Clinical Infectious Diseases

MAJOR ARTICLE

Characterizing Human Immunodeficiency Virus Antiretroviral Therapy Interruption and Resulting Disease Progression Using Population-Level Data in British Columbia, 1996–2015

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Background. Suboptimal retention is among the biggest challenges to realize the full benefits of combination antiretroviral therapy (ART). We aimed to describe ART interruption patterns and identify determinants of disease progression while off ART in British Columbia, Canada.

Methods. With population-level data on ART utilization and laboratory testing in British Columbia (1996–2015), we described the timing, frequency, and duration of ART interruptions (a gap of ≥90 days in ART dispensation records). A 4-state continuous-time Markov model was implemented to identify determinants of disease progression during individuals' first ART interruption episode. Disease progression was measured according to CD4-based state transitions (cells/μL: ≥500 to 200–499; 200–499 to <200; ≥500 to death; 200–499 to death; and <200 to death).

Results. Among individuals initiating ART, 3129 (38.6%) interrupted ART over a median 8-year follow-up (interquartile range [IQR], 4.3–13.5 years). Those interrupting ART had a median of 1 interruption (IQR, 1.0–3.0), with the first interruption occurring 12.8 (IQR, 4.0–36.1) months after ART initiation, lasting for 7.5 (IQR, 4.1–20.3) months. The proportion of individuals interrupting ART within the first year of ART initiation decreased over time; however, the absolute number of individuals interrupting ART remained high. In a multivariable analysis, age, historical plasma viral load, and ART regimen changes prior to interruption were associated with increased hazard of CD4 decline and death.

Conclusions. Our results demonstrate that ART interruptions are common even in a high-resource setting with universal free access to human immunodeficiency virus care. Further efforts are needed to promote ART reengagement and may consider prioritizing individuals with poorer prognostic factors.

Keywords. HIV/AIDS; antiretroviral therapy; treatment retention; CD4; disease progression.

The use of combination antiretroviral therapy (ART) has successfully transformed human immunodeficiency virus (HIV) disease from an acute fatal condition into a chronic condition [1]. Along with early diagnosis and treatment initiation [2], continuous ART retention is essential to achieving sustained HIV suppression [3], decreased emergence of drug resistance [4], and improved survival and quality of life [5–7], as well as reduced HIV transmission [8]. Ensuring ART retention is critical to HIV treatment-as-prevention strategies and ultimately reaching the goal of an AIDS-free generation [9].

Poor adherence and continuity of care are among the biggest challenges to realize the full benefits of ART in both high-income and resource-limited settings [9, 10]. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has established its 90-90-90 target to address gaps in the cascade of HIV care [11]—that is, by 2020, 90% of people living with HIV (PLHIV) will be diagnosed, 90% of those diagnosed will receive ART, and 90% of those on ART will have suppressed plasma viral loads (pVLs) [11]. In British Columbia (BC), Canada, progress has been made in improving the HIV care continuum over time [12], but gaps exist at each stage of cascade including achieving suppressed pVL [13]. Similar gaps have been reported globally [14], underscoring the pressing need to optimize ART continuation.

Existing evidence supports benefits of several interventions in improving adherence and viral suppression, including text messages, cognitive-behavioral therapy, and peer navigators, although their effects appear to be modest and wane over time [15]. Previous studies have also identified risk factors associated with ART nonadherence/interruption, including younger

Received 1 March 2017; editorial decision 13 June 2017; accepted 28 June 2017; published online July 1, 2017.

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Clinical Infectious Diseases® 2017;65(9):1496–503

DOI: 10.1093/cid/cix570

age [16–19], injection drug use [16, 18, 19], poor patient–provider relationship [20], and higher levels of regimen complexity [21]. Knowledge is limited, however, regarding population-level patterns of ART interruption and determinants of disease progression while off ART. This is partly due to the paucity of population-level drug dispensation data [22].

Utilizing the population-level data in BC, Canada, between 1996 and 2015, we aimed to first describe ART interruption patterns and then summarize the determinants of disease progression following the first ART interruption.

