Published in final edited form as:

AIDS. 2015 August 24; 29(13): 1681–1689. doi:10.1097/QAD.0000000000000746.

Characterizing retention in HAART as a recurrent event process: insights into ‘cascade churn’

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Abstract

Objective—The benefits of HAART rely on continuous lifelong treatment retention. We used linked population-level health administrative data to characterize durations of HAART retention and nonretention.

Design—This is a retrospective cohort study.

Methods—We considered individuals initiating HAART in British Columbia (1996–2012). An HAART episode was considered discontinued if individuals had a gap of at least 30 days between days in which medication was prescribed. We considered durations of HAART retention and nonretention separately, and used Cox proportional hazards frailty models to identify demographic and treatment-related factors associated with durations of HAART retention and nonretention.

Results—Six thousand one hundred fifty-two individuals were included in the analysis; 81.2% were male, 40.6% were people who inject drugs, and 42.8% initiated treatment with CD4 cell count less than 200 cells/μl. Overall, 29% were continuously retained on HAART through the end of follow-up. HAART episodes were a median 6.8 months (25th, 75th percentile: 2.3, 19.5),

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Author contributions: B.N. designed the study, assisted with analysis, and contributed to the preparation of the manuscript. L.L. wrote the first draft of the article and contributed to the design of the analysis. J.M. led the analysis and assisted with study design and interpretation of results. D.S. assisted in the analysis and contributed to the study design. V.D.L. and J.S.G.M. aided in study design, interpretation of results, and provided critical revisions to the article. JSGM led the procurement of the database. All authors approved the final draft.

whereas off-HAART episodes lasted a median 1.9 months (1.2, 4.5). In Cox proportional hazards frailty models, durations of HAART retention improved over time. Successive treatment episodes tended to decrease in duration among those with multiple attempts, whereas off-HAART episodes remained relatively stable. Younger age, earlier stages of disease progression, and injection drug use were all associated with shorter durations of HAART retention and longer off-HAART durations.

Conclusion—Metrics to monitor HAART retention, dropout, and reentry should be prioritized for HIV surveillance. Clinical strategies and public health policies are urgently needed to improve HAART retention, particularly among those at earlier stages of disease progression, the young, and people who inject drugs.

Keywords

British Columbia; HAART; HIV; mathematical models; medication persistence; proportional hazards model; retention

Introduction

Modern HAART has transformed the HIV epidemic in two profound ways [1]: First, at an individual level, persons living with HIV (PLHIV) today are living longer, healthier lives [2,3]. Second, at a population level, it has been established that the expansion of HAART coverage can lead to a population-level reduction in HIV incidence [4–7]. The extent of these benefits rely on the continuous lifelong use of HAART, as treatment interruptions have been associated with inferior patient outcomes, increased risk of HIV transmission, and emergence of antiretroviral drug resistance [8–10]. Structured treatment interruptions were once applied in clinical practice but have been discontinued as of 2005 following evidence-based recommendations discouraging this practice [11]. However, unstructured interruptions and poor or intermittent retention in HAART remain common [12–15]. It is therefore of vital interest to those engaged in the care of PLHIV to monitor lifelong retention on HAART [16].

The cascade of HIV care is a well established monitoring tool that measures retention in care and highlights attrition along the HIV care continuum from HIV infection to diagnosis, linkage to HIV care (often defined as the first HIV-related physician visit or diagnostic test), retention in HIV care (regular HIV-related care), to HAART retention and the ultimate goal of virologic suppression [17,18]. Attrition or ‘leakage’ at different stages along the cascade is heterogeneous, composed of individuals never accessing a given level of care and those disengaged from regular care. The latter itself is a heterogeneous group comprised of those dropping out of treatment for the first time, those with multiple treatment discontinuations, as well as those lost to HIV care entirely (i.e., discontinued regular physician follow-up and diagnostic testing). The sometimes cyclical process of engagement, disengagement, and reengagement in HIV care has been referred to as cascade ‘churn’, and has been cited as a crucial component of HIV monitoring [19–22]. HAART persistence or sustained engagement (as opposed to adherence, which measures the number of prescribed doses of HAART that were ingested) [23,24] is of particular interest as the ultimate goal of sustained viral suppression cannot be achieved without it.

