OBJECTIVE: To assess the impact of clinical and social factors unique to HIV-infected adults in Saskatoon, Saskatchewan, regarding the rate of CD4⁺ count change, and to identify factors associated with a risk of CD4⁺ count decline.

METHODS: A retrospective longitudinal cohort study from medical chart reviews at two clinics was conducted in Saskatoon. Univariate and multivariate linear mixed effects models were used to assess the impact of selected factors on CD4⁺ count change.

RESULTS: Four hundred eleven HIV-infected patients were identified from January 1, 2003 to November 30, 2011. Two hundred eighteen (53%) were male, mean ± SD age was 35.6 ± 10.1 years, 257 (70.8%) were First Nations or Métis, 312 (80.2%) were hepatitis C virus (HCV) coinfection, and 300 (73.3%) had a history of injection drug use (IDU). In univariate models, age, ethnicity, HCV, IDU, antiretroviral therapy and social assistance were associated with significantly lower CD4⁺ counts in multivariate models. Older age and social assistance were associated with significantly lower CD4⁺ counts in models 1 and 3. Age was marginally significant in model 2 (P=0.055). Not prescribed antiretroviral therapy was associated with a significantly negative CD4⁺ count slope in all multivariate models.

CONCLUSION: The unique epidemiology of this HIV-infected population may be contributing to CD4⁺ count change. Increased attention and resources focused on this high-risk population are needed to prevent disease progression and to improve overall health and quality of life.

Key Words: CD4⁺ count; First Nations; HCV; HIV; IDU; Métis; Rapid progression

The HIV epidemic in Saskatchewan has been growing at an alarming rate since 2003 (1,2). At the present time, the incidence of HIV in Saskatchewan is the highest in Canada (19.6 per 100,000 in 2011), at more than double the national average (7.6 per 100,000) (3). Importantly, the highest recorded incidences have occurred in the most recent years (23.8 per 100,000 in 2009; 20.3 in 2010 and 19.6 in 2011), indicating that the epidemic in this province is not approaching resolution (3).

The epidemiology of HIV in Saskatchewan is unique to Canada in that female sex and/or individuals self-identifying as being of First Nations and Métis ethnicity are over-represented compared with other HIV-infected populations across Canada (4-6). The unfortunate prevalence of low socioeconomic status among First Nations and Métis in Canada poses barriers to achieving optimum health. Such challenges include poverty and the associated housing insecurity and malnutrition, in addition to increased rates of incarceration, injection drug use (IDU) and mental illness. Another unique characteristic of the HIV epidemic in this province is that IDU is the predominant mode of transmission, in contrast to men who have sex with men, which has remained the most commonly reported exposure nationally, since the beginning of the epidemic in Canada (1,2). Given the high prevalence of IDU, this population is also afflicted with high rates of coinfection with hepatitis C virus (HCV), which has been shown to be 10 times more transmissible through IDU than HIV (7-9).

Immune deficiency in AIDS is caused by the virally mediated destruction of CD4⁺ T cells (10,11). HIV disease progression is characterized by the progressive decline in CD4⁺ count over time (11-15). The
monitoring of CD4+ cell counts over time provides a surrogate measure of HIV disease progression (10). CD4+ cell counts are used by clinicians in determining when to initiate antiretroviral therapy (ART) and other prophylactic therapies in the treatment of opportunistic infections, as well as being commonly used as an end point in clinical studies (10,11,16,17). In the present study, we used CD4+ cell count to evaluate HIV disease progression. Clinicians in Saskatoon, Saskatchewan caring for HIV-infected individuals have anecdotally reported the observation of a more rapid than expected progression to immunological AIDS (CD4+ count <200 cells/µL) in recent years. The aim of the present study was to examine this phenomenon of rapid progression from HIV infection to immunological AIDS.

