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Impact of Hepatitis C Virus (HCV) on CD4$^+$ T-Lymphocyte Count < 200 cells/µL among HIV-Positive Adults: A Longitudinal Evaluation

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Authors' contributions

This work was carried out in collaboration between all authors. Author PKM performed the literature searches and data analyses and wrote the first draft of the manuscript. Author HJL participated in the design and coordination of the study, jointly developed the structure and analysis for the manuscript. Author SK collected the data. Authors SS and MS helped in writing the first draft of the manuscript and interpretation of results. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Previous research on whether Hepatitis C Virus (HCV)/HIV coinfection alters the natural history of HIV disease progression shows conflicting findings. The aim of this study is to investigate whether HCV/HIV coinfection has an adverse effect on the outcome of a CD4$^+$ count < 200 cells/µL in HIV-positive adults.
Study Design: A retrospective longitudinal study.
Place and Duration of Study: Royal University Hospital and West Side Community Clinic in Saskatoon, Canada. Individuals were diagnosed with HIV between January 1, 2005 and September 1, 2011.

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Methodology: Data were collected using medical charts. $CD4^+$ count was dichotomized into a binary variable (1 for $CD4^+$ count < 200; 0 for ≥ 200). Independent t-tests or Wilcoxon test, and Chi-square tests were used to compare quantitative and qualitative variables between groups, respectively. The risk factors for $CD4^+$ count < 200 were determined using Generalized Estimating Equations (GEE) marginal logistic regression model. Analysis was done by SAS 9.4 and $P<0.05$ was considered as statistically significant.
Results: Among 369 patients, 48.5% were female, 72.1% were Aboriginals, 82.4% were HCV/HIV-coinfected and 77.4% had history of Injection Drug Use (IDU) at diagnosis. The mean age at diagnosis was 35.5 years. In univariate GEE logistic regression model, patients with coinfection of HCV/HIV, Aboriginals ethnicity, ever use of Antiretroviral Therapy (ART), social assistance, older age, and higher viral load at baseline were significantly more likely to have $CD4^+$ count < 200. In multivariate model, HCV/HIV coinfection, age, and ART were associated with $CD4^+$ count < 200. Patients with HCV/HIV coinfection, older age, and ever use of ART had significantly higher odds of having $CD4^+$ count < 200 (adjusted odds ratios 2.21, 1.48, and 2.70 respectively).
Conclusions: HCV/HIV-coinfected patients were significantly more likely to have $CD4^+$ count < 200. Results support earlier treatment of HCV and HIV as well as increased monitoring for coinfected individuals.

Keywords: HIV; AIDS; $CD4^+$ count; ART; HCV; IDU; GEE; Aboriginals.

1. INTRODUCTION

There were 35.3 million (32.2-38.8 million) people globally living with HIV infection at the end of 2012 [1]. As a result of effective antiretroviral therapies (ARTs), HIV infection has evolved from a disease with high morbidity and mortality to become a chronic and manageable condition in high-income countries such as Canada [2]. Because of shared routes of transmission, it is estimated that approximately 20-30% of HIV patients are also infected with Hepatitis C Virus (HCV), with approximately 10 million dually infected world-wide [3] and an estimated 13,000-15,000 dually infected of the 65,000 HIV-infected persons in Canada [4].

HCV transmission is most often by a blood-borne route, explaining the high rates of HCV/HIV coinfection among injection drug users (IDUs); median prevalence is estimated to be 90% [5]. The prevalence of HCV and HIV coinfection varies between countries, even between various areas within a country [6,7]. Research has found that the prevalence of HCV coinfection among HIV-infected individuals with a background of IDU is over 90% in the US, [8] and Asia [7].

Whether HCV/HIV coinfection is associated with HIV progression is debated among researchers. Conflicting reports are found in multiple studies of the effect of HCV/HIV coinfection on the natural history of HIV disease progression. In the pre-ART era, some cohort studies have shown that HCV/HIV coinfection was associated with an increased risk of clinical progression, but not with immunologic progression [9]. Other studies found that HCV/HIV-coinfected patients had similar clinical progression compared with HIV-monoinfected patients [10]. In the post-ART era, several cohort studies reported more rapid progression to AIDS among coinfected persons [10-14]. Others have not seen the same association [8, 15, 16]. Some cohort studies found that coinfection increased the risk of mortality compared to HIV infection alone [16, 17].

