A Multi-State Model Examining Patterns of Transitioning Among States of Engagement in Care in HIV-Positive Individuals Initiating Combination Antiretroviral Therapy

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Background: Common measures of engagement in care fail to acknowledge that infrequent follow-up may occur either intentionally among patients with sustained virologic suppression or unintentionally among patients with poor clinical outcomes.

Methods: Five states of HIV care were defined within the Canadian Observational Cohort Collaboration following combination antiretroviral therapy (cART) initiation: (1) ***guidelines*** HIV care [suppressed viral load (VL) and CD4 >200 cells per cubic millimeter, no gaps in cART >3 months, no gaps in CD4 or VL measurement >6 months], (2) ***successful*** care with ***decreased*** frequency of follow-up (as above except no gaps in CD4 or VL measurement >12 months), (3) ***suboptimal*** care (unsuppressed VL, CD4 <200 cells per cubic millimeter on 2 consecutive visits, ≥1 gap in cART >3 months, or ≥1 gap in CD4 or VL measurement >12 months), (4) ***loss to follow-up*** (no contact for 18 months), and (5) ***death***. Multi-state models were used to determine factors associated with transitioning among states.

Results: In total, 7810 participants were included. Younger age, female gender, Indigenous ethnicity, and people who have injected drugs were associated with increased likelihoods of transitioning from *guidelines* to *suboptimal* care and decreased likelihoods of transitioning from *suboptimal* to *guidelines* care. One-fifth of individuals in *successful, decreased follow-up* after cART initiation (mean sojourn time 0.72 years) were in suboptimal care in subsequent years.

Conclusions: Using routinely collected data, we have developed a flexible framework that characterizes patient transitions among states of HIV clinical care. We have demonstrated that multi-state models provide a useful approach to supplement "cascade of care" work.

Key Words: HIV, engagement in care, cascade of care, combination antiretroviral therapy, multi-state model

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INTRODUCTION

Regular HIV care is critical for the achievement and maintenance of virologic suppression. Failure to adhere to antiretroviral regimens can lead to resistance, viral breakthrough, clinical progression, and increased likelihood of HIV transmission.[1,2] The HIV "cascade of care" is a commonly used framework to quantify the proportion of patients engaged at each stage of HIV medical care, from initial diagnosis to virologic suppression.[3] This framework has several limitations. Notably, patient engagement is presumed to follow a linear trajectory through the various stages, failing to capture the clinical reality that individuals may move back and forth along the continuum or choose to minimize their engagement with care for various reasons, including being otherwise well.[4,5] A model is therefore required that integrates HIV clinical outcomes and frequency of follow-up in a manner that characterizes transitions through various states of care experienced by individuals throughout the course of their illness and differentiates patterns of engagement yielding poor clinical outcomes from those where patients may be clinically well despite infrequent contact with health care providers. Such an approach would facilitate identification of factors associated with suboptimal patterns of engagement and inform the design of interventions targeted to specific groups at risk of poor outcomes. The objectives of this analysis were to describe patterns of engagement in HIV care over time among individuals receiving combination antiretroviral therapy (cART) and to determine factors associated with transitions among different states of HIV care.

METHODS

Study Population

The Canadian Observational Cohort (CANOC) is a collaboration of 8 cohorts from British Columbia (BC), Quebec, and Ontario.[6] To be eligible, patients must be HIV-positive Canadian residents older than 18 years who initiated their first antiretroviral regimen composed of at least 3 agents after January 1, 2000 and have at least 1 measurement of HIV plasma viral load (VL) and CD4 cell count within 6 months before initiating cART. Demographic, laboratory, and clinical data of eligible patients were formatted in a standardized fashion at each study site, stripped of identifying information, and compiled at the Project Data Centre in Vancouver, BC. For most Ontario and Quebec participants, start and stop dates

of ARV regimens were abstracted from patient charts. For participants from Maple Leaf Medical Clinic in Ontario and participants from BC, start and stop dates were generated using actual prescription records from electronic medical and administrative data, respectively. All participating cohorts have received approval from their institutional ethics boards to contribute non-nominal patient-specific data to CANOC. To be included in this analysis, participants must have at least 1 full year of follow-up after initiation of cART.