Although determinants of HAART retention have been studied exhaustively [25,26], less is known about the process of HAART persistence, dropout, and reengagement over time. Episodes of HAART persistence and disengagement vary in length and the determinants these episode durations may have critical implications for clinical practice and public health policy. Dynamic characterization, as afforded by advances in longitudinal data analysis [27–29], can help to shed light on the longitudinal process (i.e., pattern of HAART persistence and disengagement) in the interest of informing clinical practice. This form of analysis may also provide important information to capture within mathematical models used to estimate transmission dynamics and make resource allocation decisions.

We aimed to identify and characterize possible determinants of successive durations of HAART retention and nonretention over time. We applied Cox proportional hazards frailty models to link health administrative data captured for the population of PLHIV in British Columbia (BC) between 1996 and 2012 to address our objectives.

Methods

Study population

This study was based on a provincial-level linkage of seven health administrative databases and disease registries, including the BC Centre for Excellence in HIV/AIDS drug treatment program and virology registries [antiretroviral dispensations, plasma viral load (pVL), and CD4 cell tests]; the BC Centre for Disease Control HIV testing database (HIV diagnosis); the Medical Services Plan database (physician billing records); the discharge abstract database (hospitalizations); the BC PharmaNet database (nonantiretroviral drug dispensations); and the BC Vital Statistics database (deaths). Details regarding the construction of the population-level cohort and available databases have previously been described [30].

We considered all cohort members who accessed HAART between 1 July 1996 and 30 June 2012. As our interest was in characterizing the natural course of HAART retention, we excluded those with a documented structured treatment interruption. These interruptions were applied to a limited group of individuals between 2000 and 2005 in response to growing concerns regarding toxicity and development of resistance to antiretroviral medications. Use of these interruptions has since been discontinued [11]. We also excluded individuals who had previously accessed mono or duo-antiretroviral therapy (ART) as their disease course, given that their experience with antiretroviral medication may differ substantially from those initiating treatment in the HAART era. Thus, individuals were naïve to antiretrovirals at the point of HAART initiation. For each individual, detailed HAART dispensation data was available from the point of (within province) HAART initiation to death, administrative loss to follow-up, or censorship (ongoing care as of 30 June 2012). Administrative loss was defined as no health records in any of the linked databases for a period of at least 18 months.

The study cohort was followed in a unique environment characterized by universal free medical care, including inpatient and outpatient care, laboratory monitoring, and antiretroviral medications. PVL data capture in the BC Centre for Excellence registries are

complete for the population of individuals with HIV/AIDS in the province, and CD4 cell count data capture has previously been estimated at 80% [26]. This study received approval from the University of British Columbia/Providence Healthcare Research Ethics Board.

Measures

The dependent variable in our analysis was the duration of episodes on and off HAART, according to administrative medication dispensation records. An episode of HAART was considered discontinued if individuals had a gap of at least 30 days between days in which medication was prescribed; thus, on and off-HAART episodes were mutually exclusive and exhaustive in the classification of follow-up from the time of HAART initiation. This threshold was chosen because of the relative speed of viral rebound among those discontinuing treatment. Studies to date have shown that in the era of contemporary HAART, treatment interruptions lasting as short as a few days can be associated with virologic failure [31,32]. Parienti *et al.* [33] found that patients on a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen have a 50% probability of virologic failure (> 400 copies/ml) after a 15-day treatment interruption, although this duration likely varies depending on the HIV treatment regimen [23].

