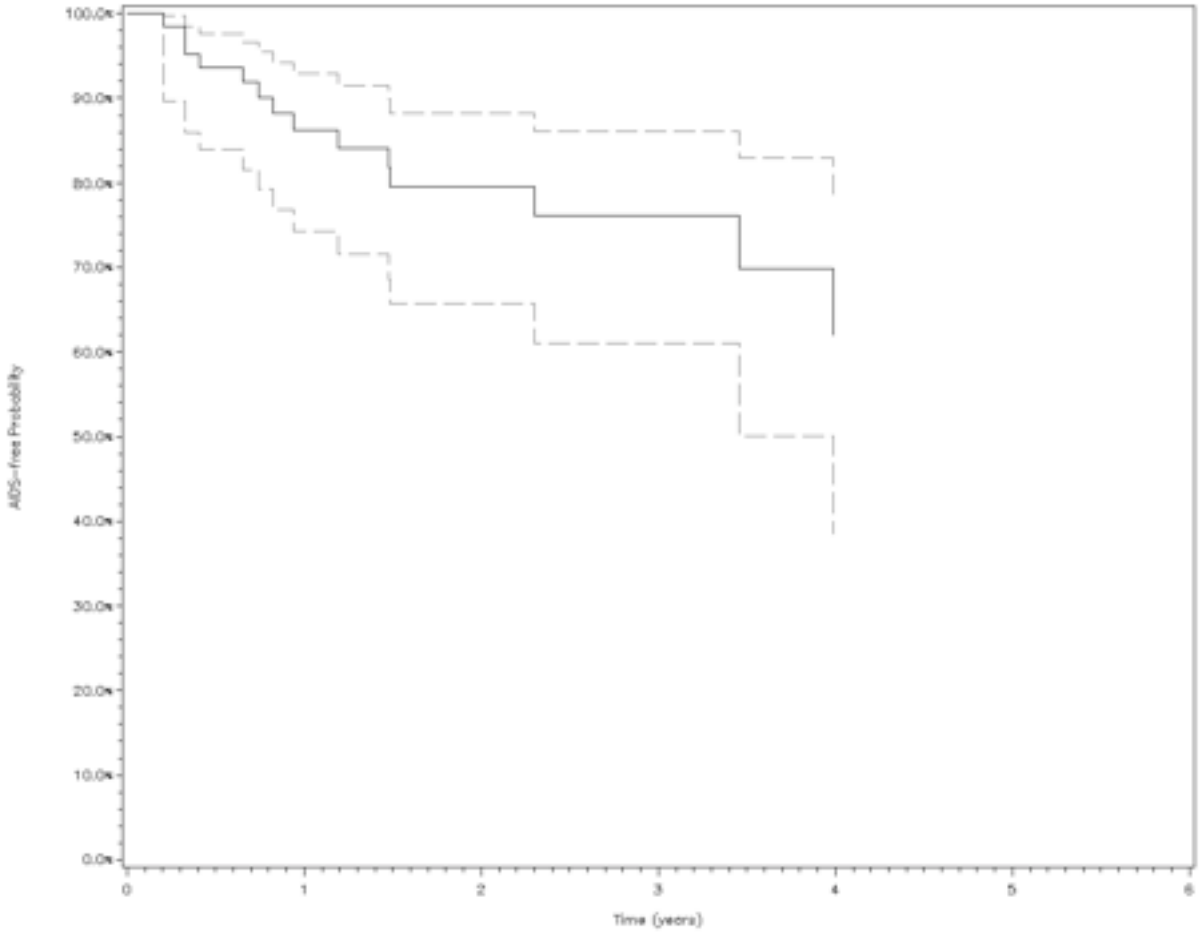
Out of the 73 patients, no deaths occurred during the follow-up.

4.5.3. Survival analysis

Time to CD4 count <200cells/µl

The mean and median follow-up time was 1.91 years and 1.56 years, respectively. The median time to immunological AIDS was not able to be determined. However, there was a 25% probability of progression to immunological AIDS in 3.45 (lower 95%CI: 0.94), Figure 4.7.

Figure 4.7. Survival curve for immunological AIDS from HIV infection



Kaplan Meier graphs showed no significant differences by gender, IDU, HCV coinfection, Aboriginal ethnicity, treatment, year of seroconversion (dichotomous), incarceration, or social assistance.

Given the high proportion of Aboriginal ethnicity, IDU, and HCV coinfections, this cohort is inadequate to further study the effects of these three variables. In both univariable and multivariable analysis, none of the covariates were significant predictors of time to immunological AIDS.

4.6. Summary of survival analysis

HIV disease progression was measured from HIV diagnosis to immunological AIDS and death and from HIV seroconversion to immunological AIDS in a subgroup with estimable dates of seroconversion. As no deaths occurred for this subgroup, this outcome was not assessed. Table 4.19 summarizes the probability of progression at 1, 3 and 5 years post diagnosis and infection.

Table 4.19. Summary of percentage without immunological AIDS and survival of HIV positive patients

	Percent AIDS free		Percent surviving	
	%	**95% CI**	**%**	**95% CI**
After HIV Diagnosis				
1 year	77.8	72.1, 82.5	97.6	95.0, 98.8
3 years	53.2	44.8, 60.9	88.7	81.8, 93.1
5 years	33.2	19.2, 47.8	77.0	61.2, 87.0
After HIV Seroconversion				
1 year	86.2	74.2, 92.9	n/a	n/a
3 years	76.2	61.0, 86.0	n/a	n/a
5 years	n/a	n/a	n/a	n/a

CI, confidence intervals; n/a, not available

5. Discussion

5.1. Summary of findings

This study was based on retrospective data from 343 HIV positive patients receiving care at the PLP or WCC in Saskatoon, Saskatchewan. It characterized HIV disease progression among this study population and identified factors associated with disease progression. This section will briefly summarize the findings of this study, compare these findings to the literature, discuss the potential implications of these findings, and comment on the strengths and limitations of the study.

Characterizing HIV disease progression

Following HIV diagnosis, we found that the 3-year and 5-year immunological AIDS free probability was 53% and 33%, respectively. The 3-year and 5-year survival probability were 89% and 77%, respectively. In efforts to obtain the true rate of progression, unbiased by delay in diagnosis, we performed a subgroup analysis with patients who had an estimated seroconversion date. Among this seroconversion cohort, we found that 3 years after seroconversion the probability of being immunological AIDS free was 76%. No deaths occurred among this subgroup.