States of Care

We developed a system to classify states of HIV care using routine data, such as laboratory tests and medication records. Each year of follow-up after the initial 12-month period following cART initiation was classified into 1 of 5 states of HIV care: (1) HIV care following ***guidelines*** (suppressed VL, CD4 >200 cells per cubic millimeter, no gaps in cART >3 months, and no gaps in CD4 or VL measurement >6 months), (2) ***successful*** care with ***decreased*** frequency of ***follow-up*** (as above except no gaps in CD4 or VL measurement >12 months), (3) ***suboptimal*** care (unsuppressed VL, CD4 <200 cells per cubic millimeter on 2 consecutive visits, 1 or more gaps in cART >3 months, or 1 or more gaps in VL or CD4 measurement >12 months), (4) ***loss to follow-up*** (LTF, no contact for 18 months), and (5) ***death***. These states differentiate individuals who infrequently access care but are otherwise well (state 2) from those who have poor laboratory or clinical outcomes (states 3, 4, and 5).

The frequencies of VL and CD4 count measurement were used as surrogates of access to HIV care,[7] with laboratory test results used to classify the clinical status of the patient. A threshold of 6 months between CD4 and VL measurements was chosen as a significant departure from the recommendations to monitor patients every 3 or 4 months.[8] Virologic suppression was defined as per United States

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Department of Health and Human Services guidelines,[9] where nonsustained increases in VL were not considered evidence of unsuppressed VL. A value of 200 cells per cubic millimeter for CD4 counts was chosen because the CDC definition for stage 3 HIV infection (AIDS) was based on this threshold[10] and because of its association with disease progression[11] and increased mortality.[12,13] A gap in treatment was defined to be 3 months or more to ensure administrative phenomena resulting from non-uniform prescription refill data were not counted as gaps, and because results from structured treatment interruption trials showed gaps in treatment of 3 months or less, it had no significant impact on future clinical outcomes.[14]

Each year of follow-up after cART initiation was classified according to the predominant state, that is, for each participant, the state in which he or she spent the greatest time during that year. We classified states of care for each 1 year timeframe rather than for each CD4 or VL measurement to eliminate the dependency of the state classification on time because this would have violated assumptions of multi-state models. The 1 year duration was selected to allow sufficient time for observation of gaps in access to care. States were censored in the last year of follow-up when partial years occurred because of the administrative end of the study period as there was insufficient information to determine the predominant state. Patients who died or were lost to follow-up were classified as such regardless of length of follow-up in the last year.

Explanatory Variables

Fixed covariates were used to examine associations with transitions among care states of demographic and clinical characteristics, including age, sex, ethnicity, HIV risk factors [men having sex with men, people who have injected drugs (PWID)], province, hepatitis C infection, CD4 count at cART initiation, initial third agents, AIDS defining illness at baseline, and calendar year of cART initiation. For the purposes of modeling, missing data were included using indicator variables for unknown race, risk factor, and hepatitis C status.

Statistical Methods

We compared characteristics among patients included and excluded from the analysis and among patients with different patterns of engagement in care with Wilcoxon rank sum tests for continuous variables and chi-square or Fisher exact tests, as appropriate for categorical variables.

We used multi-state time-homogeneous Markov modeling to identify factors associated with transitioning among care states after the first year of cART using the *msm* package in R.[15–17] These models assume that the sojourn time, that is, the time spent in a state on a single occasion, follows an exponential distribution and does not depend on previous states. Because of small numbers of events, we collapsed LTF and death into a single, absorbing state. We assumed that transitions between the *successful decreased follow-up* and *LTF/death* states went through the *suboptimal* state as too few individuals transitioned directly from *successful decreased follow-up* to *LTF/death*. The transition matrix then consisted of 8 possible transitions: state 1 to each state 2, 3, and 4/5; state 2 to states 1 and 3; state 3 to each state 1, 2, and 4/5; as shown in Figure S1, Supplemental Digital Content, http://links.lww.com/QAI/A852. For different values of key covariates, we estimated the mean sojourn times and the probabilities of moving to different states. Age, sex, ethnicity, and PWID were considered for inclusion in the multivariable model based on a priori knowledge.[4,18–20] As multi-state models estimate parameters for each transition by each covariate level, inclusion of additional covariates was dependent on model precision and fit. Goodness-of-fit model was assessed by comparing observed and expected numbers of transitions among states using a modified, Pearson-type χ^2 test.[17,21]