A range of covariates previously hypothesized to impact HAART retention were incorporated including patient demographics [age at episode initiation (<30, 30–39, 40–49, 50+), sex, known aboriginal ethnicity, HIV risk group – known MSM, known history of injection drug use, or other], medical comorbidity (Charlson comorbidity index score [34–36] in the year prior to episode initiation), HIV disease history at episode initiation [time from diagnosis, CD4 cell count and pVL (undetectable vs. detectable), AIDS status], calendar year of HAART initiation (1996–1999, 2000–2003, 2004–2007, 2008–2012), HAART treatment regimen at episode initiation (traditional regimens including zidovudine, lamivudine, didanosine, stavudine, nevirapine, abacavir, nelfinavir, and ritonavir; contemporary regimens including lamivudine + tenofovir, emtricitabine + tenofovir, tipranavir, maraviroc, raltegravir, etravirine, atazanavir, enfuvirtide, efavirenz, and ritonavir + other protease inhibitor or boosted protease inhibitor-based regimens; multidrug resistance regimens including five or more drugs), and physician contact during 1 year prior to episode initiation (number of visits to general practitioner/specialist and visits related to HIV). We note that the threshold for pVL undetectability has decreased from 500 copies/ml in 1996, to 400 copies/ml in 1997, to 50 copies/ml in 1999 and 40 copies/ml in 2008 [4]. Finally, a variable, indicating whether a given on or off-HAART episode was the individuals' first, second, and so on, was created to assess whether the duration of successive treatment and off-treatment episodes changed over time.

Statistical analysis

The determinants of the time to discontinuation of HAART and off-HAART episodes were analyzed using time-to-event data statistical techniques. Mantel–Haenszel tests were conducted for each independent variable considered in the analyses. The assumption of proportionality for each of the study variables was assessed by visual inspection of Schoenfeld residual plots and weighted residuals score tests [37]. Nonproportional hazards were accepted if the variation in $\beta(t)$ was not large in comparison with the parameter

estimate. The resulting parameter estimates were therefore time-averaged regression effects. Given the simple structure of the regression model (i.e., no random effects on covariates), nonproportionality of the covariates did not bias the estimates of the variance components [38].

Proportional hazards γ frailty models were fitted to account for the dependence in the length of individuals' repeated HAART episodes [28,29]. The proportional hazards γ frailty model can be expressed as $h_{ij}(t) = h_0(t)v_j \exp(\beta'Z_{ij})$, wherein $h_0(t)$ is the unspecified baseline hazard, Z_{ij} is the fixed-effect covariate matrix for episode $i = 1, \dots, n_j$ among individuals $j = 1, \dots, m$, and β is a vector of regression coefficients. The unobserved random effect, or frailty, for the j th individual (v_j) was assumed to follow a γ distribution ($v_j \sim \chi(1/\theta, 1/\theta)$). Frailties are unobservable random variables corresponding to each individual's underlying modification of the baseline hazard function. They represent unobserved covariates common across multiple treatment episodes for each individual. Furthermore, the proportional hazards γ frailty model captures the correlation in episode lengths within an individual; conditional on the frailty terms, the episode lengths are independent [27].

In addition, we executed a parallel proportional hazards frailty model on the 'gap times' between treatment discontinuation and reinitiation among those with at least one 30-day gap. In doing so, the aforementioned set of covariates was updated according to the date of HAART discontinuation (and thus 1 day prior to the start of the 'gap time' initiation). As a sensitivity analysis to determine whether patterns of the duration of successive HAART and off-HAART episodes was consistent over time, we included models in which the HAART and off-HAART episode count variable was interacted with the calendar year of HAART initiation. Analysis was executed using SAS version 9.3 and R version 2.5.1.

Results

Table 1 provides a description of the 6152 individuals included in the analysis, at the point of HAART initiation. Briefly, 81.2% were male, 40.6% were people who inject drugs (PWID), and 42.8% initiated treatment with a low (<200 cells/ μ l) CD4 cell count.

Durations of HAART and off-HAART episodes are described in Table 2. In total, we observed 18 695 HAART and 13 975 off-HAART episodes. The median (25th, 75th percentile) duration of all HAART episodes was 6.8 months (2.3, 19.5), with 21.5% lasting at least 24 months. First episodes tended to last longer, a median 12.7 months (3.7, 35.8), with 34.9% lasting at least 2 years. Over 29% of the individuals included in the study were continuously retained on HAART from initiation of their first episode to the end of follow-up, whereas 29.8% had 12 or more distinct treatment episodes. In contrast, off-HAART episodes lasted a median 1.9 months (1.2, 4.5), with little difference across successive episodes (not adjusting for other covariates). Over 10% (12.0%) of individuals discontinuing their initial HAART episode never reentered treatment.