Determinants of HIV disease progression

Determinants of disease progression to immunological AIDS among the seroprevalent cohort (i.e. from HIV diagnosis) were history of IDU, HCV coinfection, treatment use, and year of diagnosis, when controlling for age at diagnosis and baseline CD4 counts. Ethnicity and gender were not significant predictors. Since three separate models were built because of the high collinearity between variables, we cannot state that HCV coinfection or a history of IDU were independent predictors of each other.

With regards to survival, only treatment use was found to be a significant predictor. HCV coinfection was marginally significant (p=0.082), while a history of IDU, ethnicity, gender, age at diagnosis, and year of diagnosis were not.

Among the seroconversion cohort (i.e. from estimated seroconversion dates), the high representation of patients reporting a history of IDUs, having HCV coinfection, and an Aboriginal ethnicity made it difficult to assess these variables in further detail. However, we did assess year of diagnosis, year of seroconversion and age at seroconversion and did not find these variables to be significant predictors of progression to immunological AIDS.

5.2. Comparison of findings

Characterizing HIV disease progression

HIV disease progression in our study was similar to that reported among IDUs in the United States. This recent analysis in 2009 of 27,572 IDUs from 33 US states similarly found a 49%

probability of progression to AIDS (defined as an AIDS defining illness or CD4 count <200) within 3 years of HIV diagnosis.[58] The probability of survival 3 years after HIV diagnosis was 86%. Information on treatment was not available. In contrast, similar analysis among the MSM population (i.e. excluding those in the MSM/IDU) found an AIDS-free probability of 71% three years after HIV diagnosis. Both of these studies included patients diagnosed during the HAART era (i.e. post-1996).

Other US studies have found a lengthier time to immunological AIDS. Diamond et al[79] reported a median time to immunological AIDS ranging from 4.8 to 6 years from study enrollment in 2001. Unlike our study, they reported a higher percentage of patients on treatment and IDUs accounted for less than 50% of the study population. Baum et al[163] followed 133 drug users in Miami, Florida for 30 months in 2009. At 2.5 years following study enrollment, they found the probability of progression to immunological AIDS ranged from 15 to 25% depending on crack-cocaine use. However, understanding the significance of these differences is difficult as the delays in diagnosis and varying origin points (e.g. study enrollment) were used. Analysis based on seroconversion cohorts are better suited for these comparisons.

Time from HIV infection was slightly faster for this study than what other studies have reported. Piroth et al[130] reported a median time to immunological AIDS of 6 years and 8 months in France. Fifty-seven percent of patients were treated with antiretroviral therapy before the endpoint event. In a meta-analysis, Zwahlen et al[164] reported similar median duration to CD4 <200 cells/μl among low and middle-income countries, at 6.1 years. Only 14% of study population,

established in the 1990s, had received ART. In another study based on the pre-HAART era, Lepri et al[44] found a median time to immunological AIDS of 6 years for women. There was a 25% probability of progression to immunological AIDS at 4 years for women and 4.5 years for men. Most of these studies had a low proportion of IDUs. In comparison, this study found a 25% probability of progression at 3.5 years. However, given the availability of HAART during this study period (2005-2010), one would have expected to see a slower progression in HIV disease.

Determinants of HIV disease progression

Baseline CD4 cell count was the most important predictor of progression to immunological AIDS, a finding consistent with numerous previous reports.[30, 79] However, unlike these studies, we did not find baseline CD4 counts to be a predictor of survival. This could be due to the short follow-up period of this study, which did not allow for these differences to become significant.

While it may seem contradictory, a positive association between treatment and disease progression was observed in our study, as in other studies[30, 162] and is due to the preferential prescription of ART for persons with advanced disease.[165] Such situations have been phrased "confounding by severity," in which the decision to treat are dependent on indicators of prognosis.[166] This study did not attempt to prove the efficacy of treatment. If this was the case, the nonrandom allocation of the treatment would need to be accounted for. Thus, conclusions regarding the association of ART use and immunological parameters cannot be made.

Similar to other seroprevalent cohort studies,[127, 128] our analysis showed IDU and HCV coinfection were associated with faster progression, independent of baseline CD4 counts. Various factors could explain the observed differences. For instance, both smoking and alcohol use, factors highly prevalent among HIV populations, have also been shown to be associated with HIV progression.[95, 113] These factors could not be controlled for in this study. Disparities in receipt of, and/or adherence to ART could be another critical confounder.[167] On a positive note, we found that among those eligible for treatment (CD4 count <350 cells/μl), there were no differences in the percentage of patients ever on ART between IDUs and non-IDUs or those mono-infected or coinfected with HCV. However, information on when treatment was initiated was not available, and therefore we cannot rule out that the prescription of treatment may have been delayed for IDUs in comparison to non-IDUs. Adherence information was also not available.

Similar to other studies,[46] individuals in this study reported multiple highly correlated risk behaviours, making it difficult to distinguish between direct and indirect effects. Due to the high collinearity of IDU and HCV coinfection, we could not assess the affect of one of these variables independent of the other. Greub et al[128] however, have found that HCV seropositive individuals and active intravenous drug use were independent predictors in a large Swiss prospective cohort. It is possible that either one, both of these factors, or confounders, are negatively affecting disease progression in our study population.

Calendar time has been shown to be an important predictor of disease progression, but this is generally due to differences in treatment across time. The importance of year of diagnosis (2005-2008 vs. 2009-2010) was not clearly understood. It was noted that baseline CD4 counts were significantly lower among those diagnosed in the last two years, than those diagnosed from 2005 to 2008. However, when controlling for baseline CD4 counts year of diagnosis remained a significant predictor. Nevertheless, in the seroconversion cohort, this variable was not significant, suggesting that this variable is not a true predictor of disease progression. This finding may suggest an increased delay in diagnosis of HIV in the later years (2009-2010) as the epidemic has unfolded resulting in late diagnosis and consequently a faster progression to AIDS.