We conducted 2 sensitivity analyses. In the first, we included only participants from BC, to determine if the population-based data available for that province influenced the results. In the second, we omitted the criterion requiring a CD4 cell count above 200 cells per cubic millimeter. This analysis was conducted to acknowledge that some patients who initiate cART with low CD4 counts may not achieve this level of immune recovery despite good adherence to cART and regular follow-up with their HIV care provider.[22]

RESULTS

As of December 2012, data were available for 9694 CANOC participants. We excluded participants who died (n = 236) or were lost to follow-up (n = 237) within the first year of cART initiation, active participants who had less than 1 year of follow-up (n = 697), and participants with a VL <200 copies per millimeter on or before the date of cART initiation as possible non-antiretroviral naïve participants (n = 714). Of the 7810 included CANOC participants, 81% were male and the median age was 40 years (interquartile range: 33–46 years) (Table 1).

The median duration of follow-up was 5.0 years (interquartile range: 2.9–8.1 years). The number and rate of transitions between states are shown in Table S1, Supplemental Digital Content, http://links.lww.com/QAI/A852. Following the first year of cART therapy, 52% of the patients transitioned to *guidelines* care, 31% to *suboptimal*, 1.5% to *successful decreased* engagement, and 3.8% were LTF or died. Of the 2494 patients who transitioned to *suboptimal* care in the second year of cART, 76% had unsuppressed VL, and 22% had discordant virologic and immunologic responses with suppressed VL and CD4 <200 cells per cubic millimeter. Participants transitioning to *guidelines* care in the second year of cART were more likely to be male participants, men having sex with men, and have higher baseline CD4 counts than those transitioning to *suboptimal* care in that year (Table 2).

The estimated sojourn times were 5.17 years [95% (CI): 4.92 to 5.43], 0.72 years (95% CI: 0.66 to 0.78), and 2.72 years (95% CI: 2.61 to 2.83) for the *guidelines*, *successful decreased follow-up*, and *suboptimal* care states, respectively. The estimated probabilities of transitioning among states, according to the care state occupied in the second year of cART, are shown in Table 3. Although most participants who

TABLE 1. Baseline Demographic and Clinical Characteristics of Included and Excluded Participants

	Included (>12-mo Follow-up) (N = 7810)	Less Than 12-mo Follow-up (N = 697)	Died or Lost Within 12 mo (N = 473)	*P*
Year of cART initiation	2007 (2003–2009)	2012 (2012–2012)	2005 (2003–2008)	<0.0001
Province (%)				
Quebec	1595 (20)	182 (26)	100 (21)	<0.0001
Ontario	2475 (32)	138 (20)	95 (20)	
British Columbia	3740 (48)	377 (54)	278 (59)	
Age at cART initiation	40.0 (33.0–46.0)	39.0 (31.0–48.0)	42.0 (35.0–48.0)	<0.01
Male (%)	6333 (81)	589 (85)	386 (82)	0.08
Race (%)				
Caucasian	2305 (30)	104 (15)	65 (14)	<0.0001
Black/African/Caribbean	716 (9)	39 (6)	34 (7)	
Indigenous people	386 (5)	16 (2)	42 (9)	
Other	624 (8)	29 (4)	30 (6)	
Unknown	3779 (48)	509 (73)	302 (64)	
Risk factors (not mutually exclusive) (%)				
MSM	2999 (38)	275 (39)	120 (25)	0.0002
PWID	1792 (23)	103 (15)	126 (27)	<0.0001
Endemic country	671 (9)	42 (6)	35 (7)	0.14
Unknown	1240 (16)	143 (21)	135 (29)	
Hepatitis C positive (%)	1952 (25)	110 (16)	145 (31)	<0.0001
Unknown status	439 (6)	60 (9)	89 (19)	
Hepatitis B positive (%)	540 (7)	23 (3)	31 (7)	0.003
Unknown status	2113 (27)	237 (34)	202 (43)	
ADI at cART initiation (%)	1183 (15)	50 (7)	89 (19)	<0.0001
BL CD4 count (cells/mm^3)	217 (120–311)	350 (220–480)	150 (50–265)	<0.0001
>500 (%)	459 (6)	159 (23)	15 (3)	<0.0001
350–500 (%)	1069 (14)	200 (29)	50 (11)	
200–350 (%)	2802 (36)	186 (27)	121 (26)	
<200 (%)	3480 (45)	152 (22)	287 (61)	
BL VL ($\log_{10}$ copies/mL)	4.9 (4.4–5.1)	4.7 (4.3–5.2)	5.0 (4.5–5.2)	<0.0001
>5.0 (%)	3304 (42)	241 (35)	253 (53)	<0.0001
4.5–5.0 (%)	2206 (28)	186 (27)	97 (21)	
4.0–4.5 (%)	1316 (17)	169 (24)	82 (17)	
<4.0 (%)	984 (13)	101 (14)	41 (9)	
First cART regimen (%)				
PI-based	3846 (49)	284 (41)	255 (54)	<0.0001
NNRTI-based	3602 (46)	324 (46)	188 (40)	
Other	362 (5)	89 (13)	30 (6)	