There is fairly consistent evidence that HCV/HIV coinfection is associated with either smaller $CD4^+$ count increases after initiation of ART [10, 12, 13, 17-21] or a delayed $CD4^+$ count response [22]. However, other studies have reported that early differences in $CD4^+$ count response diminish over time, [23, 24] while other studies have not observed such an association [8, 14, 15, 25]. Recent analyses based on combined data from four randomized studies showed that HCV/HIV-coinfected patients had, over time, a mean of 39.2 cells/μL lower $CD4^+$ count and 33.8 cells/μL smaller $CD4^+$ count increase from baseline than HIV-monoinfected patients [18]. In another study, HCV-positive individuals had significantly slower recovery of $CD4^+$ count compared with those who were HCV RNA-negative [21]. A review of 8 cohort studies found that after receiving ART the $CD4^+$ count response for co-infected patients was less than that for patients with HIV infection alone by an average 33.4 cells/μL [19]. The findings suggested that HIV-infected patients were more likely to have a better immunological response to antiretroviral therapy compared to co-infected

patients. These inconsistent findings may be explained by the heterogeneous populations studied, the limited baseline information collected, and the different ART regimens studied. An improved understanding of HCV coninfection among people living with HIV has important implications for both HCV and HIV treatment decisions. This study examines longitudinal data to determine the immunological effects of HCV coinfection among patients living with HIV.

2. MATERIALS AND METHODS

2.1 Study Population

The population of this study was drawn from the Canadian province of Saskatchewan, where incidence of HIV dramatically increased from 3.3 per 100,000 populations in 2002 to 20.8 per 100,000 populations in 2008; this was the highest in Canada and more than twice the national average [26]. This study was a retrospective observational longitudinal study of HIV infected adult patients (age ≥ 18 years) followed at two sites in Saskatoon, Canada specializing in the care of HIV/AIDS population. The Positive Living Program (PLP), located at Royal University Hospital (Saskatoon, Saskatchewan), provides services to adults and children with HIV and/or HCV who reside in Central and Northern Saskatchewan. The Westside Community Clinic (WSCC), located in Saskatoon's core area, serves residents of this area.

2.2 Data Collection

Data for HIV diagnosed patients were extracted from medical charts from both study sites. HIV-positive adults, diagnosed between January 1, 2005 and September 1, 2011, with at least one $CD4^+$ measurement after HIV diagnosis were eligible for inclusion in this study. Patients data included information pertaining to demographics (age, gender, ethnicity), social history (history of ever IDU, incarceration, receiving social assistance), date of HIV diagnosis, date of clinical AIDS diagnosis, laboratory testing ($CD4^+$ count, viral load) and use of anti-retroviral therapy. HCV/HIV coinfection was determined based on an HCV antibody positive test. Ethnicity was categorized as self-identified Aboriginal ethnicity (First Nations or Metis) or non-Aboriginal ethnicity. First $CD4^+$ count and viral load measurement within six months of HIV diagnosis was considered as baseline $CD4^+$ count and viral load.

2.3 Statistical Analyses

Baseline demographic and clinical characteristics were compared between HCV/HIV-coinfected and HIV-monoinfected participants using *t*-tests or Wilcoxon rank-sum test as appropriate for continuous variables, and Pearson's chi-square test for categorical variables. We fitted marginal logistic regression models using generalized estimating equations (GEE) to estimate the effect of HCV/HIV coinfection on $CD4^+$ count < 200 while adjusting for covariates and correlation among multiple outcomes within individuals [27]. The GEE method is used to analyze longitudinal and other correlated data, especially when they are binary or in the form of counts. We created a binary outcome variable with values 1 and 0 using $CD4^+$ count < 200 and $CD4^+$ count ≥ 200 respectively. Given a data set consisting of repeated measures, a GEE model allows the correlation of outcomes within an individual to be estimated and taken into appropriate account in the formulae which generate the regression coefficients and their standard errors. We applied GEE approach in place of basic regression approaches because outcomes with an individual may be correlated. Several models were fitted using different correlation structures such as; exchangeable, autoregressive (1), and independent. The quasi-likelihood information criterion (QIC) statistics was similar in all models [28]. However, we used exchangeable correlation structure in the final model. The level of significance was set at 0.05. Covariates which had a p value of less than 0.05 in the univariate models were included in the multivariate regression model to control for possible confounding effects. All analyses were conducted using SAS v 9.4 (SAS Institute, Cary, NC, U.S.A.).