Mutlivariable analysis of both the seroprevalent and seroconversion cohorts indicated gender was not a significant predictor in our study, a finding consistent with a review of seroconversion cohorts in 2005.[70] However, similarly to the articles included in the review, significant differences were noted in CD4 counts and VL at diagnosis between females and males; females had a mean CD4 count of 80 cells/μl higher, and mean $\log_{10}$VL of 0.50 higher than males. These findings may point to an earlier diagnosis among females, as they are more likely to be routinely screened for HIV as part of prenatal care. Other research, however, has shown that after seroconversion VL is lower among women than men.[69] One would thus expect these differences to translate to differences in disease progression, but despite this the rate of progression has been shown to be the same. This observation is not clearly understood, but could relate to biological differences. [69, 70]

5.3. Study limitations

There were several limitations to our study. First, this was a retrospective cohort, limiting the availability and quality of data collected. There were additional variables, such as treatment adherence or alcohol use, that would have been beneficial to capture. As described in the conceptual framework, many micro and macro-level factors are influencing disease progression. However, data was unavailable, poorly recorded, or recorded inconsistently preventing the assessment of these variables, limiting the factors which could be examined in this study. The inability to gather all important factors and to gather the data through validated measures prevented the discernment between direct and indirect effects, a further limitation of this study. Moreover, all exposure categories were self-reported, limiting the accuracy and completeness of the data potentially leading to information bias, such as misclassification. Given the use of the exposure category hierarchy, that any individual reporting at least one instant of IDU was differentially misclassified as belonging to that group. This differential misclassification could have masked the effect of IDU on HIV disease progression.

In addition, this study only included HIV positive individuals who attended clinics. This has likely biased towards a more stable study population and could have potentially biased against rapid progressors. For instance, seroconverters who progressed rapidly and died may have been less likely to attend clinics, and thus not be represented in this study. A review of community hospitalization data in Saskatoon for HIV patients from 2008-2009 indicated a 28% mortality

among this population when followed to May 1, 2010.[168] Among patients in our study, the mortality rate was 6.5%. Moreover, rapid progressors may have been excluded from the first analysis, time from HIV diagnosis to immunological AIDS, as they were more likely to be diagnosed with a CD4 count below 200 cells/μl. In short, the findings of this study may not be generalizable to all HIV patients in Saskatoon, but rather only to patients in care.

We attempted to reduce problems related to possible low reliability of the case definition (i.e. event) by including different outcomes/endpoints. Initially, clinical AIDS was one of these outcomes. However, since clinical AIDS was not collected at the WCC, we were unable to use time to clinical AIDS as the third outcome. This is a further limitation, as many other studies do use this important measure of disease progression.

The seroconversion cohort introduced further limitations. Only a small proportion (25%) of HIV-infected individuals had a previous documented negative antibody test. Those who did have a documented negative HIV test tended to be IDUs, which brings into question the representativeness of this seroconversion. For example, heterosexuals acquiring the virus through sexual contact are perceived to be of lower risk, and are therefore less likely to have had a previous HIV test. This is a common issue for many seroconversion cohorts.[26] We attempted to reduce this problem by not selecting too narrow a window period, which would inevitably result in the selection of a group of individuals undergoing frequent HIV testing. In addition, when reviewing all cases that dropped below a CD4 count of 200 cells/μl, those which had a single CD4 count where excluded from the analysis, as we could not conclude if this was a temporary

dip in CD4 counts or immunological AIDS. This exclusion may have biased results towards slower disease progression.

5.4. Study strengths

This project also had some important strengths, including the serocoversion cohort, the unique study population, and the assessment of some under-studied factors. There is high variability in the time from HIV infection to diagnosis. The use of diagnosis time as a proxy may introduce a substantial amount of noise, resulting in the attenuation of coefficients towards the null. If the time to diagnosis depends on factors, such as sex or socioeconomic status, there is also the potential for systemic bias. The subgroup analysis of the seroconversion cohort was able to provide a true measure of disease progression, a major strength of this study.

Furthermore, this study is based on an important and unique population in which little research has been done. The province of Saskatchewan has the highest incidence rate of HIV in the country and its population sharply contrasts from the national statistics, with an overrepresentation of females, Aboriginals and IDUs. Any research that further helps to understand the present situation is vital to assisting in the prevention and control of the HIV epidemic.

Moreover, while other studies have examined many potential determinants of disease progression, minimal research has assessed ethnicity, and much less Aboriginal ethnicity. The Aboriginal people are a particularly vulnerable population in Canada, and assessing ethnicity

aids in the acquisition of knowledge of disparities in health among ethnic groups. Our study highlighted that HIV positive Aboriginals were particularly burdened by IDU and hepatitis C coinfections. A higher percentage of smoking, incarceration and social assistance were also noted among Aboriginal people compared to non-Aboriginals. Fortunately, when controlling for other important factors, particularly CD4 counts at diagnosis, ethnicity did not appear to be a predictor of disease progression within our follow-up period. Nevertheless, these other differences are important determinants of health, and need to be addressed.

Finally, our study was further strengthened by the large study population. This strength is not only seen in numbers, but also in the overall representation of the HIV-infected population. Between the years of 2005 and 2008, Saskatchewan diagnosed 481 cases. Our study sample contained 224 patients diagnosed within that same period, which corresponds to a representation of 47% of all HIV diagnoses for the province. While the results of this study cannot be generalized to the entire province, it does represent much of the HIV positive population in and around Saskatoon.

5.5. Study implications

The rate of HIV disease progression is concerning for this study population. From diagnosis, this cohort progressed to AIDS and death at similar rates to IDUs in the United States, a country without universal health care. From seroconversion, the population progressed at rates similar or slightly faster to those in the pre-HAART era. Many issues appear to inflict this population, which could explain the faster progression. The vast majority of the population is highly

burdened by co-morbidities, addiction, and low socioeconomic status, which can lead to issues of access, engagement and retention into care.[167] Within our study, at diagnosis (+6 months), 50.2% of patients had CD4 counts below 350 cells/µl, which can be seen as an indicator of access to care. Moreover, a survey administered among IDUs in Saskatoon found 46% of participants reported they did not go to health care centers even when they thought they should; discrimination was the most commonly reported reason for not seeking care.[21] A review of hospitalization data in Saskatoon, SK from 2008-2010 found that among HIV-infected patients not newly diagnosed and eligible for treatment (CD4 <350 cells/µl), only 29% were actively on HAART,[169] further indicating poor access to care, through low treatment initiation. These issues are not only concerning for the individual, but also signifies a large economic burden for the province.

Issues of access, engagement and retention into care can also translate into substantial health care cost for the province. As mentioned above, in this study, half of the patients were diagnosed at CD4 counts below 350 cells/µl, and thus considered eligible for treatment. Twenty percent had CD4 counts below 200 cells/µl. In Calgary, Alberta, Krentz et al[170] found that the direct costs of medical care in the year following HIV diagnosis for late presented (CD4 <200 cells/µl) was more than twice as high as those for early presenters (CD4 >200 cells/µl). The mean cost was $18,448 for late presenters compared to $8,455 for early presenters. These additional costs were attributable to HIV-related hospital care costs (15 times higher for late presenters) and immediate initiation of antiretroviral therapy. The economic impact of early diagnosis is likely to be quite substantial for Saskatchewan.