Table 3 provides results of multiple Cox proportional hazards frailty regression models for on and off-HAART episodes. Controlling for other covariates, among individuals with multiple treatment attempts, successive HAART episodes tended to decrease in duration

(i.e., greater adjusted hazard of episode discontinuation). Second episodes were 24% shorter than first episodes [adjusted hazard ratio: 1.24; 95% confidence interval (CI): (1.17, 1.31)], third episodes were 47% shorter than first episodes [1.47 (1.38, 1.57)], and sixth or more episodes were 76% shorter than first episodes [1.76 (1.63, 1.91)]. Younger age, a history of injection drug use, and First Nations ethnicity were all associated with shorter HAART episode durations. Those with higher CD4 cell counts or detectable pVL at episode initiation tended to have shorter treatment durations, whereas those initiating treatment with a contemporary treatment regimen tended to have longer treatment durations than those initiating with traditional or multidrug resistance regimens. Those with a high volume of general practitioner visits (>10 in the past 12 months) tended to have shorter subsequent HAART episodes, whereas those with regular specialist visits (>3 in the past 12 months) had longer treatment episodes. Finally, those initiating HAART in later years tended to have longer HAART episodes, controlling for other factors. In particular, those initiating treatment in 2008–2012 remained in treatment 27% longer than those initiating in 1996–1999 [0.73 (0.67, 0.80)].

In contrast, successive off-HAART episodes were similar in duration from first episodes after controlling for relevant covariates and adjusting for intraindividual correlation, although fourth and fifth episodes tended to be 12–13% shorter in duration. Older age was associated with shorter off-HAART episodes, heterosexuals tended to have shorter off-HAART episodes compared with individuals with other HIV risk behaviors, whereas those with a prior AIDS diagnosis had substantially shorter off-HAART episodes [1.55 (1.46, 1.64)] than others. Those initiating HAART in more recent years had substantially shorter off-HAART episodes, compared with those initiating in 1996–1999 [2004–2007: 1.26 (1.18, 1.36); 2008–2012: 1.59 (1.47, 1.71)].

We explored the temporal relationship of successive on and off-HAART episode durations further by testing the interaction between the constructed episode count variable and the temporal phase of the episode initiation. Results (shown in Fig. 1) indicate that the pattern of decreasing durations of on-HAART episodes is consistent across temporal phases of HAART initiation, with successively wider CIs in later phases likely because of smaller cell sizes for later episodes. Off-HAART episodes again showed no distinct pattern in terms of durations of successive episodes across temporal phases. Although off-HAART episodes tended to increase in duration among 2008–2012 HAART initiators, CIs were exceptionally wide and results were not statistically significant.

Discussion

Our results demonstrate a substantial level of treatment dropout and reinitiation, or ‘churn’, among individuals on HAART in a high-resource setting with universal access to treatment and routine HIV care. Successive HAART episodes tended to decrease in duration, whereas off-HAART episodes remained relatively constant. Nonetheless, the duration of HAART episodes was greater for individuals initiating HAART in later years, whereas off-HAART episodes were shorter. In particular, durations of HAART episodes for those initiating treatment after 2008 were 27% longer than those initiating between 1996 and 1999, whereas off-HAART episodes were 59% shorter.

The observed increasing durations of HAART episodes (and diminishing durations of off-HAART episodes) in more recent years (2008–2012) is encouraging, and corroborates previously reported findings of improving treatment outcomes, in terms of both virological [39] and mortality outcomes [40,41]. This is likely largely attributable to improvements in the treatment regimens themselves, with reduced pill burdens and improved safety and tolerability profiles boosting treatment adherence.