MATERIALS AND METHODS

Study Population

We considered all individuals who were antiretroviral naive at age ≥19 years and initiated combination ART between 1 August 1996 and 30 September 2015, as observed in the BC Centre for Excellence in HIV/AIDS (BC-CfE) Drug Treatment Program data. The study cohort is followed in a unique environment characterized by universal medical care, including free in- and outpatient care, laboratory monitoring, and antiretroviral drugs. Antiretroviral drugs are centrally distributed by the BC-CfE according to provincial treatment guidelines [23], which remain consistent with those put forward by the International AIDS Society (IAS) [24]. The initial fill of HIV medications is usually a 1-month supply, and refills for stable patients are usually a 2- to 3-month supply [25]. Both CD4 and pVL are also monitored according to these guidelines [23].

Our data capture complete antiretroviral drug dispensation, drug resistance, and pVL test data, and an estimate of 80% CD4 test data in the province [26]. The study sample is comprised of individuals infected mostly with subtype B virus [27]. The study was approved by the University of British Columbia and Providence Health Care research ethics board.

Measures

ART interruption was defined as a minimum 90-day gap between the prescription refill date and the date when previously dispensed medications were expected to be finished. We chose ≥90 days given our clinical experience on an ongoing province-wide "reengagement and engagement in treatment for antiretroviral interrupted and naive populations" intervention, where alerts were sent to providers whose patients have a ≥60-day gap in antiretroviral drug dispensing records. We found that many of these individuals were still taking their medication (albeit with low adherence), indicating the need for a longer time period to capture true ART interruption.

Disease progression while off ART was the primary endpoint in the analysis to address the second study objective, operationalized by a matrix with 5 possible transitions (CD4 count [cells/μL] ≥500 to 200–499; 200–499 to <200; ≥500 to death; 200–499 to death; and <200 to death). We applied an "ad hoc smoothing" technique [28], whereby transitions between CD4 strata were only allowed when 2 consecutive CD4 measurements were observed, to address intraindividual variation in time between CD4 measurements. All-cause death was ascertained through a linkage to provincial vital statistics data. Off-ART deaths were classified as such if they occurred during an off-ART period, or within 90 days of reinitiating ART; the latter aimed to capture individuals who reinitiated ART as a result of advanced disease.

We considered a list of variables to examine their relationships with disease progression, including (1) fixed covariates: male (yes/no), aboriginal ethnicity (yes/no/unknown), people who inject drugs (PWID) (yes/no/unknown), hepatitis C virus positive (HCV^+) at ART initiation (yes/no/unknown), and (2) time-dependent covariates: age, year, time from ART initiation to interruption (in months), HIV drug resistance (yes/no), nadir CD4 count and historical average pVL before interruption, regimen change (yes/no), and receiving a modern regimen (yes/no). Drug resistance was considered as nonreversible, and determined as detecting mutations based on a modification of the 2014 IAS-USA mutation list [29]. Historical average pVL was measured as area under the pVL curve, as sustained high pVL periods are associated with CD4 declines. We coded missing values as a third category in several categorical covariates to avoid the exclusion of individuals due to missing covariates.

Statistical Analysis

Descriptive statistics and univariate analysis were employed to characterize ART interruption patterns among all individuals initiating ART. First, we evaluated the proportion of individuals interrupting ART during follow-up and compared their characteristics to those remaining on ART continuously. Second, we examined the number of first and subsequent interruption episodes by calendar year and, among those with a minimum 1-year follow-up, the proportions of individuals interrupting ART within the first year. Third, we investigated the proportion of individuals who received at least 1 CD4/pVL test while off ART and compared the time intervals between CD4/pVL measurements pre– and post–ART interruption among individuals having at least 2 measurements to examine their retention in HIV care while off ART.

A parametric continuous-time, multistate Markov (MSM) model [30] was implemented to identify determinants of disease progression following the first ART interruption and before ART resumption, among individuals with at least 2 observed disease status measurements (either CD4 or death) during the first off-ART period. Individuals were censored at the point of the last CD4 test during the first interruption episode. MSM models have previously been applied to model HIV disease progression by CD4 cell count strata [28, 31, 32]. These models efficiently handle heavily censored data, such as when the exact time of disease onset is unknown or when a subject is observed over a portion of his/her disease history [32]. The assumption of noninformative sampling times was satisfied in the current

study as CD4 measurements typically occur at regular intervals as part of routine care [30]. A covariate was assumed to affect each baseline transition intensity by a proportional factor.