The rate of progression highlights the need to have targeted interventions for these particularly vulnerable populations to slow disease progression. HAART has made great strides in reducing HIV-associated morbidity and mortality. [11] Avenues of increasing treatment uptake and adherence to treatment need to be further explored and implemented. For instance, direct administered therapy has been shown to increase adherence among IDUs.[171] Nevertheless, it is evident this population faces many obstacles. Many patients are dealing with numerous other issues, including homelessness, addiction, and poverty.[16, 17] The basic necessities of these individuals need also to be address through a collaborative and integrated program for this population.

5.6. Future research directions

More research is required to support these findings and to clearly determine the mechanisms by which IDUs and hepatitis C coinfected patients are more vulnerable to disease progression. More detailed variables, such as frequency of IDUs, type of drug, hepatitis C treatment, treatment adherence, and number of clinic visits, need to be collected and examined, ideally through a prospective cohort. These could further inform policy development and program planning.

In addition, it would be of value to reassess these and other variables in a study population with a longer follow-up period. While certain variables may have short-term consequences, in efforts to identify factors which may only be evident over the long-term, as has been noted in other studies,

[112] a longer follow-up period is required. The longer follow-up period would also allow the acquisition of the median time to immunological AIDS among the seroconversion cohort. This information is vital to better understanding the true rate of progression among this population; this data would allow for the distinction between a rapid progression or a late HIV diagnosis among this population.

Finally, there is also a need to characterize the influence of biological factors shown to effect HIV disease progression. These factors, such as genetic susceptibility, viral strain and immune response, continue to be the predominant predictors for disease progression.[172] The seroconversion cohort, identified through this study, is an ideal population in which to study these variables, as the population is rather homogenous.

5.6. Summary

Identification of factors influencing disease progression is vital to effectively care for patients and to improve their quality of life. In this study, we found that IDU, HCV coinfection, and baseline CD4 counts were significant predictors of disease progression. This study highlights the need for increased testing and early detection, dedicated resources for clinical care and treatment access, and for targeted interventions for these particularly vulnerable populations to slow disease progression. Moreover, this study calls for continued research on understanding the mechanisms by which disparities exist among various populations with regards to HIV disease progression. Results could further increase the understanding of other health care inequalities among other marginalized populations.

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7. APPENDICES

Appendix 1. Definition of Terms

Acquired Immunodeficiency Syndrome (AIDS)	A name given to the most advanced stage of HIV-1 infection. The diagnostic hallmark of AIDS is the development of opportunistic infections secondary to the immunosuppression caused by HIV infection
Antiretroviral Therapy (ART)	Medications for the treatment of infection by retrovirus, primarily HIV
Gender	A multidimensional social construct that is culturally based and historically specific, and thus constantly changing; Refers to the social prescribed and experienced dimensions of femaleness or maleness in a society, and is manifested at many levels[38]
Highly Active Antiretroviral Therapy (HAART)	Antiretroviral drug medication for the treatment of HIV, typically taken in a combination of three to four drugs
Human Immunodeficiency Virus (HIV)	A retrovirus that is the causative agent of AIDS

HIV Disease progression	Refers to the rate of clinical disease progression following infection with HIV; there are various definitions differing on their endpoint
Injection Drug User (*IDU)*	A person who uses an illicit substance drug (e.g. heroin, cocaine) that is administered with a needle or syringe
Incidence	The number of new events or occurrences, e.g., new cases of disease in a defined population, within a specific period time
Men who have sex with Men (*MSM)*	Men who report either homosexual or bisexual contact; an epidemiological classification for HIV transmission
Prevalence	The number of events, e.g, instances of a given disease or other condition, in a given population at a designated time
Seroconversion	The development of detectable specific antibodies to microorganisms in the blood serum as a result of infection

Sex	A multidimensional biological construct that encompasses anatomy, physiology, genes and hormones, which together affect how we are labelled and treated in the world[38]

Appendix 2. Medical Chart Forms

HIV Case Report Form

Saskatchewan Ministry of Health

HIV Case Reporting Form

Complete and forward a copy to the office of your regional Medical Health Officer. Mark it "Confidential".

This report is authorized by law. Under *The Public Health Act* it is mandatory to report all cases of HIV and AIDS to the Medical Health Officer of the regional health authority, following which mandatory information on confirmed cases will be forwarded to the Chief Medical Health Officer.

Part 1 – Patient Information

RHA Reporting	**Check (✓) applicable** ☐ New case report ☐ Updated report	Date of Last Contact with Patient (YYYY/MM/DD)	☐ Unable to contact ☐ Lost to follow-up ☐ Deceased Date: _____
HSN	Birth Date (YYYY/MM/DD)	Sex ☐ Male ☐ Female ☐ Other	Pregnant ☐ Unknown ☐ No ☐ Yes Approx ____ weeks
Patient Name *Last*	*First*	*Middle*	
Alias/Other/Maiden Name(s) *Last*	*First*		

Current Street Address	**Current** City/Town/First Nations Community	**Current** Province	**Current** Postal Code
Street Address **at time of diagnosis**	City/Town/First Nations Community **at diagnosis**	Province **at diagnosis**	Postal Code **at diagnosis**

Country of Birth	Arrival Year in Canada (YYYY/MM/DD)	Ethnicity (see over for descriptions)			
		☐ White	☐ Black Canadian	☐ South Asian	☐ Mixed ethnicity
		☐ First Nations	☐ Black African	☐ Arab/West Asian	☐ Other, *specify:*
		☐ Métis	☐ East Asian	☐ Latin-American	_____

Part 2 – Risk(s) Associated with the Transmission of HIV

Injection Risks

Yes	No	Unknown	
☐	☐	☐	Injection drug use (current or past history)

Sexual Risks **(Respond to each item)**

Yes	No	Unknown	
☐	☐	☐	Heterosexual contact
☐	☐	☐	Sex with a partner of the same gender
☐	☐	☐	Heterosexual contact of a bisexual male
☐	☐	☐	Sex trade worker
☐	☐	☐	Sexual partner is from an HIV endemic region
☐	☐	☐	Sexual partner of intravenous drug user (IDU)
☐	☐	☐	Sexual partner of a person with confirmed or suspected HIV/AIDS
☐	☐	☐	Past history of sexually transmitted infection (STI)