The HIV-infected population of Saskatchewan is afflicted with a multitude of health-compromising conditions; this population is understudied and is showing evidence of rapid progression to AIDS. The objectives of the present study were to estimate the rate of CD4+ cell depletion among HIV-infected adults in the city of Saskatoon, and to determine the effects of the following clinical and social factors regarding CD4+ cell count changes: age at diagnosis; sex; ethnicity; HCV coinfection; history of IDU; ART; incarceration during follow-up; engagement in case management services; receipt of social assistance; and presence of a sexually transmitted infection (STI).

**METHODS**

### Setting and population

The present study was a retrospective longitudinal cohort analysis of HIV-infected patients followed at two clinics in Saskatoon, specializing in the care of this population: the Positive Living Program at Royal University Hospital and the Westside Community Clinic (WSCC).

### Data collection

Data were abstracted from patient charts. Inclusion criteria included a new HIV diagnosis of patients ≥18 years of age between January 1, 2003 and November 30, 2011. Patient data abstracted from medical charts included demographics, social history, clinical variables, laboratory data and ART. First CD4+ count and viral load measurement within six months of HIV diagnosis were considered to be baseline measurements.

### Data analyses

Patient characteristics at HIV diagnosis (baseline) and during follow-up (time dependent) were summarized using descriptive statistics. A χ² test was used to assess associations between categorical variables. Pearson correlation analysis was performed. Independent variables considered included sex, age, ethnicity, HCV seropositivity, coinfection with an STI, IDU, history of incarceration, history of receipt of social assistance, case management (a program of intensive social work at the WSCC) and ART. Before fitting mixed effect models on CD4+ count outcome, the CD4+ count of an individual was summarized in three-month intervals for the first three years and in six-month intervals for the remainder of the study time. If a subject underwent more than one measurement in a given interval, the mean was used. This interval was selected because this is the standard clinical follow-up timeline for patients observed in the two clinics. The interval was increased to six months after the three-year period because there were far fewer patients followed for >3 years compared with patients followed for ≤3 years. CD4+ count was then modelled longitudinally by fitting mixed effects models with random intercept and random slope (18). A linear regression of CD4+ count change according to months since diagnosis among 10 randomly selected patients, as well as a linear regression of mean CD4+ count according to months since diagnosis was created to ensure the assumption of a robustly linear change in CD4+ count over time was not violated. Interactions among covariates were examined. Variables were identified as significant using a p < 0.05 level. All analyses were performed using SAS version 9.2 (SAS Institute, USA).

The present study was approved by the University of Saskatchewan Ethics Review Board, the Saskatoon Health Region and the WSCC.

### RESULTS

A total of 411 patients who had at least one CD4+ recorded met the study inclusion criteria. A total of 2555 CD4+ counts were recorded among all patients (Table 1). One hundred eighty-eight patients were followed at the Positive Living Program, 122 at the WSCC and 101 were followed at both sites. The mean (± SD) age at diagnosis was 35.7±10.3 years and 70.8% of patients were men. Two hundred fifty-seven (75.3%) patients were identified as being of First Nations or Métis ethnicity. The most commonly reported exposure category was IDU (75.3%), followed by heterosexual contact (14.2%) and

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**TABLE 1**

Baseline and time-dependent patient characteristics according to ethnicity (n=411)