At first, we described the frequency of observed disease state transitions, and estimated the average annual transition probabilities from the unadjusted MSM model. We then examined the association between each covariate and disease transitions using bivariate models. At last, we constructed multivariable models to summarize factors associated with disease progression. As the covariates PWID and HCV^+ were highly positively correlated, we evaluated the nested models (with both covariates vs with either of them) using likelihood ratio tests, and a P value ≤.05 was considered as favoring the more complex model. Covariate effects on 2 transitions (CD4 count ≥500 to death; and 200–499 to death) were not estimated due to small numbers of transitions [30].

To check the robustness of results, we repeated multivariable analyses among first and subsequent ART interruptions, additionally adjusting for numbers of interruption episodes, as well as among a remaining subset of individuals (n = 1657) after excluding those with any missing covariates.

All statistical analyses were executed in SAS version 9.4 and R version 3.2.5 software. The R msm package version 1.6.4 was used for MSM modeling [30].

RESULTS

A total of 8110 ART-naive individuals initiated combination ART between 1996 and 2015 in BC. Among them, 3129 (38.6%) interrupted ART for ≥90 days over a median 8-year follow-up (interquartile range [IQR], 4.3–13.5 years), resulting in 6549 off-ART episodes. Individuals interrupting ART were younger at ART initiation (38 vs 42 years) and were more likely to be aboriginal (19.7% vs 8.1%), PWID (51.0% vs 21.2%), and HCV^+ (55.1% vs 25.3%), compared with individuals remaining on ART (Table 1). Those interrupting ART had a median of 1 interruption (IQR, 1.0–3.0), with the first interruption occurring 12.8 (IQR, 4.0–36.1) months after ART initiation, lasting for 7.5 (IQR, 4.1–20.3) months (Table 1).

The proportion of individuals interrupting ART within the first year decreased from 31.7% to 18.7%, 13.5%, and 11.0%, respectively, among those initiating ART in 1996–2003, 2004–2007, 2008–2011, and 2012–2014. The decrease was statistically significant when comparing against the previous period, except for 2012–2014 (P = .077). However, absolute numbers of individuals interrupting ART the first time every year remained high (around 150), with a gradual increase from 138 in 2012 to 183 in 2014; similarly, total numbers of interruptions increased from 360 in 2011 to 500 in 2014 (Figure 1). The numbers observed in 1996 and 2015 represented partial years.

We observed a large proportion of individuals having at least 1 CD4 or pVL test during the first interruption (Figure 1), with the proportion being higher in the early 2000s. The time intervals between CD4/pVL tests were comparable among individuals interrupting and not interrupting ART during on-ART periods (Figure 2A and 2B), with 95.0% and 96.6% of observed pVL measurement pairs being less than 6 months apart, respectively. The intervals were longer for pVL measurements during off-ART periods, yet the majority (79.0%) were within 6 months apart. Similar patterns were observed over time (Supplementary Figure 1).

Individuals (2212/3129 [70.7%]) with at least 2 observed disease status measurements during the first ART interruption were included in analyses of disease progression. The median time from ART interruption to the last CD4 measurement or death was 8.3 (IQR, 3.9–21.8) months. Model estimated average probability of all-cause mortality after 1 year of ART interruption was 2%, 4%, or a remarkable 19% for those with a CD4 count of ≥500, 200–499, and <200 cells/μL, respectively, at ART dropout (Table 2).

Independent determinants of CD4 decline or death during first-ART interruption are shown in Figure 3 and Supplementary Table 1. In the multivariable analysis, we found that increased age, elevated historical pVL, and ART regimen changes prior to interruption appeared to be associated with increased hazard of CD4 decline and death. For example, the adjusted hazard ratios (aHRs) for transitions from CD4 count (cells/μL) 200–499 to <200 were 1.27 (95% confidence interval [CI], 1.14–1.40) per 10-year increase in age; 1.25 (95% CI, 1.11–1.40) per $\log_{10}$-unit increase in historical pVL and 1.35 (95% CI, 1.10–1.65) with prior ART regimen changes. Similarly, every 10-year increase in age, and every $\log_{10}$-unit increase in historical pVL were associated with 70% (95% CI, 41%–106%) and 59% (95% CI, 26%–101%) increase in the hazard of progression from CD4 count <200 cells/μL to death, respectively.

