Identifying clinical and social factors influencing changes in $CD4^+$ count in HIV infected adults in Saskatoon, Canada

Submitted to the College of Graduate Studies and Research

In Partial Fulfillment of the Requirements

For the Degree of Master of Science

In the Department of Community Health and Epidemiology

University of Saskatchewan

Saskatoon, Saskatchewan

Canada

By

Kelsey Elizabeth Hunt

Permission To Use

In presenting this thesis/dissertation in partial fulfillment of the requirements for a Postgraduate degree from the University of Saskatchewan, I agree that the Libraries of this University may make it freely available for inspection. I further agree that permission for copying of this thesis/dissertation in any manner, in whole or in part, for scholarly purposes may be granted by the professor or professors who supervised my thesis/dissertation work or, in their absence, by the Head of the Department or the Dean of the College in which my thesis work was done. It is understood that any copying or publication or use of this thesis/dissertation or parts thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of Saskatchewan in any scholarly use which may be made of any material in my thesis/dissertation.

Requests for permission to copy or to make other uses of materials in this thesis/dissertation in whole or part should be addressed to:

Head of the Department of Community Health and Epidemiology University of Saskatchewan 107 Wiggins Road Saskatoon, Saskatchewan, S7N 5E5
Canada

OR

Dean College of Graduate Studies and Research University of Saskatchewan 107 Administration Place Saskatoon, Saskatchewan S7N 5A2
Canada

Abstract

Context and Rationale: The incidence of HIV in Saskatchewan is the highest in Canada and the epidemiology in this province is unique. Clinically, rapid decline in $CD4^+$ cell count and rapid progression to AIDS has been reported. The high proportion of co-morbidities present in this population could offer some explanation for this accelerated progression. The purpose of this study was to assess the impact of selected cofactors on the rate of $CD4^+$ count change as well as to identify factors associated with an increased risk of rapid $CD4^+$ count decline among HIV-infected adults in Saskatoon, Saskatchewan.

Methods: This is a retrospective longitudinal cohort study from a medical chart review at the Positive Living Program and the Westside Community Clinic in Saskatoon. Study inclusion criteria included HIV diagnosis between January 1st, 2003 and November 30th, 2011 and at least 18 years of age at time of diagnosis. Multiple statistical analyses were used to assess the influence of selected cofactors on changes in $CD4^+$ count over time, including linear regression, mixed effects models and logistic regression.

Results: In total 457 patients were eligible for inclusion in the study. The mean follow-up time was 46.3 (SD = ± 26.8) months.

When $CD4^+$ slope was estimated by linear regression patients who were not prescribed ARV during the follow-up period had a significantly higher $CD4^+$ at diagnosis as

compared to patients who were prescribed ARV ($p<0.0001$). Hepatitis C infection (HCV) ($p=0.0079$), a history of injection drug use (IDU) ($p=0.0002$), a record of incarceration ($p=0.016$) and not having been prescribed antiretroviral therapy (ARV) during the follow-up period ($p=0.0004$) were associated with a significantly more rapid decline in $CD4^+$ count.

Due to high association between First Nation or Métis ethnicity, HCV-coinfection and IDU three separate multivariate mixed effects models were built. In the model including First Nations or Métis ethnicity, First Nations or Métis ethnicity ($p=0.028$), receipt of social assistance ($p=0.011$) and age at diagnosis ($p=0.0011$) were significantly associated with $CD4^+$ count. Receipt of ARV over time was significantly associated with a rise in $CD4^+$ count ($p=0.0089$). In another model including HCV co-infection, HCV co-infection ($p=0.0048$) and age at diagnosis ($p=0.039$) were significantly associated with $CD4^+$ count. Receipt of ARV over time ($p=0.0004$) was again associated with an increase in $CD4^+$ count. Finally, in the third model, which included history of IDU, history of IDU ($p=0.047$), receipt of social assistance ($p=0.042$) and age at diagnosis ($p=0.018$) were significantly associated with $CD4^+$ count. Receipt of ARV over time ($p=0.001$) was associated with an increase in $CD4^+$ count. Model 1 had the lowest AIC value.

Only $CD4^+$ counts recorded while patients were not receiving ARV were included in the logistic regression analysis. Two subpopulations were analyzed in these models, patients with an initial $CD4^+$ of ≥ 500 cells/mm^3 and patients with an initial $CD4^+$ count

of ≥ 300 cells/mm^3. CD4$^+$ count slopes were estimated using both linear regression and mixed effects models. In the logistic regression models of subgroups which consisted of patients with the 25% steepest and 25% shallowest CD4$^+$ count slopes, ARV was consistently significantly associated with experiencing rapid CD4$^+$ count decline.

Conclusion: HCV co-infection, a history of IDU, a record of incarceration and not receiving ARV during the follow-up period were associated with a significantly more rapid CD4$^+$ count decline. First Nations ethnicity, HCV and IDU are highly correlated, therefore the effects of each of these variables on CD4$^+$ count are likely not independent. Overall among all three multivariate mixed effects models, First Nation or Métis ethnicity, HCV co-infection, a history of IDU, receipt of social assistance, and age at diagnosis were associated with lower CD4$^+$ cell count, whereas ARV treatment was associated with increasing counts. In the logistic regression models receipt of ARV was associated with rapid CD4$^+$ count decline. Individuals exhibiting factors associated with rapid CD4$^+$ count decline or lower CD4$^+$ counts over the follow-up period could benefit from more frequent follow-up by clinicians and earlier initiation of ARV. Increased attention and resources focused on this population are needed to prevent disease progression.

Acknowledgements

I would first like to thank my supervisors Dr. Lim and Dr. Skinner for their expert guidance and assistance with this thesis project. I also wish to thank my committee members Dr. Janzen and Dr. Reeder for their valuable input and insights in this project.

I would like to thank Stephanie Konrad for collecting a large portion of the data I used for this project as well as for her input throughout this project. I would also like to thank Prosanta Mondal for his help with the statistical analyses involved in this project. I would like to acknowledge Kali Gartner who also collected data that contributed to the database I used in this project.

I am very grateful to the staff at the Positive Living Program, the administrative assistants of the physicians in the Infectious Diseases department at Royal University Hospital, and the staff at the Westside Community Clinic for their help with the data collection. This project would not have been possible without their assistance.

I would like to acknowledge the patients who were the subjects of my study. It is my sincerest hope that this project will contribute to improvements in their care.

Finally, I would like to thank my family Mom, Dad, Carrie, Mark and my grandparents for their endless love and encouragement.

Table of Contents

List of Figures

List of Tables

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral Therapy
CI	Confidence Interval
CMV	Cytomegalovirus
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSV2	Herpes Simplex Virus 2
IDU	Non-prescription injection drug users
KS	Kaposi's sarcoma
MAC	Mycobacterium Avium Complex
MACS	Multicenter AIDS Cohort Study
MRSA	Methicillin-resistant Staphylococcus aureus
MSM	Men who have sex with men
NAHIVP	Northern Alberta HIV Program
OHL	Oral Hairy Leukoplakia
OR	Odds Ratio
PCP	*Pneumocystic carinii* pneumonia
PHAC	Public Health Agency of Canada
PID	Pelvic Inflammatory Disease

PIP	Pharmaceutical Information Program
PLP	Positive Living Program
RUH	Royal University Hospital
SD	Standard Deviation
SE	Standard Error
SES	Socioeconomic Status
SHR	Saskatoon Health Region
STI	Sexually transmitted infection
TB	Tuberculosis
THC	Tetrahydrocannabinol
WIHS	Women's Interagency HIV Study
WSCC	Westside Community Clinic

1. Introduction

1.1 Study Rationale

The epidemic of Human Immunodeficiency Virus (HIV) has been growing at an alarming rate in the province of Saskatchewan since 2003 (1,2,2). Despite this troublesome trend, limited research has been dedicated to the study of this high risk and underserved HIV-infected population.

The HIV positive population of Saskatchewan is afflicted by many health-compromising conditions, including Hepatitis C (HCV), illicit injection drug use (IDU), mental illness and circumstances associated with poverty, including homelessness and malnutrition.

In Saskatchewan and throughout Canada, populations of people of First Nations, Métis and Inuit ethnicity are over-represented among cases of HIV and AIDS (1,3,4). This marginalized ethnic group also faces the challenges of lower educational attainment, lower rates of employment, lower median annual income, reduced life expectancy and overall poorer health when compared with the rest of the Canadian population (3).

Evidence of rapid progression to immunologic AIDS (defined as a $CD4^+$ count below 200 cells/ mm^3) in Saskatchewan is of particular concern. The HIV positive population of Saskatchewan is afflicted with a multitude of health-compromising conditions, is understudied and is showing evidence of rapid progression to AIDS. Studies which seek ultimately to prolong and elevate the quality of life of HIV infected individuals are urgently needed in this province. The university environment provides an advantaged perspective from which we are charged with a responsibility to study and

ultimately to assume an important role in the mitigation of the HIV epidemic in this province.

1.2 Study Purpose

The purpose of this study is to determine clinical and social factors that are associated with faster or slower rates of change in $CD4^+$ count among HIV infected adults in Saskatoon, Saskatchewan. The results of this study will lead to improvements in the quality of clinical care provided to HIV infected individuals in this community.

1.3 Research Objectives

(1) To estimate the overall average rate of $CD4^+$ count depletion over the follow-up period; specifically the differences in rates among the following groups will be investigated: Age at diagnosis; Gender; Ethnicity; HCV co-infection; History of IDU; antiretroviral therapy (ARV); Incarceration during follow-up; Individuals engaged in case management services; Individuals receiving social assistance; Individuals infected with an STI.

(2) To determine the effects of the clinical and social factors listed in objective 1 on $CD4^+$ cell count changes.

(3) To identify subjects showing "rapid"- $CD4^+$ cell count decline, and to determine clinical and social factors associated with this designation. Rapid decline will be defined by the slope of $CD4^+$ count for each individual.

1.4. Study Hypotheses

Based on our study objectives we present here the hypotheses for our study.

1.4.1. Objective 1 Hypotheses

Age H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients diagnosed HIV positive above the mean age at diagnosis among this cohort, as compared to patients below it.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period, or both between patients diagnosed HIV positive above the mean age at diagnosis among this cohort, as compared to patients below it.

Gender H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between males and females.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between males and females.

Ethnicity H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who self-identify as of First Nations or Métis ethnicity as compared to patients who do not.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who self-identify as of First Nations or Métis ethnicity as compared to patients who do not.

HCV H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were co-infected with HCV as compared to those who were not.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were co-infected with HCV as compared to those who were not.

IDU H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who had a history of IDU as compared to those who did not.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who had a history of IDU as compared to those who did not.

Incarceration H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were incarcerated during the follow-up period as compared to those who were not.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were incarcerated during the follow-up period as compared to those who were not.

Social Assistance H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who received social assistance as compared to those who did not.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who received social assistance as compared to those who did not.

Case Management H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were Case Management clients as compared to patients who did not access such services.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were Case Management clients as compared to patients who did not access such services.

STI H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were diagnosed with an STI during the follow-up period as compared to patients who did not receive such a diagnosis.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were diagnosed with an STI during the follow-up period as compared to patients who did not receive such a diagnosis.

ARV H_0: There is no difference in mean $CD4^+$ count (cells/mm^3) at diagnosis and mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were prescribe ARV during the follow-up period as compared to those who were not.

H_A: There is a difference in either mean $CD4^+$ count (cells/mm^3) at diagnosis or mean $CD4^+$count slope (cells/mm^3 per month) over the follow-up period between patients who were prescribe ARV during the follow-up period as compared to those who were not.

1.4.2. Objective 2 Hypotheses

H_0: None of the social or clinical factors listed in Objective 1 will have any significant influence on $CD4^+$ count changes (cells/mm^3 per month) over the follow up period.

H_A: At least one of the social or clinical factors listed in Objective 1 will have a significant influence on $CD4^+$ count changes (cells/mm^3 per month) over the follow up period.

1.4.3. Objective 3 Hypotheses

Age H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who are older as compared to patients who are younger at HIV diagnosis.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who are older as compared to patients who are younger at HIV diagnosis.

Gender H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among males as compared to females.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among males as compared to females.

Ethnicity H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who self-identify as of First Nations or Métis ethnicity as compared to those who do not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who self-identify as of First Nations or Métis ethnicity as compared to patients who do not.

HCV H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who were HCV co-infected as compared to patients who were not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who were HCV co-infected as compared to patients who were not.

IDU H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who had a history of IDU as compared to patients who did not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who had a history of IDU as compared to patients who did not.

Incarceration H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who were incarcerated during the follow-up period as compared to those who were not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who were incarcerated during the follow-up period as compared to those who were not.

Case Management: H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who were Case Management clients as compared to patients who were not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who were Case Management clients as compared to patients who were not.

Social Assistance: H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who were recipients of social assistance as compared to patients who were not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who were recipients of social assistance as compared to patients who were not.

STI H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who were diagnosed with an STI during the follow-up period as compared to patients who were not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who were diagnosed with an STI during the follow-up period as compared to patients who were not.

ARV H_0: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are the same among patients who were recipients of ARV as compared to patients who were not.

H_A: The odds of rapid $CD4^+$ cell count (cells/mm^3 per month) decline are significantly greater or lesser among patients who were recipients of ARV as compared to patients who were not.

2. Literature Review

2.1. HIV/AIDS

Acquired Immunodeficiency Syndrome (AIDS) was first identified in 1981 based on the diagnosis of *Kaposi's sarcoma* (KS) and *Pneumocystic carinii* pneumonia (PCP) in previously healthy homosexual men living in Los Angeles, California and New York, New York (5). By 1989 AIDS was recognized as an endemic life-threatening condition among vulnerable sub-populations namely, sex workers and their clients, men who have sex with men (MSM) and IDUs (6,7). In the developed countries of the world the HIV epidemic has mostly been confined to populations of IDU and MSM (7). In the early years of the epidemic MSM was the most severely affected population. The successful mobilization by this population against the disease resulted in a significant decrease in incident cases after the mid-1980s (7). The most prominent feature of the HIV/AIDS epidemic in the developed world is undoubtedly the development of ARV, which has substantially decreased AIDS related mortality and has enabled infected individuals to lead healthy and productive lives.

Approximately 95% of individuals ever infected with HIV are living or previously lived in developing countries (8). In 2010 greater than 60% of infected individuals lived in sub-Saharan Africa (7-9). The majority of infected individuals are of economically productive age and are thereby likely responsible for supporting both their children and elderly relatives (10). Due to the low levels of financial resources available in developing countries, most infected individuals will receive minimal care when they themselves develop AIDS (7). Additional barriers faced in the mitigation of the HIV epidemic are

that efforts to prevent HIV transmission raise universally culturally sensitive issues of sexuality, gender inequality, commercial sex, MSM and IDU (7).

At the conclusion of 2010, the HIV epidemic had killed more than 25 million people with an additional 34 million people living with HIV worldwide (8). HIV is transmitted through sexual contact, both heterosexual and homosexual, by blood and by vertical transmission from mother to infant (11). Sexual contact is the predominant mode of transmission globally (7).

After initial infection many individuals remain asymptomatic for years (11). A small proportion of individuals (10-20%) have symptoms of an acute illness at the time of infection (11). Without effective ARV intervention, infection with HIV ultimately results in the development of AIDS, usually within 8 to 12 years of seroconversion (the time at which HIV antibodies become detectable in the infected patients' blood) (12-14). AIDS results when the immune system is weakened to a point at which it is no longer able to maintain control of the HIV virus (15). In Canada an AIDS diagnosis includes a positive result on an HIV test in addition to infection with one or more AIDS-defining illnesses (16).

Presently, there is neither cure, nor vaccine available for HIV. The advent of ARV, at least in developed countries, has however dramatically increased the lifespan of HIV infected individuals and transformed HIV infection from a likely death sentence to a chronic condition (17). Encouragingly, between 2003 and 2010 there was a 16-fold increase in the number of people receiving ARV in low- and middle-income countries (8). In spite of this promising trend, effective ARV remains unavailable in many parts of the world where the spread and impact of HIV/AIDS is the most devastating (18).

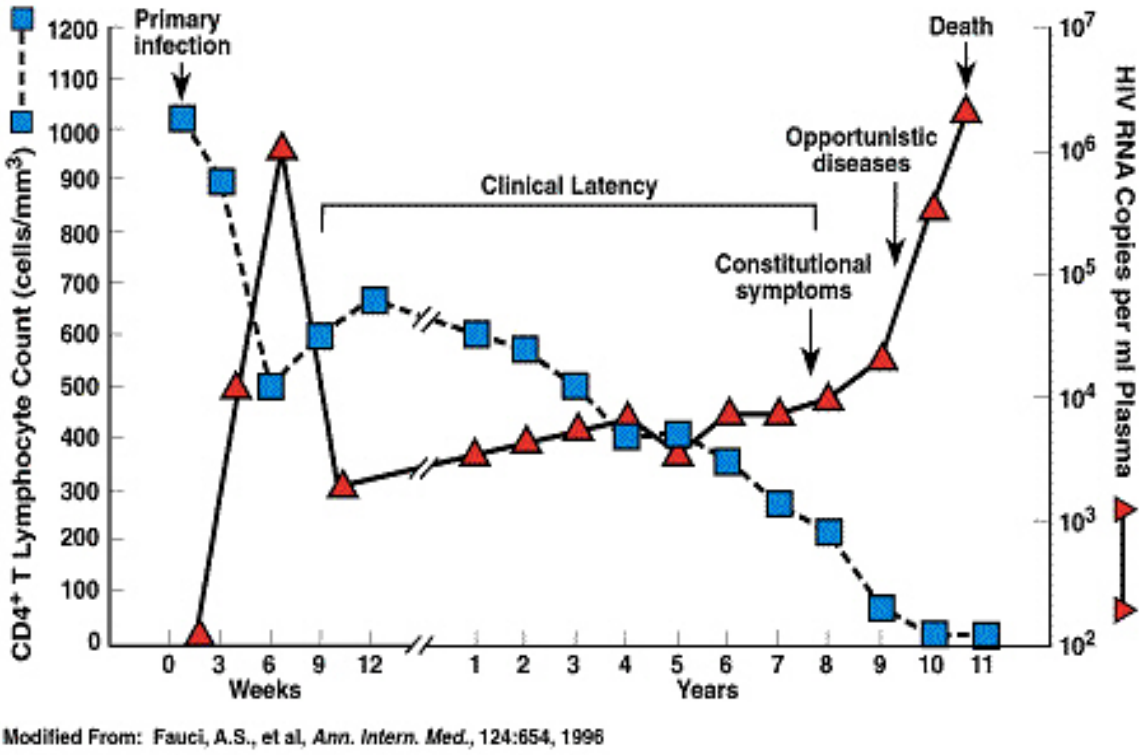
2.2. $CD4^+$ T-Lymphocyte Cells and HIV Disease Progression

HIV propagates itself in the human body through integration into the genome of $CD4^+$ cells (11,15). $CD4^+$ cells have a central role in the immune system crucial to the coordination of cellular and humoral immune responses to foreign antigens (15). Immune deficiency in AIDS is caused by the virally mediated destruction of $CD4^+$ T-cells (11,13). The loss of $CD4^+$ cell activity compromises the function of other types of immune cells (11). The HIV virus assumes control of the cellular machinery of the $CD4^+$ cells to manufacture copies of itself, which go on to infect other $CD4^+$ cells. Therefore, HIV disease progression is characterized by the progressive decline in $CD4^+$ count over time since infection (13,15,19-21). The average $CD4^+$ count of an HIV negative individual with a healthy immune system is between 800 and 1,200 cells/ mm^3 (13). Monitoring $CD4^+$ cell counts over time provides a surrogate measure of HIV disease progression (11). Advanced HIV disease can be identified by low $CD4^+$ cell counts and the presence of HIV related symptoms associated with high viral loads (20). The most commonly observed pattern of change in $CD4^+$ count is an initial steep decline following seroconversion, slowing over time until a plateau is reached (11,21,23). Viral load dynamics have also been suggested to be of importance in influencing $CD4^+$ count (24-26). A higher viral load has been correlated with a higher rate of $CD4^+$ count decline (26). $CD4^+$ count is commonly used as an end point in clinical studies of new therapies and importantly is used by clinicians in determining when to initiate ARV and other prophylactic therapies in the treatment of opportunistic infections (11,13,27,28).

Figure 1.1. depicts the average natural course of HIV infection with respect to the decline in $CD4^+$ count and corresponding increase in viral load. During the initial four to

eight weeks following virus entry (primary HIV infection) there is an explosive increase in HIV viral load (29-32). This spike in viral load is down regulated when the host's immune system mounts a partially effective immune response against the virus, characterizing the chronic phase of HIV infection (29-32). The immune system remains in a chronic activation stage typically for several years until it is no longer able to maintain control of the HIV virus resulting in an increase in viral load and in susceptibility to other microbial infections (33). These events signal the end of the chronic phase and the development of AIDS.

Figure 1.1. Average natural course of HIV infection over time as measured by $CD4^+$ count and viral load.



Source: HIV/AIDS Clinical Features, http://www.dwp.gov.uk/publications/specialist-guides/medical-conditions/a-z-of-medical-conditions/hiv-aids/clinical-features/(34)

Median time from seroconversion to AIDS diagnosis, without effective ARV intervention, is 10 years (35). An annual decline of 60 cells/μL based on an initial count

of 800 cells/ μL among ARV naive patients has been estimated (22). However, much heterogeneity exists in the rate of the clinical course of HIV infection. At one extreme are patients designated as long-term nonprogressors (LTNPs) or long-term asymptomatics (LTA) (15,36). Such individuals represent the estimated 5% of HIV-1 infected people who maintain a normal $CD4^+$ count and an undetectable viral load in the absence of ARV more than 10 years following infection (15). At the other extreme are rapid progressors, the estimated 20% of individuals developing AIDS within 5 years of infection or having a time from seroconversion to a $CD4^+$ count below 200 cells/mm^3 of less than 7.5 years (36-38). A high initial viral load followed by further increase in viral load has also been found to be characteristic of rapid progression (21).

Immune activation has been identified as probably the most important determinant of variations in HIV-1 disease progression (18). Patients with high levels of T-cell activation at presentation are at a heightened risk for rapid $CD4^+$ decline (25). The activation of host immune cells (primarily $CD4^+$ cells, macrophages and dendritic cells) in conjunction with co-infection with acute infectious illnesses may enhance HIV viral replication and consequently accelerate $CD4^+$ cell decline (18,33,39). Accelerated decline in $CD4^+$ count is associated with a shortened time to AIDS diagnosis (21). Rapid decline has been identified as a decline in $CD4^+$ count of more than 100 to 140 cell/mm^3 per year (9,15,36). Therefore, patients with the most extensive or rapid decline in $CD4^+$ cell levels are also the most likely to develop AIDS earlier (11).

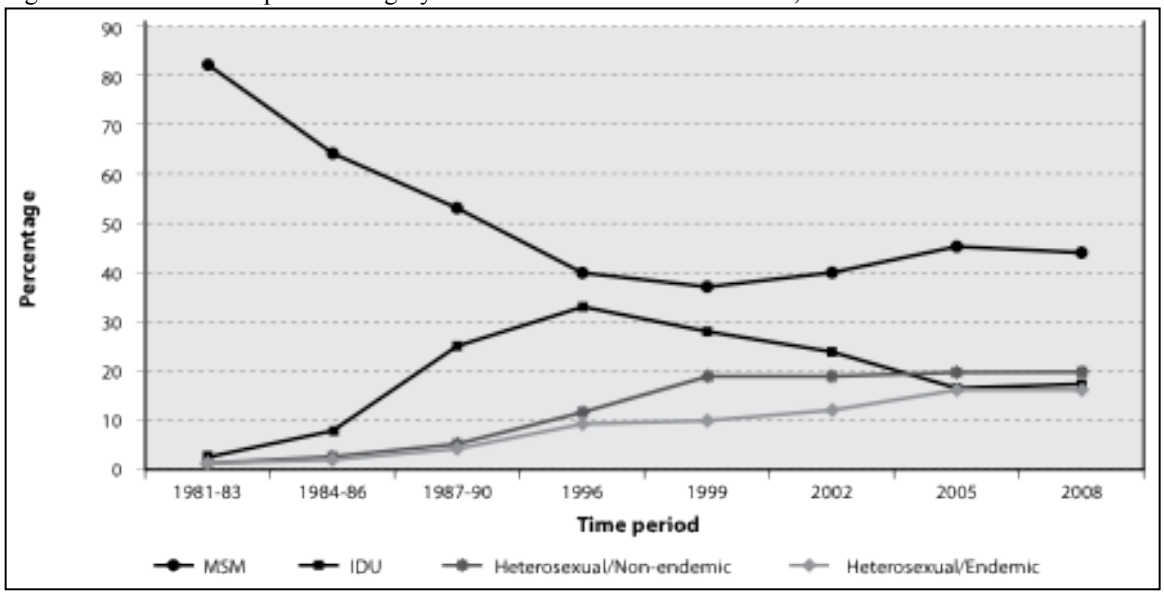
2.3. Epidemiology of HIV in Canada

In the HIV and AIDS in Canada Surveillance Report to December 31, 2009 the Public Health Agency of Canada (PHAC) documented a cumulative total of 69,844 positive HIV tests in Canada between 1985 and December 31st, 2009 (1). A total of 21,681 AIDS cases have been reported to PHAC between 1979 and December 31st, 2009. A cumulative total of 16, 452 deaths among adults have been attributed to HIV infection between 1987 and 2006.

The two most prominent historical features of the HIV epidemic in Canada are the initial peak in incidence primarily among MSM at the beginning of the epidemic (1984-1985) and the subsequent development of ARV (4). The number of cases of HIV reported to PHAC over the past 10 years has remained relatively stable. The incidence of positive HIV tests among adults in Canada in 2009 was 8.6 per 100,000.

MSM has remained the most commonly reported exposure over the entire course of the epidemic. However, the reporting of this exposure has declined over time, from 80% of cases in 1985 to 41.8% of cases in 2009, while the proportion attributed to IDU has increased, to a peak in 2007 of 33.5% of cases reporting this exposure (see Figure 1.2). In 2009, heterosexual contact was the second most commonly reported exposure category at 30.7% of incident cases, with IDU being the third most reported at 21.6% of cases.

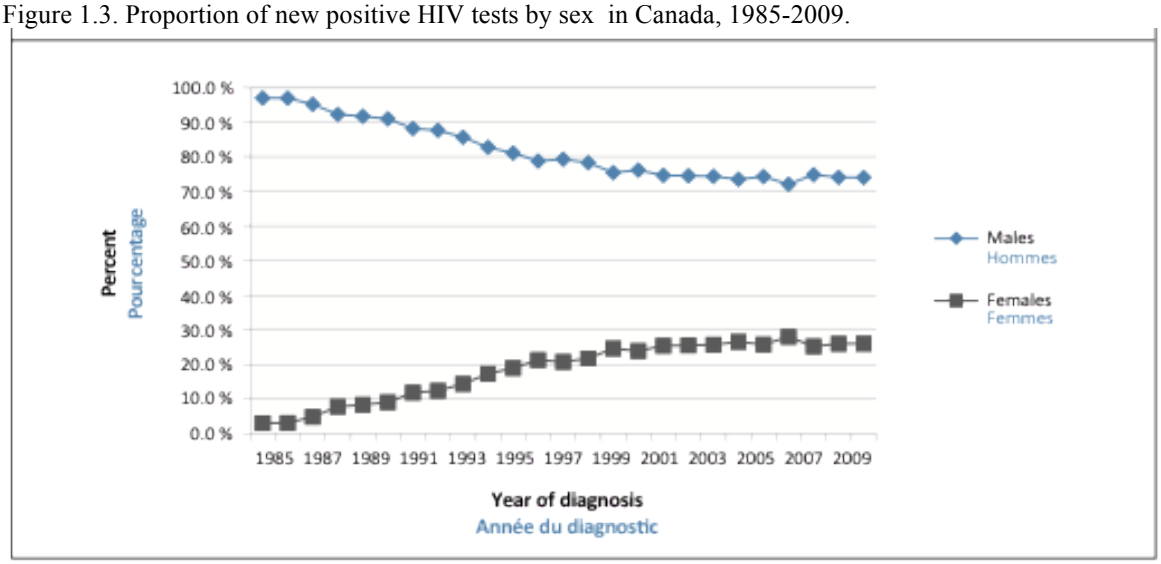
Figure 1.2. Estimated exposure category of new HIV infections in Canada, 1981-2008.



Source: HIV/ AIDS Epi Update Public Health Agency of Canada. July 2010. (4)

The number of cases among females has increased steadily since 1985. In 2009, 26 % of incident cases were reported among females (see Figure 1.3).

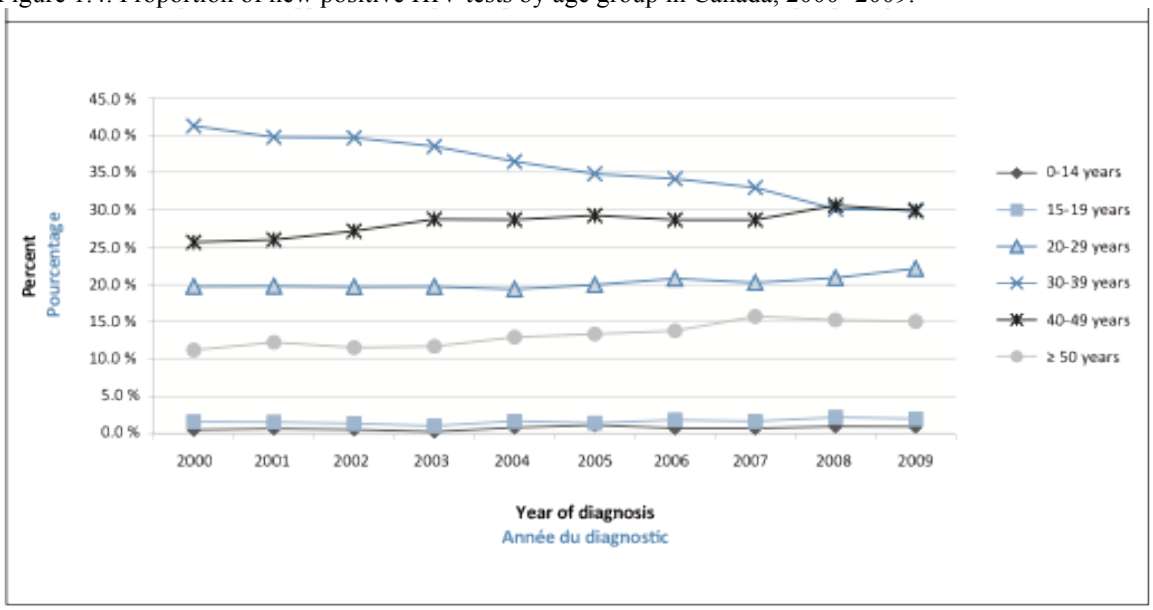
Figure 1.3. Proportion of new positive HIV tests by sex in Canada, 1985-2009.



Source: Public Health Agency of Canada. HIV and AIDS in Canada. Surveillance Report to December 31, 2009 (1).

With respect to age distribution, the 30-39 age range has encompassed the largest proportion of HIV case reports since 1985. Since 2000, the proportion of cases reported in the age range of 40-49 and over 50 has increased, while the proportion of cases reported in the 30-39 age range has decreased. For a summary of age trends among HIV cases see Figure 1.4. Since 1985, cases reported among females have generally occurred more often in the younger age groups whereas cases among males have been most often reported among the older age groups.