Values are represented as median and interquartile range or frequency and percentage.
ADI, AIDS defining illness; MSM, men having sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

follow *guidelines* care during the second year of cART are likely to be in *guidelines* care in the years following, approximately one-fifth of those who are in the *successful decreased follow-up* state in the second year of cART are likely to be in *suboptimal* care in subsequent years. The probabilities of being in *suboptimal* care 1, 2, 5, and 10 years after the second year of cART are 70%, 51%, 27%, and 17%, respectively.

Estimated sojourn times and probabilities of moving among states from univariate models are presented in Table 4. Women spent a mean of 4.04 years in *guidelines* care with an estimated 48% probability of transitioning to *suboptimal* care. Men, however, spent a mean of 5.43 years in *guidelines* care with 42% probability of transitioning to *suboptimal* care. Similar results were observed between Indigenous and non-Indigenous participants (Table 4). Moreover, Indigenous participants spent 3.93 years on average in *suboptimal* care compared to 2.70 years for non-Indigenous participants. Similar results were observed for people who have injected drugs compared to those who have not injected drugs.

The multivariable multi-state model is presented in Table 5. Among patients in *guidelines* care, people who have injected drugs were more likely to transition at any given time to *suboptimal* care than those who have not injected drugs [hazard ratio (HR) = 1.87, 95% CI: 1.59 to

TABLE 2. Demographic and Clinical Characteristics at Baseline by State of First Transition After cART Initiation

	From cART Initiation to				
	Guidelines (1) (N = 4066)	Successful Decreased Follow-up (2) (N = 120)	Suboptimal (3) (N = 2494)	Lost or Died (4/5) (N = 292)	*P*
Age	40 (34–47)	39 (31–46)	39 (33–45)	39 (33–46)	<0.0001
Male (%)	3450 (85)	98 (82)	1855 (74)	222 (75)	<0.0001
Race (%)					
Caucasian	1265 (31)	37 (31)	783 (31)	69 (23)	<0.0001
Black/African/Caribbean	379 (9)	15 (13)	248 (10)	30 (10)	
Indigenous people	117 (3)	≤6 (≤7)	219 (9)	18 (6)	
Other	338 (8)	≤6 (≤7)	192 (8)	21 (7)	
Missing	1967 (48)	54 (45)	1052 (42)	159 (54)	
Risk factors (not hierarchical) (%)					
MSM	1782 (44)	49 (41)	775 (31)	81 (27)	<0.0001
PWID	647 (16)	15 (13)	908 (36)	84 (28)	<0.0001
Endemic country	361 (9)	17 (14)	209 (8)	39 (13)	0.0006
Heterosexual contact	1070 (26)	42 (35)	835 (33)	61 (21)	<0.0001
Province (%)					
Quebec	865 (21)	40 (33)	451 (18)	69 (23)	<0.0001
Ontario	1330 (33)	61 (51)	728 (29)	99 (33)	
British Columbia	1871 (46)	19 (16)	1315 (53)	129 (43)	
Hepatitis C positive (%)	732 (18)	19 (16)	954 (38)	89 (30)	<0.0001
Hepatitis B positive (%)	276 (7)	8 (7)	190 (8)	24 (8)	0.09
Year of cART initiation	2007 (2004–2009)	2007 (2005–2009)	2005 (2002–2008)	2005 (2002–2007)	<0.0001
Baseline CD4 count (cells/mm^3)	230 (150–310)	230 (136–310)	157 (60–269)	190 (90–270)	<0.0001
Baseline CD4 < 200 (%)	1570 (39)	45 (38)	1505 (60)	158 (53)	<0.0001
VL ($\log_{10}$ copies/mL)	4.9 (4.4–5.1)	4.7 (4.2–5.0)	4.9 (4.5–5.2)	4.9 (4.4–5.1)	<0.0001
First cART regimen (%)					
PI-based	2004 (49)	73 (61)	1000 (40)	126 (42)	<0.0001
NNRTI-based	1912 (47)	43 (36)	1372 (55)	156 (53)	
Other	150 (4)	4 (3)	122 (5)	15 (5)	
AIDS defining illness at baseline	517 (13)	12 (10)	491 (20)	66 (23)	<0.0001