In addition, drug resistance and lower nadir CD4 counts (per 100 cells/μL decline) were associated with increased hazard of CD4 decline from ≥500 to 200–499 (aHRs, 1.32 [95% CI, 1.03–1.69] and 1.51 [95% CI, 1.44–1.59]), and from 200–499 to <200 cells/μL (aHRs, 1.42 [95% CI, 1.13–1.78] and 1.57 [95% CI, 1.46–1.69]), respectively. In contrast, being HCV^+ was strongly associated with increased hazard of death (2.98 [95% CI, 1.66–5.32]).

Results of the sensitivity analyses among first and subsequent ART interruptions as well as among a subset of individuals following exclusion of those with missing covariates were consistent with main findings (Supplementary Table 2).

DISCUSSION

This study examined disease progression and associated factors while off ART in a population-based setting. Our results demonstrate that ART interruptions are common even among individuals on ART in a high-resource setting with universal

Table 1. Characteristics at Antiretroviral Therapy (ART) Initiation of 8110 ART-Naive Individuals Who Initiated ART in British Columbia, by ART Interruption (≥90 Days), 1996–2015

Characteristic	Total (N = 8110)	Ever Interrupted ART (n = 3129)	Never Interrupted ART (n = 4981)	*P* Value[a]
Age, y, median (IQR)	40.7 (33.6–48.1)	38.2 (32.2–44.8)	42.4 (34.9–49.7)	<.001
Male sex	6636 (81.8)	2342 (74.8)	4294 (86.2)	<.001
White race				
Yes	4913 (60.6)	1841 (58.8)	3072 (61.7)	<.001
No	1849 (22.8)	792 (25.3)	1057 (21.2)	
Unknown	1348 (16.6)	496 (15.9)	852 (17.1)	
Aboriginal ethnicity				
Yes	1022 (12.6)	617 (19.7)	405 (8.1)	<.001
No	5740 (70.8)	2016 (64.4)	3724 (74.8)	
Unknown	1348 (16.6)	496 (15.9)	852 (17.1)	
People who inject drugs				
Yes	2651 (32.7)	1595 (51.0)	1056 (21.2)	<.001
No	3629 (44.7)	1034 (33.0)	2595 (52.1)	
Unknown	1830 (22.6)	500 (16.0)	1330 (26.7)	
CD4 count <200 cells/μL[b]				
Yes	2938 (36.2)	1162 (37.1)	1776 (35.7)	<.001
No	4513 (55.6)	1675 (53.5)	2838 (57.0)	
Unknown	659 (8.1)	292 (9.3)	367 (7.4)	
HIV drug resistance[c]	705 (8.7)	277 (8.9)	428 (8.6)	.69
Hepatitis C positive				
Yes	2984 (36.8)	1724 (55.1)	1260 (25.3)	<.001
No	4476 (55.2)	1200 (38.4)	3276 (65.8)	
Unknown	650 (8.0)	205 (6.6)	445 (8.9)	
Modern regimen[d]	5700 (70.3)	1611 (51.5)	4089 (82.1)	<.001
Calendar year				
1996–2003	2562 (31.6)	1678 (53.6)	884 (17.7)	<.001
2004–2007	1622 (20.0)	607 (19.4)	1015 (20.4)	
2008–2011	2182 (26.9)	598 (19.1)	1584 (31.8)	
2012–2015	1744 (21.5)	246 (7.9)	1498 (30.1)	
Follow-up, y, median (IQR)	5.6 (2.4–10.0)	8.0 (4.3–13.5)	4.4 (1.5–7.9)	<.001
Interruption episodes, median (IQR)	…	1.0 (1.0–3.0)	…	
Time from ART initiation to first interruption, mo, median (IQR)	…	12.8 (4.0–36.1)	…	
Duration of first interruption episode, mo, median (IQR)	…	7.5 (4.1–20.3)	…	
Duration of each interruption episode, mo, median (IQR)		6.5 (4.0–14.9)		
Total months off ART, median (IQR)	…	18.9 (7.0–41.3)	…	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Pearson χ^2 and Mann-Whitney tests were used to compare categorical and continuous variables, respectively.

[b]Baseline CD4 count was determined based on the CD4 test performed within 3 months of ART initiation.

[c]HIV drug resistance was considered as nonreversible, and determined as detecting mutations based on a modification of the 2014 International AIDS Society–USA mutation list.