Figure 1.4. Proportion of new positive HIV tests by age group in Canada, 2000 -2009.



Source: Public Health Agency of Canada. HIV and AIDS in Canada. Surveillance Report to December 31, 2009 (1).

When considering the distribution of ethnicities of new HIV cases it is noteworthy that in 2009 67.1% of cases were not accompanied by any ethnic status or race information. Among cases where information on ethnicity was available, the majority of cases were among individuals of White (44.2%), First Nations, Métis or Inuit (33.3%), and Black ethnicity (11.6%).

2.4. Epidemiology of HIV Among First Nations, Métis and Inuit Peoples in Canada

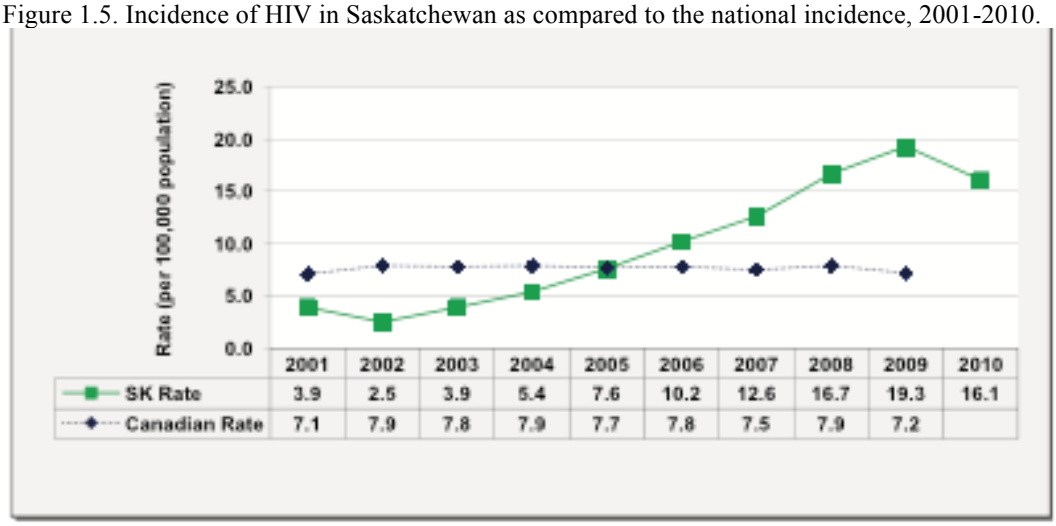
As documented by the PHAC Population Specific HIV/AIDS Status Report on Aboriginal People, First Nations, Métis and Inuit peoples are over-represented among the HIV-infected population in Canada (3). While this ethnic group represented only 3.8% of the total Canadian population (1.1 million people) on the 2006 census, this group represented 8% (4,300 to 6,100) of all people living with HIV and 12.5% (300 to 520) of incident infections in 2008. Many factors increase the vulnerability of this population to HIV infection, including increased rates of poverty, homelessness, violence, racism and the lasting effects of colonialism and the residential school system. It is important to acknowledge that First Nations, Inuit and Métis people do not comprise a homogeneous group, but rather represent distinct populations with unique cultural, linguistic, geographic and historic characteristics.

First Nations, Métis and Inuit peoples are more likely to be diagnosed with HIV at a younger age (40). In addition, a greater proportion of First Nations, Métis and Inuit women are infected as compared with other ethnic groups, as between 1998 and 2006 females comprised 48.1% of incident cases among First Nations, Métis and Inuit people, while only 20.7% of cases occurred among females in Canada's non-aboriginal population (40). IDU is the most commonly reported exposure among this ethnic group with women more often reporting this exposure than men. The second most commonly reported exposure category among both genders is heterosexual contact. Importantly, First Nations, Métis or Inuit IDU represent the fastest growing population of incident cases of HIV in Canada.

2.5. Epidemiology of HIV in Saskatchewan

In 2009 the incidence of HIV in Saskatchewan (23.6 per 100,000) exceeded the national average (of 8.6 per 100,000) by almost 3-fold, as well as more than doubled that of the province of Ontario, with the second highest incidence in Canada at 9.3 (1). Of further concern is the dramatic increase in reported cases in recent years from 26 cases in 2002 to a peak of 200 in 2009 (see Figure 1.5). This increase prompted the creation of the 'HIV Strategy for Saskatchewan' by the Saskatchewan Ministry of Health (2,41).

Figure 1.5. Incidence of HIV in Saskatchewan as compared to the national incidence, 2001-2010.



	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SK Rate	3.9	2.5	3.9	5.4	7.6	10.2	12.6	16.7	19.3	16.1
Canadian Rate	7.1	7.9	7.8	7.9	7.7	7.8	7.5	7.9	7.2	

* Canadian rates from Public Health Agency of Canada, 2010 (2010 Canadian rate not available)

Source: HIV and AIDS in Saskatchewan 2010, Annual Report prepared by Disease Prevention Unit, Population Health Branch, Saskatchewan Ministry of Health (41).

As documented in the annual report on HIV and AIDS in Saskatchewan published by the Saskatchewan Ministry of Health on November 30, 2011, the past 3 years have seen the highest incidences of HIV in the history of the province, 16.7 in 2008, 19.3 in 2009 and 16.1 in 2010 (per 100 000). This indicates that the HIV epidemic in Saskatchewan is far from its resolution. While the national rate of HIV has remained stable over the past decade, rates in Saskatchewan have been consistently increasing

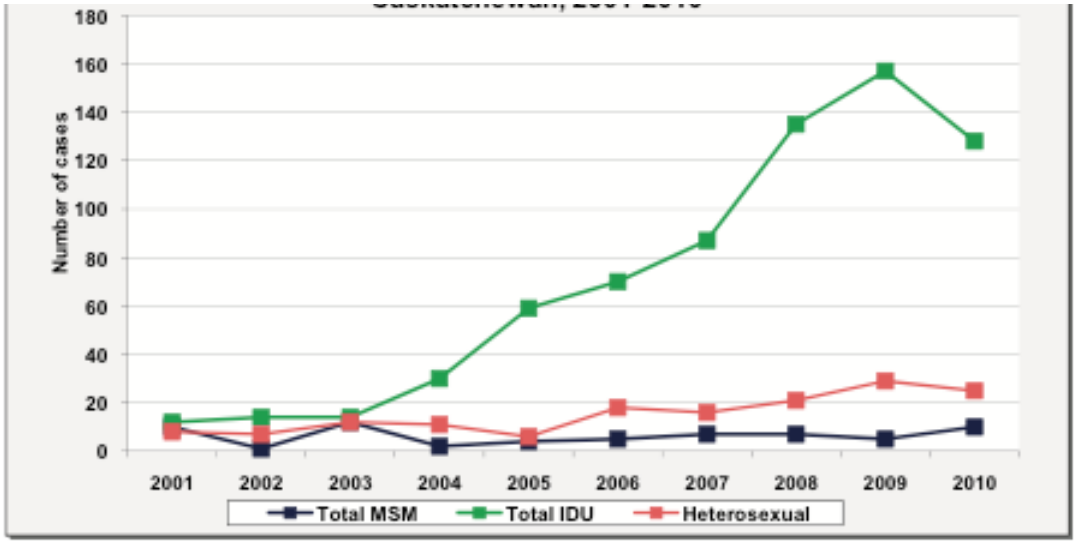
since 2002, surpassing the national rate in 2006 and remaining consistently higher (see Figure 1.5) (1,41). The cost to the provincial health care system has been estimated at more than $ 40 million annually (2).

The majority of cases have occurred in the health regions incorporating Saskatchewan's largest urban centers. Between 2004 and 2010, 45% of HIV cases were reported in the Saskatoon Health Region (SHR), 26 % in the Regina Qu'Appelle Health Region and 12 % in the Prince Albert Parkland Health Region.

From 2001 to 2010 55% of cases have occurred among men. This is a significantly lower proportion as compared to the 73.6% of cases reported at the national level among men as of 2008 (4). With respect to reported age at diagnosis in Saskatchewan, recent years have seen a rise in the number of cases among older males and among younger females.

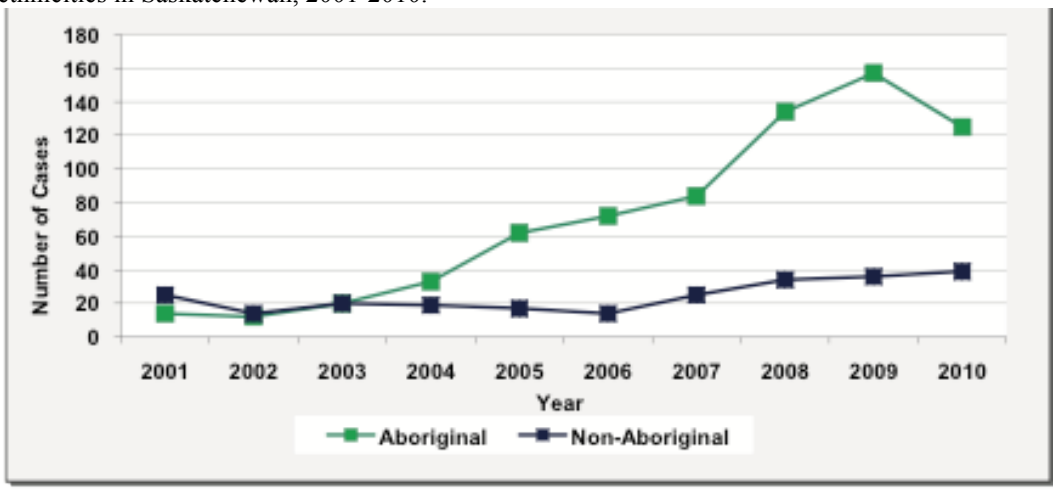
There are many aspects of the HIV epidemic in Saskatchewan that make it unique in Canada, even as compared to the neighboring provinces of Alberta and Manitoba (42). For example, while IDU-attributed HIV exposure has declined on the national scale, Saskatchewan has reported significant increases in this exposure category (1). Self-reporting of IDU as the primary HIV exposure increased from 30 % of cases in 2001 to 79 % in 2009 (see Figure 1.6). While MSM has been and continues to be the predominant mode of exposure on the national scale, MSM has not been identified as a significant risk factor for HIV transmission in Saskatchewan (1,41). Another unique aspect is the number of individuals of First Nations and Métis ethnicity represented in this epidemic (see Figure 1.7). In 2010, 73% of incident cases were reported among this ethnic group (41).

Figure 1.6. Attributable risk factors among incident HIV cases in Saskatchewan, 2001 -2010.



Source: HIV and AIDS in Saskatchewan 2010, Annual Report prepared by Disease Prevention Unit, Population Health Branch, Saskatchewan Ministry of Health (41).

Figure 1.7. Incident cases among patients of First Nations, Métis and Inuit ethnicity as compared to other ethnicities in Saskatchewan, 2001-2010.



Source: HIV and AIDS in Saskatchewan 2010, Annual Report prepared by Disease Prevention Unit, Population Health Branch, Saskatchewan Ministry of Health (41).

Since AIDS became a reportable disease in 1984, 298 cases (238 among males and 60 among females) had been recorded provincially as of 2010. Since 2004, 75% of deaths attributable to AIDS have been among males.

In a panel discussing the HIV epidemic in Saskatchewan organized on February 14th, 2011 by the Community Health and Epidemiology student group *Community Health for Community Change*, the challenges faced in the mitigation of the HIV epidemic in the province were explored and some of the topics that arose from this discussion are presented here (42). The unique characteristics of the HIV epidemic in Saskatchewan not only makes it unique in Canada but also makes it one of the most difficult populations to treat nationally. IDUs, for example may be among the members of society in the poorest of health but frustratingly for clinicians, also among the least likely to be concerned with their own health, as other aspects of their lives are likely to become secondary to their addiction. Furthermore, the high prevalence of mental illness in this HIV infected population makes it difficult for patients to initiate and even more difficult to remain adherent to treatment, which is of vital importance to the effectiveness of ARV. Poverty is also rampant among this population. Understandably, immediate concerns of housing and nourishment most often trump patient concerns of addressing potential HIV infection. In addition, the transient nature of this population makes it difficult to keep track of the locations of patients, further complicating the scheduling of follow-up visits with physicians and arranging pharmacies to dispense ARV. Initial access to health care can also be a challenge among Saskatchewan's rural inhabitants. Another significant obstacle to the mitigation of the HIV epidemic in Saskatchewan is the unwillingness of at risk individuals to be tested for or seek treatment for HIV. Such attitudes are likely due to stigma surrounding HIV. Delayed testing and treatment of this disease ultimately leads to an increased number of individuals presenting to hospital with end stage AIDS. At this stage in disease progression prognosis is much poorer than if care had been sought at an

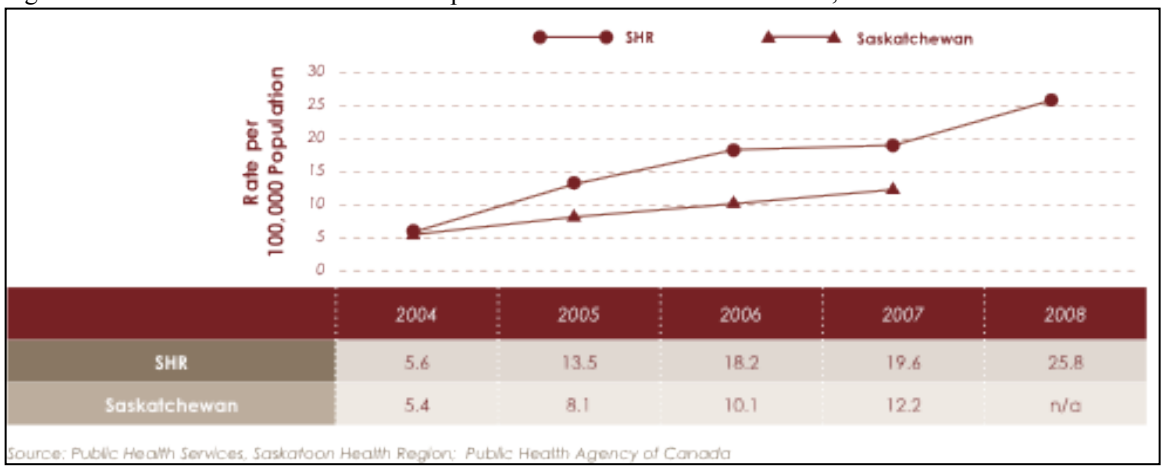
earlier stage, not to mentioned the substantial increased cost of treating an AIDS patient in hospital versus in an outpatient setting. The HIV epidemic in Saskatchewan is so severe that it has been suggested that it more closely resembles HIV epidemics in developing nations.

2.6. Epidemiology of HIV in Saskatoon

The city of Saskatoon is under the jurisdiction of the Saskatoon Health Region (SHR) and includes more than 73% of the total population serviced by the SHR (43). The SHR has a total population of 298,371, almost 29% of the entire province (44). According to the SHR Health Status Report 2008, the SHR has recorded the highest number of cases of HIV across all regional health authorities in Saskatchewan since 2005 (see Figure 1.8). It is noted that this finding most likely represents intensive HIV testing efforts; however, an increased occurrence of transmission is acknowledged in this report.

Since 2004, more than 300 cases of HIV have been reported in the SHR. The majority (77%) have been among patients of self-reported First Nations, Métis or Inuit ethnicity. Consistent with provincial trends IDU is the most commonly reported exposure for HIV infection. Between 2004 and March 2007, 80% of cases reported IDU as an exposure and an additional 73% reported sex with an IDU as an exposure. MSM, the most commonly reported exposure on the national scale, was reported among only 7.3% of cases in the SHR in this same time interval (1). Also, in contrast with national trends, the proportion of reported female cases since 2004 were almost equal to male cases (1). Unprotected sex continues to pose a risk for HIV transmission as 34% of cases reported sex with a partner in whom HIV infection was either confirmed or suspected.

Figure 1.8. Incidence of HIV in SHR compared to incidence in Saskatchewan, 2004 – 2008.



	2004	2005	2006	2007	2008
SHR	5.6	13.5	18.2	19.6	25.8
Saskatchewan	5.4	8.1	10.1	12.2	n/a

Source: Public Health Services, Saskatoon Health Region; Public Health Agency of Canada

Source: Saskatoon Health Region 2008 Health Status Report (43).

2.7. Risk Factors for Accelerated $CD4^+$ Decline

The following literature review will summarize the influence of the variables of interest in this thesis project on HIV disease progression. As $CD4^+$ count is the outcome measure of this study, an emphasis will be placed on specifically describing ways in which factors of interest influence this marker of HIV disease progression. The breadth of research published on the effects of each of these factors on HIV is too vast to be covered completely in this literature review, therefore, we will attempt to summarize the consensus, where one exists, reached by the literature. Additionally, it is important to consider that while each co-factor is presented separately in this literature review, in reality a single patient is very likely to possess multiple co-factors. Within that individual patient these multiple co-factors might cumulatively lead to a greater acceleration in $CD4^+$ decline than could be accounted for by the additive effects of single co-factors.

2.7.1. Gender

Gender inequality is an important driver in the transmission of the global HIV epidemic. This social force is ultimately responsible for an increased risk of infection among women (45). At the root of this increased risk is a women's lack of control over her body and life, especially in developing countries, where women's rights and opportunities for education and self-empowerment may be dramatically lesser as compared to those of men (45). Gender inequality means that women are often not in a position to negotiate safe sex and therefore are at risk for infection by partners in HIV endemic populations (46).

Pharmacokinetic, immunologic and genetic differences between men and women have the potential to exert differing influences on the clinical course of HIV (24). For instance, uninfected women are known to have higher $CD4^+$ counts in the general population (27,47). Women have also consistently presented with higher $CD4^+$ counts at seroconversion in cohort studies (47,48). However, whether this biological difference confers any advantage in terms of better prognosis among women is unclear. Reported effects of gender differences in rate of $CD4^+$ decline among have been mixed. Where Lodi et al. (2011) and Mocroft et al. (2000) both recorded no differences in rate of $CD4^+$ decline between genders, Anastos et al. (2000) reported a more rapid decline in $CD4^+$ count among women. However, in Anastos et al.'s (2000) study the selection of male and female cohorts for comparison may be called into question. The female cohort comprised the Women's Interagency HIV Study (WIHS) and the male cohort was the Multicenter AIDS Cohort Study (MACS) a cohort of homosexual men in the United States. Of concern were findings that women had lower $CD4^+$ counts, were significantly older, were

more likely to be black or Hispanic, to report IDU, and to have symptoms. Each of these factors found at increased prevalence among the female cohort chosen for this study has been independently associated with accelerated rates of $CD4^+$ decline (see Sections corresponding to each of these cofactor in this literature review). In addition, there was a temporal difference in the collection of data where data from the WIHS was collected from October 1994 to November 1995 and data from the MACS was collected between April 1985 and April 1987, which again may call into question the validity of conclusions drawn based on comparisons.

Gender differences in immunological response to ARV has also been the subject of conflicting reports. Giordano et. al. (2003) observed a greater mean $CD4^+$ cell count increase among women as compared to men at 6 months following initiation of ARV (24), whereas, no difference in response to treatments were recorded among patients at a clinic in Southern Alberta (47).

Implications of differences in response to ARV by gender for survival following initiation of ARV are also inconclusive. The study conducted at this Southern Alberta clinic noted a lower prevalence of AIDS among women at their first visit, however this was reportedly not cause for differences in prognoses between genders. A New York City study investigating causes of death among HIV-infected individuals in the post-HAART era found the mortality rate attributable to HIV-related causes to be higher among women (49). An analysis of data from a collaboration of 23 HIV seroconverter cohort studies in Europe, Australia and Canada concluded that overall women in developed countries survive longer following HIV seroconversion as compared to men in the post-HAART era (50). Prior to the widespread availability of ARV there was no significant differences

in risk of AIDS and death between men and women. Beginning in 1997 and ever since that time, women had a much lower risk of AIDS and death (50). It has been suggested that ARV, in lowering the risk of death from HIV, once again exposes the higher incidence of mortality among men in the general population (50). Differing risk behaviours present among study cohorts likely explain observed differences by gender in HIV prognosis following ARV initiation. Were underlying biological differences the cause of varying prognoses among genders more consistent results would be expected across multiple study cohorts.

2.7.2. Age

Age is a well-established predictor of overall health status, with older individuals at increased risk for poorer health (49). Age also has prognostic value for HIV/AIDS outcomes. Older age is associated with an increased risk of accelerated progression to AIDS and death (13,47,49,51-54). Older age at the onset of treatment has also been associated with poorer survival (13,19,55). This association between more advanced age and the greater likelihood of adverse outcomes has been observed across groups including, men, women, IDU, MSM, and those infected by heterosexual sex (52,56). It has been postulated that faster progression among older individuals may occur because on average older individuals are more likely to be infected with a greater number of opportunistic infections that might become reactivated during severe immunodeficiency (51).

The association of advancing age with accelerated decline in $CD4^+$ count, as might explain the higher incidence of AIDS and death among older individuals, is less

clear. Where Phillips et. al. (1991) found no evidence of a more rapid rate of decline in $CD4^+$ count among older patients, Lodi et. al. (2011) did find a significant influence of increasing age on accelerated $CD4^+$ decline (48,51).

2.7.3. Ethnicity

Socially and biologically produced conditions associated with ethnicity may produce worsened HIV prognoses among disadvantage groups. In developed countries, ethnic minorities are at a disproportionately high risk of acquiring HIV, and have not benefited as greatly from ARV as the general population (7). For example, findings from Louisiana show that African Americans were more likely to miss clinic visits, suggesting this ethnic group are not receiving early intervention services (57). In a study conducted in New York City, HIV-related deaths were higher among people of black and Hispanic ethnicity as compared to people of other ethnicity (49). Ethnicity was also associated with length of survival following AIDS diagnosis in a study conducted in Philadelphia, with Whites as compared to non-Whites having a longer survival time even after controlling for income (58). Minority groups are also more likely to be of a younger age at time of diagnosis, for example in the United States when comparing Hispanic individuals with individuals of Caucasian ethnicity (24).

Genetic differences between ethnicities may influence $CD4^+$ cell counts, viral "set points" (the steady state viral load reached early in infection), clinical disease progression and survival (20,26,59,60). For example, heterozygosity in the human leukocyte antigen (HLA) is associated with delayed AIDS diagnosis, whereas homozygosity is associated with rapid progession and death and HLA haplotypes are known to vary by ethnicity

(61). In addition, HLA-B35 positivity has been associated with a significantly greater rate of progression to AIDS (61,62). HIV-1 coreceptors also differ by ethnicity. For instance the Δ32 CCR5 mutation (a co-factor integral to the binding of the HIV viral envelope to the $CD4^+$ cell) is more prevalent among Caucasian populations and less prevalent in African Americans (20,63) This genetic mutation is associated with slower rates of progression to AIDS (63). Greater than 70% of our study population self-identified as of First Nations or Métis ethnicity, therefore in the following section we will examine the unique challenges faced by this ethnic group in achieving optimal health following HIV diagnosis.

2.7.4. First Nations, Métis and Inuit Ethnicity

First Nations, Métis and Inuit peoples are more likely, relative to the general Canadian population, to be afflicted with the following co-morbidities: a record of incarceration, STI infection, co-infection with HCV, and housing insecurity (3,40). As will be examined in the subsequent sections of this literature review, each of these co-factors has shown to have some association with an accelerated decline in $CD4^+$ count or an accelerated progression to AIDS or death. The causes of the increased incidences of such co-morbidities among this population are socially produced. Furthermore, not unexpectedly this ethnic group is also confronted with lower accessibility to ARV and a poorer prognosis as compared to other infected individuals in the general Canadian population (40).

The results of a study by Monette et al. (2011) highlight the social and economic disadvantage of First Nation, Métis and Inuit peoples infected with HIV living in Ontario.

They found that, in comparison to Caucasian participants, First Nations, Métis and Inuit participants were more likely to have achieved lower levels of education, to report an annual average income of less than $10,000 and to report harmful alcohol and non-medicinal drug use. First Nations, Métis and Inuit participants in this same study were also generally younger, more likely to identify as female or transgender women and heterosexual, have a history of incarceration, have a history of homelessness and live in unstable housing (i.e. hotels, shelters, motels, streets, parks, or couch-surfing). Similar conclusions were drawn in an Alberta study where additionally it was seen that Aboriginal patients suffered higher rates of all cause and HIV related mortality, as well as poorer rates of adherence to ARV (64).

2.7.5. Substance Abuse

Substance abuse and addiction has been associated with HIV/AIDS since the beginning of the epidemic. In recent years, the role of IDU in the transmission of HIV has diminished significantly in much of the developed world, Canada included (4,65). In contrast, among Canada's First Nations, Métis and Inuit peoples IDU is the category of exposure to which the greatest proportion of incident cases are attributed and this number continues to grow (4,64)

Substance abusers and drug addicts are at a heightened risk for initially contracting the HIV virus. Drug and alcohol use can lead to impaired decision making causing individuals to be more likely to engage in risky behaviours such as unsafe sex with multiple partners and the sharing of needles or other drug paraphernalia (65,66).

Importantly, infection with HIV through IDU and subsequent continued use is associated with a heightened risk of AIDS and death (49,55,67,68).

The physiological effects of illicit drugs may also have adverse effects on $CD4^+$ count. For example, there is evidence that regular cocaine use depresses $CD4^+$ counts independent of the effects of regular cocaine use on ARV adherence and HIV viral load (69). Cocaine has been shown to impair early activation events during $CD4^+$ cell stimulation potentially placing HIV-positive cocaine-abusers at heightened risk for opportunistic infections (70,71). The recent use of crack cocaine has also been seen to delay entry into clinical care (72). Furthermore, continued drug use increases the likelihood of contracting additional strains of HIV, which again has the potential to accelerate progression of the disease as well as to necessitate the implementation of increasingly complex ARV regimes to prolong life.

IDUs are less likely to be prescribed ARV and less likely to remain adherent to regimes once prescribed (50,52,64,68,73,74). Cohort studies in Europe, Australia and Canada have all found IDUs to spend smaller proportions of time on ARV as compared to individuals infected through heterosexual sex (50,52). IDUs are also less likely to have regular follow-up visits or are more likely to fail to attend scheduled visits than patients infected through other means (52,57). These observations are likely due to comordidities present among drug using populations including chronic liver disease and psychosocial issues, complicating patients' abilities to comply with therapeutic regimes and clinic attendance (75). Interruptions in treatment regimes have adverse effects on HIV outcomes (64). Encouragingly the use of injection drugs has not been seen to have a significant effect on $CD4^+$ count response to ARV (24).

2.7.6. HCV

HCV is the most commonly reported blood-bourne pathogen in the SHR (43). While on a national scale a decreasing trend in the incidence of HCV has been documented since 1997, in the SHR incidence has not declined and remains significantly higher than the national average (43). A challenge to the treatment of active HCV is that the treatment regime takes a greater physical toll on the body than treatment of HIV, therefore completion of HCV treatment requires greater social stability than treatment of HIV (42). Consequently, few patients in our study population are recipients of HCV treatment.

Co-infection with HCV among HIV infected IDUs is highly prevalent as both viruses are transmitted through multiperson use of injecting equipment (67,76-78). Transmission of HCV through the sharing of needles is 10 times more likely than transmission of HIV (5,66,79). In an international meta-analysis of HCV prevalence among IDUs the median HCV seroprevalence among HIV seropositive IDUs was 90% (80). Increased morbidity and mortality among HCV-HIV co-infected IDUs has been documented (81). As IDU is the most commonly reported exposure among newly diagnosed cases of HIV in Saskatchewan it is important to examine the effect of co-infection with HCV on $CD4^+$ cell decline in our study population.

Thus far there does not appear to be any definitive consensus as to the effects of HCV on the clinical and immunological progression of HIV among co-infected cohorts. Multiple investigations among cohorts in developed countries have found no influence of HCV co-infection on the clinical progression of HIV (77,78,82-84). Neither has HCV seropositivity been associated with lower mean $CD4^+$ counts or faster rates of decline in

$CD4^+$ counts (77,78). In contrast, some investigations found significantly slower rates of clinical progression among HCV-negative patients as compared to HCV-positive individuals, where clinical progression was defined as the occurrence of weight loss, a decrease in initial Karnofsky's index, an AIDS-defining illness or death (14).

Reports of the effects of HCV coinfection on $CD4^+$ count recovery following the initiation of ARV have also been mixed. Where Greub et. al. (2000) observed an association between HCV and delayed $CD4^+$ cell recovery following the initiation of ARV, Giordano (2003) et.al. found no significant influence of HCV seropositivity on rise of $CD4^+$ count following ARV initiation. In past years, addressing the long-term effects of chronic HCV infection was largely ignored as an HIV-related death was far more likely to occur much sooner (14,77). The prolonging of life by effective ARV now brings such concerns to the forefront among co-infected populations (14,77).

2.7.7. STIs

Infection with an STI, in particular those that are ulcerative in nature such as syphilis or herpes simplex virus 2 (HSV2), is associated with an increased risk for the sexual transmission of HIV, through increasing host infectiousness and increasing the biological susceptibility of the person exposed to HIV (18,46,66,85). Likewise, HIV infected individuals are at an increased risk of contracting STIs due to the overlap in risk behaviours leading to the contraction of these infections (86,87).

According to the Saskatoon Health Region Health Status Report 2008 rates of STI infections are increasing in the SHR, particularly in Saskatoon's core neighborhoods (King George, Riversdale, Pleasant Hill, Westmount, Meadowgreen and Confederation

Suburban Centre) (43). This report cites rates of chlamydia double those of national rates, increasing rates of gonorrhea, and a re-emergence of syphilis since 2006. Of importance to the current study and to the planning of interventions to mitigate the HIV epidemic in Saskatchewan, is the ongoing reporting of new STI infections among individuals of known HIV seropositive status. For instance, in 2007 8 individuals with previously reported HIV had a new STI.

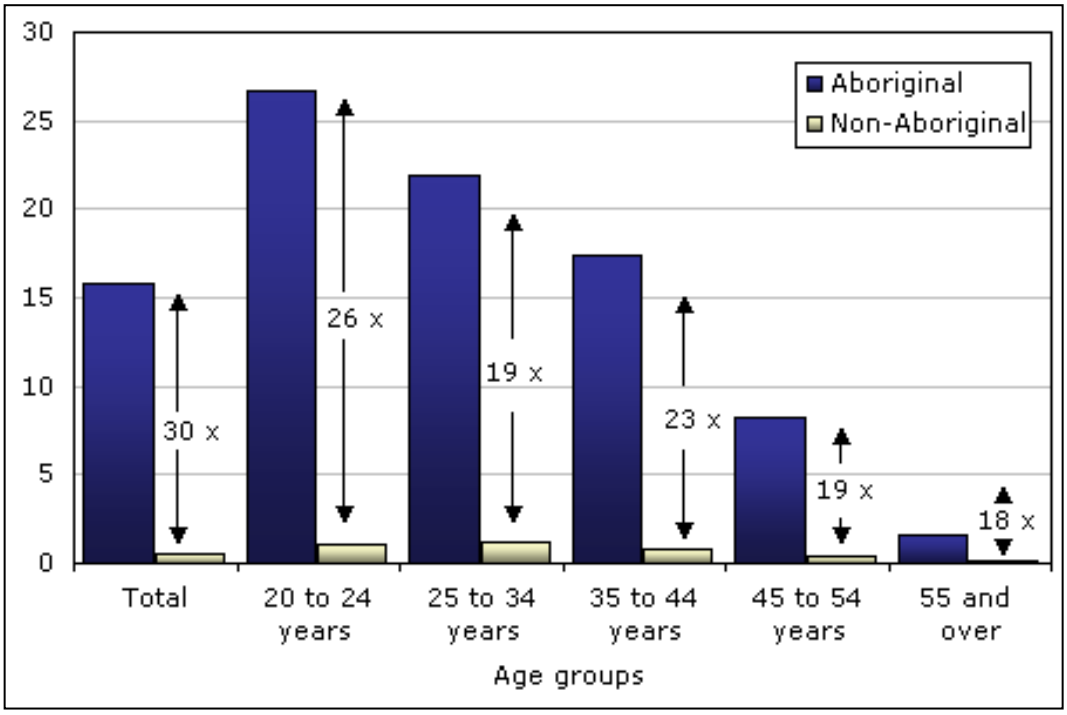
STI co-infection among HIV-positive patients has a negative impact on HIV clinical course and has been associated with an increased risk of rapid progression to AIDS (11,88). Co-infection with an STI provokes the activation of latently infected $CD4^+$ cells as the immune system responds to the infectious organisms, causing an increase in plasma viral load and a corresponding decrease in $CD4^+$ count (11,86,88-90). Syphilis, for example, has been associated with significant decreases in $CD4^+$ count in MSM, particularly among men infected with secondary syphilis who were not recipients of ARV (86,89). Secondary syphilis is a more generalized form of disease that might lead to greater immune activation than primarily syphilis(86). Encouragingly, $CD4^+$ count has been seen to recover after the successful treatment of syphilis (85,89).