It should come as no surprise that more frequent contact with medical specialists and receipt of HIV care was associated with both longer HAART episodes and shorter off-HAART episodes. The challenge remains maintaining consistent contact with the patient population at greatest risk of poor HAART persistence. These included individuals of younger age, female sex, aboriginal ethnicity, and a history of injection drug use; each of these factors was associated with both decreased treatment persistence (i.e., shorter durations on therapy) and longer treatment interruptions. These characteristics are consistent with the previous study findings [14,23]. In particular, we found that PWID experienced a high degree of churn. This finding may be partly explained by multiple competing priorities that PWID may face including multiple substance use disorders, mental health issues, as well as food and housing insecurity [36,37]. Although we did not have socioeconomic or mental health data to provide greater context, results from the study by Ing *et al.* [42] on HAART persistence among PWID showed that non-persistence of at least 7 days was highly associated with high addiction severity (adjusted odds ratio = 17.4) and high depressive symptoms (adjusted odds ratio = 5.0). As such, concurrent harm reduction, mental health, and HAART support is likely vital to ensure that PWID are consistently retained on HAART.

Decreasing durations of successive HAART episodes and relatively stable durations of off-HAART episodes call for targeted interventions for those with intermittent HAART retention. This is of concern as decreased persistence (i.e., shorter durations on therapy) is associated with virological failure, HIV drug resistance emergence, and increased mortality [9,23,43]. Understanding both treatment persistence and the frequency and duration of on-HAART episodes has become increasingly important with the advent of contemporary HAART, as studies suggest that a higher frequency and shorter durations of treatment may be a greater predictor of virologic failure among those on NNRTI-based regimens but not on protease inhibitor-based regimens [32,33,44]. This is likely attributable to the lower genetic barrier of NNRTI-based regimens [45]. In a preliminary analysis within our database for individuals with pVL measurements available both 90 days before and after treatment discontinuation (25.1% of all discontinued episodes), 38.3% of individuals previously virally suppressed experienced viral rebound (results not shown) – a conservative figure given the extent of missing data. Further study, accounting for intermittent patterns of treatment and HAART regimen switching, is required to fully demonstrate the long-term health consequences of HAART interruptions and intermittent HAART retention.

Another important and timely finding was that individuals initiating at high CD4 cell counts (> 200 cells/μl) were more likely to have shorter on-treatment HAART episode durations than those starting at less than 200 cells/μl. AIDS status was similarly associated with longer HAART durations and shorter off-HAART episodes. Similar findings have been observed

elsewhere [14,22,46,47]. Although our results suggested better retention among HAART initiators in more recent years regardless of CD4 cell count, individuals are now increasingly initiating ART at high CD4 cell counts because of relaxed HAART initiation guidelines [48,49], making monitoring of retention outcomes an increasingly critical priority. Given the growing number of treatment as prevention programs being implemented worldwide, long-term evidence-based treatment persistence support programs are necessary to minimize treatment interruptions. There is at present a paucity of research on HAART retention and reengagement among those discontinuing treatment. As noted, this is of particular importance among PWID, as well as younger individuals at earlier stages of disease progression. Interventions found to be successful to date include the use of mobile phones to act as appointment and pill reminders [50]. Improving this aspect of the cascade of HIV care is the subject of considerable focus locally and should be prioritized internationally to fully capitalize on both the individual and public health benefits of HAART.

Our analysis had several limitations. First, the study was conducted in a setting characterized by free HIV treatment, including antiretroviral medications. As such, it may be considered a 'best-case scenario', particularly among PWID, which comprises the majority of those with periods of treatment nonretention. Second, HAART durations relied on prescription refill data and were thus measured with a degree of error. Although administrative loss to follow-up was considered, it is possible, although unlikely, that individuals may have received ART dispensations out of province during periods considered off treatment. Finally, given the observational nature of the study, there is always potential for unmeasured confounding. In our case, patient-specific motivational factors and attitudes toward ART may have influenced results, however, overall patterns of HAART persistence represented that of the population of PLHIV in BC, excluding those initiating antiretroviral treatment before the HAART era or having a structured treatment interruption.

In conclusion, we found extensive evidence of churn among those on HAART in a setting with universal access to treatment and care. Incorporating monitoring of HAART churn as a part of routine HIV care surveillance is crucial to effective HIV care intervention planning. Furthermore, although HAART retention improved over time, there remains an urgent need to develop clinical strategies and public health policies to improve HAART persistence, particularly among those at earlier stages of disease progression, the young, and PWID.