3. RESULTS

3.1 Participant Characteristics

Participants' baseline characteristics are shown in Table 1. A total of 369 patients were included with a median follow-up time of 2.3 years (interquartile range [IQR]: 2.4 years). The median number of $CD4^+$ measurements was 5 (IQR: 5). The mean age at diagnosis was 35.5 years (SD = 10.2). The majority of participants were HCV/HIV coinfected (82.4%). One hundred seventy nine patients (48.5%) were female, 108 (29.3%) had record of incarceration, and 285 (77.4%) patients reported a history of IDU. 76.4% of patients were both IDUs and HCV/HIV-

coinfected. Two hundred and thirty eight persons (72.1%) self-identified as being of Aboriginal ethnicity (First Nations or Metis). Compared with non-Aboriginals, Aboriginals were more likely to have a history of injection drug use, and receive social assistance (45.7% vs. 89.5%; *P*< 0.001, 23.9% vs. 43.7%; *P*< 0.001 respectively). Median baseline $CD4^+$ count was significantly lower among individuals who were ART-exposed compared to those ART-naïve (297 cells/μL vs. 439 cells/μL; *P*< 0.001).

3.2 HCV/HIV-Coinfection

Table 1 describes characteristics of the participants by HCV/HIV coinfection status. HCV antibody positive ($HCV\text{-}Ab^+$) and HCV antibody negative ($HCV\text{-}Ab^-$) groups were significantly different with respect to most demographic and clinical variables. Mean age of HCV/HIV-coinfected patients was significantly lower than those of HIV-monoinfected (34.8 years vs. 38.7 years; *P* =0.02). Female patients (86.6% vs. 78.4%; *P* = 0.03), Aboriginal patients (94.1% vs. 50.0%; *P*< 0.001), injection drug users (98.6% vs. 26.5%; *P*< 0.001), social assistance users (92.6% vs. 76.5%; *P*< 0.001) and patients with a history of incarceration (97.2% vs. 76.2%; *P*< 0.001) were more likely to be HCV/HIV-coinfected. There were no significant differences between the two groups with respect to baseline $CD4^+$ count and ART exposure. HIV viral load was significantly higher in HCV/HIV-coinfected patients (median $\log_{10}$ HIV RNA 4.4 copies/mL vs. 4.2 copies/mL; *P* = 0.01).

3.3 $CD4^+$ Count Response

Univariate results from GEE logistic regression models for $CD4^+$ count < 200 are shown in Table 2. HCV/HIV coinfection (odds ratio [OR] = 2.35; 95% confidence interval [CI]:1.40-3.93), older age (OR = 1.24; 95% CI:1.04-1.48), Aboriginal ethnicity (OR = 1.66; 95% CI:1.06-2.62), ever use of ART (OR = 2.79; 95% CI:1.78-4.37), ever receiving social assistance (OR = 1.76; 95% CI:1.20-2.60), and higher $\log_{10}$ (HIV-RNA) at baseline (OR = 1.81; 95% CI:1.28-2.56) were associated with increased odds of $CD4^+$ count < 200. Gender, follow-up time, ever use of IDU, and history of incarceration were not significant predictors in the univariate analysis.

In the multivariate GEE logistic regression model (Table 3), HCV/HIV-coinfected patients had significantly higher odds of having $CD4^+$ count < 200 (adjusted odds ratio [aOR] = 2.21; 95% CI: 1.20-4.07) than those of HIV-monoinfected patients after controlling for age, ethnicity, ever use of ART, and ever receiving social assistance. ART-exposed patients were more likely to have $CD4^+$ count < 200 (aOR = 2.70; 95% CI: 1.65-4.42) compared to ART-naïve patients. Older age was associated with increased odds of having a $CD4^+$ count < 200 (aOR = 1.48; 95% CI: 1.20-1.83), meaning with 10-year increment of age at diagnosis, odds of having $CD4^+$ count < 200 increased by 48%. Although baseline viral load was a significant covariate in the univariate model, it was not considered in the multivariate model because of missing values, which would have excluded 30% individuals from analysis. We did not include follow-up time of $CD4^+$ measurements in the multivariate model as it was not significant in the univariate analysis. However, results were not changed after adding follow-up time in the multivariate model (data were not shown).