Other Risks **(Respond to each item)**

Yes	No	Unknown	
☐	☐	☐	Received blood/blood components before 1985
☐	☐	☐	Occupationally exposed to HIV contaminated blood or body fluids
☐	☐	☐	Other medical exposure (e.g., surgery, dental, oscopy)
☐	☐	☐	Non medical exposure (e.g., tattoo, aggravated contact with blood)
☐	☐	☐	From endemic country (see over for list)
☐	☐	☐	Perinatal transmission
☐	☐	☐	No identified risk (after asking about all risks)

Part 3 – Laboratory/Clinical Findings

Is this the first HIV test for this person? ☐ Yes ☐ No ☐ Unknown	City, province, country of first **positive** HIV test, if outside of Saskatchewan

Reason for **current** HIV test **(Check (✓) all that apply)**

☐ Immigration/visa requirement ☐ Prenatal screening ☐ STI screening ☐ Contact of an HIV infected person

☐ Needle stick injury, blood/body fluid exposure ☐ Symptomatic for disease ☐ Insurance requirement

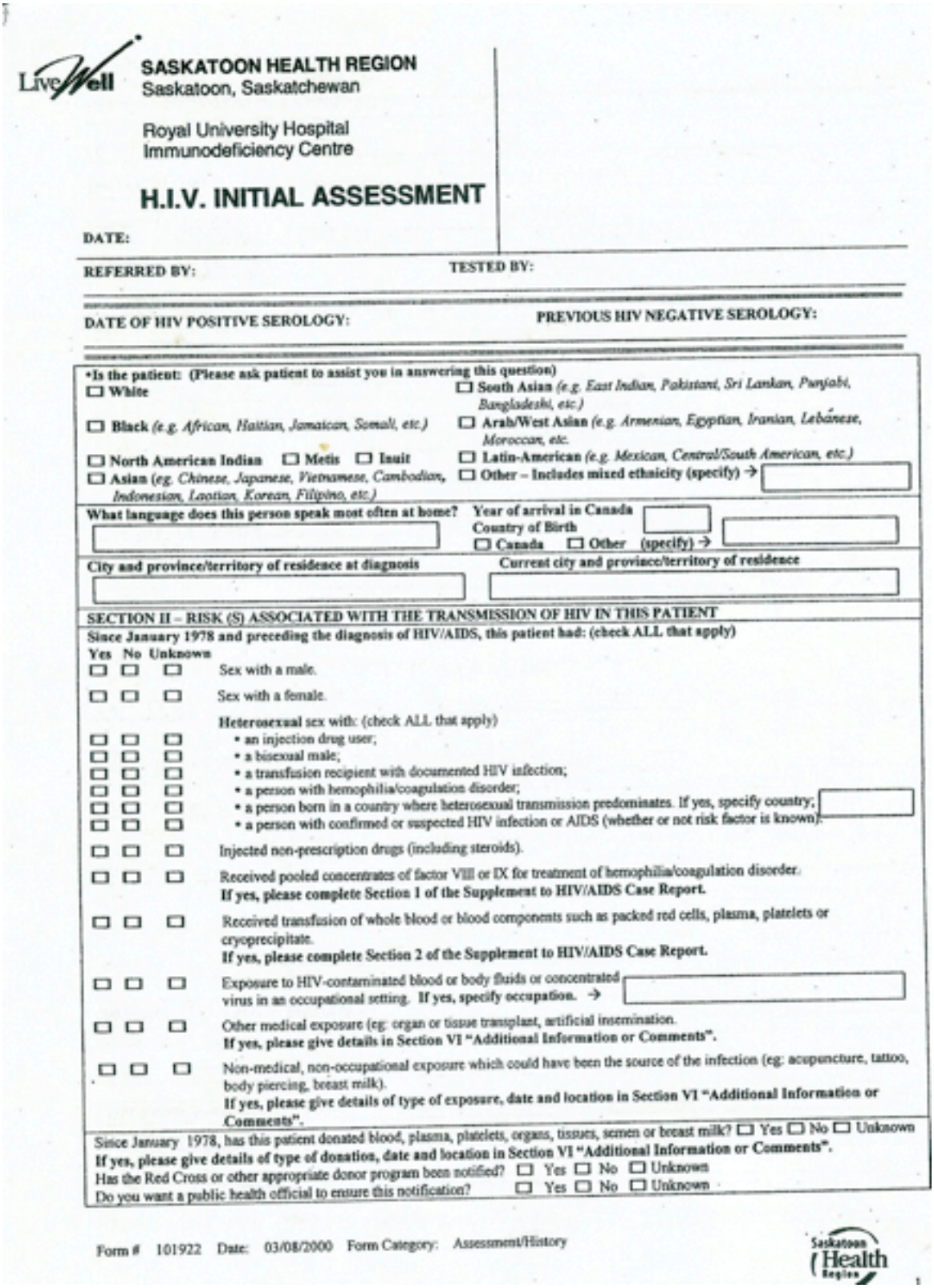
☐ History of a known risk factor, *specify:* _____ ☐ *Other, specify:*_____

Part 4 – Additional information or comments

Reporting physician's name (please PRINT):		City/town	Phone number
Referred for ongoing care ☐ Yes ☐ No	If yes, name of physician (please PRINT):	City/town	Phone number
Name of person completing this form (please PRINT)		Date report completed (YYYY/MM/DD)	Phone number

Revised January, 2011

Appendix 2. Medical Chart Forms
HIV Initial Assessment Form - 4 pages



LiveWell

SASKATOON HEALTH REGION
Saskatoon, Saskatchewan

Royal University Hospital
Immunodeficiency Centre

H.I.V. INITIAL ASSESSMENT

DATE:

REFERRED BY: **TESTED BY:**

DATE OF HIV POSITIVE SEROLOGY: **PREVIOUS HIV NEGATIVE SEROLOGY:**

***Is the patient: (Please ask patient to assist you in answering this question)**

- ☐ **White**
- ☐ **Black** *(e.g. African, Haitian, Jamaican, Somali, etc.)*
- ☐ **North American Indian** ☐ **Metis** ☐ **Inuit**
- ☐ **Asian** *(eg. Chinese, Japanese, Vietnamese, Cambodian, Indonesian, Laotian, Korean, Filipino, etc.)*
- ☐ **South Asian** *(e.g. East Indian, Pakistani, Sri Lankan, Punjabi, Bangladeshi, etc.)*
- ☐ **Arab/West Asian** *(e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan, etc.*
- ☐ **Latin-American** *(e.g. Mexican, Central/South American, etc.)*
- ☐ **Other – Includes mixed ethnicity (specify) →**

What language does this person speak most often at home?