| Variables                                | Total sample (n=411) | First Nations or Métis (n=257, 70.8%) | Others (n=154, 29.2%) |
|------------------------------------------|----------------------|--------------------------------------|------------------------|
| Follow-up time, months, median (IQR)   | 27.6 (31.9)          | 27.6 (29.9)                          | 32.6 (37.7)            |
| Variable at baseline                    |                      |                                      |                        |
| Age at enrollment, years, mean ± SD     | 35.7±10.3            | 33.7±9.1                             | 41±11.5                |
| Exposure category†                      |                      |                                      |                        |
| MSM                                      | 21 (6.5)             | 1 (0.5)                              | 20 (22.0)              |
| MSM/IDU                                  | 12 (3.7)             | 5 (2.3)                              | 6 (6.6)                |
| IDU                                      | 244 (75.5)           | 193 (89.8)                           | 36 (39.5)              |
| Heterosexual contact                    | 46 (14.2)            | 16 (7.4)                             | 29 (31.9)              |
| Site                                     |                      |                                      |                        |
| PLCC                                     | 188 (45.7)           | 100 (38.9)                           | 80 (75.5)              |
| WSCC                                     | 122 (29.7)           | 84 (32.7)                            | 7 (6.6)                |
| Both                                     | 101 (24.6)           | 73 (28.4)                            | 19 (17.9)              |
| CD4+ count, cells/µL, n, mean ± SD      | 300, 379±23            | 181, 369±218                         | 87, 376±236            |
| Missing, n                               | 111                   | 76                                   | 19                     |
| CD4+ count, cells/µL, n, mean ± SD      | 276, 43±1.0           | 167, 42±1.0                          | 85, 44±1.0             |
| Missing, n                               | 135                   | 90                                   | 21                     |
| HCV antibody positive                    | 312 (80.2)           | 227 (92.6)                           | 47 (46.5)              |
| Missing, n                               | 22                    | 12                                   | 5                      |
| History of IDU                           | 300 (73.3)           | 222 (87.1)                           | 43 (40.6)              |
| Missing, n                               | 2                     | 2                                    |                        |
| STI                                      | 134 (32.6)           | 86 (33.5)                            | 38 (35.8)              |
| Time-dependent variables                 |                      |                                      |                        |
| Incarcerated during follow-up           | 118 (28.7)           | 89 (34.6)                            | 22 (20.7)              |
| Ever use of social assistance           | 146 (35.5)           | 110 (42.8)                           | 25 (23.6)              |
| Ever use of ART                         | 257 (62.5)           | 167 (65.0)                           | 70 (66.0)              |
| ART naïve                                | 154 (37.5)           | 90 (35.0)                            | 36 (34.0)              |
| Case management                          | 54 (13.1)            | 45 (17.5)                            | 4 (3.8)                |
| Clinical AIDS                            | 30 (7.3)             | 18 (7.0)                             | 12 (11.3)              |
| All-cause mortality                      | 29 (7.1)             | 20 (7.8)                             | 8 (7.5)                |

*Data presented as n (%) unless otherwise indicated. † For MSM, the HCV antibody results were missing. *48 were missing; T88 were missing. ART Antiretroviral therapy; HCV Hepatitis C virus, IDU Injection drug use; IQR Interquartile range; MSM Men who have sex with men; PLP Positive Living Program; STI Sexually transmitted infection; WSCC Westside Community Clinic
men having sex with men (6.5%). Fifty-four (13.1%) patients were case management clients, 146 (35.5%) had a record of receiving social assistance, 134 (32.6%) acquired an STI throughout the course of their care, 312 (80.2%) were HCV seropositive, 300 (73.3%) had a history of incarceration and 257 (62.5%) were ever prescribed ART. The mean baseline CD4+ count was 379±233 cells/µL and the mean baseline log viral load was 4.3±1 copies/mL. The mean follow-up time for all patients was 32.5 months.

HCV coinfection, First Nations or Métis ethnicity, and IDU were highly correlated (Figure 1). Proportion of HCV coinfection is significantly higher in injection drug users compared with individuals who did not have a history of IDU (98.6% versus 25.8%; P<0.0001). Individuals self-identifying as of First Nations or Métis ethnicity experienced higher odds of having a history of IDU (OR 9.86 [95% CI 5.78 to 16.79]; P<0.0001) and HCV coinfection (OR 14.49 [95% CI 7.80 to 6.91]; P<0.0001). Time to ART initiation was not significantly different between First Nations or Métis and other ethnicity (P=0.43, log-rank test, Figure 2).

In the univariate mixed effects models, ethnicity, social assistance, HCV coinfection, history of IDU and ever use of ART were significant. Sex, age, incarceration, case management and STI coinfection were not significant (results are not shown for the univariate analysis).