[d]Modern regimens included those based on lamivudine plus tenofovir or emtricitabine plus tenfovir combined with efavirenz, rilpivirine, or etravirine or a boosted protease inhibitor or integrase inhibitor regimen; small numbers of individuals could have received tipranavir, maraviroc, or enfuvirtide.

free access to HIV care, and that these interruptions are associated with remarkable disease progression.

We identified that older age, higher historical pVL, and prior ART regimen changes were associated with increased hazard of CD4 decline and death. Lower nadir CD4 was associated with CD4 decline, but not with death. Potential explanations might include that individuals with lower nadir CD4 were more likely to reinitiate ART [33]. These findings were supported by another study among PLHIV in 82 centers across Europe, which reported positive associations between age, pVL, CD4 ≤200 cells/μL, and progression to AIDS or death among individuals interrupting ART. The authors did not distinguish outcomes occurring during ART interruption or after ART resumption, and current pVL/CD4 count was examined in the European study compared to historical pVL/CD4 count in our analysis [17]. Moreover, both studies did not observe an

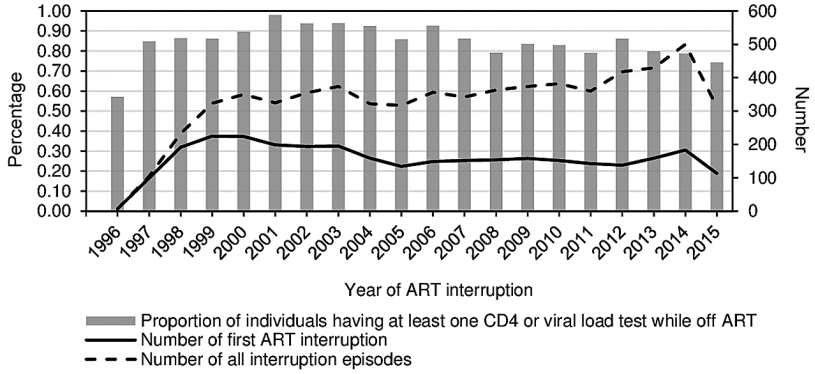

Figure 1. Longitudinal trends of antiretroviral therapy (ART) interruption and individuals' retention to human immunodeficiency virus (HIV) care (n = 3129). The study sample initiated ART between August 1996 and September of 2015 and was followed up till the end of 2015. Gray bars indicate proportion of individuals participating in HIV monitoring at least once after interrupting ART; solid line indicates total number of individuals interrupting ART the first time; dashed line indicates the total number of interruption episodes.

independent association between injection drug use and disease progression, suggesting that poorer ART treatment outcomes among PWID on ART observed by previous studies may be mediated by factors such as adherence [34]. However, about 12% of our analyzed sample had an unknown PWID status, and unknown PWID status was associated with increased hazard of progression to death. If PWID were more likely to be classified as missing, our estimates on PWID and death might be biased downward toward null.

The interpretation of factors associated with partial transitions may be limited and require evaluation in future studies. We found that receiving a modern regimen was associated with faster CD4 declines from ≥500 to 200–499 cells/μL after interruption. This might be partly explained by residual confounding associated with individuals' clinical disease status, as we observed that individuals interrupting a modern regimen had lower CD4 at ART initiation, indicating they might have more advanced disease compared to those interrupting a nonmodern