2.7.8. Incarceration

In each Canadian province and territory the representation of First Nations, Métis and Inuit adults in correctional services exceeds their representation in the general population (91). In 2008, this ethnic group was represented 77% of adult male and 90% of adult female offenders in Saskatchewan's provincial correctional facilities (3). The incarceration rate in Saskatchewan during May of 2006 is presented in Figure 1.9. and

shows the dramatic overrepresentation of First Nations, Métis and Inuit people in prisons in this province. These statistics are highly relevant to the current study as previously stated, greater than 70% of this study population self-identifies as belonging to this ethic group.

Figure 1.9. Incarceration rate in Saskatchewan on Census Day, May 16, 2006



Source: Statistics Canada. The incarceration of Aboriginal People in adult correctional services (91).

The prevalence of HIV among Canada's incarcerated population is greater than that of the general population (3). This is likely due to prison populations often being composed of individuals whose past behaviours have placed them at an increased risk of HIV infection, such as substance abuse and/or commercial sex work (92,93). Of particular relevance to the current study is the report that approximately one third of patients seen at the WSCC have a history of incarceration (42). Due to the high

prevalence of HIV among patients frequenting this clinic it is important to examine the hypothesized negative impact of such a stressful event on HIV disease progression.

A study of incarcerated inmates found that after several months of imprisonment $CD4^+$ cell count decline among HIV infected individuals was more rapid as compared to patients in an outpatient setting, among patients not taking ARVs (19). Such findings were attributed to the potential immunological impacts of the stressful living conditions in correctional facilities (19).

Incarceration also poses a significant threat to ARV adherence, which has the potential to negatively impact $CD4^+$ counts. In Canadian prisons, challenges in obtaining medications upon entry, during transfers, and upon release have been identified (94). The reported high prevalence of HIV-related discrimination present within correctional institutions, prompts HIV-infected inmates to obtain and take their medication discretely, posing further threat to adherence (94).

2.7.9. Social Assistance and Social Support

The HIV/AIDS epidemic is primarily an epidemic among impoverished and marginalized people. It is in the poorest countries, and among the poorer peoples of the richest countries of the world where the impact of this devastating epidemic is most profound (6,43,58). Therefore, a high prevalence of receipt of social assistance among this study population is expected. It is therefore not inappropriate to extrapolate this result to the conclusion that many HIV-infected individuals in Saskatoon are of low socio-economic status (SES). SES is a well-known social determinant of health and the association of lower SES with worsening overall health is well established.

Low income has also been seen to be predictive of reduced length of survival following an AIDS diagnosis (58,75). Likewise, employment has been associated with improved survival (53). In an Italian study, differences in reduced survival among individuals of lower as compared to higher income were more pronounced among women and drug users (75). Decline in SES as a function of HIV disease progression has also been documented in a study based on MACS, namely as a result of the loss of full-time employment (95). Such a finding maybe indicative of the existence of a feedback loop whereby advancing disease leads to an inability to work, leading to lowered SES, which then again feeds back to contribute to worsening disease progression.

Another prevalent condition among our study population, which could be attributed to low SES is malnourishment. Whether this condition is attributable to insufficient income to support dietary needs, IDU, alcoholism, side effects of ARV or progression of HIV disease was not differentiated in this study (91). Regardless, it has been found that even moderate degrees of malnutrition can have adverse effects on outcomes in HIV-infected persons (11,96). In a study conducted in Singapore, there was an association of low BMI with reduced $CD4^+$ response following initiation of ARV, however this trend was not significant (96). Malnutrition may impair immune reconstitution, prolonging the period during which patients remain at increased risk for opportunistic infection (96). Malnutrition may also have adverse effects on drug absorption as well as lower patient threshold for drug toxicity (96).

Denial of HIV infection and its potentially fatal consequences as well as a fear of disclosure of HIV status is common (57). Stigma attached to HIV-infected persons, isolates individuals from their support structure and increases feelings of depression

which may ultimately result in a loss of social support (57). Lack of social support has been identified as a risk factor for faster decline in $CD4^+$ count as decreased social support may compromise immune functioning (97,98). Finally, Lesermanet. al. (1999) were among the first to provide evidence to suggest that stressful life events have a measurable negative impact on disease progression among a cohort of HIV-infected men.

2.7.10. Case Management

Case Management is a relatively new program to be introduced to patients primarily cared for at the WSCC. Case managers aid their clients in accessing such services in their community as income assistance, home health care and emotional counseling in order to ameliorate the economic, social, physical, and emotional well-being of HIV infected individuals (99,100). Case Management has been shown to increase rates of linkage to care in a randomized clinical trial among a primarily low-income study population at four urban American centers (72). Additionally, case management has been shown to be effective in preventing patients from becoming unstably housed and decreasing unmet needs for supportive services (99).

2.7.11. ARV

The advent of effective ARV has been a defining feature of the HIV epidemic in the developed world and is responsible for the evolution of the virus from a fatal disease to a chronic condition. Treatment of HIV began in the early 1990s with the availability of prophylaxis against common opportunistic infections and progressed to the introduction of protease inhibitors and highly active antiretroviral therapy (HAART) by the mid-

1990s (49). ARV controls viral replication within the host's body, allowing for immunological recovery marked by a statistically significant increase in $CD4^+$ cell count (8,19,67,96). Greater decrease in viral load following initiation of ARV has been consistently associated with a greater increase in $CD4^+$ cell count (24). Therefore, ARV has resulted in a dramatic decrease in AIDS related morbidity and mortality (49,67).

As previously mentioned, $CD4^+$ cell count is used by physician as a marker of immune function in order to determine optimum timing for initiation of ARV (47). The likelihood of an increase in $CD4^+$ count in response to ARV has been observed to be greater in patients with less severely depressed immune systems. Longitudinal cohort studies and randomized clinical trials have shown those who begin therapy at a $CD4^+$ cell count between 200 and 350 have lower rates of AIDS-defining diseases and death (9,23,24,54). Therefore, the USA Panel of the International AIDS Society recommends initiation of therapy, in asymptomatic patients, before $CD4^+$ count decreases to below 350 /μL (9). The presence of other comorbidities and risk factors for HIV disease progression have been identified as to also merit consideration of initiation of ARV, these include, high viral load (> 100 000 copies/mL), rapid $CD4^+$ cell count decline (>100/μL per year), hepatitis B or C virus coinfection, HIV-associated nephropathy (HIVAN) and risk factors for non-AIDS diseases, particularly cardiovascular disease (9). Lower rates of non-HIV related mortality among HIV-infected populations has also been attributed to elevated $CD4^+$ counts following initiation of ARV (49).

Since the transformation of HIV from a fatal diagnosis to a manageable chronic condition the impact of treatment decisions are profound (9). As a chronic disease HIV infection requires continuous therapy, usually over many decades (9). The maintenance

of a $CD4^+$ count above 500 may result in a normal life expectancy, through the prevention of irreversible immunological damage associated with prolonged immune activation (9,67). Therefore, appropriate timing of initiation of ARV is important in HIV-infected patients in order to promote optimal outcomes. Furthermore, it then becomes crucial that physicians identify patients with rapid decline in $CD4^+$ count as these patients may progress to a $CD4^+$ count at which treatment should be initiated more quickly than physicians might otherwise expect. In the absence of the identification of patients with a rapid decline in $CD4^+$ count physicians may miss the optimal occasion at which to initiate ARV to the detriment of the patient.

ARV adherence is also crucial to optimal outcomes. Reduced adherence to ARV has been associated with younger age, unstable housing, low SES, lack of transportation, lack of childcare, mental illness, poor social support, presence of other severe illnesses and illicit drug use (101). These barriers to adherence as well as those associated with cofactors previously described in this literature review are highly prevalent in our study population. Lack of adherence to ARV, as well as initiation and/or discontinuation of therapy without consulting a clinician has been identified as an important barrier to achieving optimal health outcomes in our study population.

3. Methods

3.1. Theoretical Perspective

Much scientific knowledge about HIV/AIDS has been shaped through the biomedical model (102). The biomedical model is based on the ideology of individualism, focusing exclusively on biological and individual-level factors to explain the risk of acquiring HIV infection and subsequently individual characteristics associated with disease progression and the development of AIDS (102). Research conducted using this methodology is primarily focused on the analysis of data collected on individuals with or at risk of AIDS, and rarely incorporates knowledge of the social context of individuals' lives (102). Due to the clinical nature of this study and thus the focus on the individual patient and the emphasis on medical intervention to prolong and improve the lives of HIV infected individuals in this study, the biomedical models theoretical perspective is employed in most regards.

Contrasting the biomedical model of disease is the field of social epidemiology, shifting the focus from the individual to social conditions as drivers of infectious disease transmission and progression (103). Fee and Krieger (1993) emphasize the social production of HIV and raise questions "…about how the social relationships of class, race, and gender affect people's working and living conditions and thereby influence their health status…" (102).

In this study, attempts to measure social production of conditions leading to increased rates of $CD4^+$ decline are made. Through the inclusion of variables such as gender, ethnicity, receipt of social assistance, and record of incarceration this study

evaluates the effects of individuals' lives shaped by both their personal history and the social groups to which they belong on rates of $CD4^+$ cell decline (102). However, the source of data for an accurate representation of the social conditions of individual lives is greatly challenged by the source from which data was collected in this study.

3.2. Study Design

This study is a retrospective cohort study of longitudinal data collected from a medical chart review. Medical charts of HIV positive patients at the Positive Living Program (PLP) and the West Side Community Clinic (WSCC) in Saskatoon, Saskatchewan, Canada were reviewed.

3.3. Setting and Population

The two clinics, which are the focus of this study, are both located in the city of Saskatoon. Saskatoon is Saskatchewan's most populous urban center, with an estimated total population of 234, 200 as of December 31st, 2011 (104). The study population includes HIV-infected patients followed at the PLP at Royal University Hospital (RUH), the WSCC, and/ or at both sites, as some infectious disease physicians practice at both sites and thus might see a given patient at both sites. The vast majority of HIV positive patients in the SHR access HIV care through these sites. The WSCC first opened in 1975 and was re-located to its current location in May 2010 in order to increase the accessibility of its services to patients (105). This is a primary health care clinic offering programs and services specific to the First Nations and Métis, and low-income inner city population of Saskatoon (105). In May 2010 through the HIV prevention strategy the

Saskatchewan Ministry of Health increased funding to this clinic by $250,000 per year for increased physician and support staff (105). The PLP at RUH exclusively treats adults and children infected with HCV and or HIV, residing in central and northern Saskatchewan (106).

3.4. Operational and Ethics Approval

This study was initially approved by the Biomedical Review Ethics Board at the University of Saskatchewan in summer 2011 (REB no. 2011 – 96). Two subsequent amendments were submitted to this review board. The first amendment, submitted in July 2011 modified the storage of data collected from a password protected computer to a remote 'datashare', a remote server upon which stored data can only be accessed by research team members. Also modified in this first amendment was the manner in which relevant patient charts would be identified for data collection. It was decided that the administrative assistants of infectious disease physicians at RUH would pull relevant patient charts. The second amendment submitted in November 2011 was to allow for the collection of the 'Case Management' variable, as had been requested by staff at the WSCC. As data collection also occurred at the WSCC ethical approval was obtained from this organization. See Appendix 1 for copies of ethics certificates.

3.5. Data Collection

Data was previously input into the dataset used in the current study by two former students. One student collected data at the WSCC between May and July 2010 with the resulting dataset comprised of patients diagnosed between January 2007 and July 2010.

The second student collected data from the PLP between August and December 2010 with the resulting data set incorporating patients diagnosed between 2005 and December 2010. In the current study, patient data was collected at the PLP between August 2011 and November 2011, and at WSCC between November 2011 and December 2011. Throughout all of these data collection periods data was entered directly into a standardized excel spreadsheet, ensuring the collection of the same variables. Data collection in the current study focused on updating this existing database to include information on patients diagnosed in 2003 and 2004, as well as the most recently diagnosed patients as of November 30th, 2011. Patient data abstracted from medical charts included information pertaining to demographics (age, gender, ethnicity), date of HIV diagnosis, date of clinical AIDS diagnosis, risk factors (IDU, MSM, etc.), clinical variables (past medical history, co-morbidities, seroconversion illness etc.), laboratory testing ($CD4^+$ count, $CD4^+$ percentage, viral load), smoking status and ARV therapy. In order to ensure the security of this data, at the daily conclusion of data collection the spreadsheet was uploaded to the 'datashare' set up by Information Technology Services at the University of Saskatchewan. Discrepancies between information pre-existing in the data set and additions made in the current study were rectified by updating the dataset to reflect the data available from the most recent physician's note and/or lab results. Care was taken not to duplicate patient records kept at both clinic locations.

Two forms in particular were important in obtaining baseline patient characteristics, The Saskatchewan Ministry of Health HIV Case Reporting Form and the Saskatoon Health Region HIV Initial Assessment. A physician or nurse in the presence of the patient upon the occurrence of a new HIV case completes these forms. The Public

Health Agency of Canada HIV/AIDS Case Report form was used when recording clinical AIDS diagnoses among patients.

Regarding the collection of any variables involving dates, if only year was available date was recorded as January 1st and if only month was available the date was recorded as the 1st of the month. Smoking status, IDU, as well as other drug use was assessed as of the most recent physician's note present in the medical chart of a given patient. The following section describes the collection of key variables.

3.6. Variables

Last negative HIV serology- This information, when available was collected from the HIV initial assessment form or from an HIV negative lab result if contained in the chart.

Date of HIV diagnosis (day, month and year)- This information was recorded from the SHR HIV Initial Assessment Form, the Saskatchewan Ministry of Health HIV Case Report Form or directly from the lab report. Date of HIV diagnosis was recorded from results of the Western blot test. When discrepancies existed between physician's notes and laboratory results, documented laboratory results were used to determine the date of HIV diagnosis.

Gender- This variable was obtained from either the HIV Case Report or HIV Initial Assessment form, or other gender identifying information present in physicians notes or on lab results.

Age at diagnosis- This variable was calculated by subtracting patient date of birth from the date of HIV diagnosis.

Ethnicity- This variable was obtained from either the HIV Case Report or HIV Initial Assessment form. For several patient charts at the WSCC neither of these forms was available. In these instances SWITCH clinic (a student run clinic at WSCC) forms which detailed age, sex, ethnicity and neighborhood of patients was used to abstract this information.

Hepatitic C Antibodies – Lab results pertaining to HCV testing were used to determine both HCV Ab and HCV PCR status. In addition, any information indicating HCV infection prior to HIV seropositivity was recorded.

Comorbidity information- Baseline comorbidities were abstracted from the Saskatoon Health Region HIV Initial Assessment form. Any and all subsequent comorbities were recorded from physician's notes and/or results of relevant lab tests.

History of IDU- Patients were recorded as having a history of IDU if there was any indication of past injection drug use contained in their charts, even if they did not identify IDU as a risk factor for transmission of HIV. Overall, this variable indicates both those that indicated IDU as a risk factor for their acquisition of HIV and those who did not but whom nonetheless had a history of IDU.

Incarceration- Any indication of incarceration during follow-up and information regarding length of imprisonment when available, was recorded.

Social Assistance- A patient was recorded as being a recipient of social assistance by the presence of supplemental social assistance forms to be completed by physicians in order to receive additional benefits. These additional benefits would be aimed at fulfilling needs associated with the debilitating nature of HIV, in terms of chronic fatigue or weight loss, or other chronic conditions, in their medical chart. Other information, for example, that contained in physician's notes indicating that a patient was a recipient of social assistance, was also used to obtain information on this variable.

Case Management- A list of case management clients was provided by the director of the WSCC. Case management is intensive social support from a social worker. In this program social workers visit individuals in their own homes and assist with such tasks as getting to court, opening a bank account, and transportation to doctor's appointments. This program was implemented to improve HIV-infected individual's abilities to attend medical appointments regularly and remain compliant with treatment regimes, given the chaotic lives of some HIV-infected individuals in Saskatoon.

HIV Exposures- Risk factors for HIV transmission were recorded from either the HIV Case Report or HIV Initial Assessment form.

VL, $CD4^+$ Counts and $CD4^+$ % - These variables as well as the date of each count was recorded from lab results kept in patient charts. Baseline viral load and CD4 count were recorded as the earliest value recorded in a patient chart within 6 months of HIV diagnosis. The limit of detection of plasma HIV viral load was less than 40 copies/ mL.

Death (day, month, and year) –Information on the date and cause of death was obtained from the HIV/AIDS Case Report form required by PHAC or based on any other information in the chart (i.e., physician's notes, newspaper obituary clipping).

ARV therapy - Information on ARV medications was recorded from both pharmacy records and all pertinent physician notes. The medication name and the duration of the prescription was recorded. A completely accurate depiction of adherence to medication was not available from patient charts, however compliance was recorded as best was possible from these two sources of information.

3.7. Inclusion and Exclusion Criteria

All HIV positive patients treated at PLP, WSCC, or at both sites were eligible for inclusion in this study. Patients must have been diagnosed HIV positive for the first time between January 1st, 2003 and November 30th, 2011. This time period includes the rapid increase in incident cases of HIV and was thus selected as the vast majority of patients treated at the PLP and the WSCC were diagnosed during these years. Thus this study represents the cohort of patients involved in the rise in new diagnoses in Saskatchewan, which is of most interest and understanding the characteristics of this population will be of the most importance in the mitigation of the HIV epidemic in Saskatchewan. Additionally, patients under 18 years of age were excluded from this study. Inclusion and exclusion criteria are summarized below.

Inclusion criteria:

(a) HIV positive patient treated at PLP, WSCC or both and diagnosed between January 1st, 2003 and November 30th, 2011

Exclusion criteria

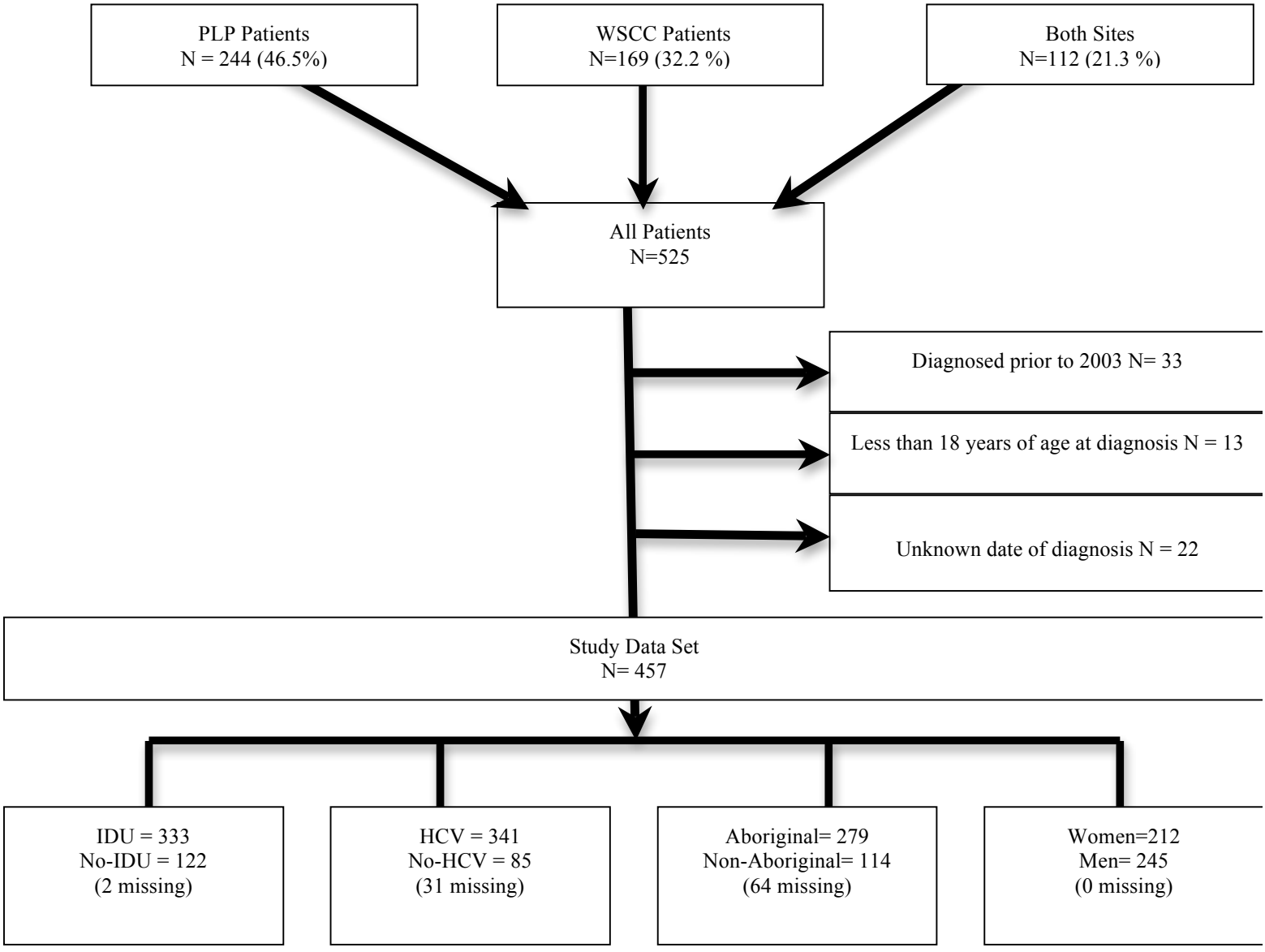
(a) Under 18 years of age at time of diagnosis

(b) HIV diagnosis prior to January 1st, 2003 or after November 30th, 2011.

Based on exclusion criteria, a number of patients were removed from the final dataset. When both the Saskatchewan Ministry of Health HIV Case Reporting Form and the Saskatoon Health Region HIV Initial Assessment form were absent in the chart in addition to the absence of any other indication of the exact date of HIV diagnosis the patient was not included in the cohort. Twenty-two patients were removed due to an undocumented date of diagnosis. Thirty-three were removed due to having been

diagnosed with HIV earlier than 2003. Lastly, thirteen patients were excluded due to being aged less than 18 years at time of diagnosis. From an initial sample size of 525, 457 patients remained in the data set. Figure 3.1 summarizes, this exclusion progress and the makeup of the final dataset.

Figure 3.1. Summary of data set.



3.8. Variable Selection.

Table 3.1 summarizes all independent variables collected and thereby available for use in analysis. However, not all variables were considered for inclusion in statistical analysis due in large part to missing information.

HIV Diagnosis date was not used as data was collected retrospectively following HIV diagnosis. Therefore, because patients were not followed prospectively from before their HIV diagnosis we cannot accurately ascertain date of HIV infection. Many individuals in this study population were likely infected several years prior to the date of their HIV diagnosis. This led to inaccuracies in recording other variables as well such as the occurrence of a seroconversion illness.

It was seen during data collection that some individuals were inconsistent in their methadone use, being on and off methadone for monthly or yearly intervals. In spite of a documented association of engagement in methadone therapy with increased adherence to ARV, this variable was not used as the extent of engagement in such therapy by an individual patient was unknown (73,107). As the duration and adherence to methadone therapy was unknown for most patients and such inconsistencies could not be accounted for in the analysis this variable was unusable.

Residency was not used, as due to the transient nature of this population and the suspected proportion of individuals who regularly experience housing instability it may not offer an accurate representation of the neighbourhoods in which study participants reside. Laboratory tests for co-infections such as Hepatitis A, Hepatitis B (HBV), tuberculosis (TB), and varicella may indicate immunity due to immunization and not evidence of prior infections, therefore these variables were not considered. The

proportion of patients with a positive Mantoux test was also difficult to ascertain as a limited number of patients returned to the clinic to have the results of the test read after it was planted.

Active IDU was also very difficult to assess, as it may not have been recorded on a regular basis in physicians' notes or a patient may not have been seen within 6 months prior to the reviewing of their chart, active IDU was defined as use of illicit injection drugs within 6 months of the most recent clinic appointment. Smoking status of both cigarettes and marijuana was also difficult to assess for similar reasons. Despite, an association of cytomegalovirus (CMV) seropositivity with more rapid development of AIDS, the prevalence of CMV antibodies was found to be so great that it would not have statistical accurate to include in the analysis (12). Likewise HLA B35 positivity has been associated with rapid progression of HIV, however this genotype occurred at a very low prevalence in this population that again it would not have been statistically appropriate to include it in the analysis (61,62).

ARV adherence was recorded principally from the Pharmaceutical Information Program (PIP), a program created by the Saskatchewan provincial government to provide health care professionals with access to a patient's medication records, if it was included in the chart (108). The PIP was supplemented by any physician's notes referencing the initiation or termination or adherence to therapy. Although, it would have been clinically relevant to include adherence to ARV this variable was excluded in statistical analysis due to multiple initiations and discontinuations of various therapeutic regiments by patients as well as an unavailability of accurate assessment of adherence. In addition, the

ARV records of patients diagnosed in other provinces or countries were not always available, or the information that was provided was not adequate for analysis.

Table 3.1. Variables available in database.

Category	Variable	Description	Type
Demographics	Gender	Female, Male or Other	Categorical
	Age	At Diagnosis	Continuous
	Ethnicity	Caucasian, First Nations, Métis, African, Asian, Inuit, Other	Categorical
	Primary Residence	Indicated by first three alpha-numerics of postal code	Categorical
	Secondary Residence	Indicated by first three alpha-numerics of postal code	Categorical
	Site of Care	PLP, WSCC, or both	Categorical
HIV Diagnosis Data	Genotype	HIV Viral Clade	Categorical
	Symptoms at diagnosis	Symptomatic At HIV testing	Categorical
	Seroconversion illness	Experienced Yes or No	Categorical
HIV Risk Factors	Sex with male, Sex with female, Heterosexual sex with IV drug user, Heterosexual sex with bisexual male, Heterosexual sex with transfusion recipient, Heterosexual sex with hemophiliac, Born in endemic country, if yes, which country, Heterosexual sex with person with HIV/AIDS (diagnosed or suspected), Injection non-prescription drug user, Received pooled Factor VII/IX concentrate, Recent transfusion, Occupational exposure, Other medical exposure, Other non-medical exposure (tattoo, acupuncture), Mother-to-child-transmission	Category of HIV Exposure	Categorical

Past Medical History	Hospitalizations/ Admissions	Yes or No, and reason for admission	Categorical
	Co-morbidities (i.e.malignancies, cardiac conditions, diabetes)	List and date of diagnosis of condition	Categorical
	Family History	List of medical conditions	Categorical
Infections	Tuberculosis (TB)	Date, Mantoux results, active TB, TB treatment	Categorical
	Result of HCV Antibody Tests	Date, Positive or Negative	Categorical
	Results of HCV PCR Tests	Date, Positive or Negative	Categorical
	HCV Genotype	1, 1a, 1b, 2b, or 3a	Categorical
	Cytomegalovirus (CMV) Ab	Present or Absent	Categorical
	Toxoplasma Ab	Present or Absent	Categorical
	Herpes simplex virus (HSV) Ab	Present or Absent	Categorical
	Varicella Ab	Present or Absent	Categorical
	Syphilis Ab	Present or Absent	Categorical
	Chlamydia Ab	Present or Absent	Categorical
	Gonorrhea Ab	Present or Absent	Categorical
Opportunistic/ Other Infections	Pneumocystis Carinii Pneumonia (PCP) Date	Date of diagnosis	Continuous
	Mycobacterium Avium Complex (MAC) Date	Date of diagnosis	Continuous
	CMV Date	Date of diagnosis	Continuous
	Oral Hairy Leukoplakia (OH) Date	Date of diagnosis	Continuous
	Candida Date	Date of diagnosis	Continuous
	Methicillin-Resistant Staphylococcus Aureus (MRSA)	Yes or No, date of diagnosis (of available)	Categorical
Females only	Pelvic Inflammatory Disease (PID) date	Date of Diagnosis	Continuous
	Vaginitis Date	Date of Diagnosis	Continuous
	Menstral History	Regular, irregular, post-menopausal	Categorical
	Last Pap	Date, results	Continuous
	Contraception	Type and frequency of use	Categorical
	Pregnancies	Number of Pregnancies during course of HIV infection	Categorical
Social	History of IDU	Ever an IDU, or never IDU, Yes or No	Categorical
	History of Incarceration	Incarcerated during follow-up, Yes or No	Categorical
	History of Social Assistance	Indication of receiving during follow-up, Yes or No	Categorical
	Case Management Client	Yes or No	Categorical
	Smoking Status (cigarettes and tetrahydrocannabinol (THC))	Current, Former and Ex-smoker	Categorical
	Methadone Treatment	Current, Previous, Referred, Never	Categorical
	Substance Abuse	List of illicit drugs used	

ARV Treatment	History of ARV ARV Initiation ARV Termination ARV Adherence	Ever on ARV, Yes or No Date of ARV Initiation Date of ARV Termination Information regarding adherence to ARV while prescribed	Categorical Continuous Continuous

Table 3.2 summarizes the independent variables that were considered in the statistical analysis for association with $CD4^+$ count rate of decline. These variables were selected both due to evidence of potential influence on $CD4^+$ count identified in the literature review and due to availability at appropriate accuracy and completeness in the dataset.

Table 3.2. Variables considered for inclusion in statistical analysis.

Category	Variable	Description	Type
Demographics	Gender	Female, Male or Other	Categorical
	Age	At Diagnosis	Continuous
	Ethnicity	Caucasian, First Nations, Métis, African, Asian, Inuit, Other	Categorical
Medical History	Result of HCV Antibody test	Positive or Negative	Categorical
	History of STI	Tested positive for an STI during follow-up, Yes or No	Categorical
Social	History of IDU	Ever an IDU, or never IDU, Yes or No	Categorical
	History of Incarceration	Incarcerated during follow-up, Yes or No	Categorical
	History of Social Assistance	Indication of receiving during follow-up, Yes or No	Categorical
	Case Management Client	Yes or No	Categorical
ARV Treatment	History of ARV	Ever on ARV, Yes or No	Categorical
	ARV Initiation	Date of ARV Initiation	Continuous

3.9. Dependent Variables

In the natural history of HIV disease progression $CD4^+$ cells decrease in number as a function of time since HIV infection. Therefore an infected person's $CD4^+$ cell count can be used to monitor disease progression.