Values are represented as median and interquartile range or frequency and percentage. 1, guidelines care; 2, successful decreased follow-up; 3, suboptimal care; 4/5, lost to follow-up and death.

cART, combination antiretroviral therapy; MSM, men having sex with men; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PWID, people who have injected drugs; VL, viral load.

2.21], those who were older were less likely to transition to *suboptimal* care (HR = 0.86 per 10 years, 95% CI: 0.78 to 0.95) or *successful decrease follow-up* care (HR = 0.74 per 10 years, 95% CI: 0.64 to 0.85) than younger individuals, and male patients were less likely than female patients (HR = 0.78, 95% CI: 0.64 to 0.94) to transition to *suboptimal* care from *guidelines* care. Among patients in *suboptimal* care, male patients were more likely to transition at any given time to *guidelines* care than were female patients (HR = 1.29, 95% CI: 1.14 to 1.46), older patients were more likely than younger individuals to transition to *guidelines* care (HR = 1.08 per 10 years, 95% CI: 1.03 to 1.14), people who have injected drugs were less likely than people who have not injected drugs to transition to *guidelines* care (HR = 0.67, 95% CI: 0.60 to 0.75), and people of Indigenous ethnicity were less likely to transition to *guidelines* care from *suboptimal* care (HR = 0.70, 95% CI: 0.56 to 0.89) than individuals not of Indigenous ethnicity.

In a sensitivity analysis where *guidelines* state did not require CD4 cell count >200 cells per cubic millimeter, the clinical inference from the multivariable model remained similar to that of the main model, with the exception that Indigenous individuals were no longer less likely to transition from *suboptimal* to *guidelines* care (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/A852).

DISCUSSION

In this study of antiretroviral-naive HIV-positive individuals initiating cART since 2000, younger age, female gender, PWID, and Indigenous ethnicity were associated with increased probabilities of transitioning from care meeting *guidelines* to *suboptimal* care and reduced likelihood of transitioning from *suboptimal* care to care meeting *guidelines*. Participants who started in care meeting *guidelines* tended to be in this care state in subsequent years while participants who started in *suboptimal* care gradually transitioned to care meeting *guidelines* over time. One-fifth of participants starting in *successful decreased follow-up* were projected to be in *suboptimal* care 1, 2, 5, and 10 years later, suggesting

TABLE 3. Estimated Probabilities of Transitions to Care States According to Initial Care State in Second Year of cART and Number of Years Following

	State After an Additional Period of Time			
State in Second Year of cART	Guidelines	Successful Decreased	Suboptimal	LTF/ Death
1 year				
Guidelines	0.86	0.04	0.08	0.02
Successful decreased	0.55	0.18	0.25	0.01
Suboptimal	0.24	0.02	0.70	0.04
2 years				
Guidelines	0.78	0.04	0.14	0.04
Successful decreased	0.63	0.06	0.27	0.04
Suboptimal	0.38	0.02	0.51	0.08
5 years				
Guidelines	0.66	0.04	0.20	0.10
Successful decreased	0.63	0.03	0.23	0.11
Suboptimal	0.53	0.03	0.28	0.16
10 years				
Guidelines	0.57	0.03	0.20	0.20
Successful decreased	0.56	0.03	0.20	0.21
Suboptimal	0.52	0.03	0.19	0.26

that interventions to re-engage individuals at high risk of transitioning to *suboptimal* care are required.

