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Modeling clinical progression and healthcare utilization of HIV-positive patients in British Columbia prior to death

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Abstract

Objectives—The extent in which clinical progression of HIV-positive patients leads to an increase in healthcare utilization, especially prior to their death, is unknown. Thus, we modeled trends in CD4 cell count and emergency department utilization and the likelihood of an emergency department visit leading to a transfer to acute care level facility prior to a patient's death from non-accidental causes.

Methods—Eligible patients initiated HAART in British Columbia between August 1996 and June 2006 (N=457). Patients were followed until their death, which occurred on or before June 30, 2007 (period in which the emergency department visit data were available). Trends were modeled using generalized mixed effects.

Results—Patients experienced a significantly steep decline in CD4 cell count and a corresponding increase in the number of emergency department visits and transfers to acute level facilities in the five years prior to death. For every 6-month interval prior to death, the CD4 cell

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Contributors: Viviane Dias Lima was the study supervisor, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Robert Hogg, Julio Montaner and Eric Grafstein contributed to the acquisition of data. Viviane Dias Lima, Benita Yip and Zishan Cui contributed to the analysis and interpretation of data. Viviane Dias Lima and Zishan Cui drafted the manuscript. All authors revised the manuscript critically for important intellectual content and approved the final version submitted for publication.

count decreased 13.22 cells/mm³, the risk of experiencing an emergency department visit increased by 9%, and among those ever admitted, the odds ratio of being transferred to an acute care level facility increased by 3%.

Conclusions—We showed that patients experienced a steep decline in CD4 cell count, which was associated with an increase in healthcare utilization prior to their death. These findings highlight the substantial residual avoidable burden that unsuccessfully managed HIV disease poses, even in the HAART era. Further strategies to enhance sustained and successful engagement in care are urgently needed to mitigate high healthcare utilization.

Keywords

CD4 cell count; emergency department visits; healthcare utilization; generalized mixed effect model; HAART; mortality; CTAS

INTRODUCTION

Since the advent of highly active antiretroviral therapy (HAART), HIV-infected patients are living longer with better quality of life [1, 2]. The main goal of HAART is to restrain the reproduction of HIV, rebuild the immune system, and consequently, decrease HIV morbidity and mortality [1, 2]. However, there are still some patients who do not fully benefit from HAART. For these patients, their clinical progression prior to death and the factors associated with their clinical progression are not well understood.

British Columbia (BC), Canada, provides a unique environment to address this gap in knowledge. BC is a resource-rich province with a fully subsidized healthcare system, which includes free access (with no co-payments or deductibles and including outpatient and inpatient hospital care) to medical services, laboratory monitoring and HAART to all its residents. Despite this favorable environment, there are still some HIV-positive individuals who die without ever assessing HIV treatment and others who still fail therapy and have a high risk of developing an AIDS-defining illness, and subsequently die prematurely of HIV-related causes [3]. Consequently, assessing the extent in which clinical progression leads to an increase in healthcare utilization by these patients, especially prior to their death, is urgently needed.

In this study, we aimed to model CD4 cell count and emergency department utilization over time prior to a patient's death. To further assess the increase in healthcare utilization, among those patients who have ever visited an emergency department, we modeled the likelihood of an emergency department visit leading to a transfer to an acute care level facility over time and prior to a patient's death. As a secondary analysis, we built exploratory models to examine which demographical and clinical factors may explain the trajectories in these outcomes. The analyses were conducted linking data from a large treatment registry of HIV-positive individuals receiving HAART and from an emergency visit administrative database in BC.

METHODS

Data and Study Population

The BC Centre for Excellence in HIV/AIDS' drug treatment program distributes antiretroviral agents at no cost to all eligible HIV-infected patients according to specific guidelines generated by the Therapeutic Guidelines Committee. These guidelines have remained consistent with the IAS-USA guidelines since the summer of 1996 and until 2012 [1].