4. DISCUSSION

Our analysis demonstrated that HCV/HIV-coinfected individuals had higher odds of developing a $CD4^+$ count of < 200 cells/μL compared with HIV-monoinfected individuals after controlling for age, ethnicity, ever receiving social assistance, and ever use of ART (adjusted OR = 2.21). According to the US Centers for Disease Control and prevention (CDC), a $CD4^+$ count of < 200 cells/μL is one of the criteria for an AIDS diagnosis; patients with a $CD4^+$ count of less than 200 cells/μL are at higher risk of opportunistic infections. This study suggests that HCV/HIV coinfected individuals have increased risk of immunological AIDS.

The result of our study was consistent with other findings. In a Swiss HIV cohort study, the hazards ratio for an AIDS-defining event or death was 1·70 (95% CI, 1·26–2·30) for HCV-seropositive patients compared with HCV seronegative patients in multivariate Cox's regression model [13]. In the study performed by De Luca et al. [12], HCV-ab+ patients had an independent increased hazard of AIDS or death (adjusted hazard ratio 1.57; 95% CI, 1.01-2.61) compared with patients without HCV markers. Stebbing et al. [14] reported that individuals with HCV-coinfection had an increased likelihood of developing a CD4+ count of < 200 cells/μL or their first AIDS-defining illness, compared with HIV-monoinfected individuals. The adjusted relative hazard of AIDS was 1.77 (95% CI, 1.15–2.73) for co-infected versus mono-infected

individuals in the study performed by Dorrucci et al. [10].

This study is unique in its analytical methodology. We used a different approach by making longitudinal $CD4^+$ counts as binary outcomes (1 for $CD4^+$ count < 200; 0 for ≥ 200) and by applying GEE marginal logistic regression model to find the effect of HCV/HIV coinfection on HIV disease progression. Most studies reported the impact of HCV/HIV coinfection on the hazard of developing a $CD4^+$ count of less than 200 cells/μL or AIDS and or death using Cox regression model or impact of HCV/HIV coinfection on $CD4^+$ count using linear regression model. However, the trajectory of an individual's $CD4^+$ count over time may not be linear. Also, we do not have seroconversion dates for many patients. Some patients experience illness first and are then diagnosed as HIV positive. These patients may have, or progress to, $CD4^+$ count below 200. However, after receiving appropriate treatment their $CD4^+$ count may return to above 200 and potentially decrease again. This phenomena is accounted for in the GEE regression analysis, a widely used statistical method in the analysis of longitudinal data in clinical and epidemiological studies. Since the outcomes from the same participant tend to be correlated, statistical analyses have to take a proper account of this correlation. Regression analysis based on GEE specifies how the average of a response variable of a subject changes with covariates while allowing for the correlation between repeated measurements on the same subject over time. The focus of this method is to estimate the regression parameters that have a population average interpretation.

Table 1. Demographic and clinical characteristics associated with HCV infection in the study participants (N = 369)

Covariates	Total sample (N = 369)	HCV Ab- (N = 65, 17.6%)	HCV Ab+ (N = 304, 82.4%)	*P*-value
Gender				
Female	179 (48.5%)	24 (13.4%)	155 (86.6%)	0.03†
Male	190 (51.5%)	41 (21.6%)	149 (78.4%)	
Age in years				
n, mean (SD)	369, 35.5 (10.2)	65, 38.7 (12.6)	304, 34.8 (9.5)	0.02‡
Ethnicity				
Aboriginal	238 (72.1%)	14 (5.9%)	224 (94.1%)	<0.001†
Non-Aboriginal	92 (27.9%)	46 (50%)	46 (50.0%)	
Missing	39			
IDU				
Yes	285 (77.4%)	4 (1.4%)	281 (98.6%)	<0.001†
No	83 (22.6%)	61 (73.5%)	22 (26.5%)	
Missing	1			
Use of social assistance				
Yes	135 (36.6%)	10 (7.4%)	125 (92.6%)	<0.001†
No	234 (63.4%)	55 (23.5%)	179 (76.5%)	
Use of ART				
Yes	233 (63.1%)	47 (20.2%)	186 (79.8%)	0.09†
No	136 (36.9%)	18 (13.2%)	118 (86.8%)	
Record of incarceration				
Yes	108 (29.3%)	3 (2.8%)	105 (97.2%)	<0.001†
No	261 (70.7%)	62 (23.8%)	199 (76.2%)	
CD4 count (cells/μL) at baseline				
n, median (IQR)	271, 340 (287)	56, 334 (190)	215, 349 (312)	0.50§
Missing	98			
Log_{10} HIV RNA (copies/mL) at baseline				
n, median (IQR)	250, 4.4 (1.0)	55, 4.2 (1.2)	195, 4.4 (1.0)	0.01§
Missing	119			
Total duration of follow-up in years				
n, median (IQR)	369, 2.3 (2.4)	65, 2.3 (2.5)	304, 2.3 (2.3)	0.13§