A total of 2, 554 $CD4^+$ count measurements were recorded among this cohort. Individual patients recorded various numbers of $CD4^+$ counts dependent on the duration of HIV infection, stage of HIV progression and clinic visit attendance, among other factors. As the infectious disease physicians treated this cohort attempted to see patients at 3 months intervals we divided the follow-up period into 3 month intervals with time zero being the time of diagnosis. If a given patient had greater than 1 $CD4^+$ count recorded in a given interval the mean of all $CD4^+$ counts recorded in this interval was used in the analyses. If a given patient did not have any $CD4^+$ counts recorded in a given interval this was recorded as missing. In addressing the three study objectives we used $CD4^+$ count as a continuous variable in Objectives 1 and 2 and as a dichotomous variable in Objective 3. Here we present more detail on the dependent variable in this study specific to each Study Objective.

Study Objective 1: To estimate the overall average rate of $CD4^+$ count depletion over the follow-up period; specifically the differences in rates among the following groups will be investigated: Age at diagnosis; Gender; Ethnicity; HCV co-infection; History of IDU; antiretroviral therapy (ARV); Incarceration during follow-up; Individuals engaged in case management services; Individuals receiving social assistance; Individuals infected with an STI.

Dependent Variable: $CD4^+$ counts of all patients with at least 3 recorded $CD4^+$ counts, where this count is a continuous repeated measurement variable over the follow-up time.

Study Objective 2: To determine the effects of the clinical and social factors listed in objective 1 on $CD4^+$ cell count changes.

Dependent Variable: All $CD4^+$ counts among all patients, again where this count is a continuous repeated measurement variable over the follow-up time.

Study Objective 3: To identify subjects showing "rapid"- $CD4^+$ cell count decline, and to determine clinical and social factors associated with this designation. Rapid decline will be defined by the slope of $CD4^+$ count for each individual.

Dependent Variable: The dependent variable for Objective 3 is dichotomous, rapid $CD4^+$ cell count decline as compared to slow $CD4^+$ count decline. Rapid decline was defined as the steepest 25% of slopes and slow decline as the shallowest 25% of slopes, as estimated from $CD4^+$ counts of patients recorded while not these patients were not receiving ARV by both linear regression and mixed effects models analyses.

3.10. Statistical Analysis

To investigate the study objectives the following statistical analyses were performed. P-values were used to determine statistical significance. Time of HIV diagnosis is equal to month since diagnosis having a value of zero.

Firstly, baseline patient characteristics were summarized by calculating the mean (SD) and of continuous variables and the frequency of count (%) variables using SAS codes *PROC MEANS*. Pearson chi-square tests were used to examine potential collinearity among cofactors using SAS code *PROC FREQ*.

To examine the first study objective, a linear regression of $CD4^+$ counts was fit for each patient with at least 3 recorded $CD4^+$ counts using SAS code *PROC REG*. Subsequently, these individuals were assigned to groups based on gender, ethnicity, HCV co-infection, history of IDU, incarceration, recipient of social assistance, case management, STI co-infection, and receipt of ARV. Ethnicity was collapsed into the two categories of First Nations/ Métis and other, including Caucasian, African and other ethnicity. This was due to the low frequency of patients identifying as African or of other ethnicity. The mean slope among all individuals in each group was calculated and t-tests and Wilcoxon rank tests were performed using the SAS codes *PROC TTEST* and *PROC NPARLWAY WILCOXON* to assess statistically significant differences. Both t-tests and Wilcoxon rank tests were performed for comparison in the event that we made incorrect assumptions regarding the normality of the distribution of $CD4^+$ count intercepts and slopes. The Wilcoxon rank test in a non-parametric test and thus does not assume any underlying distribution of the data, whereas the t-test assumes a normal distribution of the data. If the results of both of these tests are consistent we can be more confident that our observed results are closer to reflecting true differences and similarities among $CD4^+$counts at time of diagnosis and $CD4^+$ count slopes over the follow-up period.

To examine the second study objective the data was modeled longitudinally by fitting random effects models using the SAS code *PROC MIXED* with random intercept and random slope. When we model the data with mixed effects models we model the dependence of $CD4^+$count on the cofactors in the model as well as the autocorrelations among repeated $CD4^+$ counts measured for a given patient. All patients who recorded at least 1 $CD4^+$ count during the follow-up period were included in this analysis. Random

effects models calculate estimates of average linear marker trajectories over time, while accounting for correlations among repeated $CD4^+$ measurements from the same subject (21). These models allow for estimation of the $CD4^+$ count progression over time of individual patients as well as account for missing $CD4^+$ count measurements in the dataset. A univariate model was fit for each variable of interest. In these models time was continuous and in units of months. Explanatory variables with a p-value of 0.25 or less were considered for potential inclusion in a multivariate model. Due to high rates of co linearity among ethnicity, HCV-co infection and a history of IDU three multivariate models were fit. In the final multivariate models baseline covariates, which were determined to be significant in the univariate anaylsis, were adjusted for by inclusion in the mixed effects model. In practice this was done by the addition of baseline covariates to the model statement in the proc mixed code in the SAS program.

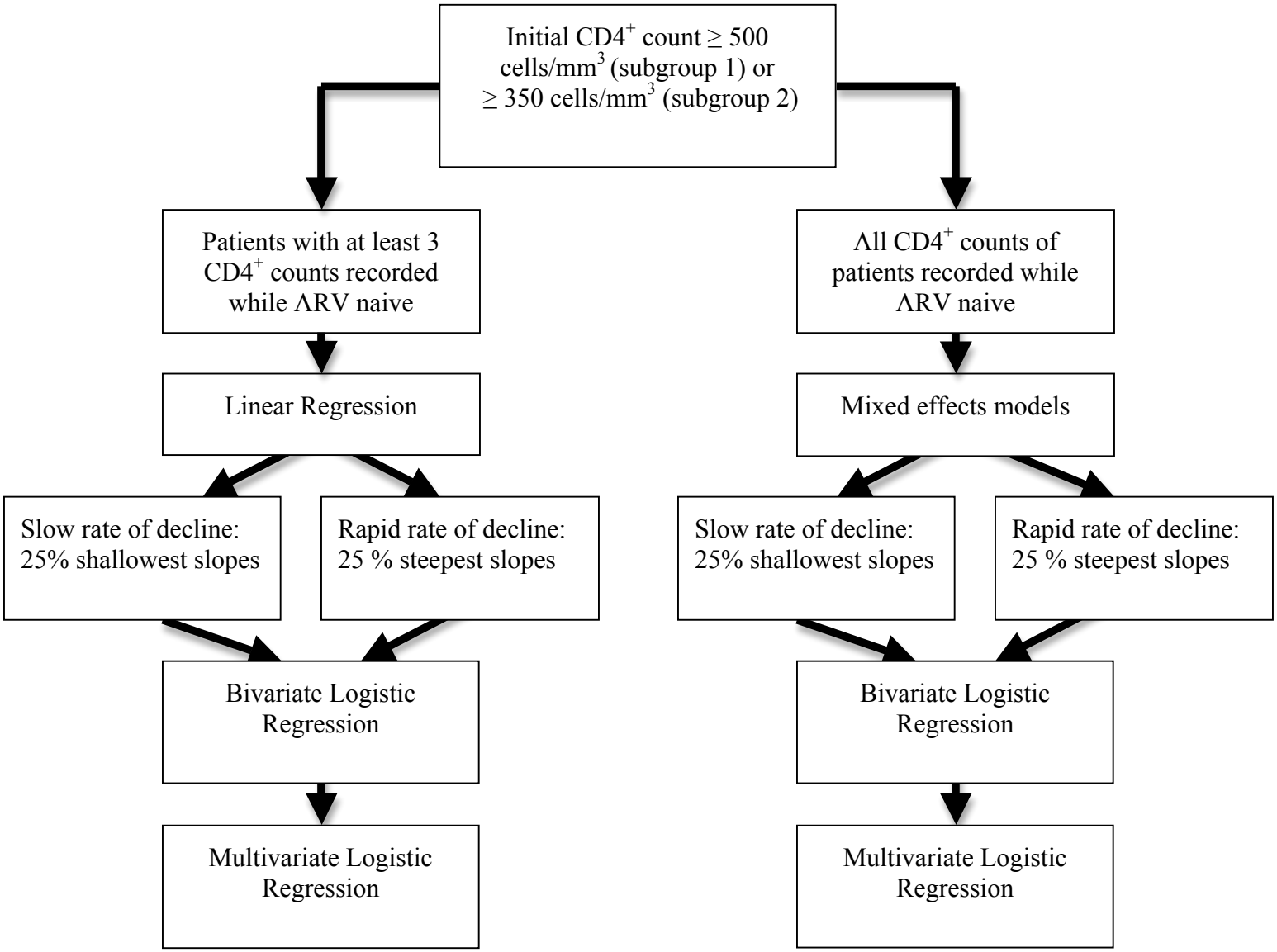
A summary of the statistical analysis performed in Study Objective 3 is presented in Figure 3.2. To examine the third and final study objective, rates of $CD4^+$ count decline were calculated by means of both linear regression and mixed effects models. Included in this analysis were $CD4^+$ counts of patients who were not prescribed ARV during the follow-up period, in addition to $CD4^+$ counts recorded before initiation of ARV therapy of patients who did receive ARV during the follow-up period. Therefore, only $CD4^+$ counts recorded while patients were ARV naïve were included in this analysis. The exclusion of $CD4^+$ counts recorded after patients were prescribed ARV, allows for the examination of the natural rate of $CD4^+$ decline. The intent to treat principle was used in this analysis and we did not account for the effects of stoppages, changes, or non-adherence to treatment regimes.

Only patients with at least 3 $CD4^+$ were included in the linear regression. The use of at least 3 $CD4^+$ counts recorded prior to initiation of ARV has previously been used in other studies to estimate $CD4^+$ slope (19,23,55). This analysis was further restricted to include only two subgroups of patients, those with a first recorded $CD4^+$ count of above 500 and above 350 cells/mm^3 (20). The outcome in this analysis was dichotomized as rapid decline or slow decline. Patients were identified as having a rapid or a slow rate of $CD4^+$ count decline by the quartile distribution of the slope of $CD4^+$ count in both linear regression and mixed effects models. Patients with the steepest 25% of slopes were designated as having a rapid rate of decline and patients with the shallowest 25% of slopes were designated as having a slow rate of decline.

A bivariate logistic regression analysis was performed for each of the variables of interest using SAS code *PROC LOGISTIC*. Variables with a p-value of less than 0.25 were considered candidates for inclusion in multivariate models. Taking into account the high collinearity between ethnicity, HCV co-infection and IDU, multivariate logistic regression models were built to estimate the associations of relevant variables to patient designations of rapid and slow decline. Interaction terms comprised of First Nations or Métis Ethnicity with ARV; HCV with ARV; and IDU with ARV were included in multivariate models to assess for significance.

The type I error rate was set at $\alpha = 0.05$. All analysis was done using SAS version 9.2.

Figure 3.2. Summary of statistical analysis to examine Study Objective 3.



4.Results

4.1 Baseline Characteristics

4.1.1. Demographics and Social Characteristics.

Baseline patient characteristics are summarized in Table 4.1. A total of 457 HIV infected patients met the inclusion criteria for this study. The average age at HIV diagnosis was 35.6 (SD ± 10.1) years. There were 245 patients who identified as of male gender (53.6%). Information describing ethnicity was not available for 64 patients. Several patients' ethnicity was designated as both Caucasian and Métis, in these instances individuals were categorized as Métis. Among those about whom information on ethnicity was available, 279 (71.0%) self-identified as First Nations (n=245, 62.3 %) or Métis (n= 34, 8.7%), and 114 (29.0 %) self-identified as being of other ethnicity. Within the group identifying as of other ethnicity, 94 (23.9 %) were Caucasian, 16 (4.1 %) were African, and 4 (1.0 %) were of other ethnicity. The most commonly reported HIV exposure category was IDU (n=324, 74.5%), followed by heterosexual contact (n=68, 15.6%), MSM (n=29, 6.7%) and MSM/IDU (n=13, 3.0%). Three-hundred and thirty three (72.9%) patients had a history of IDU or reported IDU as an exposure. Two hundred and eleven (46.1%) patients attended clinic visits exclusively at the PLP, 143 (31.3 %) exclusively at the WSCC, and 103 (22.5%) were seen at both sites. Among 212 women, 41 (19.3%) experienced at least one pregnancy during the follow-up period, 34 experienced 1 pregnancy and 7 experienced 2 pregnancies.

One hundred and fifty-nine (34.8%) patients were recipients of social assistance and fifty-five (12.0 %) were case management clients. One hundred and thirty (28.4 %)

patients were incarcerated during the follow-up time. Information about smoking status was missing for 163 patients. Among those for whom information was available 33 (11.2%) were non-smokers, 27 (9.18 %) were ex-smokers, and 234 (79.6 %) were current smokers.

4.1.2. Clinical Characteristics

Three hundred and fourteen patients (68.7%) were followed for at least 1 year. The mean follow-up time was 46.3 months (SD± 26.8). Four hundred and eleven patients had at least one recorded $CD4^+$ count; the remaining 46 patients did not have any $CD4^+$ counts recorded. Among these 411 participants, a total of 2,554 $CD4^+$ counts were recorded. Two hundred and eighty three (61.9%) patients had a baseline viral load, 301 (65.9%) patients had a baseline $CD4^+$ count and 276 (60.4%) patients had both a baseline $CD4^+$ count and a baseline viral load. In our study, the first $CD4^+$ count and viral load recorded within 6 months of diagnosis was considered as the baseline measurement. Mean baseline $CD4^+$ count was 378 (SD ± 233) cells/mm^3 and mean baseline log viral load was 4.4 (SD ± 1.0) copies/mm^3. The mean number of $CD4^+$ counts recorded per patient during the follow-up period was 5.30 (SD ± 4.28) and the mean number recorded for a given patient in a single year was 2.3 (SD ±1.16).

A total of 279 (61%) patients were recipients of ARV during the follow-up period. Three hundred and forty (74.4%) patients tested positive for HCV antibodies and 278 (65.6%) had a positive HCV polymerase chain reaction (PCR), for 31 patients there was no record in their charts of HCV testing.

Thirty three (7.2%) patients were diagnosed with clinical AIDS and 192 (42.0%) patients were classified as having immunological AIDS (defined as having recorded at least one $CD4^+$ count below 200 cells/mm^3). In total, including both clinical and immunological AIDS diagnosis, 197 (43.1%) patients were diagnosed with AIDS during the study follow-up time. Thirty-three (7.2%) patients were deceased. The vital status of one patient was unknown.

Table 4.1. Baseline patient characteristics (N=457).

Variable	Mean (± SD), Number (%)
Mean Follow-Up Time (Months)	46.3 (± 26.8)
Age (Years)	35.6 (± 10.14)
Men	245 (53.6 %)
Ethnicity	
Caucasian	94 (23.9 %)
First Nations	245 (62.3 %)
Métis	34 (8.7 %)
African	16 (4.1 %)
Other	4 (1.0 %)
Missing	64
First Nations or Métis	279 (71.0 %)
Other	114 (29.0 %)
Exposure category	
MSM	29 (6.7 %)
MSM/IDU	13 (3.0 %)
IDU	324 (74.5 %)
Heterosexual contact	68 (15.6 %)
Other	1 (0.2 %)
Missing	22
Total number of women who experienced pregnancy	41
1 pregnancy	34
2 pregnancies	7
Site	
PLP	211 (46.1 %)
WSCC	143 (31.3 %)
Both	103 (22.5 %)
Smoking Status	
Non-smoker	33 (11.2 %)
Ex-smoker	27 (9.2 %)
Current smoker	234 (79.6 %)
Missing	163
Case Management	55 (12.0 %)
Social Assistance	159 (34.8 %)
Case Management and Social Assistance	29 (6.3 %)
STI	142 (31.1 %)

ARV	279 (61.1 %)
HCV antibodies Missing	340 (74.4 %) 31
HCV PCR positive	278 (65.7 %)
IDU Missing	333 (72.9 %) 2
Incarcerated	130 (28.4 %)
At least 1 $CD4^+$ count	411 (89.9 %)
Patients with baseline $CD4^+$ count	301 (65.9 %)
Baseline $CD4^+$ count	377.7 (± 232.9) cells/mm^3
Mean Number of $CD4^+$ counts per patient during follow-up period	5.30 (± 4.28)
Mean Number of $CD4^+$ counts per patient in one year	2.32 (± 1.16)
Patients with a baseline viral load	283 (61.9 %)
Baseline Viral Load	238,473 (± 957,189) copies/mm^3
Log 10 of baseline viral load	4.4 (± 0.96) copies/mm^3
Patients with both baseline viral load and baseline $CD4^+$ count	276 (60.4 %)
Clinical AIDS	33 (7.2 %)
Immunological AIDS	192 (42.0 %)
Total AIDS	197 (43.1 %)
All Cause Mortality	33 (7.2 %)

4.2 Special Cases in Dataset

Two patients were diagnosed with cancer during the follow-up time one with diffuse B cell lymphoma and the other with Hodgkin's lymphoma. It was noted in these patients' charts that low $CD4^+$ cells counts recorded were more likely due to chemotherapy for the treatment of these malignancies as opposed to attributable to advancements in HIV disease progression. Another patient had an undetectable viral load despite not receiving any treatment and suspicion of advanced disease. It was noted in this patient's chart that there maybe a mutation in the HIV virus prohibiting amplification. One patient, was recorded as never having received ARV in spite of being prescribed atripla, because this patient took this medication for only 2 days before discontinuing the medication due to side effects without consulting a clinician. This

patient was subsequently lost to follow-up for approximately two years, after which time ARV had not been reinitiated as of the completion of follow-up time for this study.

Another condition causing depletion in $CD4^+$ count unrelated to HIV disease progression is pregnancy (109). A total of 41 (19.3% of all women) women enrolled in this study experienced at least 1 pregnancy during the course of HIV infection, with 34 women experiencing one pregnancy and 7 experiencing two pregnancies. Therefore, it is important to consider that any decline in $CD4^+$ count observed during pregnancy might be naturally occurring and thereby unrelated to HIV progression.

4.3 Association Analysis.

Table 4.2 summarizes the association among selected variables. Pearson's chi-square tests were used to assess the associations between these categorical variables. The variables of HCV co-infection, First Nations or Métis Ethnicity and IDU are highly correlated. Individuals with a history of IDU were 176.06 ($p<0.0001$) times as likely to also be HCV co-infected. Individuals self-identifying as of First Nations or Métis ethnicity were 9.95 ($p<0.0001$) times as likely to have a history of IDU and 13.97 ($p<0.0001$) as likely to be HCV co-infected. Also of note, the odds of HCV co-infection among Case Management Clients was 15.11 ($p=0.0004$) times that of patients not accessing such services and 11.43 ($p<0.0001$) times greater among patients with a history of incarceration.

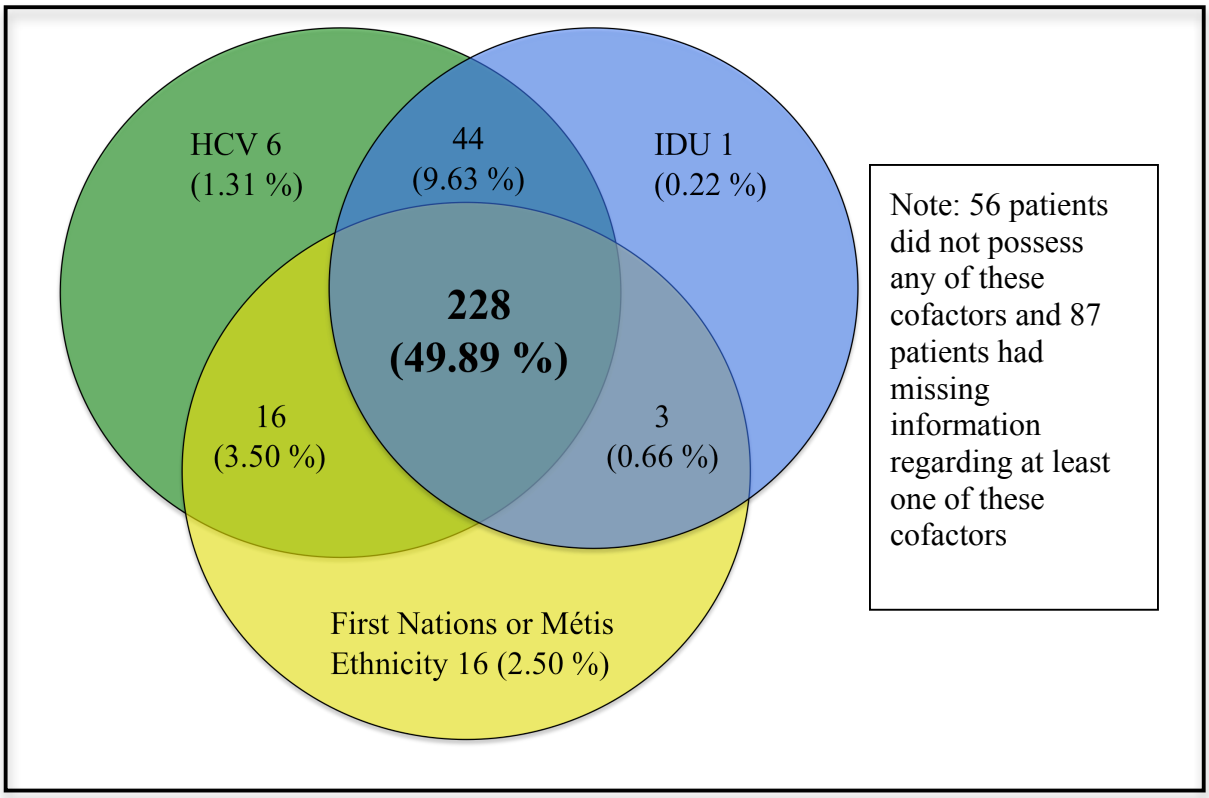
Table 4.2. Chi-Square Test of selected variables with OR and 95% CI of OR and p-value.

OR 95% CI of OR P-value	**Gender**	**First Nations or Métis Ethnicity**	**HCV co-infection**	**IDU**	**Recipient of Social Assistance**	**Case Manage-ment**	**Incar-ceration**
Gender	---	0.26 (0.16, 0.43) <0.0001	0.57 (0.35, 0.93) 0.024	0.53 (0.35, 0.82) 0.0040	0.62 (0.42, 0.91) 0.0156	0.23 (0.12,0.44) <0.0001	1.33 (0.89, 2.01) 0.17
First Nations or Métis Ethnicity		---	13.97 (7.72, 25.28) <0.0001	9.95 (5.97, 16.58) <0.0001	2.27 (1.39, 3.69) 0.0009	5.43 (1.91, 15.46) 0.0005	2.06 (1.24, 3.44) 0.0051
HCV Co-infection			---	176.06 (65.87,470.54) <0.0001	3.13 (1.72, 5.69) 0.0001	15.11 (2.06, 110.96) 0.0004	11.43 (4.09, 31.94) <0.0001
IDU				---	2.61 (1.59, 4.26) <0.0001	7.34 (2.25, 23.97) 0.0001	5.76 (2.98, 11.13) <0.0001
Recipient of Social Assistance					---	2.32 (1.31, 4.09) 0.0032	1.25 (0.82, 1.91) 0.29
Case Management						---	1.10 (0.60, 2.03) 0.75
Incarceration							---

4.4. Overlap in Highly Associated Variables among the Study Population.

Figure 4.1 summarizes the overlap of co-factors among the study population. This figure emphasizes the high degree of association among these three variables as was found in the association analysis (Table 4.2).

Figure 4.1. Overlap of patient characteristics of First Nations or Métis Ethnicity, IDU and HCV co-infection. (n= 457).



4.5. Graphical Representations of Repeated $CD4^+$ Count Measurements

The $CD4^+$ counts among 10 randomly selected patients are presented in Figure 4.2. Figure 4.3. presents the mean $CD4^+$ count among the entire population throughout the follow-up period. A series of Figures summarizing the mean $CD4^+$ count in 3-month intervals, over the follow-up time among the total population and by variables of interest are presented in Figures 4.4 through 4.11. Table 4.3. summarizes the number of patients who contributed one $CD4^+$ count to a given 3-month interval. In our study if more than one $CD4^+$ count for a given patient was available during a single interval, the mean value of these counts was used. Graphs were truncated at 72 months due to the declining number of patients contributing $CD4^+$ counts to the dataset after this many months of follow-up (see Table 4.3).

Figure 4.2. $CD4^+$ counts recorded among 10 randomly selected patients.

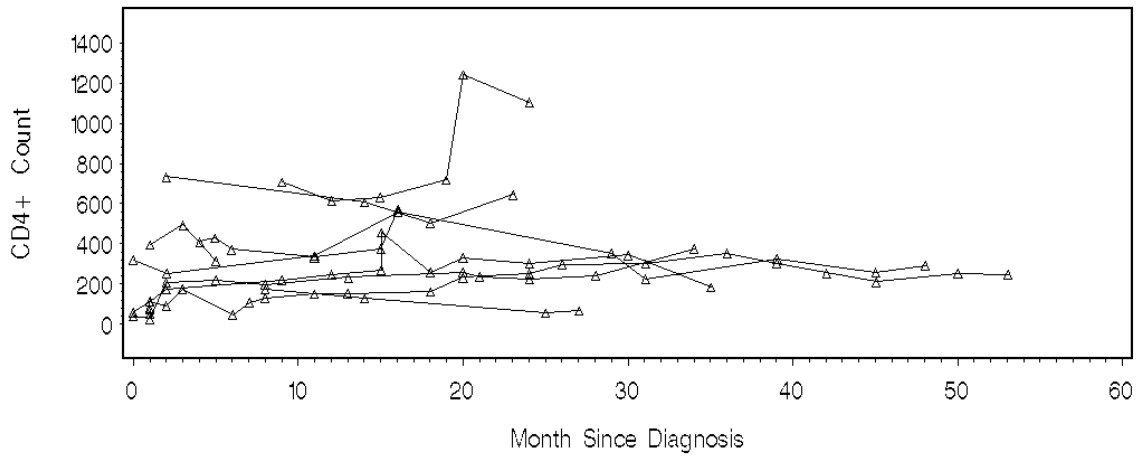


Table 4.3. Number of patients contributing at least 1 $CD4^+$ count by 3-month intervals since time of diagnosis.									
Months	**≤3**	**3-6**	**6-9**	**9-12**	**12-15**	**15-18**	**18-21**	**21-24**	**24-27**
Number	240	173	166	142	133	133	118	116	108
Months	**27-30**	**30-33**	**33-36**	**36-39**	**39-42**	**42-45**	**45-48**	**48-51**	**52-54**
Number	106	94	76	65	62	49	57	45	34
Months	**54-57**	**57-60**	**60-63**	**63-66**	**66-69**	**69-72**	**72-75**	**75-78**	**78-81**
Number	31	39	30	16	30	22	16	18	13
Months	**81-84**	**84-87**	**87-90**	**90-93**	**93-96**	**96-99**	**99-102**	**102-105**	**105-107**
Number	11	7	8	5	7	3	3	1	1

Figure 4.3. Mean $CD4^+$ count with 95% confidence limits of the 3-month intervals over follow-up time.

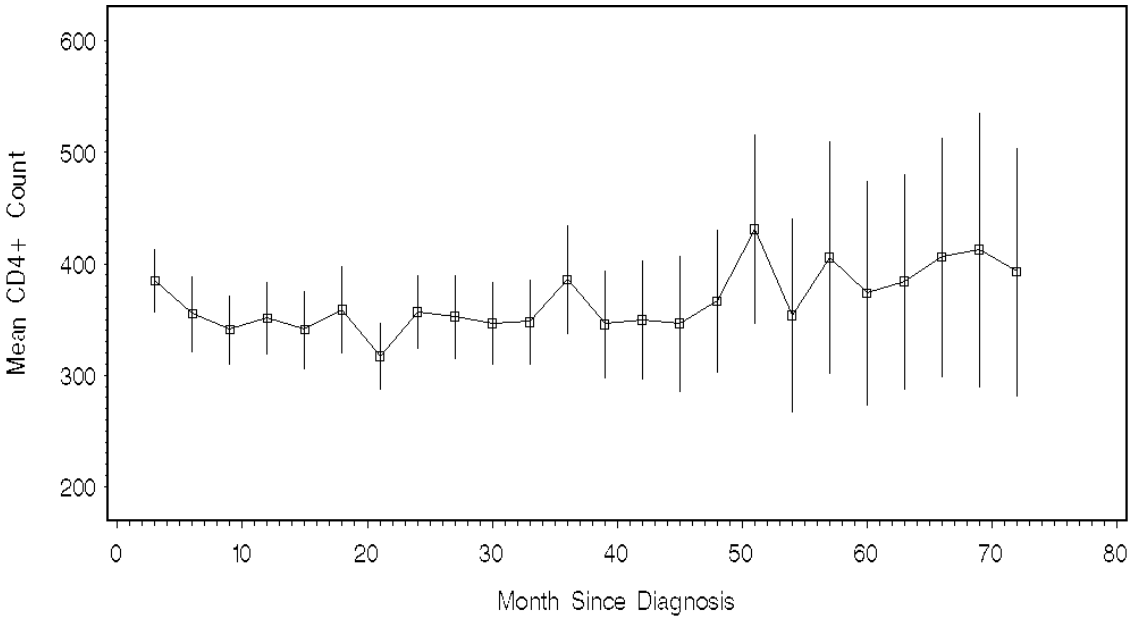


Figure 4.4. Mean $CD4^+$ count in 3 months intervals over follow-up time by age at diagnosis, where error bars represent 95% confidence intervals.

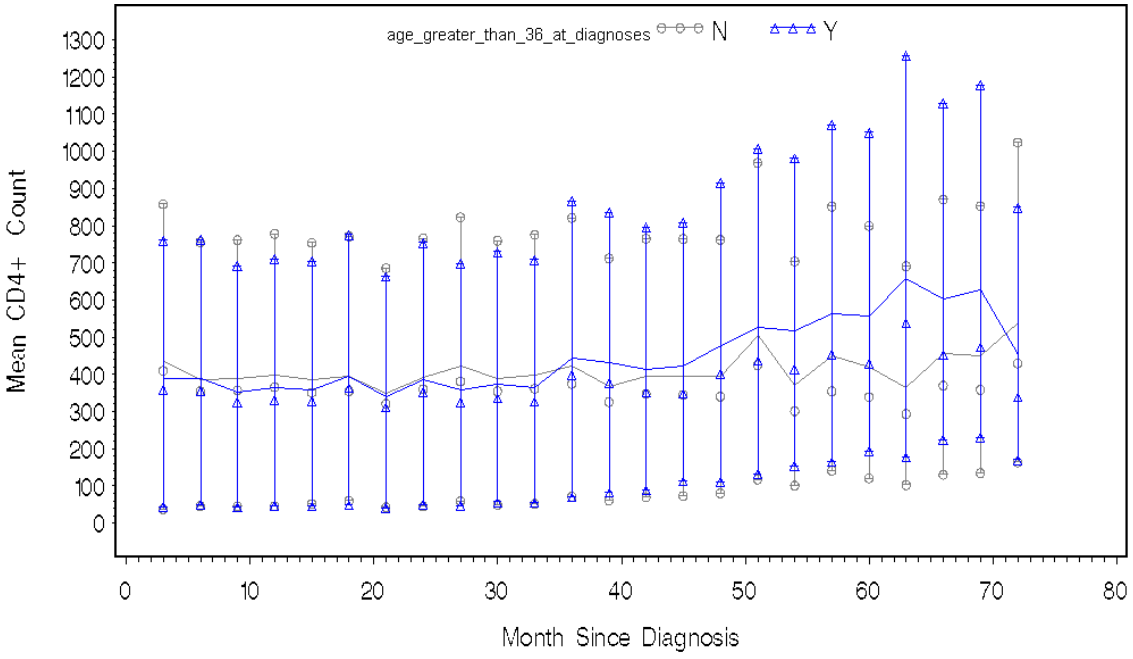


Figure 4.5. Mean CD4^{+} count in 3 month intervals over follow-up time by gender with error bars representing the standard deviation,where error bars represent 95% confidence intervals.