All significant covariates from the univariate mixed effects models analysis were included in the multivariate models. Although age was not univariately significant, it was considered to be a potential confounder and added in the multivariate models. Due to the significant correlation among ethnicity, HCV infection and IDU, the following three separate multivariate mixed effects models were built.

**Model 1:** In the first model incorporating ethnicity (Table 2), the estimated mean regression coefficient of time for the ART-naive group was −27.18 (95% CI −44.95 to −9.41), suggesting a significant decrease in CD4+ count at a rate of 27.18 cells/µL per year among ART-naive patients after controlling for other covariates. CD4+ count remained almost unchanged among ART recipients (−27.18±27.94 cells/µL per year). The rate of CD4+ count change was significantly different between these two groups (−27.18±27.94 cells/µL per year, P=0.0001). The model found an increased frequency of IDU among incarcerated populations, because patients with more extreme addictions may be at an increased risk of IDU.

**Model 2:** In the second model incorporating HCV coinfection (Table 3), CD4+ count significantly decreased at a rate of 37.17 cells/µL per year among ART-naive patients (P<0.0001). CD4+ count was not changed among ART-exposed patients (−33.72±34.08=1.67 cells/µL per year). However, the rate of CD4+ count change was significantly different between these two groups (37.17 cells/µL per year, P<0.0001). HCV antibody positivity (P=0.003) and older age at diagnosis (P=0.055) were associated with lower CD4+ counts.

**Model 3:** In the third model incorporating a history of IDU (Table 4), CD4+ count significantly decreased at a rate of 34.08 cells/µL per year among ART-naive patients after controlling for other covariates (P<0.0002). CD4+ count remained almost unchanged among ART recipients (−32.41±34.08=1.67 cells/µL per year). The rate of CD4+ count change was significantly different between these two groups (34.08 cells/µL per year, P=0.0007). A history of IDU (P=0.042), receipt of social assistance (P=0.042) and increasing age at diagnosis (P=0.026) were significant predictors of lower CD4+ counts.

**DISCUSSION**

The present study was a retrospective longitudinal cohort analysis of 411 HIV-positive patients diagnosed between January 1, 2003 and November 30, 2011 and followed by physicians at the Positive Living Program and WSCC in Saskatoon, Saskatchewan. We investigated CD4+ changes over time to explore HIV disease progression to immunological AIDS. The objective of the present study was to identify clinical and social factors associated with rates of change in CD4+ counts.

HIV and HCV are both transmitted through IDU (19-22). There is an increased frequency of IDU among incarcerated populations, because patients with more extreme addictions may be at an increased risk of IDU.
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TABLE 3
Multivariate mixed effects model (model 2) containing hepatitis C virus (HCV) coinfection (n=389)

| Covariate                | β ± SE  | 95% CI          | P     |
|-------------------------|---------|-----------------|-------|
| Intercept               | 607.7±45.34 | 518.03 to 696.32 | <0.0001 |
| Time (in years)         | −33.7±8.69   | −50.52 to −16.82 | 0.0001 |
| Time*ART (yes)          | 37.1±10.20   | 17.17 to 57.17   | 0.00003 |
| HCV (yes)               | −67.2±23.28   | −112.91 to −21.58 | 0.003 |
| Social assistance (yes) | −33.5±19.40   | −71.63 to 4.49   | 0.08  |
| Age at diagnosis        | −1.7±0.90     | −3.49 to 0.04    | 0.055 |

ART Antiretroviral therapy

Rate of incident infection control. 2010.

The identification of cofactors that can be implicated in contributing to rapid progression to AIDS and/or death has the potential to slow disease progression if the impacts of such cofactors can be mitigated. Earlier and more aggressive ART may be beneficial to patients who can be identified as higher risk for rapid progression to AIDS.