Eligible study patients, aged 18 years or older, initiated HAART between August 1996 and June 2006, and died from non-accidental causes on or before June 30, 2007 (period in which the emergency department visit data were available). In addition, only patients who had CD4 cell count tests done within 5 years prior to their deaths and who visited the emergency department at the St. Paul's hospital, a main tertiary referral hospital for HIV/AIDS-related issues in BC, were eligible for this analysis. In our database, deaths were ascertained through ongoing data linkages with the BC Vital Statistics Agency and through physician reporting.

Clinical and demographic data were obtained through the BC Centre for Excellence in HIV/AIDS' drug treatment program. Data regarding emergency visits and whether or not the visits led to a transfer to an acute care level facility were provided by the emergency administrative database at St. Paul's Hospital.

Outcomes and Explanatory Factors

The primary time-varying outcomes were CD4 cell count and the number of emergency department visits, which were assessed at every 6-month period during the five years prior to each patient's death. We considered time-varying covariates such as AIDS diagnosis results, HAART regimen class, as well as non-time-varying covariates, including gender, age and history of injection drug use (IDU). The HAART regimen class was set up as a four-level categorical variable (use of only non-nucleoside reverse transcriptase inhibitors (NNRTI), use of only protease inhibitors (PI), use of both NNRTI and PI, use of drugs other than PI or NNRTI). CD4 cell count was modeled as a continuous measure, and the number of emergency visits as counts. Plasma viral load measurements were obtained with the standard Roche viral load assay until 1999 and with the ultrasensitive Roche assay thereafter. Therefore, plasma viral load measurements were recoded to range from 500 to 10^5 copies/mL, to standardize the viral load range over time. CD4 cell counts were measured by flow cytometry (Beckman Coulter, Inc, Mississauga, Ontario).

We conducted a sub-analysis to model the number of emergency visits that led to a transfer to an acute care level facility also assessed at every 6-month period during the five years prior to each patient's death. The non-time-varying covariates were the same as in the previous analyses. In addition to the previous time-varying covariates, we also considered the Canadian Triage and Acuity Scale (CTAS) [4]. The CTAS is administered to all persons visiting the emergency department, and it is a standardized measure of urgency to define low and high acuity. The CTAS level colour assignment and assessment is as follows: Level 1 (blue) – resuscitation, Level 2 (red) – emergent, Level 3 (yellow) – urgent, Level 4 (green) –

less urgent, and Level 5 (white) – non urgent. Thus, low acuity visits were defined as those visits with a CTAS score 4 or 5 and high acuity visits were visits with CTAS score 1 to 3. We also considered as time-varying the arrival mode to the emergency department, and it was modeled as a four-level categorical variable as: arrived by walking, by wheelchair, by ambulance, and by other means.

Statistical Analyses

We fitted three separate multivariable models. A linear mixed effect model for CD4 cell count trajectory, a generalized mixed effect model with Poisson distribution for the number of emergency department visits over time, and a generalized mixed effect model with logistic distribution to model the probability of emergency visits leading to a transfer to an acute care level facility [5, 6]. Model selection was conducted for each model using a backward elimination procedure based on AIC and Type III p-value [7]. Significance level was set at 0.05 and all analyses were performed using SAS software version 9.3 (SAS Institute Inc.).

RESULTS

Overall Cohort Characteristics

Between August 1996 and June 2006, 457 patients (80% males) initiated HAART and had died of a non-accidental cause. At baseline, before starting HAART, the median age was 41 years [25th–75th percentiles (Q1–Q3): 34–48 years], median CD4 cell count was 140 cells/mm³ [Q1–Q3: 40–270 cells/mm³], median plasma viral load was 5.00 log₁₀ copies/mL [Q1–Q3: 4.85–5.00 log₁₀ copies/mL], and 80% of these patients had a history of IDU.