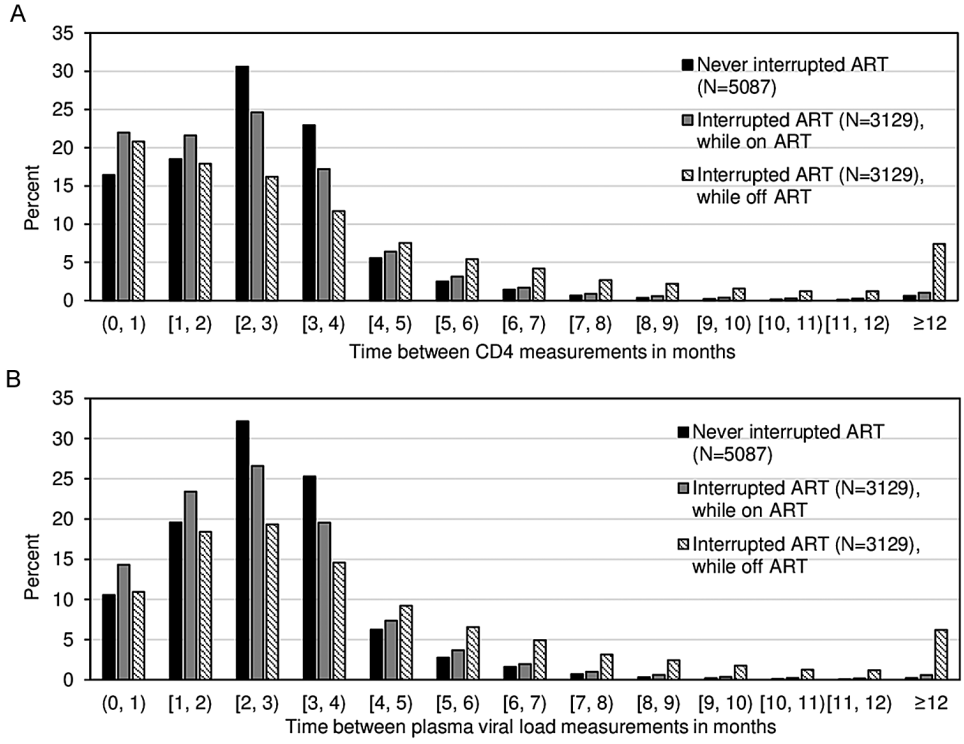

Figure 2. Distributions of time between CD4 measurements (*A*) and time between plasma viral load measurements (*B*) before and after all interruption episodes (1996–2015). Time between CD4 and plasma viral load tests was measured among those having at least 2 tests. Abbreviation: ART, antiretroviral therapy.

Table 2. Frequency of the Observed Disease State Transitions and the Estimated Average Annual Transition Probabilities During the First Antiretroviral Therapy Interruption Episode (N = 2212)[a]

CD4 Strata at time t, cells/μL	CD4 Strata at Time t+1, Cells/μL			
	≥500	200–499	<200	Death[b]
	Observed CD4 Transitions			
≥500	2073	446	19	13
200–499	0	5097	484	42
<200	0	0	2133	108
Model-Estimated Annual Transition Probabilities				
≥500	0.49	0.41	0.08	0.02
200–499	0	0.70	0.26	0.04
<200	0	0	0.81	0.19

[a]Transition probabilities were estimated using a 4-state continuous-time Markov model among individuals who had at least 2 observed disease status measurements (either CD4 measurements or death) during the first episode of antiretroviral therapy (ART) interruption.

[b]Off-ART deaths, classified as such if they occurred during off-ART period, or within 90 days of reinitiating ART.

regimen. We also observed a strong association between HCV^+ and progression from CD4 <200 cells/μL to death; although HCV^+ was highly positively correlated with PWID, the observed association remained large whether adjusting or not adjusting for PWID (aHR, 2.98 [95% CI, 1.66–5.32] vs 1.92 [95% CI, 1.15–3.19]). As our study considered all-cause mortality instead of AIDS-related death, the association may be partly attributable to HCV-related death. Nevertheless, a previous study found a lack of association between time-dependent HCV status and AIDS or death among individuals interrupting ART [17].

Our findings suggest a need to improve and maintain ART retention among an increasing number of PLHIV. Prior studies reported pervasive ART interruptions in both high- and low-resource settings [16, 18, 19, 35]. More than 38% of our study sample had interrupted ART by end of 2015. However, it was encouraging that the proportion of individuals interrupting ART within the first year of initiation decreased over time. The same trend was observed among PLHIV participating in a Canadian multisite cohort in BC, Quebec, and Ontario [19]. Moreover, 1 study among the same BC population reported a decline in durations of interruption, where interruption was defined as a gap of ≥30 days [16]. Despite improvements in individuals' retention to ART, we found the absolute number ART interruptions remained high, with an increase since 2012, corresponding to changes in ART initiation guidelines put