Acknowledgements

The authors would like to acknowledge Michelle Olding for assistance with manuscript preparation, as well as the BCMoH and Vancouver Coastal Health Decision Support Staff involved in data access and procurement, including Monika Lindegger, Clinical Prevention Services, BC Centre for Disease Control; Elsie Wong, Public Health Agency of Canada; Al Cassidy, BC Ministry of Health Registries; and Joleen Wright and Karen Luers, Vancouver Coastal Health decision support.

This study was funded by the National Institutes of Health/National Institute on Drug Abuse grant no. R01-DA032551 and the BC Ministry of Health-funded 'Seek and treat for optimal prevention of HIV and AIDS' pilot project.

B.N. is otherwise supported by a Michael Smith Foundation for Health Research Scholar Award, and V.D.L. is supported by the Michael Smith Foundation for Health Research Scholar and a CIHR New Investigator Award. J.S.G.M. has received grants from Abbott, Biolytical, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. He is also supported by the Ministry of Health Services and the Ministry of Healthy Living and Sport, from the Province of British Columbia; through a Knowledge Translation

Award from the Canadian Institutes of Health Research (CIHR); and through an Avant-Garde Award (No. 1DP1DA026182) from the National Institute of Drug Abuse, at the US National Institutes of Health. He has also received support from the International AIDS Society, United Nations AIDS Program, World Health Organization, National Institute on Drug Abuse, National Institutes of Health Research-Office of AIDS Research, National Institute of Allergy and Infectious Diseases, The United States President's Emergency Plan for AIDS Relief (PEPFAR), Bill and Melinda Gates Foundation, French National Agency for Research on AIDS and Viral Hepatitis (ANRS), and Public Health Agency of Canada.

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Fig. 1. Adjusted hazards of time to HAART and off-HAART episode discontinuation

Hazard ratios were estimated by including interaction terms between (multinomial) episode count and temporal era variables in a multiple regression model, controlling for all covariates noted in Table 3. 95% CI, 95% confidence interval; epi, episode.

Table 1
Descriptive statistics of study patients at HAART initiation

Characteristics	N (%)
Age (years)	
<30	805 (13.1)
30–39	2087 (33.9)
40–49	2102 (34.2)
50	1158 (18.8)
Male	4994 (81.2)
First Nations status (known)	973 (15.8)
HIV risk behavior	
Heterosexual	862 (14.1)
PWID	2032 (33.0)
MSM	1772 (28.8)
MSM/PWID	463 (7.5)
Unknown	1023 (16.6)
AIDS status	891 (14.5)
CD4 cell count	
<200 cells/ μ l ³	2580 (41.9)
200–349 cells/ μ l	1881 (30.6)
350–499 cells/ μ l	935 (15.2)
500 cells/ μ l	756 (12.3)
Undetectable viral load	385 (6.3)
Time since HIV diagnosis (years) (median (Q1, Q3))	1 (0–4)
Calendar year of HAART initiation	
1996–1999	1234 (20.1)
2000–2003	1075 (17.5)
2004–2007	1523 (24.8)
2008–2012	2320 (37.7)
GP visits, past 12 months	
0 visits	1309 (21.3)
1–10 visits	3347 (54.4)
>10 visits	1496 (24.3)
Specialist visits, past 12 months	
0 visits	2664 (43.3)
1–3 visits	2361 (38.4)
>3 visits	1127 (18.3)
HIV-related visits, past 12 months	
0 visits	4668 (75.9)
1 visit	1484 (24.1)
Inpatient care days, past 12 months	
0 days	4370 (71.0)

Characteristics	<i>N</i> (%)
1 day	1782 (29.0)
CCI score	
0	5495 (89.3)
1	657 (10.7)
Therapeutic class of initial HAART regimen	
Contemporary regimen	4009 (65.2)
Multidrug resistance regimen	19 (0.3)
Traditional regimen	2124 (34.5)

CCI, Charlson comorbidity index; GP, general practitioner; PWID, people who inject drugs – indication of history of injection drug use.