CD4 Cell Count Trajectory Analysis

CD4 cell count monitoring was done at six months intervals prior to each patient's death. For example, the CD4 cell count at month 18 prior to death was the CD4 result closest to month 18 prior to the death date. Only 36% of the patients had a CD4 measurement at year 5 prior to death, with a median value of 325 cells/mm³ [Q1–Q3: 170–495 cells/mm³], while 81% had a CD4 measurement at month 6 prior to death, with a median value of 140 cells/mm³ [Q1–Q3: 30–260 cells/mm³]. This decreasing trend in CD4 cell count is illustrated in Figure 1 (p-value < 0.0001).

Examining the relationship between each covariate and the CD4 trajectory over time, we observed a consistent downward trend in CD4 prior to death for each of the variables in Figure 2. Based on the results from the linear mixed effect model, for every six-month interval prior to death, the CD4 cell count decreased 13.22 (95% CI: –16.27, –10.18) cells/mm³ (Table 1). Compared with the patients without a history of IDU, those who had a history of IDU had an additional loss in CD4 cell count of 15.43 (95% CI: –27.61, –3.26) cells/mm³. Compared to the patients whose HAART regimen did not include a NNRTI or a PI, those whose regimens included both NNRTI and PI had an additional loss in CD4 cell count of 35.51 (95% CI: –59.50, –11.51) cells/mm³, those on NNRTI only had an additional loss in CD4 cell count of 39.91 (95% CI: –56.51, –23.31) cells/mm³, and those on PI only had an additional loss in CD4 cell count of 22.81 (95% CI: –38.27, –7.34) cells/mm³.

Compared with the patients who did not visit the emergency department, those who visited had an additional loss in CD4 cell count of 15.43 cells/mm³. For each log₁₀ increase in plasma viral load, the CD4 cell count decreased by 46.51 (95% CI: -51.04, -41.99) cells/mm³ (Table 1).

Number of Emergency Department Visits Analysis

The number of emergency visits for patients was recorded for every six months prior to each patient's death. Among the 457 patients, only 41 (9%) of them visited emergency room five years prior to death, and the number increased to 188 (41%) during the last six months prior to death. This increasing trend is shown in Figure 3.

Examining the relationship between each covariate and the number of patients visiting an emergency room over time, we observed a consistent increasing trend for all covariates in Figure 4. Based on the results from the generalized mixed effect model, for every six-month interval prior to death, the risk of experiencing an emergency department visit was 1.09 times higher (95% CI: 1.05, 1.13) (Table 1). Compared with patients without a history of IDU, those who had a history of IDU had a risk 1.65 times higher (95% CI: 1.07, 2.56). Compared with patients who did not have an AIDS diagnosis during follow-up, those who had an AIDS diagnosis had a risk 0.64 times lower (95% CI: 0.47, 0.88). Compared to the patients whose HAART regimen did not include a NNRTI or a PI, those patients whose regimens included both NNRTI and PI had a risk 1.25 times higher (95% CI: 0.99, 1.60), those on NNRTI only had a risk 1.35 times higher (95% CI: 1.14, 1.60), and those on PI only had a risk 1.54 times higher (95% CI: 1.31, 1.79). Older patients had a lower risk of visiting the emergency department (0.95; 95% CI: 0.93, 0.97), and patients with higher CD4 cell count had a lower risk of visiting the emergency department (0.89; 95% CI: 0.85, 0.93) (Table 1).