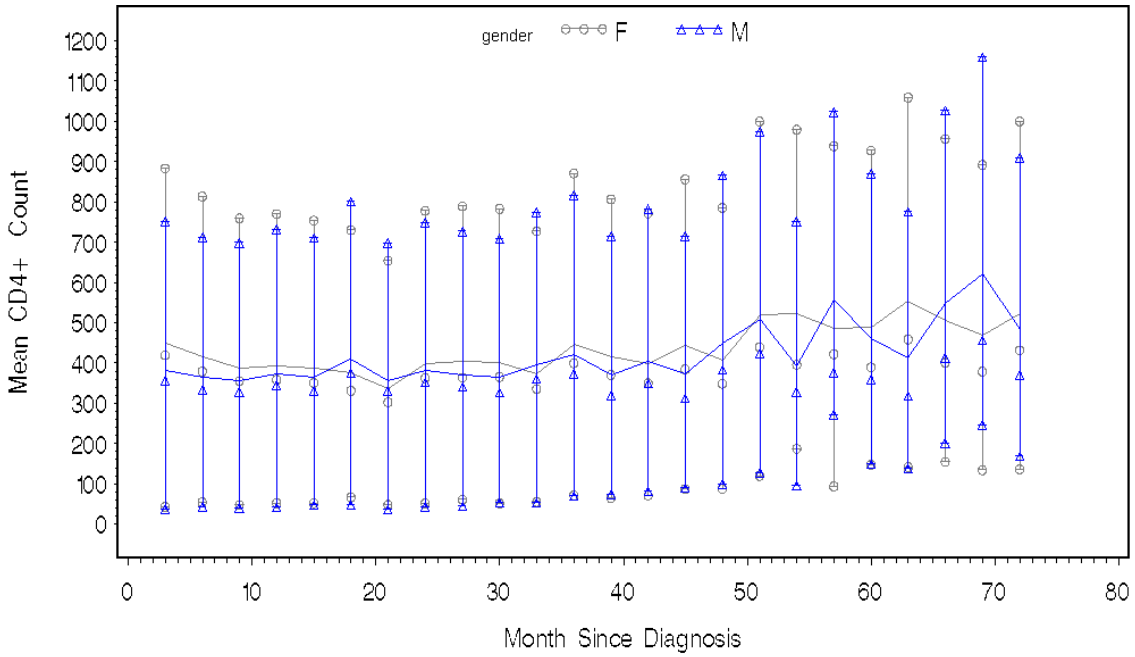


Figure 4.6. Mean CD4^{+} count in 3 month intervals over follow-up time by ethnicity, where error bars represent 95% confidence intervals.

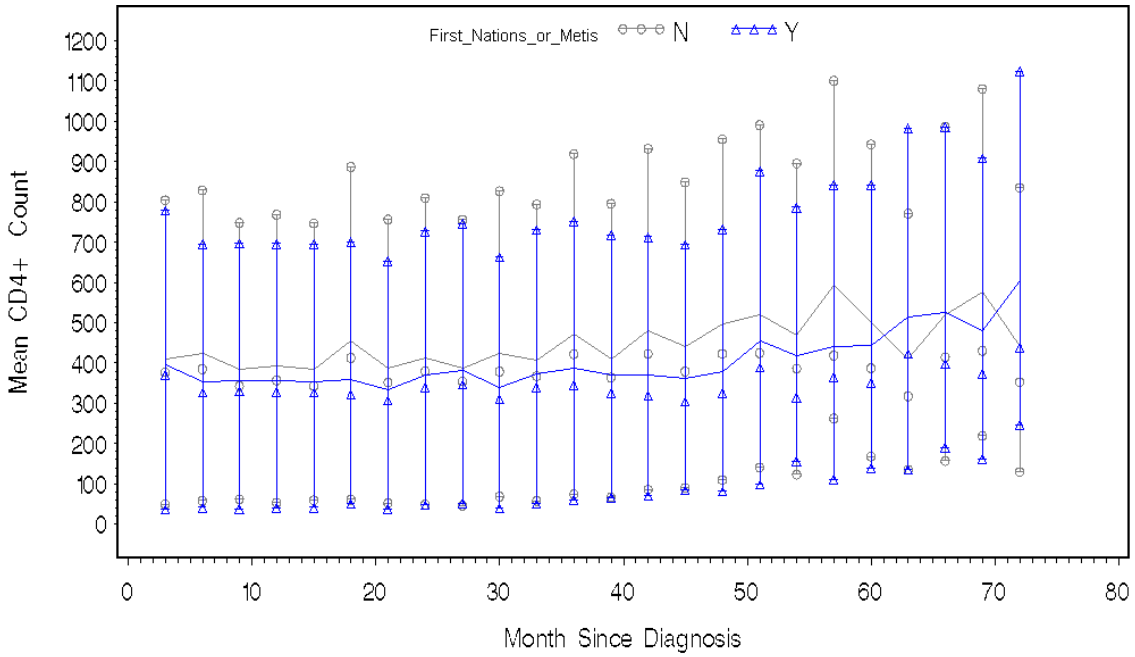


Figure 4.7. Mean CD4^{+} count in 3 month intervals over follow-up time by HCV infection status, where error bars represent 95% confidence intervals.

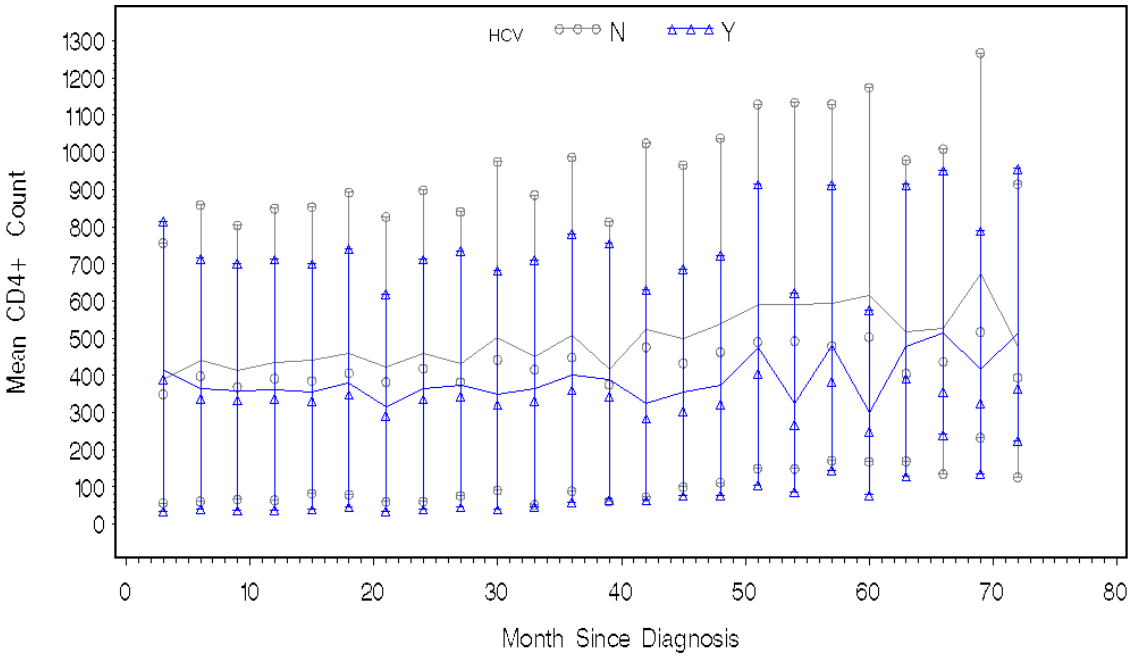


Figure 4.8. Mean CD4^{+} count in 3 month intervals over follow-up time IDU status, where error bars represent 95% confidence intervals.

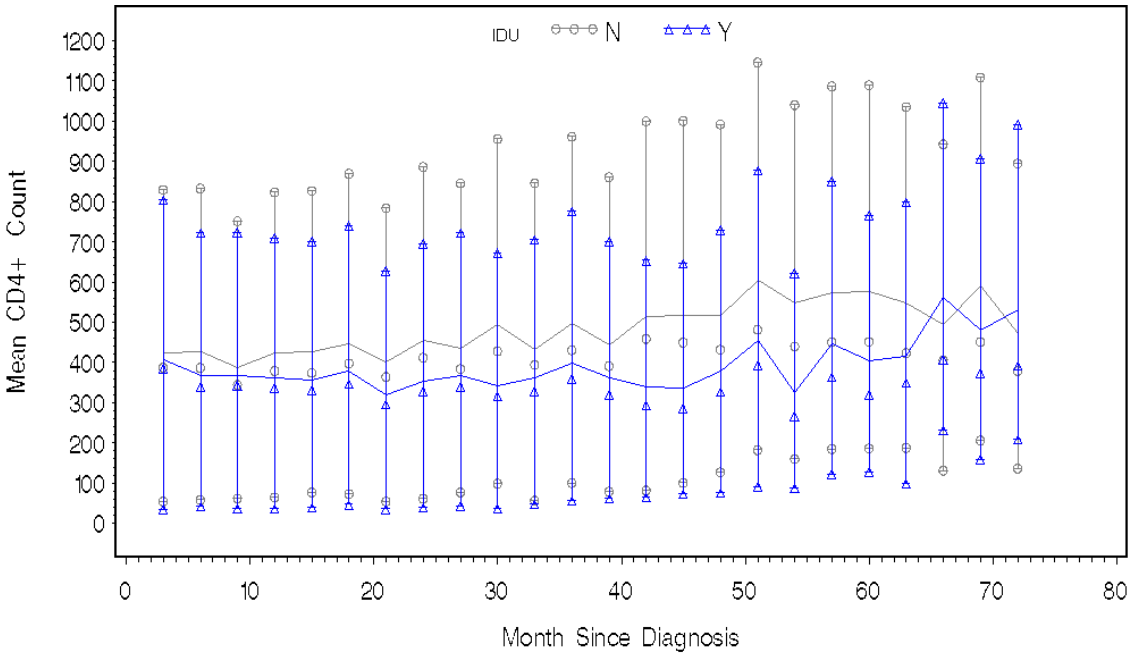


Figure 4.9. Mean CD4^{+} count in 3 month intervals over follow-up time by receipt of social assistance, where error bars represent 95% confidence intervals.

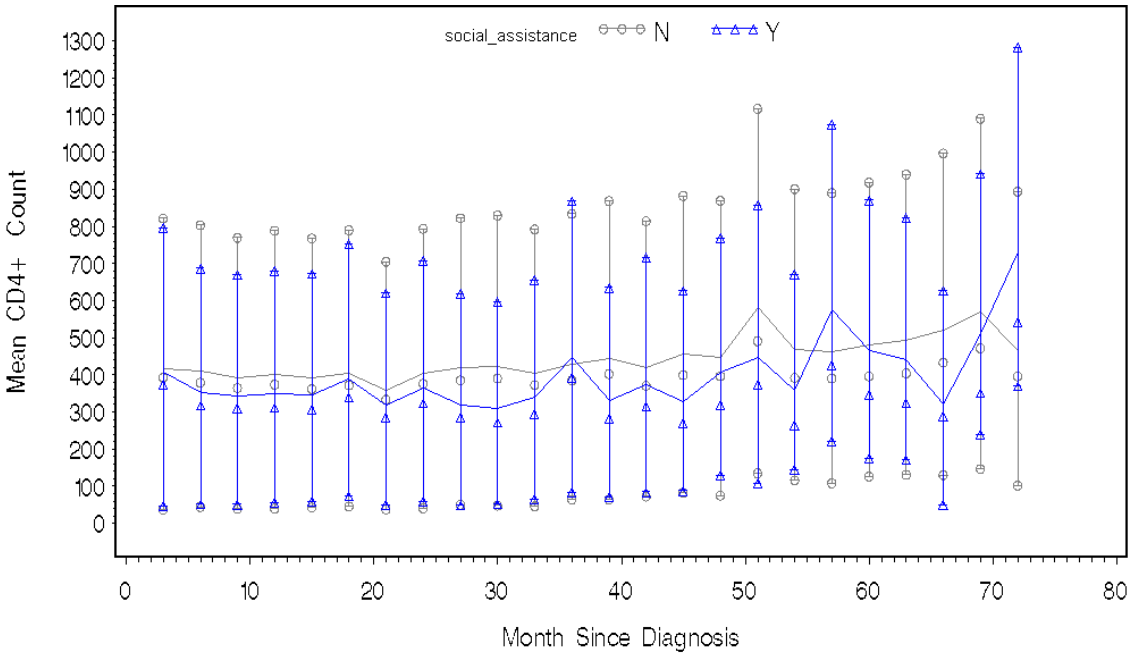


Figure 4.10. Mean CD4^{+} count in 3 month intervals over follow-up time among case management clients as compared to non-clients, where error bars represent 95% confidence intervals.

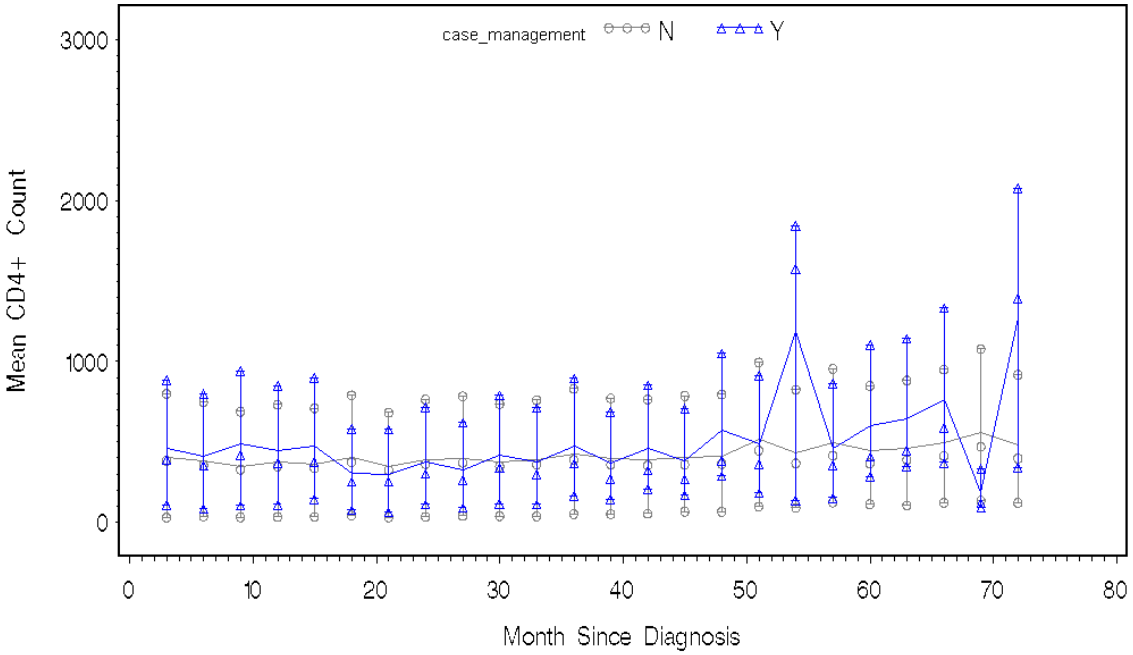


Figure 4.11. Mean CD4^{+} count in 3 month intervals over follow-up time among patients diagnosed with an STI during follow-up as compared to those who were not, where error bars represent 95% confidence intervals.

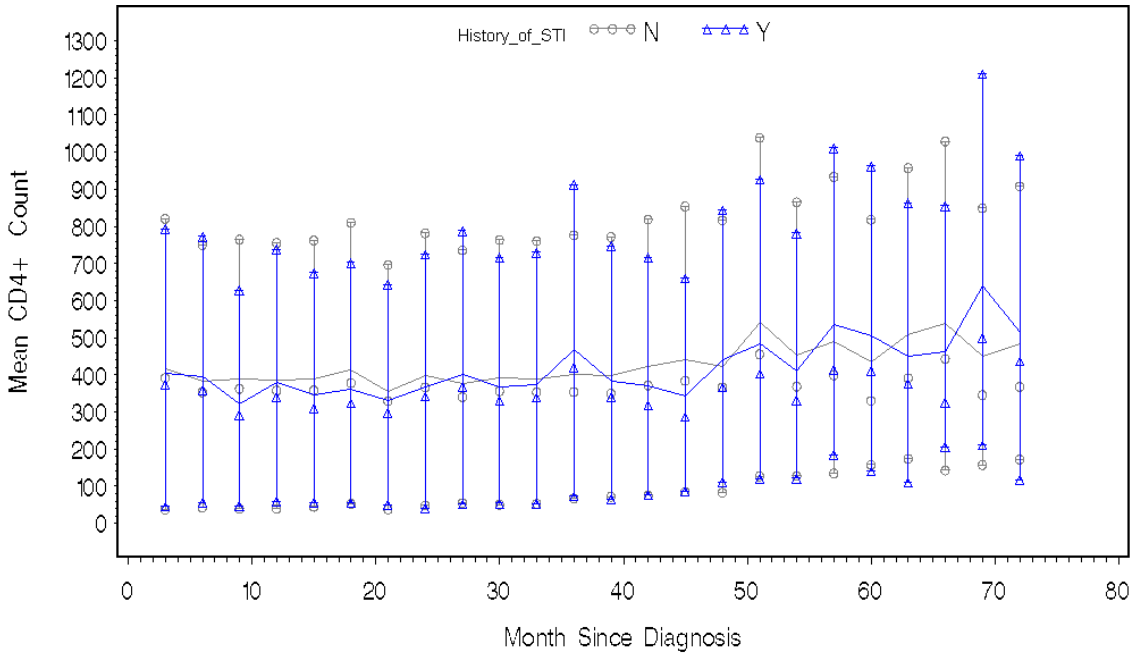


Figure 4.12. Mean CD4^{+} count in 3 month intervals over follow-up time by incarceration during follow-up status, where error bars represent 95% confidence intervals.

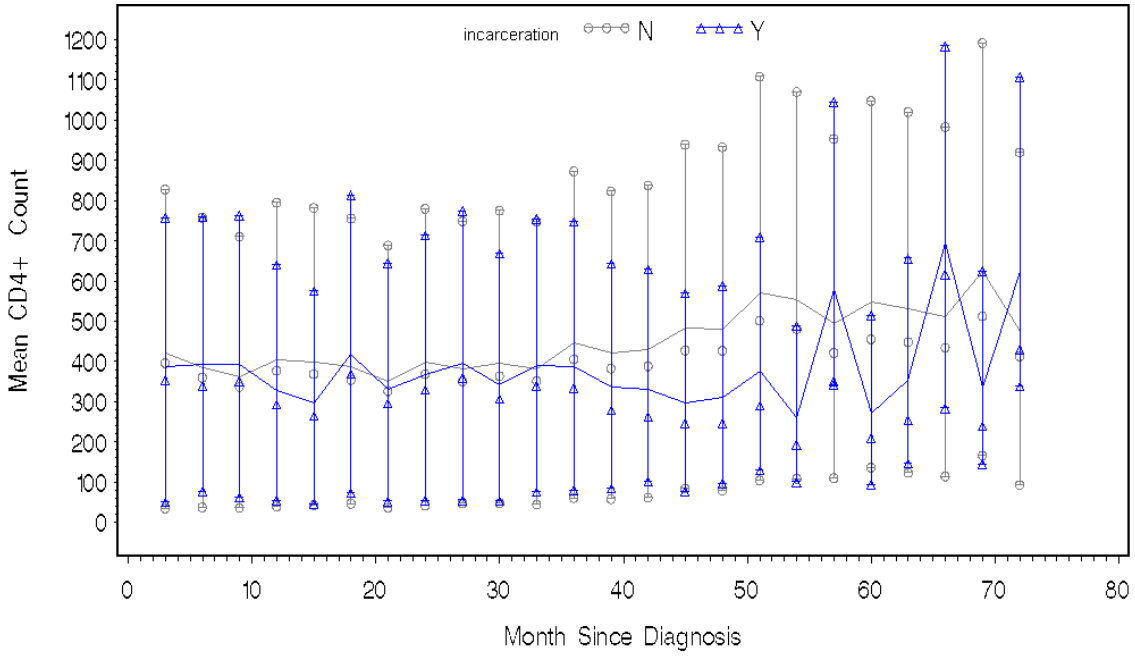
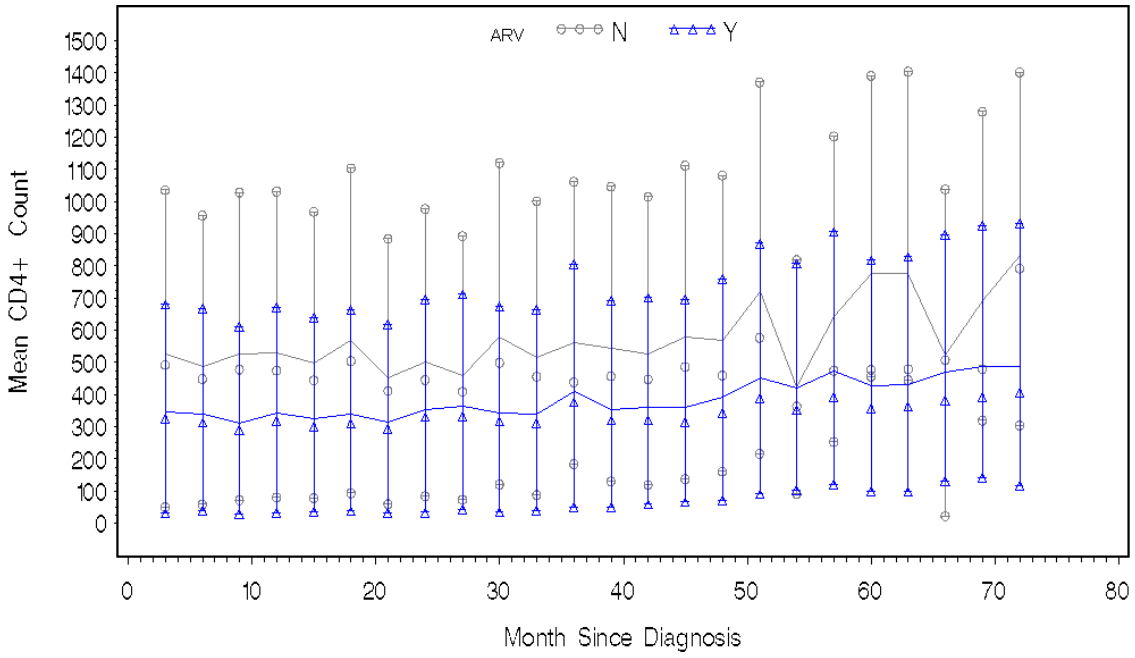


Figure 4.13. Mean $CD4^+$ count in 3 month intervals over follow-up time by receipt of ARV status (at any time during follow-up period) , where error bars represent 95% confidence intervals.



4.6. Objective 1: Results from Linear Regression Analysis

4.6.1. Overall Rate of Change in $CD4^+$ Count Determined by Univariate Linear Regression.

The mean rate of change in $CD4^+$ count over the follow-up period was estimated using linear regression. In this analysis we included all patients with a minimum of 3-recorded $CD4^+$ counts. This resulted in a total of 284 (62.1%) patients meeting the inclusion criteria. The mean intercept among included patients was 370.5 (SE = ± 259.6) cells/mm^3 and the mean slope was -0.67 (SE=±10.2) cells/mm^3 per month.

4.6.2. Study Objective 1: $CD4^+$ Rate of Change Among Groups of Interest.

In order to examine differences in rates of change in $CD4^+$ count associated with cofactors of interest slope of $CD4^+$ count was first estimated for each patient using linear regression. Subsequently, the mean slope among patients possessing a given cofactor was calculated and compared to the mean slope among patients in whom the same cofactor was absent. In order to examine older as compared to younger age at diagnosis patients were categorized as above or below the mean age at diagnosis (36 years of age). T-tests as well as non-parametric Wilcoxon Rank Tests were used to compare the mean $CD4^+$ intercepts and mean slope between groups. The results of study objective 1 are summarized in Table 4.4. Equations generated by this analysis follow the formula: $y = \beta_0 + \beta_1 X_1 + \varepsilon$.

Where Y is the estimated $CD4^+$ count at a given month since time of HIV diagnosis, β_0 is the intercept ($CD4^+$ count at months since diagnosis equal to zero, or at time of diagnosis) and β_1 is the slope of $CD4^+$ count in units of cells/mm^3 per month since diagnosis.

Examples of the equations generated are given for the cofactors gender and ethnicity.

Table 4.4. Estimates of $CD4^+$ count intercept and slope as determined by univariate linear regression among patients with 3 or greater recorded counts (N=284).

Variable	Intercept (± SE)	p-value*	Slope (± SE)	p-value **
Age				
≤ 36	385 (280)	0.28 (0.13)	-1.53 (10.78)	0.10 (0.059)
> 36	351 (230)		0.46 (9.40)	
Male	355 (262)	0.53 (0.47)	-0.96 (11.41)	0.62 (0.89)
Female	387 (257)		-0.36 (8.82)	
First Nations or Métis Ethnicity				
Yes	371 (246)	0.78 (0.92)	-1.28 (10.65)	0.23 (0.09)
No	362 (241)		0.35 (8.82)	
HCV				
Yes	380 (260)	0.36 (0.60)	-1.54 (11.07)	**0.0079 (0.0005)**
No	346 (256)		2.37 (6.92)	
IDU				
Yes	389 (257)	0.058 (0.075)	-2.05 (10.56)	**0.0002 (<0.0001)**
No	322 (265)		3.03 (8.36)	
Incarceration				
Yes	385 (269)	0.54 (0.71)	-3.26 (11.39)	0.06 **(0.02)**
No	364 (256)		0.51 (9.47)	
Social Assistance				
Yes	353 (240)	0.33 (0.30)	-1.83 (10.90)	0.13 (0.24)
No	384 (272)		0.051 (9.77)	
Case Management				
Yes	400.60 (272)	0.40 (0.48)	-1.27 (9.06)	0.67 (0.14)
No	364.78 (257)		-0.56 (10.46)	
STI				
Yes	332 (229)	0.07 (0.16)	-0.26 (10.59)	0.62 (0.24)
No	391 (273)		-0.90 (10.07)	
ARV				
Yes	307 (235)	**<0.0001 (<0.0001)**	0.58 (10.21)	**0.0004 (<0.0001)**
No	555 (239)		-4.30 (9.51)	

T-tests were performed with results of Wilcoxon Rank Test in parentheses. Bolded p-values are significant at the 0.05 level.

* Group difference in intercept

** Group difference in slope

4.6.3. Gender

Among patients of male gender the mean intercept was 355 cells/mm^3 (SE= ± 262) and the mean slope was -0.96 cells/mm^3 per month (SE = ±11.4). Among patients of female gender the mean intercept was 387 cells/mm^3 (SE ±257) and the mean slope was -0.36 cells/mm^3 per month (SE ± 8.8).

The equation for CD4+ count among men as estimated by linear regression analysis is as follows:

$CD4^+ = 355 - 0.96$ (month)

Therefore, among men the estimated $CD4^+$ at time of diagnosis is 355 cells/mm^3 and $CD4^+$ count is declining at a rate of -0.96 cells/mm^3 per month.

Among women the equation is:

$CD4^+ = 387 - 0.36$ (month)

Therefore, among women the estimated $CD4^+$ at time of diagnosis is 387 cells/mm^3 and $CD4^+$ count is declining at a rate of -0.36 cells/mm^3 per month. Females have a higher mean $CD4^+$ count at time of diagnosis, however this value is not significantly greater than that among males (p=0.31). Females in this population are experiencing a slower rate in $CD4^+$ decline as compared to men, however this difference is not statistically significant (p=0.53).

4.6.4. Ethnicity

Patients who self-identified as of First Nations or Métis ethnicity had a mean intercept of 371 (SE = ± 246) cells/mm^3 and a mean slope of -1.28 (SE = ± 10.64)

cells/mm^3 per month. The equation for CD4$^+$ count as estimated by linear regression among patients of First Nations or Métis ethnicity is as follows:

CD4$^+$ = 371.03 - 1.28 (month)

Patients who self-identified as of other ethnicity had a mean intercept of 362 cells/mm^3 (SE = ± 241) and a mean slope of 0.35 (SE = ± 8.8) cells/mm^3 per month. The equation for CD4$^+$ count as estimated by linear regression among patients of ethnicity other than First Nations or Métis is as follows:

CD4$^+$ = 361.7 + 0.35 (month)

Patients of First Nations or Métis ethnicity had a higher CD4$^+$ count at diagnosis and a steeper decline in CD4$^+$ count. Neither CD4$^+$ at time of diagnosis (p=0.78) nor CD4$^+$ slope (p=0.23) was significantly different between these groups.

4.6.5. HCV

The mean intercept in patients among whom HCV antibodies were present was 380 (SE = ± 260) cells/mm^3 and the mean slope was -1.6 (SE = ± 11.1) cells/mm^3 per month. The mean intercept among HCV negative patients was 346 (SE = ± 256) cells/mm^3 and the mean slope was 2.4 (SE = ± 6.9) cells/mm^3 per month. The mean intercept at time of diagnosis among HCV antibody positive patients was higher than among HCV un-infected patients, however this difference was not significant (p=0.36). The mean slope among patients in whom HCV antibodies were present was significantly steeper than among patients who were HCV antibody negative (p=0.0079).

4.6.6. IDU

The mean intercept among patient with a history of IDU was 389 cells/mm^3 (SE = ± 257) and the mean slope was -2.1 (SE = ± 10.6) cells/mm^3 per month. Among patients without a history of IDU the mean intercept was 322 (SD = ± 265) cells/mm^3 and the mean slope was 3.0 (SE = ± 8.4) cells/mm^3 per month. At time of diagnosis $CD4^+$ count among patients with a history of IDU was higher than among patients without a history of IDU and this difference was very close to statistically significant (p=0.06). Patients with a history of IDU had a significantly steeper decline in $CD4^+$ count as compared to those who had never been IDUs (p=0.0002).

4.6.7. Incarceration

Patients who were incarcerated during follow-up had a mean intercept of 385 (SE = ± 269) cells/mm^3 and a mean slope of -3.3 (SE = ± 11.4) cells/mm^3 per month. Patients who were not incarcerated have a mean intercept of 364 (SE = ± 256) and a mean slope of 0.49 (SE = ± 9.5). Mean $CD4^+$ count at time of diagnosis was higher among incarcerated patients, this difference was not significant (p=0.54). $CD4^+$ count slope among individuals incarcerated during follow-up was almost significantly steeper than the slope among individuals not incarcerated during this time (p=0.06) and was significantly steeper when tested using the non-parametric Wilcoxon Rank Test (p = 0.02).