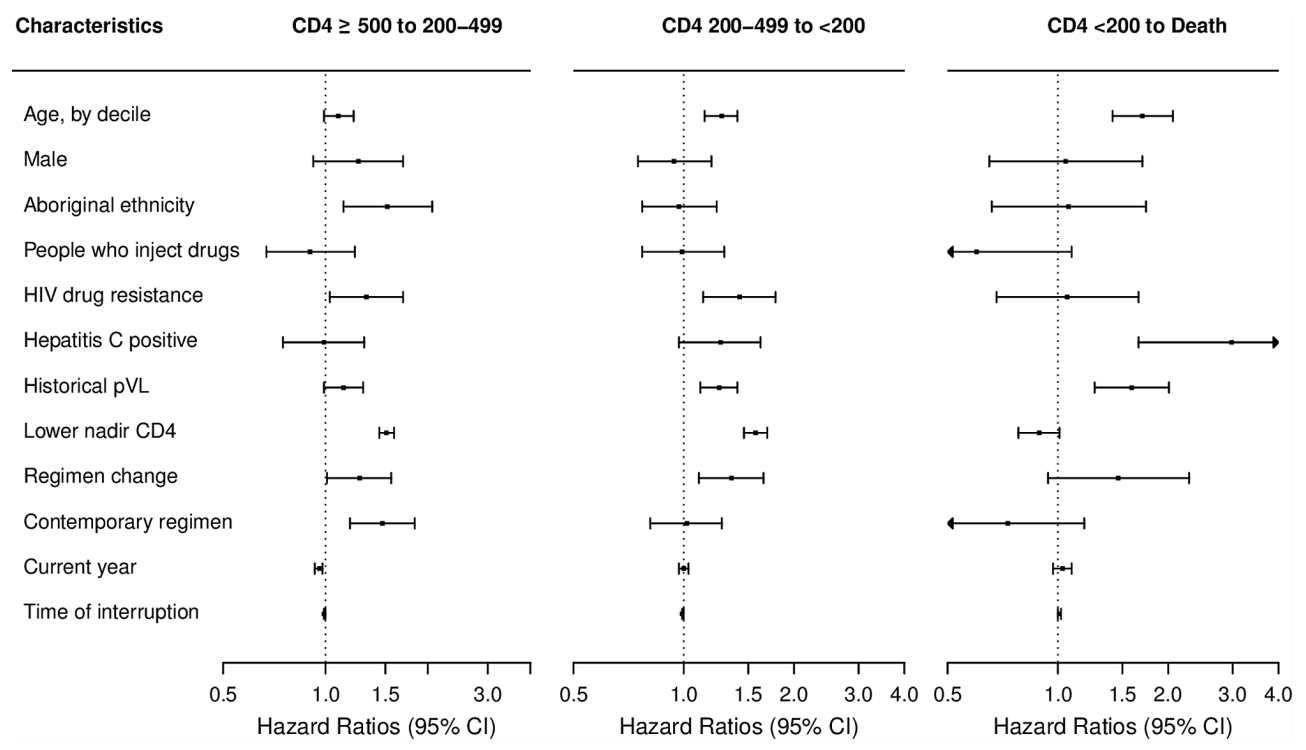

Figure 3. Adjusted hazard ratios associated with disease state transition intensities during the first antiretroviral therapy (ART) interruption episode among 2212 individuals. Four-state Markov models estimated the baseline transition intensities for each of the 5 possible transitions (CD4 count [cells/μL] ≥500 to 200–499; 200–499 to <200; ≥500 to death; 200–499 to death; and <200 to death); covariate effects of the 2 transitions (≥500 to death; and 200–499 to death) was not estimated due to the small observed transition number; results of the missing categories of the covariates were not shown. HIV drug resistance was considered as nonreversible, and determined as detecting mutations based on a modification of the 2014 International AIDS Society–USA mutation list. Historical plasma viral load (pVL) was measured as area under the pVL curve prior to ART interruption. Modern (contemporary) regimens included those based on lamivudine + tenofovir or emtricitabine + tenfovir combined with efavirenz, rilpivirine, or etravirine or a boosted protease inhibitor or integrase inhibitor regimen; small numbers of individuals could have received tipranavir, maraviroc, or enfuvirtide. Time of interruption was measured by time from ART initiation to interruption in months. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; lower nadir CD4, lowest CD4 cell count prior to antiretroviral therapy interruption, per 100 cells/μL decline; pVL, plasma viral load.

forward in 2012, offering ART to all PLHIV regardless of CD4 count [24].