Table 2
Summary statistics on durations of HAART retention

		Duration of episode (in months)		6 months	12 months	24 months	Censored
	<i>N</i>	Mean (SD)	Median (Q1, Q3)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)
HAART episodes							
1st episode	6152	25.6 (32.2)	12.7 (3.7, 35.8)	4095 (66.6)	3170 (51.5)	2144 (34.9)	1811 (29.4)
2nd episode	3556	18.2 (25.5)	8.0 (2.8, 22.1)	2025 (56.9)	1419 (39.9)	849 (23.9)	836 (23.5)
3rd episode	2330	13.6 (19.6)	6.1 (2.0, 16.3)	1192 (51.2)	761 (32.7)	399 (17.1)	406 (17.4)
4th episode	1684	11.6 (17.9)	4.9 (2.0, 12.6)	761 (45.2)	443 (26.3)	224 (13.3)	266 (15.8)
5th episode	1242	10.5 (16.1)	4.8 (2.0, 11.5)	558 (44.9)	299 (24.1)	129 (10.4)	194 (15.6)
6th episode	916	9.3 (13.8)	4.7 (2.0, 10.3)	387 (42.2)	194 (21.2)	84 (9.2)	134 (14.6)
7th episode	704	8.9 (13.4)	4.4 (2.0, 9.5)	283 (40.2)	143 (20.3)	61 (8.7)	106 (15.1)
8th episode	536	8.0 (11.7)	4.0 (2.0, 8.8)	199 (37.1)	91 (17.0)	37 (6.9)	71 (13.2)
9th episode	408	7.7 (12.2)	3.8 (2.0, 8.4)	138 (33.8)	73 (17.9)	24 (5.9)	57 (14.0)
10th episode	320	7.5 (11.9)	3.5 (2.0, 7.4)	103 (32.2)	51 (15.9)	23 (7.2)	47 (14.7)
11th episode	242	7.8 (10.9)	4.1 (2.0, 9.2)	92 (38.0)	40 (16.5)	18 (7.4)	36 (14.9)
12th episode	605	6.9 (9.1)	3.6 (2.0, 8.1)	203 (33.6)	94 (15.5)	31 (5.1)	106 (17.5)
All episodes	18 695	17 (25.2)	6.8 (2.3, 19.5)	10 036 (53.7)	6778 (36.3)	4023 (21.5)	17 (25.2)
Off-HAART episodes							
1st episode	4043	8.6 (18.6)	2.0 (1.2, 5.8)	1003 (24.8)	669 (16.5)	388 (9.6)	487 (12.0)
2nd episode	2585	7.2 (15.3)	1.9 (1.3, 5.3)	612 (23.7)	376 (14.5)	180 (7.0)	255 (9.9)
3rd episode	1853	6.4 (13.1)	1.9 (1.3, 5.0)	418 (22.6)	233 (12.6)	117 (6.3)	168 (9.1)
4th episode	1374	5.2 (11.7)	1.8 (1.2, 3.5)	234 (17.0)	128 (9.3)	61 (4.4)	132 (9.6)
5th episode	1013	4.3 (7.7)	1.8 (1.3, 3.4)	156 (15.4)	80 (7.9)	29 (2.9)	97 (9.6)
6th episode	761	4.9 (9.7)	1.9 (1.3, 3.9)	127 (16.7)	64 (8.4)	33 (4.3)	57 (7.5)
7th episode	585	5.2 (10.3)	1.9 (1.2, 4.0)	96 (16.4)	52 (8.9)	28 (4.8)	48 (8.2)
8th episode	459	4.7 (10.5)	1.9 (1.3, 3.8)	72 (15.7)	27 (5.9)	16 (3.5)	51 (11.1)
9th episode	340	3.5 (4.9)	1.8 (1.3, 3.1)	40 (11.8)	19 (5.6)	3 (0.9)	20 (5.9)
10th episode	269	5.0 (9.8)	1.9 (1.4, 4.2)	46 (17.1)	22 (8.2)	12 (4.5)	27 (10)
11th episode	203	3.1 (4.0)	1.9 (1.2, 3.0)	23 (11.3)	9 (4.4)	1 (0.5)	22 (10.8)
12th episode	490	3.2 (5.4)	1.8 (1.2, 3.0)	51 (10.4)	15 (3.1)	6 (1.2)	65 (13.3)
All episodes	13 975	6.5 (14.3)	1.9 (1.2, 4.5)	2878 (20.6)	1694 (12.1)	874 (6.3)	1429 (10.2)

(Q1, Q3), 25th, 75th percentiles; SD, standard deviation.