Probability of Having an Emergency Visit Leading to an Acute Care Hospital Admission Analysis

Among patients who have ever visited the emergency department during the follow-up in our study, 28% were ever transferred to an acute care level facility. Based on the results from the multivariable model, for every six-month interval prior to death, the odds ratio of being transferred to an acute care level facility was 1.03 times higher (95% CI: 1.02, 1.04) (Table 2). Females had an odds ratio 1.07 (95% CI: 1.01, 1.15) times higher than males. Compared to the patients whose HAART regimens did not include a NNRTI or a PI, those patients whose regimens included both NNRTI and PI had an odds ratio 1.04 times higher (95% CI: 0.96, 1.13), those on NNRTI only had an odds ratio 1.02 times higher (95% CI: 0.97, 1.07), and those on PI only had an odds ratio 1.09 times higher (95% CI: 1.03, 1.15) for being transferred to an acute care level facility. Compared to the patients with a low acuity level, those with a high acuity level had an odds ratio 1.13 times higher (95% CI: 1.04, 1.22) for being transferred to acute care after the emergency visit. Compared to patients who walked into the emergency department, those who arrived by wheelchair had an odds ratio 1.16 times higher (95% CI: 1.07, 1.26), and those arriving by ambulance had an odds ratio 1.18 times higher (95% CI: 1.13, 1.22). Patients with higher CD4 cell count

had a lower odds ratio for being transferred to an acute level facility (0.98; 95% CI: 0.96, 0.99) (Table 2).

DISCUSSION

Our results confirmed that prior to death, HIV-positive patients incur high healthcare utilization. We showed that during the previous five years to death, the CD4 cell count of these patients significantly decreased, the number of emergency department visits increased, and the risk of being transferred to an acute level facility also increased. Within our study population 80% of patients had a history of IDU, and these patients experienced a significantly higher CD4 cell count loss and higher healthcare utilization prior to death when compared to non-IDU patients.

Previous studies have examined the factors associated with hospital or emergency department admission among different cohorts of HIV-positive individuals [8–14]. These studies concluded that highly marginalized sub-groups of the population, and individuals with advanced HIV disease were at a higher risk of being admitted to a hospital. There are several implications for these and our findings. Nosyk et al. showed that these individuals were likely to have a longer hospital stay, and consequently incur a higher hospitalization cost [6].

Of note, individuals with a history of IDU are more likely to experience treatment interruptions due to their chaotic lifestyle, which in turn promotes disease progression and HIV transmission, by having an elevated plasma viral load and a low CD4 cell count [15]. In addition, highly marginalized individuals are known to receive primary care from the emergency department, and to present to an emergency department with advanced disease progression when the management of their disease is extremely difficult and the risk of mortality is quite elevated. Providing treatment to these individuals can be extremely expensive to the healthcare system and interventions should be targeted to ensure that these individuals are properly linked and retained into care [16].

Several features of our study are worth mentioning. This study was based on a large registry of patients in BC with unrestricted and fully free of cost access to laboratory monitoring, antiretroviral treatment and medical care. Thus, we believe that our results were not influenced by typical financial barriers to access health services and therapy, a factor that has often compromised the interpretation of other cohort studies. Secondly, we only included individuals who visited the emergency department at the St. Paul's hospital, given that this was the only data linkage available to our analysis. Although this emergency department carries the highest burden of HIV/AIDS in BC, caution is warranted to extrapolate our results to other settings. Thirdly, we only included patients with follow-up between August 1996 and June 2007, due to the availability of the data linkage. We have adjusted all our analyses to follow-up time. However, our group has demonstrated that individuals (IDU or not) receiving modern HAART regimens were less likely to die and more likely to maintain viral load suppression over time. Whether these facts translate into a lower healthcare utilization or into a different CD4 trajectory prior to death is yet to be

shown. Lastly, as in any cohort study unmeasured differences may still exist in our study population, and for this reason, our findings should be interpreted cautiously.

In conclusion, patients experienced a steep decline in CD4 cell count that was associated with an increase in healthcare utilization prior to their death. We showed that hard-to-reach individuals, especially those with a history of IDU, had a sharper decline in CD4 cell count and a higher healthcare utilization. These findings highlight the substantial residual avoidable burden that unsuccessfully managed HIV disease poses, even in the HAART era. Further strategies to enhance sustained and successful engagement in care are urgently needed to mitigate high healthcare utilization.