In the context of relatively sparse evidence on effective and cost-effective interventions to improve ART persistence [9, 15, 18, 36, 37], evidence to inform development, optimization, and prioritization of interventions should be carefully examined. The prognostic factors identified in our study should be considered in parallel with risk factors for ART interruption/nonadherence to inform ART retention and reengagement interventions. For instance, strategies to prevent ART interruptions might focus on individuals with younger age and PWID, who had poorer ART adherence [16–19, 35]; however, interventions to reengage individuals who already interrupted ART might prioritize those with increased risk of disease progression, including older individuals, and those with prior experience in switching ART regimens, higher historical pVL level, lower nadir CD4 count, and drug resistance.

The current study also reveals that individuals interrupting ART continue participation in CD4/pVL tests, suggesting that there may be barriers specific to ART retention, but not to HIV monitoring care. These barriers may include avoiding medication side effects and being suspicious of treatment effectiveness, which were identified in a systematic review [38] as well as among a selected cohort of PLHIV in BC [35]. Future studies on different barriers to ART retention and routine clinical care may provide more insights on improving ART continuation.

Finally, our model-based disease transition probability estimates while off ART provide important parameter inputs for mathematical models used to estimate HIV transmission dynamics and make resource allocation decisions. These estimates were lacking in the literature, and disease progression among ART-discontinuing PLHIV was often assumed to be identical to ART-naive untreated PLHIV [39, 40], which ignored potential effect of prior regimens.

Our study has several limitations. First, structured treatment interruptions existed before 2006 [7, 24] but could not be distinguished from patient-initiated interruptions, which should be considered when interpreting the trends of ART interruption and HIV care receipt patterns over time. Second, the determination of ART interruption relied on medication dispensation data along with a 90-day threshold and were thus measured with some unavoidable degree of misclassification. Regardless, our definition aimed to balance the trade-off between sensitivity and specificity, and would capture interruptions and/or very low adherence, which warrant attention. Third, our analysis on disease progression did not include individuals who were lost to follow-up or did not participate in CD4 tests while off ART, who might have different disease progression. We explicitly compared their characteristics and our study sample in Supplementary Table 3. Fourth, covariate effects could not be estimated for all transitions due to small numbers of certain observed transitions. Fifth, although we summarized associations between a number of covariates and disease progression, there is always potential for unmeasured confounding in observational studies. However, the residual confounding might be less critical in the case when identification of subgroups of high risk rather than causal inference was of particular interest. Finally, the study was conducted in a setting with universal free HIV care, so certain findings may not be applicable elsewhere.

To conclude, our findings provide population-level estimates of ART interruption patterns and prognostic factors of disease progression while off ART. These factors should be communicated with health providers and PLHIV, and be considered together with risk factors for interruption to inform ART retention strategies. Despite observed improvement over time, further efforts are needed to promote ART reengagement and may consider prioritizing individuals with older age, higher levels of historical pVL, and prior ART regimen change experience.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We acknowledge all BC Ministry of Health (BCMoH) and Vancouver Coastal Health (VCH) decision support staff involved in data access and procurement, including Miranda Compton (VCH), Theodora Consolacion (BC Centre for Disease Control [BC-CDC]), Monika Lindegger (BC-CDC), Al Cassidy (BCMoH), and Joleen Wright and Karen Luers (VCH). We also acknowledge Ciro Panessa, Nancy South, and Mark Gilbert for their contributions to the STOP HIV/AIDS study group. Finally, we acknowledge Kathy Lepik (BC Centre for Excellence in HIV/AIDS) for providing her clinical insights on the HIV antiretroviral drug dispensing practice in BC.

Financial support. This work was supported by the BC Ministry of Health–funded "Seek and Treat for Optimal Prevention of HIV & AIDS" pilot project; a grant from the National Institutes of Health (NIH)/National Institute on Drug Abuse (grant number R01-DA-041747); and by Genome Canada (142HIV), the Canadian Institutes of Health Research, Genome British Columbia, and Genome Quebec funding to P. R. H. and J. S. G. M. In addition, B. N. is supported by a Michael Smith Foundation for Health Research Scholar award.

Potential conflicts of interest. J. S. G. M. is supported with grants paid to his institution by the British Columbia Ministry of Health and by the NIH (R01-DA-036307). He has also received limited unrestricted funding, paid to his institution, from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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