* Censored indicates episodes that were ongoing as of the end of follow-up.

Table 3
Results of multivariate Cox proportional hazards frailty models for on and off-HAART episodes

	On-HAART episodes			Off-HAART episodes		
	AHR	95% CI		AHR	95% CI	
Episode 1	Reference			Reference		
Episode 2	1.24	1.17	1.31	1.05	0.99	1.11
Episode 3	1.47	1.38	1.57	1.03	0.96	1.09
Episode 4	1.61	1.49	1.73	1.13	1.05	1.22
Episode 5	1.61	1.48	1.76	1.12	1.03	1.22
Episode 6	1.76	1.63	1.91	0.95	0.88	1.02
Female	1.12	1.05	1.20	0.96	0.90	1.02
Age						
<30	1.60	1.46	1.75	0.68	0.61	0.74
30–39	1.27	1.19	1.35	0.77	0.72	0.82
40–49	1.11	1.04	1.17	0.89	0.84	0.95
50	Reference			Reference		
First Nations status (known) ^a	1.24	1.16	1.32	1.02	0.96	1.09
MSM ^a	Reference			Reference		
PWID ^a	1.98	1.85	2.13	0.90	0.84	0.97
MSM/PWID ^a	1.72	1.56	1.89	0.91	0.83	1.00
Heterosexual ^a	1.43	1.31	1.57	1.12	1.02	1.23
Other/Unknown ^a	1.58	1.45	1.73	0.89	0.82	0.98
Time from diagnosis (years)	0.99	0.98	1.00	1.04	1.03	1.04
Year of HAART initiation						
1996–1999 ^a	Reference			Reference		
2000–2003 ^a	0.90	0.84	0.97	1.01	0.95	1.08
2004–2007 ^a	0.86	0.80	0.93	1.26	1.18	1.36
2008–2012 ^a	0.73	0.67	0.80	1.59	1.47	1.71
AIDS status	0.99	0.93	1.05	1.55	1.46	1.64
CD4						
<200	Reference			Reference		
200–349	1.10	1.05	1.16	0.91	0.85	0.96
350–499	1.14	1.08	1.21	0.89	0.84	0.95
500	1.22	1.15	1.30	0.86	0.81	0.92
Undetectable pVL	0.86	0.82	0.90	1.29	1.23	1.34
GP visits, past 12 months						
0	0.92	0.86	0.98	0.96	0.90	1.03
1–10	0.98	0.93	1.03	1.04	0.98	1.09

	<u>On-HAART episodes</u>			<u>Off-HAART episodes</u>		
	AHR	95% CI		AHR	95% CI	
>10	Reference			Reference		
Specialist visits, past 12 months						
0	1.27	1.20	1.34	0.92	0.87	0.97
1–3	1.16	1.10	1.22	0.92	0.87	0.97
>3	Reference			Reference		
HIV-related visit: 0 vs. >0	1.18	1.12	1.24	0.94	0.89	0.99
CCI: 0 vs. >0	0.81	0.76	0.86	1.03	0.97	1.11
Therapeutic class						
Contemporary	Reference					
Traditional	1.27	1.20	1.34			
MDRT	1.25	1.03	1.50			

95% CI, 95% confidence interval; AHR, adjusted hazard ratio; CCI, Charlson comorbidity index; GP, general practitioner; MDRT, multidrug resistant therapy; NNRTI, nonnucleoside reverse transcriptase inhibitor; PWID, people who inject drugs.

^aFixed (nontime-varying) covariates.