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Ethical approval: The Centre's HIV/AIDS Drug Treatment program has received ethical approval from the University of British Columbia Ethics Review Committee at its St. Paul's Hospital site. The program also conforms to the province's Freedom of Information and Protection of Privacy Act.

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FIGURE 1.

CD4 cell count (cells/mm³) trend during the five years prior to the patients' death.

Footnote: For each time point, from bottom to top are the 25th percentile, the median and the 75th percentile; the p-value for trend was < 0.0001.

FIGURE 2.

CD4 cell count (cells/mm³) trend by different covariates during the five years prior to the patients' death.

Footnote: IDU: injection drug use; ED: emergency department; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors.

FIGURE 3.

Emergency department visit trend during the five years prior to the patients' death.

Footnote: The p-value for trend was < 0.0001 .

FIGURE 4.

Emergency department (ED) visits trend by different covariates during the five years prior to the patients' death.

TABLE 1

Multivariable models for the two main outcomes.

Factors	Multivariable Models	
	CD4 cell count (cells/mm ³) ¹	Number of emergency department visits ²
Gender		
Male	NS	NS
Female		
Injection drug use history		
No	Reference	Reference
Yes	-49.01 (-84.16, -13.26)	1.65 (1.07, 2.56)
AIDS diagnosis[¶]		
No	NS	Reference
Yes		0.64 (0.47, 0.88)
HAART regimen class[¶]		
Neither	Reference	Reference
PI only	-39.91 (-56.51, -23.31)	1.35 (1.14, 1.60)
NNRTI only	-22.81 (-38.27, -7.34)	1.54 (1.31, 1.79)
Both NNRTI and PI	-35.51 (-59.50, -11.51)	1.25 (0.99, 1.60)
Number of emergency department visits[¶]		
No	Reference	NA
Yes	-15.43 (-27.61, -3.26)	
Age (years)	NS	0.95 (0.93, 0.97)
Follow-up time (years)	-13.22 (-16.27, -10.18)	1.09 (1.05, 1.13)
Plasma HIV-1 RNA level (log₁₀ copies/mL)[¶]	-46.51 (-51.04, -41.99)	NS
CD4 cell count (per 100 cells/mm³)[¶]	NA	0.89 (0.85, 0.93)

[¶]Variables were time-varying.

NS: Not selected to be in the final model.

NA: Not applicable to be included in the model.

¹This outcome was modeled as a continuous variable. Values in brackets are the 95% confidence interval limits.²This outcome was modeled as counts, thus the values can be interpreted as risk. Values in brackets are the 95% confidence interval limits.

NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors.

TABLE 2

Multivariable model for the probability of having an emergency visit leading to an acute care hospital admission.

Factors	Multivariable Model
	Odds Ratio (95% Confidence Interval)
Gender	
Male	1.00
Female	1.07 (1.01, 1.15)
Injection drug use history	
No	NS
Yes	
AIDS diagnosis[¶]	
Yes	NS
No (ref)	
Regimen[¶]	
Neither	1.00
PI only	1.09 (1.03, 1.15)
NNRTI only	1.02 (0.97, 1.07)
Both NNRTI and PI	1.04 (0.96, 1.13)
CTAS[¶]	
Low acuity (4,5)	1.00
High acuity (1,2,3)	1.13 (1.04, 1.22)
Arrival mode[¶]	
Walking	1.00
Wheelchair	1.16 (1.07, 1.26)
Ambulance	1.18 (1.13, 1.22)
Other	1.05 (0.82, 1.35)
Age (years)	NS
Follow-up Time	1.03 (1.02, 1.04)
Plasma HIV-1 RNA level (log₁₀ copies/mL)[¶]	NS
CD4 cell count (per 100 cells/mm³)[¶]	0.98 (0.96, 0.99)

[¶]Variables were time-varying.

NS: Not selected to be in the final model.

NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; CTAS: Canadian Triage and Acuity Scale.