4.6.8. Social Assistance and Social Support

Recipients of social assistance had a mean intercept of 353 (SE = ± 240) cells/mm^3 and a mean slope of -1.9 (SE = ± 10.9) cells/mm^3 per month. Patients without a history of receiving social assistance had a mean intercept of 383.5 (SD = ± 271) cells/mm^3 and a mean slope of 0.05 (SE = ± 9.8) cells/mm^3 per month. The mean $CD4^+$ count at time of diagnosis was greater among patients who did not receive social assistance, this difference was not significant (p=0.33). The $CD4^+$ count slope among recipients of social assistance was not significantly different as compared to that among patients who did not receive social assistance (p=0.13).

4.6.9. Case Management

The mean intercept among case management clients was 401 (SE = ± 272) cells/mm^3 and the mean slope was -1.27 (SE = ± 9.1) cells/mm^3 per month. The intercept among patients who were not case management clients was 365 (SE = ± 257) cells/mm^3 and the mean slope was -0.57 (SE = ± 10.5) cells/mm^3 per month. The mean $CD4^+$ count at time of diagnosis was higher among case management clients, however this difference was not significant (p=0.40). The mean slope was not significantly different between these two groups (p=0.67).

4.6.10. STIs

The mean intercept among patients with a history of STI co-infection was 333 (SE = ± 229) cells/mm^3 and the mean slope was -0.29 (SE = ± 10.6) cells/mm^3 per month. The mean intercept among patients without a history of STI co-infection was 391

(SE = ± 273) cells/mm^3 and the mean slope was -0.90 (SE = ± 10.1) cells/mm^3 per month. $CD4^+$ count at time of diagnosis was greater among patients who had not contracted an STI and this difference neared statistical significance (p=0.07). The slope of $CD4^+$ count was not significantly different between these two groups (p=0.62).

4.6.11. ARV

The mean intercept among patients who received ARV was 307 (SE = ± 235) cells/mm^3 and the mean slope was 0.57 (SE = ± 10.2) cells/mm^3 per month. The mean intercept among patients who were not prescribed ARV during the follow-up period was 555 (SE = ± 239) cells/mm^3 and the mean slope was -4.3 (SE = ± 9.5) cells/mm^3 per month. The mean $CD4^+$ count at time of diagnosis among patients not receiving ARV during the follow-up period was significantly higher than patients who did receive ARV (p<0.0001). The mean slope among patients who were not prescribed ARV was significantly steeper than that among patients who were prescribed ARV (p=0.0004).

4.6.12. Summary of Objective 1: Results from Univariate Linear Regression

HCV co-infection, a history of IDU, a record of incarceration and not being prescribed ARV during the follow-up period were independently associated with negative slopes in $CD4^+$ count, which were significantly steeper as compared to patients not characterized by such cofactors. Patients who were not prescribed ARV during the follow-up period had a significantly higher $CD4^+$ count at diagnosis. There was no significant difference in $CD4^+$ count at diagnosis, nor in $CD4^+$ count slope among the

remaining cofactors of interest including, gender, ethnicity, receipt of social assistance, case management, or diagnosis with an STI during follow-up.

4.7. Objective 2: Results from Mixed Effects Analysis

In this study objective, mixed effects model were built to describe the effects of cofactors examined in Study Objective 1 on the $CD4^+$ count of an individual patient.

4.7.1. Results of Univariate Mixed Effects Analysis.

The results of univariate analyses conducted for each variable of interest are summarized in Table 4.5. In these analyses we are making the assumption of a normal distribution of the dependent variable $CD4^+$ count. The general form for equations generated by mixed effects models is:

$$Y_{ij} = \beta_0 + \beta_1(\text{group}) + \beta_2\,(\text{month}) + \beta_3\,(\text{group*month}) + \mu_0 + \mu_1\,(\text{month}) + \varepsilon.$$

Mixed effects models regression parameters have both population and individual level interpretations. Where y_{ij} represents the $CD4^+$ cell count of the i^{th} patient at the j^{th} month, β_0 represents the population mean intercept, β_1 represents the group effect on the population and β_3 represents the interaction between the effect of a cofactor with time since diagnosis, again on the population mean. Individual effects are modeled by μ_0 representing random intercept and by μ_1 representing the $CD4^+$ count random slope, both for the i^{th} patient. Examples of the equations generated by these mixed effects models are given for the variables of gender and age. In these examples we provide the population level interpretations of parameters in these equations.

Table 4.5. Univariate mixed effects models (n=411).				
Covariate	**Variable**	β	**95% CI (β)**	**p-value**
Gender	Intercept	388	(354, 422)	<0.0001
	Male	-45.26	(-91.88, 1.36)	0.057
	Month	-1.18	(-2.23, -0.14)	0.026
	Male*Month	0.95	(-0.52, 2.43)	0.20
Age	Intercept	443	(360, 526)	<0.0001
	Age at diagnosis	-2.85	(-4.43, 0.03)	0.053
	Month	-2.85	(-5.45, -0.02)	0.032
	Age at diagnosis* Month	0.06	(-0.01, 0.13)	0.093
Ethnicity	Intercept	366	(323, 409)	<0.0001
	First Nations or Métis Ethnicity	-9.20	(-60.85, 42.44)	0.73
	Month	0.39	(-1.87, -0.019)	0.56
	First Nations or Métis Ethnicity * Month	-1.41	(-3.00,0.19)	0.084
HCV	Intercept	355	(303, 407)	<0.0001
	HCV	12.82	(-45.66, 71.31)	0.67
	Month	1.88	(0.47, 3.30)	0.0092
	HCV*Month	-3.36	(-5.00, -1.72)	**<0.0001**
IDU	Intercept	361	(316, 406)	<0.0001
	IDU	7.82	(-44.78, 60.42)	0.77
	Month	1.14	(-0.18, 2.46)	0.092
	IDU* Month	-2.62	(-4.19, -1.05)	**0.0011**
Incarceration	Intercept	367	(340, 395)	<0.0001
	Incarceration	-11.99	(-63.84,39.86)	0.65
	Month	-0.27	(-1.15, 0.62)	0.56
	Incarceration*Month	-1.24	(-2.83,0.35)	0.13
Case Management	Intercept	359	(334, 384)	<0.0001
	Case Management	34.44	(-34.84, 103.73)	0.33
	Month	-0.25	(-1.04, 0.54)	0.53
	Case Management * Month	-2.68	(-4.68, -0.67)	**0.0089**
Social Assistance	Intercept	380	(351, 409)	<0.0001
	Social Assistance	- 42.70	(-90.93, 5.53)	0.083
	Month	-0.46	(-1.39, 0.47)	0.33
	Social Assistance* Month	-0.70	(-2.23, 0.82)	0.37
STI	Intercept	370	(341, 399)	<0.0001
	STI	-16.28	(-65.43, 32.87)	0.52
	Month	-0.86	(-1.81, 0.09)	0.076
	STI*Month	0.44	(-1.07, 1.96)	0.57
ARV	Intercept	474	(437, 511)	<0.0001
	ARV	-169	(-215, -123)	**<0.0001**
	Month	-2.64	(-4.02, -1.26)	0.0002
	ARV*Month	2.91	(1.29, 4.53)	**0.0004**

Bolded p-values indicate group differences significant at the 0.05 level.

4.7.2. Gender

The estimate of the univariate mixed effects model describing the effect of gender is presented in this section:

$CD4^+ = 388 – 45.26$ (gender) -1.18 (month) + 0.95 (gender*month)

For example, females (gender =1) at month =2;

$CD4^+ = 388 – 45.26$ (1) -1.18 (2) + 0.95 (1*2)

$= 388 – 45.26 – 2.36 + 1.9$

$= 344.64$ cells/mm^3

Therefore, a patient of female gender at time 2 months after HIV diagnosis will have an estimated mean CD4+ count of 344.64 cells/mm^3.

For examples, males (gender = 2) at month = 2;

$CD4^+ = 388 – 45.26$ (2) -1.18 (2) + 0.95 (2*2)

$= 388 – 90.52 – 2.36 + 3.8$

$= 298.92$ cells/mm^3

Therefore, a patient of male gender at time 2 months after HIV diagnosis will have an estimated mean $CD4^+$ count of 298.92 cells/mm^3. Rate of $CD4^+$ count change is not significantly different over time by gender (p=0.20).

4.7.3. Age

The univariate mixed effects model describing the effect of age at diagnosis on $CD4^+$ status is presented in this section:

$CD4^+ = 443 – 2.20$ (age at diagnosis) -2.85 (month) + 0.06 (age at diagnosis*month)

For example a patient aged 35 at diagnosis, at month = 2;

$CD4^+ = 443 – 2.20\ (35)\ -2.85\ (2) + 0.06\ (35*2)$

$= 443 – 77 – 5.7 + 4.2$

$= 364.5\ cells/mm^3$

Therefore, a patient 35 years of age at diagnosis at time 2 months after HIV diagnosis will have an estimated mean $CD4^+$ count of 364.5 cells/mm^3. Rate of $CD4^+$ count change is not significantly different overtime with increasing age at diagnosis.

A summary of the univariate mixed effects models including the remaining cofactors follows.

4.7.4. Ethnicity

$CD4^+$ count among individuals self-identifying as First Nations or Métis was not significantly different as compared to individuals identifying as of other ethnicity ($p=0.73$). Time since diagnosis (in months) was not significant in this model ($p=0.58$), nor was the interaction term of time with First Nations or Métis ethnicity ($p=0.084$).

4.7.5. HCV

$CD4^+$ count was not significantly different between HCV co-infected patients as compared to uninfected patients ($p=0.67$). Months since time of diagnosis was significant ($p=0.0092$) as was the interaction term between month and HCV co-infected ($p<0.0001$).

Therefore, rate of $CD4^+$ decline was significantly more rapid among co-infected patients as compared to those who were uninfected.

4.7.6. IDU

$CD4^+$ count was not significantly different when comparing patients with a history of IDU to those without such a history (p=0.77). Month since diagnosis was not significant in this model (p=0.092). The interaction term of IDU with month since diagnosis was significant (p=0.0011).

4.7.7. Incarceration

$CD4^+$ count was not significantly different between patients who were incarcerated during follow-up up as compared to those who were not (p=0.65). Month since diagnosis also was not significant (p=0.56), nor was the interaction between incarceration and time since diagnosis (p=0.13).

4.7.8. Case Management

$CD4^+$ count was not significant different between patients who were case management clients as compared to those who were not (p=0.33). Month since diagnosis was also not significant (p=0.53). However, the interaction term between case management and time since diagnosis was significant (p=0.0089).

4.7.9. Social Assistance

$CD4^+$ count was not significantly different between recipients of social assistance as compared to those who did not receive such social services (p=0.083). Month since diagnosis was not significant in predicting $CD4^+$ count (p= 0.33), nor was the interaction between receipt of social assistance and time since diagnosis (p=0.37).

4.7.10. STI

There was no significant difference in $CD4^+$ count between those diagnosed with an STI during follow-up as compared to those who were not diagnosed with such an infection (p=0.52). Time since diagnosis was not a significant predictor of $CD4^+$ count in this model (p=0.076), nor was the interaction of STI infection with month since diagnosis (p=0.57).

4.7.11. ARV

ARV was a significant predictor of $CD4^+$ count (p<0.0001). Time since diagnosis was a significant predictor of $CD4^+$ count (p=0.0002). Receipt of ARV was associated with a positive $CD4^+$ count slope, which was significantly different that the negative slope of $CD4^+$ count among those who did not receive ARV at any time throughout the follow-up period (p=0.0004)

4.7.12. Summary of Objective 2: Results from Univariate Mixed Effects Models.

HCV co-infection, history of IDU, and case management were associated with a negative $CD4^+$ slope and a significantly more rapid rate of decline in $CD4^+$ count.

Receipt of ARV was associated with a positive $CD4^+$ slope. Gender, age, ethnicity, incarceration, social assistance and STI co-infection were not significantly associated with $CD4^+$ count, nor were there any significant interactions between these variables and month since diagnosis.

4.7.13. Multivariate Analysis of Factors Associated with Trends in $CD4^+$ count.

Three separate mixed effects models were built due to the high degree of colinearity between First Nations and Métis ethnicity, HCV co-infection and IDU. This is due to the fact that when one or more of the independent variables are correlated and these correlated variables are input together in the same model estimated regression coefficients can be highly unreliable.

From the univariate mixed effects models analysis, gender, time since diagnosis, First Nations and Métis ethnicities, presence of HCV antibodies, history of IDU, incarceration, case management clients, recipients of social assistance, recipients of ARV and age at diagnosis, merit consideration for inclusion in the multivariate model based on a p-value of less than 0.25.

4.7.14. Ethnicity (Model 1)

The estimated mixed effects model including ethnicity was as follows:

$CD4^+ = 617 - 145.16$ (ARV) -2.23 (month) +– 46.36 (ethnicity) – 49.61 (social assistance) -3.01 (age at diagnosis) + 2.31 (ARV*month)

$CD4^+$ count increased at a rate of 2.31 cells/mm^3 per month among recipients of ARV after controlling for other covariates. First Nations Ethnicity (p=0.029), receipt of social

assistance (p=0.0097) and age at diagnosis (p=0.0013) were also independent significant predictors of $CD4^+$ count. Gender, a history of incarceration and being a case management client were not significant predictors and were therefore excluded from the model. The interaction between First Nations or Métis Ethnicity and ARV was tested and found not to be significant, therefore was also excluded. The AIC statistic for this model was 29683.8 . This model is summarized in Table 4.6.

Table 4.6. Multivariate Mixed Effects Model containing First Nations or Métis Ethnicity (n=362).

Cofactor	β	95% CI (β)	p-value
Intercept	616	(526.91, 706.15)	<0.0001
ARV	-145	(- 193, - 97.0)	<0.0001
Month	- 2.23	(- 3.70, - 0.76)	0.013
Month * ARV	2.31	(0.60, 4.01)	0.0079
First Nations or Métis Ethnicity	- 46.36	(- 88.01, -4.66)	0.029
Social Assistance	- 49.63	(- 87.20, -12.06)	0.0097
Age at diagnosis	-3.01	(-4.83, -1.18)	0.0013

4.7.15. HCV Co-infection (Model 2)

The estimated mixed effects model including HCV co-infection was as follows:

$CD4^+$ = 606 -170 (ARV) -2.76 (month)– 65.73 (HCV) – 33.51 (social assistance) -1.83 (age at diagnosis) + 3.02 (ARV*month)

$CD4^+$ count increased at a rate of 3.02 cells/mm^3 per month among recipients of ARV after controlling for other covariates. HCV antibody positivity (p=0.0046) and age at

diagnosis (p=0.042) were independently associated with lower $CD4^+$ counts. Social assistance was forced into the model despite it having a p-value of less than 0.05, to allow for comparisons between the three models. Case management, a history of incarceration and gender were not significantly associated with $CD4^+$ count and were therefore removed from the model. The interaction between receipt of ARV and HCV co-infected was tested and found not to be significant; therefore it also was not included in this model. The AIC statistic for this model was 30859.0 This model is summarized in Table 4.7.

Table 4.7. Multivariate Mixed Effects Model containing HCV co-infection (n=387).

Cofactor	β	95% CI (β)	p-value
Intercept	606	(517, 695)	<0.0001
ARV	-170	(- 218, -122)	<0.0001
Month	-2.76	(- 4.17, -1.35)	0.0032
Month* ARV	3.02	(1.37, 4.67)	0.0003
HCV	- 65.76	(- 111.19, -20.33)	0.0046
Social Assistance	- 33.51	(- 71.48, 4.46)	0.084
Age at diagnosis	-1.83	(-3.59, -0.065)	0.042

4.7.16. IDU (Model 3)

The estimated mixed effects model including HCV co-infection was as follows:

$CD4^+ = 590 - 163$ (ARV) -2.65 (month)– 41.67 (IDU) – 38.85 (social assistance) - 2.06 (age at diagnosis) + 2.76 (ARV*month)

$CD4^+$ count increased at a rate of 2.76 cells/mm^3 per month among recipients of ARV after controlling for other covariates. A history of IDU (p=0.047), receipt of social assistance (p=0.0424) and increasing age at diagnosis (p=0.20) were independently associated with lower $CD4^+$ counts. Case management, a history of incarceration and gender were not significantly associated with $CD4^+$ count and were therefore removed from the model. The interaction between a history of IDU and receipt of ARV was tested and found not to be significant and was therefore also excluded from the final model. The AIC value for this model is 31615.2. The final model is summarized in Table 4.8.

Table 4.8. Multivariate Mixed Effects Model containing history of IDU (n=407).

Cofactor	β	95% CI (β)	p-value
Intercept	590	(506, 673)	<0.0001
ARV	- 163	(-209, -117)	<0.0001
Month	-2.65	(- 4.03, -1.28)	0.0022
Month* ARV	2.76	(1.15, 4.38)	0.0008
IDU	- 41.69	(- 82.79, -0.59)	0.047
Social Assistance	- 38.86	(- 76.38, -1.34)	0.042
Age at diagnosis	-2.06	(- 3.79, - 0.32)	0.020

4.7.17 Summary of Objective 2: Multivariate Mixed Effects Models

Common to all three models was the interaction between ARV and months. Age was also independently significant in all three models. Social assistance was independent significant in models 1 and 3 and marginally significant in model 2. Ethnicity, a history of IDU and HCV co-infection were each significant predictors of $CD4^+$ count status in each of their respective models. Model 1 which included ethnicity had the lowest AIC.

4.8. Objective 3: Results from Logistic Regression Analysis

In this study objective we define rapid $CD4^+$ decline in this population and subsequently identify cofactors associated with an increased risk of rapid decline. This analysis was undertaken amongst two subpopulations, patients with an initial $CD4^+$ count of 500 cells/mm^3 or greater and patients with an initial $CD4^+$ count of 350 cells/mm^3 or greater. Rapid decline was defined as the steepest 25% of $CD4^+$ count slopes as estimated by both linear regression and mixed effects models among these two sub populations. Slow decline was defined as the shallowest 25% of $CD4^+$ count slopes among these two subpopulations, again as estimated by both linear regression and mixed effects models.

4.8.1. Results of Bivariate Logistic Regression Models Among Subgroup of Patients with First $CD4^+$ Count ≥ 500 cells/mm^3

4.8.2. Linear Regression

Among patients with an initial $CD4^+$ count greater than or equal to 500 cells/mm^3 with at least 3 recorded $CD4^+$ counts while not receiving ARV, rapid decline was defined as a slope, as determined by linear regression analysis, of ≤ -12.58 cells/mm^3 per month and slow decline was defined by a slope of ≥ - 2.19 cells/mm^3 per month. By these definitions 16 patients were identified as having rapid $CD4^+$ cell count decline and 16 patients were identified as having slow decline. A total of 32 patients were included in this analysis. The results of this analysis are summarized in Table 4.9.

Table 4.9. Bivariate logistic regression analysis of variables of interest among patients with first $CD4^+$ count ≥ 500 cells where slope was estimated with linear regression (n=32).			
Covariates	**OR***	**95% CI****	**p-value**
Gender	2.83	(0.67, 12.02)	0.16
Age	0.98	(0.92, 1.04)	0.54
First Nations or Métis Ethnicity	1.07	(0.23, 5.02)	0.93
HCV	3.50	(0.56, 21.81)	0.18
IDU	4.20	(0.70, 25.26)	0.12
Case Management	1.00	(0.12, 8.13)	0.99
Social Assistance	7.00	(1.19, 41.36)	0.03
Incarceration	4.33	(0.88, 21.31)	0.07
STI	0.51	(0.10, 2.62)	0.42
ARV	5.57	(1.13, 27.52)	0.04

* OR = Odds Ratio
**CI= Confidence Interval

4.8.3. Gender

The bivariate analysis for the cofactor of gender is presented here:

Y = 1 if rapid $CD4^+$ count decline

Y = 0 if slow $CD4^+$ count decline

$Logit\ (Y) = \beta_0 + \beta_{gender}gender + \varepsilon$

[illegible] = -0.45+ 1.040 (gender)

Odd Ratio (OR) = Exp (β) = $e^{1.040}$ = 2.83

95% CI for e^{β} = exp [$\beta \pm 1.96$ ($S.E._{\beta}$)]

95% CI for e^{β}= exp [1.040±1.96 (0.74)] = ($e^{-0.41}$, $e^{2.49}$) = (0.67, 12.02)

In this example female gender is the reference category. Therefore, we interpret this OR as the risk of rapid $CD4^+$ decline is 2.83 times greater among males as compared to females. This result is not significant as the 95% CI includes the value of 1.

4.8.4. Age

An increase in age at diagnosis by one year resulted in an individual being 0.98 as likely to be designated as having rapid decline in $CD4^+$ count, this OR was not significant (p=0.54).

4.8.5. Ethnicity

Patients of First Nations or Métis ethnicity were 1.07 times as likely to be designated as having rapid decline in $CD4^+$ count, which was not significant (p=0.93).

4.8.6. HCV

Patients who were HCV co-infected were 3.50 as likely to be identified as having rapid decline in $CD4^+$ count, this was not significant (p=0.18).

4.8.7. IDU

Patients with a history of IDU were 4.20 times more likely to be identified as having rapid decline in $CD4^+$ count, this was not significant (p=0.12).

4.8.8. Case Management

Case Management clients were no more likely to be identified as having rapid decline in $CD4^+$ count as compared to non-clients (OR = 1.00, p=0.999).

4.8.9. Social Assistance

Recipients of Social Assistance were 7.00 times as likely to be designated as having rapid decline in $CD4^+$ count as compared to patients who never received social assistance and this was a significant difference between the groups (p=0.032).

4.8.10. Incarceration

Patients who were incarcerated during follow-up were 4.33 times as likely to be designated as having rapid decline in $CD4^+$ count as compared to patients who were not incarcerated during this period. This result was not significant (p=0.071).

4.8.11. STIs

Patients infected with an STI during follow-up were 0.51 times as likely to be designated as having rapid decline as compared to those who were uninfected. This result was not significant (p=0.42).

4.8.12. ARV

Patients who were prescribed ARV over the course of follow were 5.57 times more likely to be identified as having a rapid decline in $CD4^+$ count as compared to patients who were not prescribed ARV in this same period. This result was significant (p=0.035).

4.8.13. Summary of Bivariate Analysis among Patients with First $CD4^+$ Count ≥ 500 cells/mm^3, where Slope was Estimated using Linear Regression

Receipt of social assistance and ARV were each significantly associated with an increased risk of rapid $CD4^+$ cell count decline. Gender, age, ethnicity, HCV co-infection, history of IDU, case management, incarceration and STI infection did not significantly increase the risk of such a designation among patients.

4.8.14. Multivariate Analysis among Patients with First $CD4^+$ Count ≥ 500 cells/mm^3, where Slope was Estimated using Linear Regression

In the bivariate analyses among patients with an initial $CD4^+$ count of 500 cells or greater, with at least 3 $CD4^+$ counts recorded while not receiving ARV and where $CD4^+$ rate of change was determined by linear regression, gender, HCV co-infection, a history of IDU, receipt of social assistance, a history of incarceration and receipt of ARV will be considered candidates for inclusion in the multivariate model based on a p-value of less than 0.25.

In no constructed multivariate model did more than one covariate remain an independent significant predictor of an increased likelihood of designation with a rapid

$CD4^+$ count decline. The models including the covariates which most closely approached significance are summarized in Table 4.10.

Table 4.10 Multivariate logistic regression model among patients with an initial $CD4^+ \geq 500$, where slope was estimated using linear regression (n=32).

	Covariates	OR*	95% CI**	p-value
Rapid decline $\leq$ -12.58 cells/mm^3 per month Slow decline $\geq$ -2.19 cells/mm^3 per month	**IDU**	5.82	(0.74, 45.65)	0.094
	ARV	7.06	(1.19, 42.02)	0.032
	HCV	5.16	(0.63, 42.33)	0.13
	ARV	6.64	(1.12, 39.51)	0.037

*OR= Odds Ratio
** CI=confidence interval

The model containing IDU and ARV resulted in the most significant terms and is further examined here.

Y = 1 if rapid $CD4^+$ count decline

Y = 0 if slow $CD4^+$ count decline

$Logit\ (Y) = \beta_0 + \beta_{IDU}IDU + \beta_{ARV}ARV$

[redacted] = -2.05 + 1.76 (IDU) + 1.95 (ARV)

OR for IDU

$OR = e^{1.76} = 5.82$

95% CI for $e^{\beta} = \exp[\beta \pm 1.96\ (S.E._{\beta})] = \exp[1.76 \pm 1.96\ (1.05)] = (e^{-0.30}, e^{3.82}) =$

(0.74, 45.65)

OR for ARV

$OR = e^{1.95} = 7.06$

95% CI for $e^{\beta} = \exp[\beta \pm 1.96 (S.E._{\beta})] = \exp[1.95 \pm 1.96 (0.91)] = (e^{0.17}, e^{3.74}) =$

(1.19, 42.02)

In this model patients with a history of IDU are 5.82 times more likely to experience rapid decline in $CD4^+$ count. The 95% CI of this OR includes the value of 1 suggesting that history of IDU is not significantly influencing the risk of such a classification. Receipt of ARV is associated with 7.06 times greater odds of experiencing a rapid decline in $CD4^+$ count. The 95% CI of this OR does not include the value of 1, indicating that this association is statistically significant.

4.8.15. Mixed Effects

When using a mixed effects model to determine $CD4^+$ slope and among patients with an initial $CD4^+$ count of 500 or greater recorded while not receiving ARV, rapid decline was defined as a slope of $\leq$ -3.33 cells/mm^3 per month and slow decline as $\geq$ 2.80 cells/mm^3 per month. A total of 50 patients were included in this analysis, 25 with a rapid decline and 25 with a slow decline. The results of this analysis are summarized in Table 4.11.

Table 4.11. Bivariate logistic regression analysis of variables of interest among patients with first $CD4^+$ count ≥ 500 cells, where slope was estimated using mixed effects models (n=50).			
Covariates	**OR***	**95% CI****	**p-value**
Gender	1.00	(0.33, 3.03)	0.99
Age	0.99	(0.94, 1.04)	0.56
First Nations or Métis Ethnicity	1.62	(0.45, 5.78)	0.46
HCV	3.83	(0.69, 21.30)	0.12
IDU	2.85	(0.64, 12.64)	0.17
Case Management	0.55	(0.12, 2.58)	0.44
Social Assistance	2.14	(0.60, 7.68)	0.24
Incarceration	2.67	(0.75, 9.45)	0.13
STI	1.96	(0.62, 6.19)	0.25
ARV	6.00	(1.69, 21.26)	0.01

OR = Odds Ratio
** CI=confidence interval

4.8.16. Gender

There is no difference in the likelihood of being classified as having a rapid $CD4^+$ decline between genders (OR = 1.00, p = 0.99).

4.8.17. Age

Y = 1 if rapid $CD4^+$ count decline

Y = 0 if slow $CD4^+$ count decline

Logit (Y) = $\beta_0 + \beta_{age}$ age

[ ] = 0.52 -0.0152(age)

OR = $e^{-0.0152} = 0.99$

95% CI for e^{β} = exp [$\beta \pm 1.96$ ($S.E._{\beta}$)]

95% CI for e^{β} = exp [-0.015 ±1.96 (0.026)] = ($e^{-0.066}$, $e^{0.036}$) = (0.94, 1.036)

Therefore, this OR is interpreted as for each 1 year increase in age at diagnosis a patient is 0.985 times as likely to be designated as having a rapid decline in $CD4^+$ count. As the 95% CI of this OR contains the value of 1 this OR is not significant.

4.8.18. Ethnicity

Patients of First Nations or Métis ethnicity were 1.62 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to patients of other ethnicity. This result was not significant (p=0.46).

4.8.19 HCV

Patients who were HCV co-infected were 3.83 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to uninfected patients. This result was not significant (p=0.12).

4.8.20. IDU

Patients with a history of IDU were 2.85 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to patients without such a history. This result was not significant (p=0.17).

4.8.21. Case Management

Case Management clients were 0.55 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to non-clients. This result was not significant (p=0.44).

4.8.22. Social Assistance

Recipients of social assistance were 2.14 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to patients who did not receive such funds. This result was not significant (p=0.24).

4.8.23. Incarceration

Patients who were incarcerated during follow-up were 2.67 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to patients who were not incarcerated during this period. This result was not significant (p=0.13).

4.8.24. STIs

Patients who were diagnosed with an STI during follow-up were 1.96 times as likely to be designated as having a rapid decline in $CD4^+$ count as compared to those who remained uninfected. This result was not significant (p=0.25).

4.8.25 ARV

Patients who were prescribed ARV during the follow-up period were 6.00 times as likely to be designated as having a rapid $CD4^+$ count decline as compared to patients who were not prescribed ARV in this same time period. This result was significant (p=0.0055).

4.8.26. Summary of Bivariate Analysis among Patients with First $CD4^+$ Count ≥ 500 cells/mm^3, where Slope was Estimated using Mixed Effects

In this bivariate analysis of covariates of interest only receipt of ARV was significantly associated with an increased risk of rapid $CD4^+$ count decline. Gender, age at diagnosis, ethnicity, HCV co-infection, history of IDU, case management, receipt of social assistance, incarceration and co-infection with an STI were not significantly associated with an increased likelihood of this outcome.

4.8.27. Multivariate Analysis among Patients with First $CD4^+$ Count ≥ 500 cells/mm^3, where Slope was Estimated using Mixed Effects Models.

In the bivariate analyses among patients with an initial $CD4^+$ count of 500 cells or greater using $CD4^+$ counts recorded before ARV was prescribed to define $CD4^+$ slope

with a mixed effects model HCV co-infection, history of IDU, receipt of social assistance, history of incarceration and receipt of ARV are eligible for inclusion in the multivariate model based on a p-value of less than 0.25.

As previously mentioned in none of the constructed multivariate model was more than 1 variable independently significantly associated with a higher or lower likelihood of rapid or slow rate of $CD4^+$ decline. The models including the covariates which most closely approached significance are summarized in Table 4.12.

Table 4.12. Multivariate logistic regression model among patients with an initial $CD4^+ \geq 500$, where slope was estimated using mixed effects models (n=50).

	Covariates	OR*	95% CI**	p-value
Rapid decline $\leq$ - 3.33 cells/mm^3 per month Slow decline $\geq$ 2.80 cells/mm^3 per month	IDU	3.62	(0.68, 19.27)	0.13
	ARV	6.70	(1.77, 25.36)	0.01
	HCV	4.64	(0.70, 30.74)	0.11
	ARV	6.24	(1.64, 23.74)	0.0072

*OR = Odds Ratio
**CI= confidence interval

The model including HCV and ARV most closely approached significance and is further investigated here.

Y = 1 if rapid $CD4^+$ count decline

Y = 0 if slow $CD4^+$ count decline

$Logit\ (Y) = \beta_0 + \beta_{HCV}HCV + \beta_{ARV}ARV$

[redacted] = -1.98 + 1.53 (HCV) + 1.83 (ARV)

OR for HCV

$OR = e^{1.53} = 4.64$

95% CI for e^{β} = exp [β±1.96 ($S.E._{\beta}$)] = exp [1.53 ± 1.96 (0.96)] = ($e^{-0.35}$, $e^{3.41}$) = (0.70, 30.74)

OR for ARV

OR = $e^{1.83}$ = 6.24

95% CI for e^{β} = exp [β±1.96 ($S.E._{\beta}$)] = exp [1.83 ± 1.96 (0.68)] = ($e^{-0.50}$, $e^{3.16}$) = (1.64, 23.74)

In this model HCV co-infected patients were 4.64 times more likely to experience rapid $CD4^+$ count decline. However co-infection with HCV did not significantly influence rapid $CD4^+$ count decline as the value of 1 was present in the CI for this OR. Patients who were prescribed ARV were 6.24 times more likely to experience rapid $CD4^+$ cell count decline. This result was significant as the value of 1 was not included in the CI of this OR.