Strengths of the present study include the unique epidemiology of the study population; namely, an over-representation of individuals of First Nations or Métis ethnicity, HCV coinfection, a history of IDU, older age and receipt of social assistance to be associated with significantly lower CD4+ counts in multivariate models. Not being exposed to ART was significantly associated with a negative CD4+ count slope in multivariate mixed effects models.

The mixed effects models have the potential to be developed into clinical tools. These clinical tools may predict the CD4+ counts of patients at follow-up visits and, therefore, potentially be helpful in the identification of patients at risk for rapid progression. By identifying these patients early in the clinical course of HIV disease progression, interventions to mitigate risk factors for rapid progression may be initiated; for example, increased social support to mitigate the effects of low socioeconomic status such as poor nutrition. Such increased social support has recently been introduced at the WSfCC in the form of case management service. Associations between engagement in case management services and improvements in overall health among HIV-infected individuals have been previously reported (30-32). Although we did not observe a significant association with increased CD4+ counts and involvement with case management services, this finding was likely due to dataset limitations.

Socioeconomic disadvantages, which are unfortunately prevalent among First Nations and Métis communities, HCV coinfection, a history of IDU, receipt of social assistance and older age at diagnosis were associated with lower CD4+ counts. CD4+ count significantly decreased over time among patients who were never prescribed ART. The present study highlights the urgent need for both clinical, as well as social, interventions to address the HIV epidemic in Saskatchewan.

The findings of the present study may contribute to improvements in clinical care in that these findings may aid clinicians in the identification of HIV-infected patients who may be at risk for rapid progression. The identification of cofactors that can be implicated in contributing to rapid progression to AIDS and/or death has the potential to slow disease progression if the impacts of such cofactors can be mitigated. Earlier and more aggressive ART may be beneficial to patients who can be identified as higher risk for rapid progression to AIDS.

Strengths of the present study include the unique epidemiology of the study population; namely, an over-representation of individuals of First Nations or Métis ethnicity and therefore, an increased prevalence of social and economic disadvantage that unfortunately exists among this population; a high prevalence of HCV coinfection; and a high prevalence of IDU. Another strength is that the follow-up period of the present study incorporates the course of the emergence of the dramatic increase in incidence of HIV in Saskatchewan.

Limitations of the present study include those of all retrospective data sets, in that we were limited to information that was previously recorded in patient medical records, which may not always have included all of the variables of interest. For example, absolute lymphocyte count, leukocyte count, and information regarding alcohol use and abuse among patients were not available. Alcoholism has known effects on CD4+ counts in HIV-infected patients (33,34). Another limitation of this dataset was an unknown date of seroconversion among many patients, which poses a challenge to an accurate depiction of the entire clinical course of HIV. We were able to arrive at a more accurate depiction of the effects of selected cofactors on the clinical course of HIV through the use of multiple analyses and comparisons of the results of these analyses.

Future studies should include the creation of a prospective cohort database, ideally enrolling at-risk individuals while seronegative, to establish date of seroconversion and, therefore, enable a more accurate and complete depiction of the individual and population-level clinical course of HIV infection. In addition, studies with a longer follow-up period would also allow for a more comprehensive picture of the course of HIV among Saskatchewan patients. Finally, a study examining social factors contributing to the HIV epidemic in Saskatchewan and, in particular, the contribution of social factors to the phenomenon of a rapid progression to AIDS would be of particularly importance to this unique population.

SUMMARY

The HIV-infected population of Saskatoon is characterized according to unique social and clinical factors, which may conspire to contribute to an accelerated progression to AIDS. The variables of HCV coinfection, First Nations or Métis ethnicity and IDU were highly correlated. Ethnicity, receipt of social assistance, older age at diagnosis, HCV coinfection, a history of IDU and ever use of ART were significantly associated with lower CD4+ counts. Patients presenting as HIV positive with one or more of these cofactors can be considered to be at risk for accelerated progression to AIDS. The early identification by clinicians of patients with these risk factors and the implementations of targeted interventions to mitigate the negative health effects of these cofactors may contribute to improved health and quality of life for this HIV-infected population.

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