Year of arrival in Canada

Country of Birth
☐ **Canada** ☐ **Other** (specify) →

City and province/territory of residence at diagnosis

Current city and province/territory of residence

SECTION II – RISK (S) ASSOCIATED WITH THE TRANSMISSION OF HIV IN THIS PATIENT

Since January 1978 and preceding the diagnosis of HIV/AIDS, this patient had: (check ALL that apply)

Yes	No	Unknown	
☐	☐	☐	Sex with a male.
☐	☐	☐	Sex with a female.
			Heterosexual sex with: (check ALL that apply)
☐	☐	☐	• an injection drug user;
☐	☐	☐	• a bisexual male;
☐	☐	☐	• a transfusion recipient with documented HIV infection;
☐	☐	☐	• a person with hemophilia/coagulation disorder;
☐	☐	☐	• a person born in a country where heterosexual transmission predominates. If yes, specify country;
☐	☐	☐	• a person with confirmed or suspected HIV infection or AIDS (whether or not risk factor is known).
☐	☐	☐	Injected non-prescription drugs (including steroids).
☐	☐	☐	Received pooled concentrates of factor VIII or IX for treatment of hemophilia/coagulation disorder. **If yes, please complete Section 1 of the Supplement to HIV/AIDS Case Report.**
☐	☐	☐	Received transfusion of whole blood or blood components such as packed red cells, plasma, platelets or cryoprecipitate. **If yes, please complete Section 2 of the Supplement to HIV/AIDS Case Report.**
☐	☐	☐	Exposure to HIV-contaminated blood or body fluids or concentrated virus in an occupational setting. **If yes, specify occupation.** →
☐	☐	☐	Other medical exposure (eg: organ or tissue transplant, artificial insemination. **If yes, please give details in Section VI "Additional Information or Comments".**
☐	☐	☐	Non-medical, non-occupational exposure which could have been the source of the infection (eg: acupuncture, tattoo, body piercing, breast milk). **If yes, please give details of type of exposure, date and location in Section VI "Additional Information or Comments".**

Since January 1978, has this patient donated blood, plasma, platelets, organs, tissues, semen or breast milk? ☐ Yes ☐ No ☐ Unknown
If yes, please give details of type of donation, date and location in Section VI "Additional Information or Comments".
Has the Red Cross or other appropriate donor program been notified? ☐ Yes ☐ No ☐ Unknown
Do you want a public health official to ensure this notification? ☐ Yes ☐ No ☐ Unknown

Form # 101922 Date: 03/08/2000 Form Category: Assessment/History

Saskatoon Health Region

NAME: _____

Was a Conversion Illness Experienced?

Location of Infection:

Was Partner Notification Completed upon Diagnosis? Current Partners Notified? Explain.

MEDICAL / FAMILY HISTORY:

STD'S:

G.C. [Y] [N] Hepatitis [B] [C] [NO] Warts [Y] [N] Syphilis [Y] [N] Chlamydia [Y] [N] HSV II [Y] [N]

OPPORTUNISITIC INFECTIONS:

Candida [Y] [N] _____ PCP [Y] [N] _____

OHL [Y] [N] _____ MAC [Y] [N] _____

TB [Y] [N] _____ Other _____

FEMALES:

PID [Y] [N] _____ Vaginitis [Y] [N] _____

Menstrual History

Last Pap Smear _____ Result _____ Contraception _____

MEDICATION HISTORY:

ANTIRETROVIRALS	OTHER Rx	COMPLIMENTARY THERAPIES

ALLERGIES: _____

PREVIOUS IMMUNIZATIONS:

Pneumovax [Y] [N] Date: Hepatitis B [Y] [N] Date:

Influenza [Y] [N] Date: dT [Y] [N] Date:

Hib [Y] [N] Date: Other [Y] [N] Date:

Mantoux [Y] [N] Date: Result:

SASKATOON DISTRICT HEALTH
SASKATOON, SASKATCHEWAN
ROYAL UNIVERSITY HOSPITAL
CENTRAL SASKATCHEWAN
IMMUNODEFICIENCY CLINIC

H.I.V. INITIAL ASSESSMENT

Yes	No	SYMPTOM CHECKLIST	DESCRIBE	Yes	No	SYMPTOM CHECKLIST	DESCRIBE
[ ]	[ ]	Fever\Night Sweats		[ ]	[ ]	Dysphagia	
[ ]	[ ]	Fatigue		[ ]	[ ]	Odynophagia	
[ ]	[ ]	Nausea		[ ]	[ ]	Headache	
[ ]	[ ]	Vomiting		[ ]	[ ]	Peripheral Neuropathy	
[ ]	[ ]	Diarrhea		[ ]	[ ]	Oral Lesions	
[ ]	[ ]	Weight Loss		[ ]	[ ]	Genital	
[ ]	[ ]	Cough		[ ]	[ ]	Vision	
[ ]	[ ]	SOB		[ ]	[ ]	Skin Lesions	
[ ]	[ ]	Other		[ ]	[ ]	Other	

CURRENT CONCERNS:

PHYSICAL EXAM: (WNL [✓]) WT _____HT_____BP_____PULSE _____RR_____TEMP_____

GENERAL	
LYMPHADENOPATHY	[ ]
ENT	[ ]
EYES / FUNDI	[ ]
DENTAL	[ ]
SKIN	[ ]
PULMONARY	[ ]
CARDIOVASCULAR	[ ]
ABDOMEN	[ ]
GENITO-URINARY	[ ]
RECTAL	[ ]
NEUROLOGICAL	[ ]
M. SKELETAL	[ ]

Form # 101922 Date: 03/08/2000 Form Category: Assessment/History

EMOTIONAL \ MENTAL ASSESSMENT:

PROBLEMS:

PLANS:

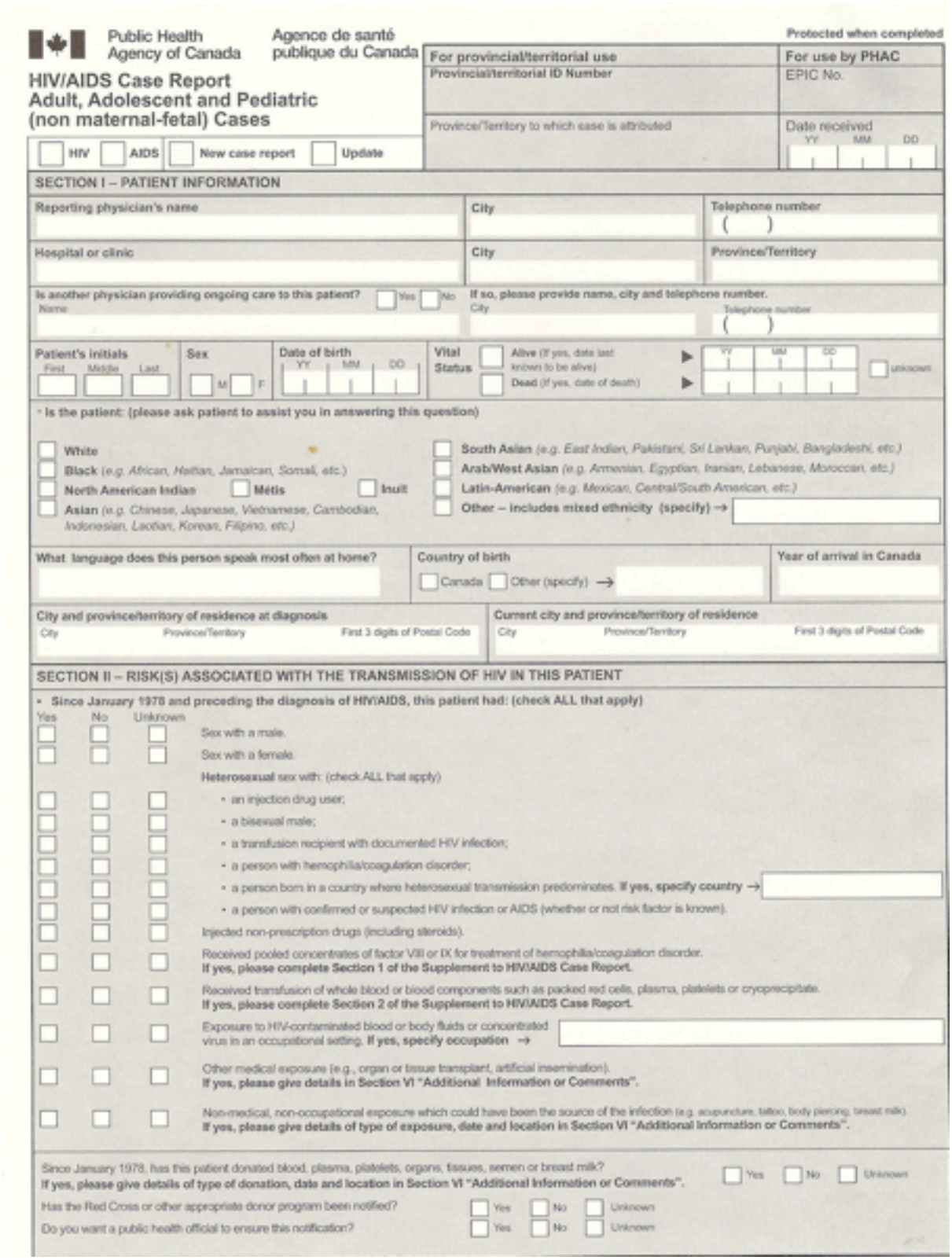
COUNSELLING:

FOLLOW-UP:

Interviewer's Signature RN _____ **Physician's Signature** _____

Appendix 2. Medical Chart Forms

HIV/AIDS Case Report - 2 pages



Public Health Agency of Canada / Agence de santé publique du Canada

Protected when completed

HIV/AIDS Case Report
Adult, Adolescent and Pediatric
(non maternal-fetal) Cases

For provincial/territorial use — Provincial/territorial ID Number

For use by PHAC — EPIC No.

Province/Territory to which case is attributed

Date received (YY MM DD)

☐ HIV ☐ AIDS ☐ New case report ☐ Update

SECTION I – PATIENT INFORMATION

Reporting physician's name | City | Telephone number ( )

Hospital or clinic | City | Province/Territory

Is another physician providing ongoing care to this patient? ☐ Yes ☐ No — If so, please provide name, city and telephone number.
Name | City | Telephone number ( )

Patient's initials (First, Middle, Last) | Sex ☐ M ☐ F | Date of birth (YY MM DD) | Vital Status ☐ Alive (If yes, date last known to be alive) ▶ (YY MM DD) ☐ unknown ☐ Dead (If yes, date of death) ▶ (YY MM DD)

* Is the patient: (please ask patient to assist you in answering this question)

☐ White
☐ Black (e.g. African, Haitian, Jamaican, Somali, etc.)
☐ North American Indian ☐ Métis ☐ Inuit
☐ Asian (e.g. Chinese, Japanese, Vietnamese, Cambodian, Indonesian, Laotian, Korean, Filipino, etc.)
☐ South Asian (e.g. East Indian, Pakistani, Sri Lankan, Punjabi, Bangladeshi, etc.)
☐ Arab/West Asian (e.g. Armenian, Egyptian, Iranian, Lebanese, Moroccan, etc.)
☐ Latin-American (e.g. Mexican, Central/South American, etc.)
☐ Other – includes mixed ethnicity (specify) →

What language does this person speak most often at home?

Country of birth ☐ Canada ☐ Other (specify) →

Year of arrival in Canada

City and province/territory of residence at diagnosis — City | Province/Territory | First 3 digits of Postal Code

Current city and province/territory of residence — City | Province/Territory | First 3 digits of Postal Code

SECTION II – RISK(S) ASSOCIATED WITH THE TRANSMISSION OF HIV IN THIS PATIENT

* Since January 1978 and preceding the diagnosis of HIV/AIDS, this patient had: (check ALL that apply)