4.8.28. Summary of Results of Logistic Regression among Patients with Initial $CD4^+$ Count ≥ 500 cells/mm^3

In the bivariate logistic analysis among this sub population where slope was estimated using linear regression receipt of social assistance and ARV were associated with an increased risk of rapid $CD4^+$ cell count decline. In the multivariate logistic regression only ARV remained significantly associated with increased risk for rapid decline.

In the bivariate logistic analysis among this sub population where slope was estimated using mixed effects methods only receipt of ARV was associated with an increased risk of rapid $CD4^+$ count decline. ARV remained the only significant factor in the multivariate model. Similar results from both linear regression analysis and mixed effects models were observed.

4.8.29. Subgroup of Patients with First $CD4^+$ Count ≥ 350 cells/mm^3

An identical analysis of which the results are presented in sections 4.7.1. through 4.7.28. was undertaken among patients with an initial $CD4^+$ of at least 350 cells/mm^3 or greater.

4.8.30. Results of Bivariate Logistic Regression Models among Subgroup of Patients with First $CD4^+$ Count ≥ 350 cells/mm^3

4.8.31. Linear Regression

Among patients with an initial $CD4^+$ count equal to or greater than 350 cells and at least 3 recorded $CD4^+$ counts while not receiving ARV rapid decline was defined as a slope, as determined by linear regression analysis, of ≤ -12.01 cells/mm^3 per month and slow decline was defined by a slope of ≥ - 2.29 cells/mm^3 per month. By this definition 27 patients were identified as showing a rapid rate of $CD4^+$ decline and 27 patients were identified as showing a slow rate of $CD4^+$ decline. Therefore, a total of 54 patients were included in this analysis.

4.8.32. Summary of Bivariate Analysis among Patients with First $CD4^+$ Count ≥ 350 cells/mm^3, where Slope was Estimated using Linear Regression

In a bivariate analysis of each variable of interest only receipt of ARV (OR=3.57, p=0.03) was associated with a greater likelihood of showing a rapid rate of $CD4^+$ progression. Gender (OR=1.35, p=0.59), age at diagnosis (OR=1.00, p=0.95), ethnicity (OR= 1.48, p=0.51), HCV (OR=3.04, p=0.10), IDU (OR=3.38, p=0.07), Case management (OR=1.00, p=0.99), social assistance (OR=1.60, p=0.40), incarceration (OR=2.06, p=0.24) and STI co-infection (OR=0.49, p=0.24) were not shown to significantly influence the risk of $CD4^+$ count rapid decline. Bivariate analysis results for each factor of interest are summarized in Table 4.13.

Table 4.13. Bivariate analysis of variables of interest among patients with a first $CD4^+$ count ≥ 350 cells , where slope was estimated using linear regression (n=54).			
Covariates	**OR***	**95% CI****	**P-value**
Gender	1.35	(0.46, 3.93)	0.59
Age at diagnosis	1.00	(0.95, 1.05)	0.95
First Nations or Métis Ethnicity	1.48	(0.46, 4.78)	0.51
HCV	3.04	(0.80, 11.55)	0.10
IDU	3.38	(0.91, 12.64)	0.07
Case Management	1.00	(0.18, 5.46)	0.99
Social Assistance	1.60	(0.53, 4.82)	0.40
Incarceration	2.06	(0.62, 6.82)	0.24
STI	0.49	(0.15, 1.61)	0.24
ARV	3.57	(1.13, 11.25)	0.03

* OR=Odds ratio
** CI=Confidence Interval

4.8.33. Summary of Multivariate Analysis among Patients with First $CD4^+$ Count ≥ 350 cells/mm^3, where Slope was Estimated using Linear Regression

Given a p-value of less than 0.25 HCV co-infection, a history of IDU, a record of incarceration, STI infection and receipt of ARV were eligible for inclusion in the multivariate model. In constructing the multivariate logistic regression models for this

analysis separate models were fit for HCV co-infection and IDU, due to the high degree of colinearity between these two variables. In the final multivariate models a history of IDU (OR = 4.10, p =0.052) and HCV co-infection (OR= 3.80, p = 0.07) approached statistical significance, however only ARV (OR = 4.15, p=0.02; OR = 3.99, p=0.027) remained significantly associated with an increased likelihood of rapid $CD4^+$ cell count decline. Incarceration and STI infection were not significantly associated with increased risk of rapid $CD4^+$ decline. A summary of this analysis is presented in Table 4.14.

Table 4.14. Multivariate model among patients with an initial $CD4^+ \geq 350$, where slope was estimated using linear regression (n=54).

	Covariates	OR	95% CI	p-value
Rapid decline ≤ -12.01 cells/mm^3 per month **Slow decline ≥ -2.29 cells/mm^3 per month**	**IDU**	4.10	(0.99, 17.01)	0.052
	ARV	4.15	(1.22, 14.17)	0.02
	HCV	3.80	(0.90, 16.05)	0.07
	ARV	3.99	(1.17, 13.65)	0.027

* OR=Odds ratio
** CI=Confidence Interval

4.8.34. Mixed Effects Model

Among patients with an initial $CD4^+$ count of 350 cells or greater using a mixed effects model to determine individuals showing rapid and slow rates of $CD4^+$ cell count decline among $CD4^+$ counts recorded while patients were not receiving ARV, rapid decline was defined as a slope of ≤ -3.71 cells/mm^3 per month and slow decline a slope of ≥ 2.64 cells/mm^3 per month. A total of 87 individuals were included in this analysis, 44 individuals with a rapid rate of decline and 43 with a slow rate of decline.

4.8.35. Summary of Results of Logistic Regression among Patients with Initial $CD4^+$ Count ≥ 350 cells/mm^3

In the bivariate analysis patients that would eventually receive ARV were more likely to be identified as having a rapid rate of $CD4^+$ decline (OR 5.54, p=value=0.0003). Gender (OR=1.15, p=0.74), age at diagnosis (OR=1.00, p=0.90), ethnicity (OR=1.13, p=0.81), HCV (OR=2.70, p=0.09), IDU (OR=1.95, p=0.19), case management (OR=0.97, p=0.97), receipt of social assistance (OR=1.02, p=0.96), incarceration (OR=1.08,p= 0.87), or co-infection with an STI (OR=1.18, p=0.72) did not significantly influence the risk of $CD4^+$ count rapid decline in this population. This bivariate analysis for variables of interest is summarized in Table 4.15.

Table 4.15. Bivariate analysis of factors of interest among patients with a first $CD4^+$ count ≥ 350 cells , where $CD4^+$ count slope was estimated by mixed effects models (n=87).			
Covariates	**OR***	**95% CI****	**P-value**
Gender	1.15	(0.50, 2.67)	0.74
Age at diagnosis	1.00	(0.96, 1.04)	0.90
First Nations or Métis Ethnicity	1.13	(0.44, 2.90)	0.81
HCV	2.70	(0.85, 8.59)	0.09
History of IDU	1.95	(0.71, 5.33)	0.19
Case Management	0.97	(0.29, 3.29)	0.97
Social Assistance	1.02	(0.43, 2.44)	0.96
Incarceration	1.08	(0.43, 2.74)	0.87
STI	1.18	(0.49, 2.81)	0.72
ARV	5.54	(2.20, 13.89)	0.0003

*OR= Odds Ratio
**CI= confidence interval

4.8.36. Summary of Multivariate Models among Patients with First $CD4^+$ Count ≥ 350 cells/mm^3, where Slope was Estimated using Mixed Effects

HCV co-infection and a history of IDU were eligible for inclusion in the multivariate model given a p-value of less than 0.25 in the bivariate analysis. In constructing the multivariate logistic regression models for this analysis separate models were fit for these two variables due to their high degree of colinearity. Receipt of ARV (OR=5.52, p =0.0003; OR = 6.34, p=0.0002) was a significantly associated with an

increased risk of rapid $CD4^+$ count decline. HCV co-infection (OR =3.39, p=0.06) approached statistical significance, whereas a history of IDU (OR= 1.93, p=0.24) did not. The results of these multivariate models are summarized in Table 4.16.

Table 4.16. Multivariate model among patients with an initial $CD4^+ \geq 350$, where $CD4^+$ count slope was estimated using mixed effects models (n=87).

	Covariates	OR*	95% CI **	p-value
Rapid ≤ - 3.71 cells/mm^3 per month **Slow ≥ 2.64 cells/mm^3 per month**	IDU	1.93	(0.65, 5.78)	0.24
	ARV	5.52	(2.18, 13.97)	0.0003
	HCV	3.39	(0.94, 12.23)	0.06
	ARV	6.34	(2.40, 16.77)	0.0002

*OR= Odds Ratio
**CI= confidence interval

4.7.37. Summary of Results of Logistic Regression among Patients with Initial $CD4^+$ Count ≥ 350 cells/mm^3

Receipt of ARV was significantly associated with an increased risk of rapid $CD4^+$ count decline in bivariate logistic regression analysis where slope of $CD4^+$ count was defined using both linear regression and mixed effects models. ARV was also the only significant cofactor in the multivariate models, again where $CD4^+$ count slope was defined by both linear regression and mixed effects models.

4.7.38. Overall Conclusion for Objective 3

The results from the two subgroups, one with an initial $CD4^+ \geq 500$ and the other with an initial $CD4^+ \geq 350$ were similar. When $CD4^+$ count slope was estimated by both linear

regression and mixed effects model ARV was the only significant factor to consistently distinguish between slow and fast rate in $CD4^+$ count decline.

5. Discussion

5.1.Summary of Findings

This study is a retrospective longitudinal cohort study of 457 HIV positive patients diagnosed between January 1st, 2003 and November 30th, 2011 at the PLP and WSCC in Saskatoon, Saskatchewan. In this study we investigated the suspected phenomenon of a high prevalence of rapid progression to AIDS and death in Saskatoon, Saskatchewan. The primary objective of this study was to identify clinical and social factors associated with accelerated rates of decline in $CD4^+$ counts among individual patients.

Estimates of $CD4^+$ slope obtained by linear regression analysis identified patients in possession of the following characteristics: HCV co-infection, a history of IDU, incarceration during follow-up, and not receiving ARV as likely to experience significantly steeper rates of $CD4^+$ decline. Subsequently, patient $CD4^+$ counts were modeled longitudinally. Mixed effects models identified individuals who self-identified as being of First Nations or Métis ethnicity, HCV co-infection, a history of IDU and receipt of social assistance to be independently associated with $CD4^+$ count in multivariate models. Whereas receipt of ARV was significantly associated with a positive $CD4^+$ count slope. Finally, a logistic regression model with the outcome of rapid versus slow rate of $CD4^+$ decline, based on the 25% steepest as compared to the 25% shallowest slopes, found receipt of social assistance and receipt of ARV to be significantly associated with an increased likelihood of being classified as having a rapid rate of $CD4^+$ decline in bivariate analysis. In multivariate logistic regression only the receipt of ARV remained significantly associated with an increased likelihood of experiencing rapid $CD4^+$ count decline.

5.2. Demographic Factors

The proportion of individuals in this cohort who self-identified as being of First Nations, Métis or Inuit ethnicity is significantly greater than in any other study cohort of HIV infected patients in Canada, as was the proportion of patients identifying as female (40,64,68). For example, in an Ontario study examining social and economic inequities among HIV-infected First Nations, Inuit and Métis peoples as compared to individuals of other ethnicities, 15% of participants were of First Nations, Inuit or Métis and 85% were Caucasian (40). As compared to our study population where 71 % of participants self-identified as being of First Nations or Métis ethnicity and only 24% as Caucasian.

As previously mentioned, another unique characteristic of the HIV infected population in Saskatchewan, and in the city of Saskatoon, is the high proportion of cases attributed to exposure through IDU. This same trend was seen in the neighboring province of Alberta in a study published in 2011 using data collected by the Northern Alberta HIV Program (NAHIVP) (64). Although the percent of individuals exposed to HIV through IDU was much higher in our study population. In summary, the proportion of cases attributed to IDU in our study is much higher than in any other HIV infected population in the literature (49,67)

Due to the high association between HCV infection and IDU in our study population it is not possible to distinguish the independent influence of either of these variables on $CD4^+$ count. As is seen in Figure 4.1, only one patient who had a history of IDU was not also co-infected with HCV and only six patients who were infected with HCV had no history of IDU. This result is not surprising due to the increased ease of transmission of

HCV as compared to HIV and to the sharing of needles and other drug paraphernalia as modes of transmission for these two viruses (5,66,79).

5.3. Factors Associated with More Rapid $CD4^+$ Decline as Estimated by Linear Regression

Linear regression was used as an exploratory analyses in Study objective 1 to identify cofactors which might be identified as significant in analyses performed in response to subsequent study objectives. The use of linear regression to models estimate the slope of $CD4^+$ counts collected from patients in a longitudinal study is not without precedent in HIV research literature (19,78).

In this section we will examine each of the statistical assumptions of the linear regression model to see which of the assumptions are met and which are violated when we model our longitudinal $CD4^+$ count data using this method. The first statistical assumption of a linear regression model is the assumption of existence and this assumption is met with our data. The second assumption is the assumption of independence. This second assumption is violated in our study as the Y-values ($CD4^+$ count) are not statistically independent of one another; an association exists between multiple $CD4^+$ counts taken at different times from the same individual. The third statistical assumption of the linear regression model is the assumption of linearity, whereby the mean value of the dependent variable ($CD4^+$ count in this study) is a linear function of independent variables. We have tested this assumption by plotting the $CD4^+$ counts of sets of 10 randomly selected patients over month since diagnosis (see Figure 4.2). By examining Figure 4.2 it is seen that this assumption of linearity is met in our

study. The fourth statistical assumption of a linear regression model is homoscedasticity, the assumption of equal variances for the dependent variable for any given independent variable. It was not practical to assess this assumption as we would have to assess equal variance of errors for the dependent variables of 411 different patients. The fifth statistical assumption of a linear regression is normality, a normal distribution of the dependent variable for a fixed value of an independent variable. $CD4^+$ count values were graphed to test this assumption. The assumption of a normal distribution of $CD4^+$ count was not seen to be overtly violated. Furthermore, neither log transforming nor taking the square root of $CD4^+$ count was seen to improve normality of this dependent variable, therefore it was analyzed in its untransformed state.

Cofactors identified as significantly associated with a significantly more rapid rate of $CD4^+$ count decline as estimated using a linear regression model included, HCV co-infection, a history of IDU, being incarcerated during follow-up and not receiving ARV. Each of these factors has previously shown associations with each other in other published studies. For example, HIV and HCV are both transmitted through IDU (67,76-78). Also, there is an increased frequency of IDU among incarcerated populations, as patients with more extreme addictions may be at an increased likelihood to incur criminal charges(92,93). Finally, both IDU and incarceration has been found to be associated with a lower uptake of and adherence to ARV (50,52,64,73,101).

Dorrucci et al. (1995) also compared the slopes of $CD4^+$ count as estimated by linear regression among HIV patients with at least 3 recorded counts among HCV co-infected and HCV uninfected patients. However, in contrast to our findings, these researchers found no significant difference between the distributions of the estimated

linear regression slopes in the two groups. Discrepancy in these findings as compared to those among our study population might be explained by differing prevalence of HIV transmission mode between the two populations. Where our population had a larger proportion of patients reporting IDU as their mode of HIV transmission and a much smaller population reported MSM. HCV co-infection among IDU in our study population was approximately 99 % and the co-occurrence of these factors may lead to an accelerated rate of decline, or IDU may be solely responsible for the accelerated decline.

In our study IDUs had a higher estimated $CD4^+$ at diagnosis. This observation might be explained by an increased likelihood of testing at needle exchanges and of being identified as a high-risk individual, leading to an HIV diagnosis earlier in the clinical course of the disease. As IDU are at a substantially increased risk for co-infection with HCV, the representation of IDU among the HCV co-infected population likely also explains the higher $CD4^+$ count at time of diagnosis among HCV co-infected patients as compared to HCV uninfected patients.

Griffin et al.'s (1996) study of HIV-infected incarcerated inmates found a mean $CD4^+$ cell count decrease of 10.5 cells/ month during the first three months of incarceration and a subsequent 17 cells/month decrease over the following 7 months among patients who were not on ARV (19). The follow-up period of this study was only 1 year due to the fact that most inmates were transferred to a state prison or released within this time period. In our study the average decrease in $CD4^+$ count among patients incarcerated during follow-up was a decrease of 3.26 cells/mm^3 month. However, our analyses includes all patients with at least 3-recorded $CD4^+$ counts regardless of ARV status. Additionally, the mean patient follow-up time in our study was 3.9 years. These

two factors might account for differences in the rate of decrease seen in the present study as compared to that found by Griffin et. al. (1996). Nevertheless, in both ours and Griffin et. al.'s (1996) study, incarceration during follow-up was associated with a more rapid decrease in $CD4^+$ count. The stress of the prison environment has been found to contribute to a faster rate of decline in $CD4^+$ count among prisoners than would be expected in a clinic environment (19). Another hypothesis to explain this association might be the increased prevalence of IDU among prisoners (92,93)

Following patients who are incarcerated has been identified as a significant obstacle to ensuring continuity of care among the HIV positive patients in Saskatoon. As previously mentioned, an estimated one third of WSCC patients have a history of incarceration (42). The tracking of patients through the prison systems in this province has been identified as a barrier to ensuring continuity of care among incarcerated HIV-positive individuals, in particular in ensuring continual supply of ARV. This reduced ability to track a patient's incarceration, duration and release also likely led to an underrepresentation of the true prevalence of incarceration in this study population.

5.4. Factors Associated with More Rapid $CD4^+$ Decline with Longitudinal Modeling

When we modeled patients' $CD4^+$ count using linear regression in our exploratory analysis we ignored the correlations that exist among repeated $CD4^+$ counts collect from a given patient. Statistical consequences of ignoring these correlations include incorrect estimates of β values through incorrect inferences and less precise estimates as well increasing bias in regression parameters caused by $CD4^+$ counts missing in the data set. $CD4^+$ counts may be missing from the data set for multiple reasons, for example patients

may have been deceased before the end of the follow-up period, may have been lost to follow-up, or simply may have failed to attend their scheduled clinic appointment. The use of mixed effects models allow for consideration of the correlation structure present within repeated measurements taken for a given patient as well as accounts for missing values among the dependent variable.

In these analyses, as well as the analyses conducted in objective 3, age was included as a continuous variable as a difference in age of one year in this cohort may be clinically significant.

The mixed effects model, which was found to best estimate rate of change in $CD4^+$ count, was model 1 containing ethnicity. It is hypothesized that this may be due to the fact that as mentioned in the previous section, HCV co-infection is associated with IDU, which is also the exposure to which the largest proportion of HIV infections among First Nations or Métis people is attributed. The First Nations and Métis ethnicity factor also likely takes into account the impoverished living conditions due to the inferior economic and social conditions, which unfortunately are prevalent among First Nations or Métis communities, or to ongoing IDU.

Limitations in the study dataset make comparison with other studies difficult. In particular unknown dates of seroconversion among this population make comparisons between $CD4^+$ slopes estimated in the analysis of this study data and estimated slopes in other studies inappropriate. Were more simple comparisons possible conclusions about the presence of rapid progression among HIV infected patients in Saskatoon could be more easily reached. Estimates of average declines in $CD4^+$ count among other cohorts while not receiving ARV among patients with known dates of seroconversions are

provided here. Lewden et al (2010) found an average decline in $CD4^+$ count, while not on ARV, as estimated by mixed effect models, among two cohorts in Cote d'Ivoire and France of -63 cells/mm^3 per year (95% CI = -80, -46) among individuals enrolled in care 6 months after seroconversion (110). Deeks et al (2004), also using mixed effects modeling, found a mean decrease of 8 $CD4^+$ cells/mm^3 per month (- 96 cells/ mm^3 per year) among untreated patients in their San Francisco based cohort. Inclusion criteria for their study consisted of evidence of acute or recent HIV infection. When we examine the results of our mixed effects models we see an average rate of monthly decline among ARV naive patients of between -2.23 cells/mm^3 and -2.65 cells/mm^3, depending on which of the three multivariate mixed effects models we employ. This is an average yearly decline of between – 26.76 cells/mm^3 and – 31.8 cells/mm^3. Therefore, our study population has a shallower slope of annual decline in $CD4^+$ count as compared to these two published studies. However, we must note, as mentioned above, that we have unknown seroconversion dates among our study, whereas patients in these published studies had known dates of seroconversion.

When comparing findings from our study regarding individual cofactors significantly influencing trends in $CD4^+$ count, Staples et al (1999) found no difference in mean or median values of $CD4^+$ count between HCV co-infected and HCV uninfected patients in their study among patients followed at the Atlanta Veterans Affairs Medical Center. However, out of 350 patients in their cohort only 70 were IDU (77). In our study we found that mean $CD4^+$ count decline was more rapid among HCV co-infected as compared to uninfected individuals.

Further difficulties in assessing the impacts of HCV co-infection on trends in $CD4^+$ counts are the unknown dates of HCV infection as well as HIV infection. This same limitation was identified in a study by Piroth et al (2000). Therefore, the duration that these two infections have co-occurred in an individual patient is unknown, and the time that an individual's immune system has been infected with these two viruses is unknown.

Caution in interpreting the results of estimates of the effects of case management on $CD4^+$ slope is required as the number of clients was small and the timing of entry into the program was not recorded in this dataset. We cannot reject the hypothesis that case management may be a mitigating factor in slowing $CD4^+$ cell decline (which would be the desired outcome of such a program using the outcome measure in the current study to gauge its success) as we do not known the time at which this intervention occurred. Additionally, the small sample may not have allowed for sufficient power to ascertain differences in rate of $CD4^+$ decline between clients and non-clients.

Among recipients of social assistance, it is suspected that the number of people recorded as being recipients of social assistance is likely an underrepresentation of the true number of individuals among this population who are beneficiaries of this service. Patients in our study have many social and medical needs and therefore likely access care at other clinics or through social services. Information on the receipt of social assistance was for the most part derived from the inclusion of physician completed forms with patient charts requesting additionally funds due to debilitations associated with advanced HIV or other medical conditions. Patients in our study may have accessed social assistance funds at other locations, and this information may not have been accurately

recorded in reviewed charts. Furthermore, advancing disease progression has been associated with a lowering in SES (95). Therefore, it may be difficult to determine if a lower SES contributed to accelerated $CD4^+$ cell decline or whether an accelerated $CD4^+$ decline necessitated receipt of social assistance.

5.5. Identification of Patients with Rapid Decline in $CD4^+$ Count

The number of studies published focusing specifically on defining rapid $CD4^+$ cell count decline was quite limited. When definitions of slow or rapid progression were provided they were most often specific to the given study population and therefore likely not generalizable to other population, especially one as unique as ours (38). It was challenging to identify rapid progressors among this population as seroconversion date was not known for every patient. Therefore, it was not possible to calculate slope of $CD4^+$ over the entire course of HIV infection, because the duration of infection was unknown. Identification of rapid progressors was further complicated by the finding that 91 patients had an initial $CD4^+$ count equal to or below 200 cells/ mm^3, therefore the immune systems of these patients were already severely compromised. Including these patients in an analysis to identify rapid progressors was problematic as due to their depressed $CD4^+$ count their calculated slope would likely either remain stable or increase. As such, in primary analyses, these patients who were at the most advanced stage of HIV progression were classified as slow progressors. This was an erroneous classification as these patients had already progressed to immunological AIDS.

Delays in testing among at risk populations and subsequent delays in presentation to care among infected individuals is an important obstacle in the management of the

HIV epidemic particularly in developed countries (22) The occurrence of individuals who are first diagnosed as HIV positive at the same time as they receive an AIDS diagnoses is a major concern and the SHR has identified this as such (43). Kissingger et al (1995) found that the most severely immunocompromised clients were more likely to miss scheduled clinic visits (57). Severity of immunosuppression at initiation of ARV has previously been associated with the likelihood of immune recovery, with a rise in $CD4^+$ count occurring more frequently in patients with higher $CD4^+$ counts at the initiation of ARV (23). Therefore, it is important to initiate ARV at the clinically appropriate time in HIV disease progression in order to maximize the likelihood of immune recovery and subsequent maintenance of a healthy immune system in an HIV infected patient. If HIV is not diagnosed early in its clinical course and/ or if patients are not followed by clinicians at appropriate intervals, the likelihood of prevention of progression to AIDS is reduced, not to mention the substantially increased costs of treating an AIDS patient in hospital as opposed to an HIV patient in an outpatient setting (57). Krentz, Auld and Gill (2004) calculated the direct costs of care in the 12 months following HIV-diagnosis in Southern Alberta for patients presenting with a $CD4^+$ count below 200 cells/ μL to be more than twice that of a patient presenting with a $CD4^+$ count above 200 cells/μL (111)

Due to the unavailability of date of seroconversion among all patients and therefore an inability to accurate define duration of HIV infection rapid and slow progression was assessed among two sub group of patients with initial $CD4^+$ counts equal to or greater than 500 and 350 cells/mm^3. These values were selected because a $CD4^+$ count of 500 or greater is associated with a normal life expectancy among HIV infected patients and initiation of ARV is recommended before $CD4^+$ count declines below 350

cells (9). Therefore, patients who entered care above these $CD4^+$ counts were more likely to record $CD4^+$ counts prior to initiation of ARV, therefore allowing for observation of the natural course of HIV infection. In addition, we estimated $CD4^+$ count slope using two methods, linear regression and mixed effects models. Under the circumstances of this analyses the assumption of a linear relationship between the independent and dependent variables is justified as $CD4^+$ counts included in this analysis are those recorded while patients were not on ARV and it is reasonable to expect that $CD4^+$ counts should show a linear pattern of decline prior to initiation of ARV. The use of two statistical methods to estimate $CD4^+$ count slope is further justified by an absence in the literature of any precedent of methods by which patients should be identified as rapid progressors and how rapid progression should be defined with respect to $CD4^+$ count. In our analyses similar results were obtained between the two $CD4^+$ count slope estimation methods this consistency allows for a higher level of confidence in our results.

In this analysis only $CD4^+$ counts of patients who did not receive ARV during the follow-up period and $CD4^+$ counts of patients who were prescribed ARV recorded before the date of ARV initiation were used. Other authors have also restricted evaluation of $CD4^+$ cell count slopes over time to participants with initial $CD4^+$ counts greater than 500 in order to minimize the number or participants likely to initiate ARV after their baseline visit (20). Although this inclusion criteria reduced the study sample size it resolved the issue of the erroneous classification of end stage HIV patients as slow progressors.

Co-infection with HCV, a history of IDU and receipt of ARV were the variables most strongly associated with an increased likelihood of having a rapid rate of $CD4^+$ decline, although only receipt of ARV was statistically significant. This may indicate that

patients exhibiting rapid $CD4^+$ count decline were more likely to be prescribed ARV or were more likely to progress to a $CD4^+$ count at which initiation of ARV was recommended. Receipt of social assistance was significantly associated with an increased likelihood of rapid $CD4^+$ decline among patients with an initial $CD4^+$ count of equal to or greater than 500 where slope was estimating using linear regression in bivariate analysis.

In our study median rate of decline, estimated by linear regression, among patients with at least 3 $CD4^+$ counts recorded among patients who did not receive ARV during the follow-up period were similar between the two sub-groups. Among patients with an initial $CD4^+$ count of 500 cells or greater, median rate of decline was - 6.85 cells/mm^3 per month and among patients with an initial $CD4^+$ count of 350 cells or greater median rate of decline was -6.45 cells/month. Easterbrook et al (1993) included patients with at least 3 $CD4^+$ counts recorded prior to initiation of therapy to determine a median rate of decrease of 4-11 cells per month as determined by linear regression stratified by $CD4^+$ count at initiation ARV, which is consistent with our study (23). In another study using data from the ongoing MACS cohort of homosexual and bisexual men collected before January 1990, in order to avoid influence of ARV, a highly significant linear decline of 109 cells/mm^3 per year in the first 3 years of follow-up after seroconversion was observed (21). The rates of decline in $CD4^+$ count in our study are comparable to those recorded by Easterbrook and slightly less than those found in the MACS study. However, the validity of comparing the $CD4^+$ slopes estimated in our study to these analyses of data collected in the late 1980s and early 1990s is questionable as the characteristics of patients not receiving ARV are likely different. Among our study population, effective ARV was widely available and patients meeting immunological

guidelines for the initiation of ARV were in high likelihood recipients of this therapy. Patients who did not receive ARV during the follow-up time were likely those whose $CD4^+$ were sufficiently elevated to levels where ARV is not required. Whereas, in the studies from the late 1980s and early 1990s effective ARV may not have been available to all patients and consequently despite recording $CD4^+$ counts where ARV would have been recommended by today's guidelines these patients likely did not receive such therapies.

5.6. Clinical Implications of Findings

It is important that the findings of our study be beneficial to the patients enrolled in this study cohort. Due to the nature of this study these benefits are primarily in improving clinical practices. An essential goal of our study was to contribute information to aid clinicians in the identification of patients in Saskatoon at risk of rapid progression based on the individual social and clinical characteristics of patients. The identification of cofactors in progression to AIDS and/or death has the potential to slow disease progression if the impacts of such cofactors can be mitigated (12). The presence of coinfections or a high risk of certain opportunistic diseases, can provide a strong rationale for earlier initiation of therapy (9). Early and more aggressive ARV might be beneficial to patients with more rapid disease progression (23).

The mixed effects models built in our study have the potential to be developed into a clinical tools for use by clinical care providers in predicting $CD4^+$ counts of patients at follow-up visits. By such means patients at particular risk of attaining low $CD4^+$ counts in relatively short time intervals could be identified and steps could be taken

to mitigate this risk and/ or to prepare patients for initiation of ARV. For example, although we did not see a significant association with increased $CD4^+$ counts and involvement with case management services likely due to dataset limitations in our study, it is a reasonable expectation that enrollment in case management services should have a positive impact on $CD4^+$ count. Associations with engagement in case management services and improvements in overall health among HIV infected individuals have been previously recorded (72,99,100). Through the use of such a tool clinicians would be better able to identify patients who would most benefit from engagement in Case Management services and thereby better allocate this limited resource.

5.7. Study Strengths

One of the important strengths of this study is that it investigates a unique and understudied population that is facing an HIV epidemic that is at present far from its resolution. This unique population is characterized by three important factors, each of which potentially place HIV infected individuals at risk for rapid progression. These factors include an overrepresentation of individuals of First Nations or Métis ethnicity and therefore the social and economic disadvantage that exists at increased rates among this population, and a high prevalence of HCV co infection and IDU. Additionally, the follow-up period of this study incorporates the course of the emergence of the dramatic increase in incidence of HIV in the province of Saskatchewan. This study was also set in the most severely affected health region in the province, as the SHR has reported the highest number of cases of HIV across all regional health authorities in Saskatchewan since 2005 (43).

Another strength of this study is that data was derived from patient charts complied by clinicians providing ongoing care to patients, therefore one can be confident that information contained within these charts is accurate to the best of the abilities of these clinicians.

Importantly, this study advances HIV epidemiological research by contributing a definition of rapid HIV disease progression with respect to $CD4^+$ count decline. Such a definition is valuable due to limited numbers of studies offering any definition of rapid progression, especially with respect to decline in $CD4^+$ count. This study provides important insights into the phenomenon of rapid HIV disease progression in the province of Saskatchewan and in doing so has the potential to improve clinical care to these patients and ultimately improve their quality of life. Finally, as First Nations, Métis and Inuit IDU comprise the fastest growing proportion of incident HIV infections in Canada, a more throughout understanding of HIV disease progression among this population will become essential to the mitigation of the HIV epidemic in Canada (3).