To our knowledge, this is the first study to use multi-state models to describe associations of patient characteristics with bidirectional transitions among states of HIV care engagement over time, as recently suggested by Powers and Miller.[23] There have been a number of studies examining associations between patient characteristics and the HIV "cascade of care" and retention.[4,18–20] Our findings were similar to those of Burchell et al,[18] who found that younger individuals, women, Indigenous people, and people who have injected drugs had lower continuous engagement in care, ART use, and VL suppression. A similar study of HIV-positive individuals in care in North America between 2000 and 2008 also reported that younger individuals and people who have injected drugs were at greater risk of incomplete care; however, women were more likely to be engaged in complete care.[4]

Our work has several important clinical implications. Notably, our findings that women and people who have injected drugs were more likely to transition to *suboptimal* care following the first year of antiretroviral therapy highlight subgroups of vulnerable individuals for whom interventions to maximize successful engagement in care are warranted. Although further research is required to characterize the reasons these subgroups of individuals transition to *suboptimal* care shortly after initiating antiretroviral therapy, possible interventions could include enhanced integration of addiction management into HIV primary care, peer patient navigators, and assistance with costs associated with child care and transportation to appointments.

Using the multi-state model framework, we were also able to estimate the time spent in each care state and the probabilities of transitioning among states according to patient characteristics. These estimates are useful for the design of interventions to enhance engagement in care. Further strengths of the multi-state framework include flexibility in the definitions of both states and trajectories of transitions among states.[24] For example, patients can be assumed to transition through *suboptimal* care before being lost to follow-up, as per physician experience, or state definitions can exclude CD4 criterion, as in our sensitivity analysis. Multi-state models also allow for censoring of the state itself, when the patient is known to be alive but there is insufficient information available to classify the individuals' care state, as was done in our analysis.

There are some limitations to multi-state models. First, a modest number of associations could be evaluated in a multivariable model, as coefficients for each covariate were estimated for each transition, and the power of multi-state models is related to the number of observed transitions. Second, the "memoryless" property that the future state depends only on the current state and time[17] does not allow the incorporation of previous, clinically informative CD4 cell counts in the model. Third, we assumed time homogeneity in our models. To ensure that the definitions of states did not depend on time, we classified participants within each year of follow-up, according to the state they were in for the greatest period during that year. This "predominant" care state was chosen over the first or last state held within the year because it was felt to be more representative of the clinical care received by the individual. Future work could explore the use of hidden continuous-time Markov models to address possible misclassification of the states.[24] Despite these limitations, we believe the approach of examining transitions among states is useful. Multi-state models have been used in disease progression modeling of HIV.[25–27]

Strengths of our study include its large sample size, universal health care setting, homogeneity of participants with regard to era of antiretroviral therapy exposure and diversity of participants regarding geographic area, HIV risk factor, age, and gender. A limitation of our study was the large amount of missing data on ethnicity and HIV risk factor and lack of data on socioeconomic status, adherence, antiretroviral drug coverage, and injection drug use over time. Furthermore, we were unable to distinguish CD4 and VL measurements ordered as part of routine clinical care from those ordered because of hospitalizations, emergent care, or unscheduled visits with patients' regular physicians. Consequently, gaps in routine, structured care may be underestimated. We were also unable to distinguish whether decreases in the frequency of follow-up were because of the patient's or the physician's initiative. There were important differences among provinces regarding data collection and participant enrolment. The BC cohort is population-based, including all individuals prescribed cART since 2000. The cohorts from Ontario and Quebec are clinic-based and are not necessarily representative of all HIV-positive individuals who initiated cART since 2000 in these provinces. Transfers between clinics are captured in 2 cohorts, BC and the Ontario HIV Treatment Network Cohort Study. Transfers from other cohorts are not captured or for individuals transferring out of province. LTF may therefore be overestimated. Deaths in BC were ascertained through monthly