Yes	No	Unknown	
☐	☐	☐	Sex with a male.
☐	☐	☐	Sex with a female.
			Heterosexual sex with: (check ALL that apply)
☐	☐	☐	• an injection drug user;
☐	☐	☐	• a bisexual male;
☐	☐	☐	• a transfusion recipient with documented HIV infection;
☐	☐	☐	• a person with hemophilia/coagulation disorder;
☐	☐	☐	• a person born in a country where heterosexual transmission predominates. **If yes, specify country** →
☐	☐	☐	• a person with confirmed or suspected HIV infection or AIDS (whether or not risk factor is known).
☐	☐	☐	Injected non-prescription drugs (including steroids).
☐	☐	☐	Received pooled concentrates of factor VIII or IX for treatment of hemophilia/coagulation disorder. **If yes, please complete Section 1 of the Supplement to HIV/AIDS Case Report.**
☐	☐	☐	Received transfusion of whole blood or blood components such as packed red cells, plasma, platelets or cryoprecipitate. **If yes, please complete Section 2 of the Supplement to HIV/AIDS Case Report.**
☐	☐	☐	Exposure to HIV-contaminated blood or body fluids or concentrated virus in an occupational setting. **If yes, specify occupation** →
☐	☐	☐	Other medical exposure (e.g., organ or tissue transplant, artificial insemination). **If yes, please give details in Section VI "Additional Information or Comments".**
☐	☐	☐	Non-medical, non-occupational exposure which could have been the source of the infection (e.g. acupuncture, tattoo, body piercing, breast milk). **If yes, please give details of type of exposure, date and location in Section VI "Additional Information or Comments".**

Since January 1978, has this patient donated blood, plasma, platelets, organs, tissues, semen or breast milk? ☐ Yes ☐ No ☐ Unknown
If yes, please give details of type of donation, date and location in Section VI "Additional Information or Comments".

Has the Red Cross or other appropriate donor program been notified? ☐ Yes ☐ No ☐ Unknown

Do you want a public health official to ensure this notification? ☐ Yes ☐ No ☐ Unknown

SECTION III – LABORATORY DATA

• Does this case have evidence, as defined in the above instructions, of HIV infection?
☐ Yes ☐ No ☐ Unknown

Date of first positive HIV test (if known) — Year | Month

Current CD4 count (if known) — cells/µ l

SECTION IV – DISEASES INDICATIVE OF AIDS

DISEASES	Date of Diagnosis Year	Month	Diagnostic method Definitive	Presumptive
Bacterial pneumonia, recurrent			☐	☐
Candidiasis (bronchi, trachea or lungs)			☐	
Candidiasis (esophageal)			☐	☐
Cervical cancer, invasive			☐	
Coccidioidomycosis (disseminated or extrapulmonary)			☐	
Cryptococcosis (extrapulmonary)			☐	
Cryptosporidiosis (chronic intestinal, >1 mo. duration)			☐	
Cytomegalovirus disease (other than in liver, spleen or nodes)			☐	
Cytomegalovirus retinitis (with loss of vision)			☐	☐
Encephalopathy, HIV-related (dementia)			☐	
Herpes simplex: chronic ulcer(s) (>1 mo. duration) or bronchitis, pneumonitis or esophagitis			☐	
Histoplasmosis (disseminated or extrapulmonary)			☐	
Isosporiasis, chronic intestinal (>1 mo. duration)			☐	
Kaposi's sarcoma			☐	☐
Lymphoma, Burkitt's (or equivalent term)			☐	
Lymphoma, immunoblastic (or equivalent term)			☐	
Lymphoma, primary in brain			☐	

DISEASES	Date of Diagnosis Year	Month	Diagnostic method Definitive	Presumptive
Mycobacterium avium complex or *M. kansasii* (disseminated or extrapulmonary)			☐	☐
Mycobacterium of other species or unidentified species			☐	☐
M. tuberculosis (disseminated or extrapulmonary) **(Please complete SECTION V)**			☐	

Specify Site:
☐ Miliary ☐ Pleurisy ☐ Other respiratory
☐ C.N.S. ☐ Bone and joint ☐ Genitourinary
Other (specify) →

M. tuberculosis (pulmonary) **(Please complete SECTION V)**			☐	☐
Pneumocystis carinii pneumonia			☐	☐
Progressive multifocal leukoencephalopathy			☐	
Salmonella septicemia, recurrent			☐	
Toxoplasmosis of brain			☐	☐
Wasting syndrome due to HIV			☐	

Diseases affecting pediatric cases only (<15 years old)

Bacterial infections, multiple or recurrent (excluding recurrent bacterial pneumonia)			☐	
Lymphoid interstitial pneumonia and/or Pulmonary lymphoid hyperplasia			☐	☐

SECTION V – TUBERCULOSIS

1. **Before the diagnosis of AIDS, was this patient ever treated for tuberculosis?** ☐ Yes – when? → Year | Month ☐ No ☐ Unknown
2. **Has this patient ever had a PPD skin test?** ☐ Yes – What was the size in mm? → mm ☐ No ☐ Unknown
3. **If the PPD test was negative, was the patient anergy tested?** ☐ Yes ☐ No ☐ Unknown If yes, were any sites positive? ☐ Yes ☐ No ☐ Unknown

SECTION VI – ADDITIONAL INFORMATION OR COMMENTS

(Please use this section for information of interest about the acquisition of the virus, etc.)

Person completing this form

Telephone number ( )

Date report completed YY MM DD

FOR PROVINCIAL/TERRITORIAL USE: To which exposure category has this patient been assigned?

☐ Men who have sex with men (MSM) ☐ Injection drug user (IDU) ☐ MSM and IDU ☐ Heterosexual – Endemic ☐ NIR – Heterosexual
☐ Blood transfusion recipient ☐ Clotting factor recipient ☐ Occupational exposure ☐ Heterosexual – Partner at risk ☐ NIR – Other

Appendix 3. Exposure Category (Risk Factor) Hierarchy

Individuals having a new positive HIV test may belong to more than one exposure category. These individuals are assigned to the exposure category listed first (or highest) in the following hierarchy, in accordance with PHACs surveillance reporting.

1. **MSM**: Male who reports having male sex partner(s), this includes men who report either homosexual or bisexual contact
2. **MSM/IDU:** Men who have had sex with men and have injected drugs.
3. **IDU:** Person who reports current or prior history of injection drug use
4. **Blood / blood product recipient:** Person who reports receipt of whole blood or blood product (e.g., packed red cells, plasma, platelets, cryoprecipitate, pooled concentrates of clotting factor).
5. **Heterosexual contact:** Male who reports having female sex partner(s) only, and females who report having male sex partner(s).
6. **Occupational exposure:** Exposure to HIV contaminated blood or body fluids, or concentrated virus in an occupational setting.
7. **Perinatal transmission:** Transmission of HIV from an HIV-infected mother to her child either in utero, during childbirth, or through breastfeeding.
8. **Other:** Cases in which the mode of HIV transmission is known but cannot be classified into any of the major exposure categories listed here

9. **NIR (No Identified Risk):** Where the history of exposure to HIV through any of the modes listed is unknown, or there is no reported history.