Our study results may additionally prove to be influential at a policy level if the conclusions drawn from the research in this study may contribute to a greater allocation of funding to HIV prevention and care in Saskatchewan. Furthermore, as our study arrives at the conclusion that the unique epidemiology of HIV in Saskatchewan does contribute to making this infected population one that is uniquely vulnerable interventions can be tailored to the most high-risk individuals among this population. For example, based on this study it would appear that interventions targeted at reducing HIV transmission via IDU in First Nations and Métis communities would be particularly effective in reducing HIV incidence in Saskatchewan.

5.8. Study Limitations

Limitations of this study include those inherent in all retrospective studies, namely data was collected from a source, medical charts, not designed for scientific studies. On multiple occasions the data source was missing information or there was a lack of sufficient detail for inclusion in statistical analysis of variables of interest. In addition, records of patients who migrated to Saskatchewan from other provinces, territories or countries were often incomplete with regards to variables of interest in this study.

A further limitation is the possible exclusion of eligible patients due to the use of multiple lists in the identification of patients, as no centralized list of HIV infected patients followed at the PLP and WSCC existed or was accessible to the M.Sc. student collecting the data. As consequence the student had to identify patients based on several master lists as created by past contributors to the database, as well as a new referrals binder kept by administrative assistants in the Infectious Disease Department at RUH.

Unknown seroconversion dates among many of the patients in the dataset is another important limitation of this study, as it renders investigators unable to assess $CD4^+$ count decline over the entire duration of HIV infection. An absence of information on ARV adherence among patients receiving such therapies is another limitation in this study. In addition periods of discontinuation of ARV and changes in therapeutic regime are difficult to assess statistically and as a result were not accounted for in our study. It was also not possible to assess the impact of housing insecurity on $CD4^+$ count, which is an important limitation in our study as a significant number of patients likely experienced housing insecurity. Active IDU was also absent in our analysis due to difficulties in assessing this variable, as a physician may not have recorded this information in a patient

chart or the patient may not have been seen within the past 6 months, as the definition of active IDU included IDU in the last 6 months. The impact of the HLA-B*57 MHC class type was also not investigated in this population due to the limited number of individuals in possession of this phenotype, despite recognition of the association of this allele with rapid progression to AIDS (61). Finally, we did not factor into any analyses the impact on population means of including individuals mentioned in the special cases section (Section 4.2) such as pregnant women. Inclusion in analyses of individuals with other conditions also negatively affecting $CD4^+$ count may have caused an overestimation of the magnitude of decline in $CD4^+$ count. Were we to account for the influence of pregnancy on $CD4^+$ count in our analyses we might consider either excluding pregnant females from the analyses or only excluding $CD4^+$ counts recorded during time of pregnancy.

The impact of stressful life events as well as the loss of social support is not well measured in the present study. This may be a weakness of this study as many of the patients in this study likely have lost partners or family members, whether it be to HIV or another causes attributable to turbulent lives. Such losses results in both a loss of social support as well as represent an extremely stressful life event. Diminished social support and stressful life events have both been associated with lowered immunological function and therefore may be associated with a more rapid course of HIV infection (97,98).

In Study Objective 3 subgroup inclusion criteria resulted in a significant reduction in sample size particularly when the inclusion criteria was 3 $CD4^+$ counts recorded while not receiving ARV and an initial $CD4^+$ count of $\geq$ 500 cells/ mm^3. In this instance the sample size was reduced to only 32 patients. Therefore, these analyses may not have had

a sufficient sample size to allow for adequate power to detect significant associations between cofactors and rate of $CD4^+$ count decline.

Another significant limitation of this study is that it is difficult statistically to measure the potential cumulative negative impacts of the co-occurrence within an individual of HCV co-infection, IDU and the social and economical disadvantages often associated with First Nations or Métis ethnicity on rate of $CD4^+$ decline, due to the high colinearity between these three variables. In general, it was difficult to represent multiple health compromising conditions present amongst some patients in statistical models and even more difficult to evaluate the potential synergistic impacts of these conditions on $CD4^+$ cell decline. It may be possible to create a function combining these three variables to be incorporated into one model. However, the use of such a new variable in a model to estimate the effect of these three highly associated cofactors is questionable. Some areas of concern include the unknown duration of HCV infection, an unknown duration of IDU as well as difficulty in accounting for the differing effects of various drugs on the immune system and finally in identifying the social factors that contribute to First Nations and Métis ethnicity influencing CD4+ count. As such we would recommend caution in utilizing such a variable as well as to recommend that it be validated using a larger data than the one in this study prior to any scientific use. This presence of co-factors amongst a single patient, all potentially associated with accelerated $CD4^+$ decline, is undoubtedly also a challenge faced by infectious disease physicians in the clinical management of these patients.

Finally, our decision to use the upper and lower quartiles of $CD4^+$ slope to define rapid and slow progression in the third objective of our study was arbitrary and therefore, might not represent the best method by which to make such distinctions.

6. Conclusion and Future Studies

Rates of $CD4^+$ decline among HIV-1 infected individuals vary considerably, while some individuals maintain stable counts for long periods of time, others experience rapid decline. In this study we investigated social and clinical factors that might be associated with some of the observed heterogeneity in rates of $CD4^+$ cell decline with the goal of improving the quality of care provided to HIV infected patients in Saskatoon. In summary, a history of incarceration, co-infection with HCV, a history of IDU, First Nations and Métis ethnicity, age at diagnosis, receipt of social assistance and not receiving ARV had a negative influence on trends in $CD4^+$ count.

At the beginning of the HIV epidemic HIV-positive people were likely to die within 10 years of infection. The development of ARV has transformed, at least for people living in developed countries, this infection into a chronic treatable condition. Therefore, decisions regarding HIV therapies are arguably of greater importance today than ever before in the history of the HIV/AIDS epidemic. Results of this study have the potential to influence physician decisions of timing of initiation of ARV. For example in this study a history of IDU was identified as associated with an increased risk of a rapid rate of decline in $CD4^+$ count. Thereby a physician may recommend initiation of ARV at an earlier time for a patient with a history of IDU than for a patient without such a history, in order to initiate ARV at the optimal time.

Other research questions of interest generated over the course of the completion of this thesis included, whether or not ethnicity affects HIV prognosis after the initiation of treatment, quantifying the response of $CD4^+$ count to treatment in this population, determining patient factors that predict a rise in $CD4^+$ count to 500 cells and lastly, differentiating between factors that influence $CD4^+$ rate of decline on-treatment as compared to off treatment. The investigation of the effects of other prevalent cofactors such as mental illness and smoking status, which could not be included in the current study due to data limitations, on rate of $CD4^+$ decline would also be of use to clinicians as they plan for the clinical management of patients. Smoking, for example, has been associated with significantly higher $CD4^+$ counts among HIV negative individuals (27).

The establishment of a prospective cohort among this study population will be instrumental in improving the quality of data available for analysis and enabling a much clearer estimation of the clinical and immunological course of HIV in this population. The conducting of qualitative studies among this cohort would also be extremely powerful because of the tumultuous lives led by many of the individuals in this study. The stories of these individuals' lives would give important insights into the HIV epidemic in Saskatchewan and hopefully lead to a strong call to action to improve the lives of those afflicted. Such studies would also follow the conclusions of Fee and Krieger (1993) that the development of more effective prevention and health care strategies will be greatly aided by making "…the experiences and views of those hit hardest by the epidemic….more central to the conduct of scientific research and the establishment of health policy" (102).

For many individuals in our study being infected with HIV is one of many challenges faced in daily life among others including, drug addiction, mental illness, and poverty. More than clinical interventions are required if there can be hope for meaningful and sustained improvements in these individuals' lives. Monette et al (2011) support this notion that policies and services that integrate income and employment support with affordable and stable housing may have the potential to reduce health disparities and improve health outcomes for First Nations, Métis and Inuit peoples living with HIV (40). Fee and Krieger (1993) reiterate this notion that, "…AIDS…cannot be understood or addressed solely within the parameters of the health care system." (102). Multiple and sustained social interventions will be required in addition to a throughout understanding of the clinical course of the HIV virus in Saskatoon, in order to turn the tide on the HIV epidemic in this city and in this province.

7. References

(1) Public Health Agency of Canada. HIV and AIDS in Canada. Surveillance Report to December 31, 2009. Surveillance and Risk Assessment Division, Centre for Communicable Diseases and Infection Conrtol. 2010.

(2) Saskatchewan Ministry of Health, Population Health Branch. HIV Strategy for Saskatchewan 2010-2013.

(3) Public Health Agency of Canada. Population-Specific HIV/AIDS Status Report: Aboriginal Peoples. 2010.

(4) Public Health Agency of Canada. HIV/AIDS Epi Updates – July 2010, Chapter 1: National HIV Prevalence and Incidence Estimates in Canada for 2008. 2011; Available at: http://www.phac-aspc.gc.ca/aids-sida/publication/epi/2010/1-eng.php#note5. Accessed March/12, 2012.

(5) Montaner JSG, Le T, Hogg R, Ricketts M, Sutherland D, Strathdee SA, et al. The changing spectrum of AIDS index diseases in Canada. AIDS 1994;8(5):693.

(6) Fee E, Fox DM. The contemporary historiography of AIDS. Journal of Social History 1989;23(2):303-314.

(7) Morison L. The global epidemiology of HIV/AIDS. Br Med Bull 2001;58(1):7.

(8) World Health Organization. HIV/AIDS. November, 2011; Available at: http://www.who.int/mediacentre/factsheets/fs360/en/index.html. Accessed March/11, 2012.

(9) Hammer SM, Eron JJ, Jr Reiss, Peter Schooley,Robert T., Thompson MA, Walmsley, Sharon Cahn, Pedro Fischl,Margaret A., Gatell JM, et al. Antiretroviral Treatment of

Adult HIV Infection: 2008 Recommendations of the International AIDS Society-USA Panel. JAMA 2008 August 6;300(5):555-570.

(10) Gillies P, Tolley K, Wolstenholme J. Is AIDS a disease of poverty? AIDS Care 1996 06;8(3):351-363.

(11) SELIGMANN M, PINCHING AJ, ROSEN FS, FAHEY JL, KHAITOV RM, KLATZMANN D, et al. Immunology of human immunodeficiency virus infection and the acquired immunodeficiency syndrome. Ann Intern Med 1987;107(2):234-242.

(12) Webster A. Cytomegalovirus as a possible cofactor in HIV disease progression. JAIDS J Acquired Immune Defic Syndromes 1991;4(6):S47.

(13) McCune JM. The dynamics of CD4 T-cell depletion in HIV disease. Nature 2001;410(6831):974-979.

(14) Piroth L, Grappin M, Cuzin L, Mouton Y, Bouchard O, Raffi F, et al. Hepatitis C virus co-infection is a negative prognostic factor for clinical evolution in human immunodeficiency virus-positive patients. Journal of Viral Hepatitis 2000;7(4):302-308.

(15) Rowland-Jones S, Pinheiro S, Kaul R. New insights into host factors in HIV-1 pathogenesis. Cell 2001;104(4):473.

(16) Public Health Agency of Canada. A Guide to HIV/AIDS Epidemiological and Surveillance Terms. 2006.

(17) Hammer SM, Eron Jr JJ, Reiss P, Schooley RT, Thompson MA, Walmsley S, et al. Antiretroviral Treatment of Adult HIV Infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA: The Journal of the American Medical Association 2008;300:555.

(18) Bentwich Z, Maartens G, Torten D, Lal AA, Lal RB. Concurrent infections and HIV pathogenesis. AIDS 2000;14(14):2071.

(19) Griffin MM, Ryan JG, Briscoe VS, Shadle KM. Effects of incarceration on HIV-infected individuals. J Natl Med Assoc 1996;88(10):639.

(20) Anastos K, Gange SJ, Lau B, Weiser B, Detels R, Giorgi JV, et al. Association of race and gender with HIV-1 RNA levels and immunologic progression. JAIDS J Acquired Immune Defic Syndromes 2000;24(3):218.

(21) Lyles RH, Muñoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. J Infect Dis 2000;181(3):872.

(22) Samet JH, Freedberg KA, Savetsky JB, Sullivan LM, Stein MD. Understanding delay to medical care for HIV infection: the long-term non-presenter. AIDS 2001;15(1):77.

(23) Easterbrook PJ, Emami J, Gazzard B. Rate of CD4 cell decline and prediction of survival in zidovudi net reated patients. AIDS 1993 July;7(7):959-968.

(24) Giordano TP, Wright JA, Hasan MQ, White Jr AC, Graviss EA, Visnegarwala F. Do sex and race/ethnicity influence CD4 cell response in patients who achieve virologic suppression during antiretroviral therapy? Clinical infectious diseases 2003;37(3):433-437.

(25) Deeks SG, Kitchen CMR, Liu L, Guo H, Gascon R, Narváez AB, et al. Immune activation set point during early HIV infection predicts subsequent CD4 T-cell changes independent of viral load. Blood 2004;104(4):942.

(26) Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4 lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997;126(12):946.

(27) Maini M, Gilson R, Chavda N, Gill S, Fakoya A, Ross E, et al. Reference ranges and sources of variability of CD4 counts in HIV-seronegative women and men. Genitourin Med 1996;72(1):27-31.

(28) Tsouska C, Bernard N. Markers Predicting Progression of Human Immunodeficiency Virus-Related DIsease. Clinical microbiology reviews 1994;7(1):14-28.

(29) Tindall B, Cooper DA. Primary HIV infection: host responses and intervention strategies. AIDS 1991;5(1):1-14.

(30) Clark SJ, Saag MS, Decker WD, Campbell-Hill S, Roberson JL, Veldkamp PJ, et al. High Titers of Cytopathic Virus in Plasma of Patients with Symptomatic Primary HIV-1 Infection. N Engl J Med 1991 04/04; 2012/07;324(14):954-960.

(31) Daar ES, Moudgil T, Meyer RD, Ho D, D. Transient High Levels of Viremia in Patients with Primary Human Immunodeficiency Virus Type 1 Infection. N Engl J Med 1991;324:961-964.

(32) Graziosi C, Pantaleo G, Butini L, Demarest JF, Saag MS, Shaw GM, et al. Kinetics of human immunodeficiency virus tyoe 1 (HIV-1) DNA and RNA synthesis during primary HIV-1 infection. PNAS 1993;90(14):6405-6409.

(33) Pantaleo G, Fauci AS. New concepts in the immunopathogenesis of HIV infection. Annu Rev Immunol 1995;13(1):487-512.

(34) Fauci AS. Typical Course of HIV Infection. Available at: http://www.dwp.gov.uk/publications/specialist-guides/medical-conditions/a-z-of-medical-conditions/hiv-aids/clinical-features/. Accessed July/7, 2012.

(35) Buchbinder S, Vittinghoff E. HIV-infected long-term nonprogressors: epidemiology, mechanisms of delayed progression, and clinical and research implications. Microb Infect 1999;1(13):1113-1120.

(36) Klein MR, van Baalen CA, Holwerda AM, Garde SRK, Bende R, Keet I, et al. Kinetics of Gag-specific cytotoxic T lymphocyte responses during the clinical course of HIV-1 infection: a longitudinal analysis of rapid progressors and long-term asymptomatics. J Exp Med 1995;181(4):1365-1372.

(37) Yu XF, Wang Z, Vlahov D, Markham RB, Farzadegan H, Margolick JB. Infection with dual-tropic human immunodeficiency virus type 1 variants associated with rapid total T cell decline and disease progression in injection drug users. J Infect Dis 1998;178(2):388.

(38) Audigé A, Taffé P, Rickenbach M, Battegay M, Vernazza P, Nadal D, et al. Low postseroconversion CD4 count and rapid decrease of CD4 density identify HIV fast progressors. AIDS Res Hum Retroviruses 2010;26(9):997-1005.

(39) Sulkowski M, Chaisson R, Karp C, Moor R, Margolick J, Quinn T. The effect of acute infectious illnesses on plasma human immunodeficiency virus (HIV) type 1 load and the expression of serologic markers of immune activation among HIV-infected adults. 1998;178(6):1642-1648.

(40) Monette LE, LLB, Rourke SB, PhD, Gibson K, Bekele TM, MPH, Tucker R, Greene S, et al. Inequalities in Determinants of Health Among Aboriginal and Caucasian Persons

Living With HIV/AIDS in Ontario: Results From the Positive Spaces, Healthy Places Study. Canadian Journal of Public Health 2011 May/Jun 2011;102(3):215-219.

(41) Disease Prevention Unit, Population Health Branch, Saskatchewan Ministry of Health. HIV and AIDS in Saskatchewan 2010. 2011 November 30, 2011.

(42) HIV in Saskatchewan Panel Discussion; February 14, 2011.

(43) Neudorf C, Marko J, Wright J, Ugolini C, Kershaw T, Whitehead S, et al. Health Status Report 2008: A Report of the Chief Medical Health Officer. Saskatoon 2009.(Saskatoon Health Region).

(44) Saskatchewan Ministry of Health. Covered population, 2008. 2008; Available at: http://www.health.gov.sk.ca/covered-population2008/CovPopBook2008.pdf. Accessed March 20, 2012.

(45) Carovano K. More than mothers and whores: redefining the AIDS prevention needs of women. International Journal of Health Services 1991;21(1):131-142.

(46) Morison L. The global epidemiology of HIV/AIDS. Br Med Bull 2001;58(1):7.

(47) Mocroft A, Gill MJ, Davidson W, Phillips AN. Are There Gender Differences in Starting Protease Inhibitors, HAART, and Disease Progression Despite Equal Access to Care?[Miscellaneous Article]. JAIDS J Acquired Immune Defic Syndromes 2000 August 15;24(5):475-482.

(48) Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiébaut R, et al. Time From Human Immunodeficiency Virus Seroconversion to Reaching CD4 Cell Count Thresholds< 200,< 350, and< 500 Cells/mm3: Assessment of Need Following Changes in Treatment Guidelines. Clinical infectious diseases 2011;53(8):817-825.

(49) Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. Ann Intern Med 2006;145(6):397.

(50) Jarrin I, Geskus R, Bhaskaran K, Prins M, Perez-Hoyos S, Muga R, et al. Gender differences in HIV progression to AIDS and death in industrialized countries: slower disease progression following HIV seroconversion in women. Am J Epidemiol 2008;168(5):532.

(51) Phillips AN, Lee CA, Elford J, Webster A, Janossy G, Timms A, et al. More rapid progression to AIDS in older HIV-infected people: the role of CD4 T-cell counts. J Acquir Immune Defic Syndr 1991;4(10):970.

(52) Pezzotti P, Phillips AN, Dorrucci M, Lepri AC, Galai N, Vlahov D, et al. Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion. BMJ 1996;313(7057):583-586.

(53) Chaisson RE, Keruly JC, Moore RD. Race, Sex, Drug Use, and Progression of Human Immunodeficiency Virus Disease. N Engl J Med 1995 09/21; 2012/04;333(12):751-756.

(54) Moore AL, Kirk O, Johnson AM, Katlama C, Blaxhult A, Dietrich M, et al. Virologic, immunologic, and clinical response to highly active antiretroviral therapy: the gender issue revisited. JAIDS J Acquired Immune Defic Syndromes 2003;32(4):452.

(55) Wolbers M, Babiker A, Sabin C, Young J, Dorrucci M, Chêne G, et al. Pretreatment CD4 Cell Slope and Progression to AIDS or Death in HIV-Infected Patients Initiating Antiretroviral Therapy--The CASCADE Collaboration: A Collaboration of 23 Cohort Studies. PLoS Medicine 2010 02;7(2):1-9.

(56) Pezzotti P, Phillips AN, Dorrucci M, Lepri AC, Galai N, Vlahov D, et al. Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion. BMJ 1996;313(7057):583-586.

(57) Kissinger P, Cohen D, Brandon W, Rice J, Morse A, Clark R. Compliance with public sector HIV medical care. J Natl Med Assoc 1995;87(1):19.

(58) Fife D, Mode C. AIDS incidence and income. J Acquir Immune Defic Syndr 1992;5(11):1105.

(59) Lyles RH, Muñoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. J Infect Dis 2000;181(3):872.

(60) Engels EA, Rosenberg PS, O'Brien,T.R., Goedert JJ. Plasma HIV viral load in patients with hemophilia and late-stage HIV disease: a measure of current immune suppression. Multicenter Hemophilia Cohort Study. Ann Intern Med 1999 08/17;131(4):256-264.

(61) Carrington M, Nelson GW, Martin MP, Kissner T, Vlahov D, Goedert JJ, et al. HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. Science 1999 03/12;283(5408):1748-1752.

(62) Itescu S, Mathur-Wagh U, Skovron ML, Brancato LJ, Marmor M, Zeleniuch-Jacquotte A, et al. HLA-B35 is associated with accelerated progression to AIDS. JAIDS J Acquired Immune Defic Syndromes 1992;5(1):37.

(63) Dean M, Carrington M, Winkler C, Huttley G, Smith M, Allikmets R, et al. Genetic Restriction of HIV-1 Infection and Progression to AIDS by a Deletion Allele of the CKR5 Structural Gene. Science 1996;273:1856-1862.

(64) Martin LJ, Houston S, Yasui Y, Wild TC, Saunders LD. All-cause and HIV-related mortality rates among HIV-infected patients after initiating highly active antiretroviral therapy: the impact of Aboriginal ethnicity and injection drug use. Canadian Journal of Public Health 2011;102(2):90-96.

(65) Roy E, Richer I, Morissette C, Leclerc P, Parent R, Claessens C, et al. Temporal changes in risk factors associated with HIV seroconversion among injection drug users in eastern central Canada. AIDS; 2011; 25(15):1897-1903.

(66) Des Jarlais DC, Arasteh K, McKnight C, Hagan H, Perlman DC, Semaan S. Associations between herpes simplex virus type 2 and HCV with HIV among injecting drug users in New York City: the current importance of sexual transmission of HIV. Am J Public Health 2011;101(7):1277.

(67) Lewden C, Chêne G, Morlat P, Raffi F, Dupon M, Dellamonia P, et al. HIV-infected adults with CD4 cell count above 500/mm3 on long term combination antiretroviral therapy reach same mortality rates as the general population. JAIDS Journal of Acquired Immune Deficiency Syndromes; 2007; 46(1):72-77.

(68) Cohn SE, Jiang HY, McCutchan JA, Koletar SL, Murphy RL, Robertson KR, et al. Association of ongoing drug and alcohol use with non-adherence to antiretroviral therapy and higher risk of AIDS and death: results from ACTG 362. AIDS Care; 2011;23(6):775-785.

(69) Rafie C, Campa A, Smith S, Huffman F, Newman F, Baum MK. Cocaine reduces thymic endocrine function: another mechanism for accelerated HIV disease progression. AIDS Research and Human Retroviruses; 2011;27(8): 815-822.50.

(70) Chiappelli F, Frost P, Manfrini E, Lee P, Pham L, Garcia C, et al. Cocaine blunts human CD4 cell activation. Immunopharmacology 1994;28(3):233-240.

(71) Baldwin GC, Roth MD, Tashkin DP. Acute and chronic effects of cocaine on the immune system and the possible link to AIDS. J Neuroimmunol 1998; 3/15;83(1–2):133-138.

(72) Gardner LI, Metsch LR, Anderson-Mahoney P, Loughlin AM, Rio C, Strathdee S, et al. Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. AIDS 2005;19(4):423.

(73) Palepu A, Tyndall MW, Joy R, Kerr T, Wood E, Press N, et al. Antiretroviral adherence and HIV treatment outcomes among HIV/HCV co-infected injection drug users: The role of methadone maintenance therapy. Drug Alcohol Depend 2006 9/15;84(2):188-194.

(74) Hinkin CH, Barclay TR, Castellon SA, Levine AJ, Durvasula RS, Marion SD, et al. Drug use and medication adherence among HIV-1 infected individuals. AIDS and Behavior 2007;11(2):185-194.

(75) Rapiti E, Porta D, Forastiere F, Fusco D, Perucci CA. Socioeconomic status and survival of persons with AIDS before and after the introduction of highly active antiretroviral therapy. Epidemiology 2000;11(5):496.

(76) Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy. JAMA: the journal of the American Medical Association 1999;282(23):2220-2226.

(77) Staples J, C., Rimland D, Dudas D. Hepatitis C in the HIV (Human Immunodeficiency Virus) Atlanta V.A. (Veterans Affairs Medical Center) Cohort Study

(HAVACS): The Effect of Coinfection on Survival. Clinical Infectious Diseases 1999;29(1):150-154.

(78) Dorrucci M, Pezzotii P, Phillips A, Lepri A, Rezza G. Coinfection of Hepatitis C Virus with Human Immunodeficiency Virus and Progression to AIDS. The Journal of Infectious Diseases 1995;172(6):1503-1508.

(79) Des Jarlais D, Semaan S. HIV and other sexually transmitted infections in injection drug users and crack cocaine smokers. Sexually transmitted diseases.4th ed.New York: McGraw Hill 2008:237-255.

(80) Hagan H, Scheinmann R, Des Jarlais DC, et. al., editors. Meta-analysis of HIV/HCV co-infection in injecting drug users. National HIV Prevention Conference; 2006; Atlanta, GA; 2006.

(81) Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. The Lancet 2000;356(9244):1800-1805.

(82) Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. JAMA: the journal of the American Medical Association 2002;288(2):199.

(83) Haydon GH, Flegg PJ, Blair CS, Brettle RP, Burns SM, Hayes PC. The impact of chronic hepatitis C virus infection on HIV disease and progression in intravenous drug users. Eur J Gastroenterol Hepatol 1998;10(6):485.

(84) Zylberbeg H, Pol S. Reciprocal Interactions Between Human Immunodeficience Virus and Hepatitis C Virus Infections. Clinical Infections Diseases 1996;23:1117-1125.

(85) Boerma J, Weir SS. Integrating demographic and epidemiological approaches to research on HIV/AIDS: the proximate-determinants framework. J Infect Dis 2005;191(Supplement 1):S61.

(86) Buchacz K, Patel P, Taylor M, Kerndt PR, Byers RH, Holmberg SD, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004;18(15):2075.

(87) Eaton M. Syphilis and HIV: old and new foes aligned against us. Curr Infect Dis Rep 2009;11(2):157-162.

(88) Sheth PM, Sunderji S, Shin LYY, Rebbapragada A, Huibner S, Kimani J, et al. Coinfection with herpes simplex virus type 2 is associated with reduced HIV-specific T cell responses and systemic immune activation. J Infect Dis 2008;197(10):1394-1401.

(89) Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. Sex Transm Dis 2006;33(3):143.

(90) Palacios R, JimenezOnate F, Aguilar M, Galindo MJ, Rivas P, Ocampo A, et al. Impact of Syphilis Infection on HIV Viral Load and CD4 Cell Counts in HIV-Infected Patients. JAIDS J Acquired Immune Defic Syndromes 2007 March 1;44(3):356-359.

(91) Perreault S. The incarceration of Aboriginal people in adult correctional services. 2009; Available at: http://www.statcan.gc.ca/pub/85-002-x/2009003/article/10903-eng.htm. Accessed April 8, 2012.

(92) Spaulding A, Stephenson B, Macalino G, Ruby W, Clarke JG, Flanigan TP. Human immunodeficiency virus in correctional facilities: a review. Clinical Infectious Diseases 2002 Aug 1;35(3):305-312.

(93) Freudenberg N. Jail, Prisons, and the Health of Urban Populations: A Review of the Impact of the Correctional System on Community Health. Journal of Urban Health: Bulletin of the New York Academy of Medicine 2001;78(2):214-235.

(94) Small W, Wood E, Betteridge G, Montaner J, Kerr T. The impact of incarceration upon adherence to HIV treatment among HIV-positive injection drug users: a qualitative study. AIDS Care 2009;21(6):708-714.

(95) Kass NE, Munoz A, Chen B, Zucconi SL, Bing EG. Changes in employment, insurance, and income in relation to HIV status and disease progression. The Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr 1994;7(1):86.

(96) Paton NI, Sangeetha S, Earnest A, Bellamy R. The impact of malnutrition on survival and the CD4 count response in HIV-infected patients starting antiretroviral therapy. HIV Med 2006 07;7(5):323-330.

(97) Schuster R, Bornovalova M, Hunt E. The Influence of Depression on the Progression of HIV: Direct and Indirect Effects. Behav Modif 2011.

(98) Leserman J, Jackson ED, Petitto JM, Golden RN, Silva SG, Perkins DO, et al. Progression to AIDS: the effects of stress, depressive symptoms, and social support. Psychosom Med 1999;61(3):397.

(99) Katz MH, Cunningham WE, Fleishman JA, Andersen RM, Kellogg T, Bozzette SA, et al. Effect of Case Management on Unmet Needs and Utilization of Medical Care and Medications among HIV-Infected Persons. Ann Intern Med 2001 October 16;135(8 (Part 1)):557-565.

(100) Fleishman JA, Mor V, Piette J. AIDS case management: the client's perspective. 1991 10; 2012/7;26(4):447+.

(101) Mehta S, Moore RD, Graham NMH. Potential factors affecting adherence with HIV therapy. AIDS 1997;11(14):1665.

(102) Fee E, Krieger N. Understanding AIDS: historical interpretations and the limits of biomedical individualism. Am J Public Health 1993 Oct;83(10):1477-1486.

(103) Poundstone K, Strathdee S, Celentano D. The social epidemiology of human immunodeficiency virus/acquired immunodeficiency syndrome. Epidemiol Rev 2004;26(1):22-35.

(104) City of Saskatoon. Population Estimate & Projection. 2011; Available at: http://www.saskatoon.ca/DEPARTMENTS/Community%20Services/PlanningDevelopment/FutureGrowth/DemographicAndHousingData/Pages/PopulationEstimateProjection.aspx. Accessed March 26, 2012.

(105) Community Health Services (Saskatoon) Association Ltd. Background Information Westside Community Clinic October 19th, 2010. 2010; Available at: http://www.saskatooncommunityclinic.ca/pdf/2010-10-19-fact-sheet.pdf. Accessed March 16, 2012.

(106) Saskatoon Health Region. Livewell Chronic Disease Management (CDM) Livewell Positive Living Prgram. 2012; Available at: http://www.saskatoonhealthregion.ca/your_health/ps_cdm_positive_living_program.htm. Accessed March 16, 2012.

(107) Krüsi A, MILLOY MJ, Kerr T, Zhang R, Guillemi S, Hogg R, et al. Ongoing drug use and outcomes from highly active antiretroviral therapy among injection drug users in a Canadian setting. Antivir Ther (Lond) 2010;15(5):789-796.

(108) Government of Saskatchewan. Pharmaceutical Information Program (PIP). 2007; Available at: http://www.health.gov.sk.ca/pip. Accessed July/13, 2012.

(109) Castilla J, Rueda R, Luisa Vargas M, González-Gómez F, García-Olivares E. Decreased levels of circulating CD4+ T lymphocytes during normal human pregnancy. J Reprod Immunol 1989 5;15(2):103-111.

(110) Lewden C, Thiébaut R, Boufassa F, Coulibaly A, Malateste K, Seng R, et al. Comparison of early CD4 T-cell count in HIV-1 seroconverters in Cote d'Ivoire and France: the ANRS PRIMO-CI and SEROCO cohorts. JAIDS J Acquired Immune Defic Syndromes 2010;53(2):260.

(111) Krentz HB, Auld MC, Gill MJ. The high cost of medical care for patients who present late (CD4<200/ μL) with HIV infection. HIV Medicine 2004;5:93-98.