TABLE 4. Estimated Sojourn Time (in Years) Spent in Each State and Probability of Moving to Other States in Next Year of Follow-up From Univariate Multistate Models by Level of Covariates

	Guidelines (1)				Successful (2)			Suboptimal (3)			
	Sojourn Time (yr)	Probability of Moving to State			Sojourn Time (yr)	Probability of Moving to State		Sojourn Time (yr)	Probability of Moving to State		
Covariate	Mean (95% CI)	2	3	4/5	Mean (95% CI)	1	3	Mean (95% CI)	1	2	4/5
Overall	5.17 (4.92 to 5.43)	0.48	0.43	0.09	0.72 (0.66 to 0.78)	0.75	0.25	2.72 (2.61 to 2.83)	0.79	0.06	0.15
Male	5.43 (5.14 to 5.73)	0.49	0.42	0.09	0.72 (0.66 to 0.80)	0.75	0.25	2.49 (2.38 to 2.61)	0.80	0.07	0.13
Female	4.04 (3.61 to 4.51)	0.44	0.48	0.07	0.68 (0.55 to 0.84)	0.76	0.24	3.44 (3.16 to 3.75)	0.76	0.04	0.20
Indigenous people	3.84 (2.98 to 4.95)	0.34	0.53	0.13	0.46 (0.26 to 0.83)	0.81	0.19	3.93 (3.38 to 4.58)	0.66	0.05	0.29
Non-Indigenous	5.15 (4.82 to 5.50)	0.47	0.44	0.09	0.71 (0.63 to 0.80)	0.77	0.23	2.70 (2.55 to 2.86)	0.85	0.04	0.11
Age 30	4.21 (3.92 to 4.52)	0.53	0.41	0.06	0.75 (0.66 to 0.85)	0.74	0.26	3.02 (2.85 to 3.20)	0.78	0.06	0.16
Age 50	6.19 (5.75 to 6.66)	0.43	0.45	0.12	0.66 (0.57 to 0.77)	0.78	0.22	2.38 (2.24 to 2.53)	0.80	0.06	0.14
PWID	4.11 (3.72 to 4.54)	0.31	0.60	0.09	0.69 (0.55 to 0.86)	0.78	0.22	3.49 (3.24 to 3.75)	0.75	0.04	0.21
Non-PWID	5.46 (5.14 to 5.80)	0.51	0.40	0.09	0.73 (0.66 to 0.81)	0.73	0.27	2.37 (2.24 to 2.50)	0.82	0.06	0.11
Province											
BC	6.40 (5.94 to 6.89)	0.28	0.62	0.10	0.60 (0.50 to 0.72)	0.73	0.27	2.93 (2.77 to 3.10)	0.79	0.03	0.18
Ontario	4.56 (4.18 to 4.97)	0.60	0.31	0.09	0.71 (0.63 to 0.82)	0.81	0.19	2.67 (2.47 to 2.88)	0.80	0.08	0.12
Quebec	4.09 (3.70 to 4.53)	0.62	0.31	0.07	0.75 (0.64 to 0.88)	0.66	0.34	2.23 (2.04 to 2.45)	0.76	0.13	0.11
cART initiation											
2000	4.97 (4.59 to 5.39)	0.42	0.47	0.11	0.68 (0.59 to 0.79)	0.74	0.26	3.05 (2.85 to 3.25)	0.73	0.05	0.21
2004	5.18 (4.93 to 5.45)	0.48	0.43	0.09	0.72 (0.66 to 0.79)	0.75	0.25	2.65 (2.54 to 2.76)	0.80	0.06	0.14
2008	5.32 (4.81 to 5.87)	0.54	0.38	0.07	0.76 (0.63 to 0.91)	0.76	0.24	2.22 (2.04 to 2.41)	0.84	0.07	0.09
Baseline CD4 (cells/mm^3)											
<200	5.22 (4.87 to 5.59)	0.49	0.42	0.09	0.71 (0.63 to 0.80)	0.77	0.23	2.75 (2.61 to 2.90)	0.80	0.04	0.16
200–349	5.22 (4.82 to 5.65)	0.44	0.46	0.10	0.76 (0.65 to 0.88)	0.76	0.24	2.39 (2.21 to 2.58)	0.79	0.08	0.13
350–500	5.01 (4.27 to 5.88)	0.57	0.38	0.05	0.64 (0.49 to 0.83)	0.66	0.34	2.94 (2.56 to 3.38)	0.72	0.14	0.14
>500	4.04 (3.02 to 5.39)	0.48	0.42	0.09	0.57 (0.32 to 1.05)	0.78	0.22	4.01 (3.27 to 4.91)	0.78	0.02	0.20