† P-value is based on Chi-square test, ‡ p-value is based on T-test, § p-value is based on Wilcoxon test, IQR = Interquartile range

Table 2. Characteristics associated with $CD4^+$ lymphocyte count < 200 cells/μL based on univariate GEE logistic regression model

Covariates	Odds ratio	95% confidence interval	*P*-value
HCV infection	2.35	(1.40, 3.93)	0.001
Male	1.00	(0.68, 1.45)	0.98
Age (per 10 years)	1.24	(1.04, 1.48)	0.02
Follow-up time (years)	1.05	(0.96, 1.15)	0.27
Aboriginal ethnicity	1.66	(1.06, 2.62)	0.02
IDU	1.41	(0.89, 2.24)	0.14
Use of ART	2.79	(1.78, 4.37)	<0.001
Use of social assistance	1.76	(1.20, 2.60)	0.004
Record of incarceration	1.06	(0.71, 1.60)	0.76
Log_{10}HIV RNA (copies/mL) at baseline	1.81	(1.28, 2.56)	<0.001

Table 3. Characteristics associated with $CD4^+$ lymphocyte count < 200 cells/μL based on multivariate GEE logistic regression model

Covariates	Odds ratio	95% confidence interval	*P*-value
HCV-infection	2.21	(1.20, 4.07)	0.01
Age (per 10 years)	1.48	(1.20, 1.83)	<0.001
Aboriginal ethnicity	1.59	(0.90, 2.80)	0.11
Use of ART	2.70	(1.65, 4.42)	<0.001
Use of social assistance	1.45	(0.95, 2.22)	0.08

This study represents a unique epidemiology of HIV and HCV within the population including an overrepresentation of individuals of Aboriginal ethnicity (72.1%), a high prevalence of HCV coinfection (82.4%) and a high prevalence of IDU (77.4%). Two hundred nine (63.5%) of the participants were Aboriginals with both history of IDU and HCV coinfection. History of IDU was not a significant predictor for lower $CD4^+$ count in the univariate analysis and therefore, it was not included in the multivariate model. Both HCV coinfection and ethnicity were included in the multivariate model. However, ethnicity was not significant in adjusted analyses. Hence HCV coinfection was the most influential predictor for $CD4^+$ count < 200 among these three covariates.

There are limitations in our study. Firstly, this was a retrospective cohort study and hence, we were limited to the information that was previously recorded in patient medical records; information on ARV adherence, for example, was not available, and cannot be assessed in this study. In addition, due to the retrospective nature of the study, there was some missing data, which could lead to potential biases. Secondly, this study only included HIV-infected individuals who were in care. The effect of HCV/HIV coinfection on disease progression among those not in care could thus not be examined.

5. CONCLUSION

HCV/HIV-coinfected patients had significantly higher odds of having $CD4^+$ count < 200 cells/μL compared with HIV-monoinfected patients. Older age, and ever use of ART were also significantly associated with $CD4^+$ count < 200. It is essential to understand the impact of HCV infection on the progression of HIV for the management of care for coinfected patients. The results of this study indicate that HCV/HIV coinfection is a determinant of HIV disease outcome. Coinfection may complicate the treatment and management of HIV infection. Therefore, HCV-infected patients should be screened regularly for HIV coinfection, particularly if they are in high-risk groups. Increased progression to AIDS in coinfected individuals may require earlier and more aggressive treatment for both infections and intensive follow-up. For coinfected persons, HCV treatment might have an important role not only in improving HCV related outcomes, but also for HIV-related prognosis. These considerations are particularly important in the context of increasing calls for use of both HIV and HCV treatment as preventive tools at a population level [29, 30].

CONSENT

It is not applicable.

ETHICAL APPROVAL

This study was approved by the University of Saskatchewan Research Ethics Board, the Saskatoon Health Region and the Westside Community Clinic.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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