1, Guidelines care; 2, successful care with decreased follow-up; 3, suboptimal care; 4/5, combined lost to follow-up and death.
BC, British Columbia; cART, combination antiretroviral therapy; CI, confidence interval; PWID, people who have injected drugs.

linkage with the BC Vital Statistics Database, whereas deaths in Ontario were passively reported to individual clinics and may be undercounted. However, a sensitivity analysis that included only participants from BC yielded similar results (data not shown). Generalizability of our findings is limited to patients receiving care in a universal health care setting and to patients who remained engaged in care for at least 1 year. Finally, because our cohort included only HIV-positive individuals who have initiated cART, we were not able to address factors earlier in the "treatment cascade" associated with HIV testing and initial engagement in HIV care.

TABLE 5. Estimated Hazard Ratios From a Multivariable Multistate Model

Transitions	Age (per 10 yrs), HR (95% CI)	Male, HR (95% CI)	Indigenous,* HR (95% CI)	PWID,† HR (95% CI)
Guidelines (1) to				
Successful (2)	0.74 (0.64 to 0.85)	0.87 (0.63 to 1.20)	0.73 (0.34 to 1.56)	0.77 (0.54 to 1.09)
Suboptimal (3)	0.86 (0.78 to 0.95)	0.78 (0.64 to 0.94)	1.18 (0.89 to 1.58)	1.87 (1.59 to 2.21)
LTF/death (4/5)	1.13 (1.00 to 1.27)	0.95 (0.68 to 1.32)	1.82 (1.09 to 3.02)	1.17 (0.86 to 1.60)
Successful (2) to				
Guidelines (1)	1.04 (0.90 to 1.22)	0.90 (0.62 to 1.31)	1.28 (0.61 to 2.69)	1.09 (0.73 to 1.65)
Suboptimal (3)	0.96 (0.73 to 1.25)	0.92 (0.57 to 1.50)	0.53 (0.11 to 2.48)	0.91 (0.51 to 1.63)
Suboptimal (3) to				
Guidelines (1)	1.08 (1.03 to 1.14)	1.29 (1.14 to 1.46)	0.70 (0.56 to 0.89)	0.67 (0.60 to 0.75)
Successful (2)	0.93 (0.68 to 1.27)	2.71 (0.86 to 8.55)	0.84 (0.16 to 4.46)	0.50 (0.22 to 1.13)
LTF/death (4/5)	1.08 (0.97 to 1.20)	0.88 (0.71 to 1.09)	1.72 (1.24 to 2.39)	1.15 (0.92 to 1.44)

1, Guidelines care; 2, successful care with decreased follow-up; 3, suboptimal care; 4/5, combined lost to follow-up and death.
*Reference: non-Indigenous; indicator for unknown Indigenous ethnicity not shown.
†Reference: non-PWID; indicator for unknown PWID status not shown.
CI, confidence interval; HR, hazard ratio; LTF, lost to follow-up; PWID, people who have injected drugs.

In conclusion, we have developed a flexible framework and model that characterizes patient transitions among states of HIV clinical care. Our work provides evidence that patterns of engagement and adherence are often established within the first year of cART. We also found that incomplete adherence to monitoring guidelines can be meaningfully separated into that occurring within the context of successful therapy and that occurring within the context of failing therapy, with very different management implications. These findings are relevant for policy, planning, and recommendations for care and highlight the unique information that can be gleaned from using multi-state models to evaluate engagement in HIV care.

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