

# Characterizing retention in HAART as a recurrent event process: Insights into 'cascade churn'

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## Background

- The individual and public health benefits of highly active antiretroviral therapy (HAART) rely on continuous lifelong treatment retention, as treatment interruptions have been associated with poorer patient outcomes, increased risk of HIV transmission and antiretroviral drug resistance.
- We aim to identify and characterize possible determinants of successive duration of HAART retention and non-retention over time ("HAART churn").

## Methods

- Using linked health administrative data, we considered all ARV-naïve individuals in British Columbia, Canada, initiating HAART between July 1996-June 2012.
- The dependent variable in our analysis was 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.
- 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.
- Proportional hazards frailty models were fitted to account for dependence in the length of individuals' repeated HAART episodes.
- We executed a parallel proportional hazards frailty model on the 'gap times' between treatment discontinuation and re-initiation.

## Results

### Duration of HAART retention (Table 1)

- 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.
- In contrast, off-HAART episodes lasted a median 1.9 months (1.2, 4.5), with little difference across successive episodes.

### Covariates associated with cascade churn (Table 2)

- Among individuals with multiple treatment attempts, successive HAART episodes tended to decrease in duration, while off-HAART episodes remained relatively constant.
- The duration of HAART episodes was greater for individuals initiating HAART in later years, while off-HAART episodes were shorter.
- 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.
- More frequent contact with medical specialists and receipt of HIV care were associated with longer HAART episodes and shorter off-HAART episodes.

### Trends in on-HAART and off-HAART episodes over time (Figure 1)

- The pattern of decreasing durations of on-HAART episodes was consistent across temporal phases of HAART initiation.
- Off-HAART episodes showed no distinct pattern in terms of durations of successive episodes across temporal phases.

**Table 1. Summary statistics on durations of HAART retention**

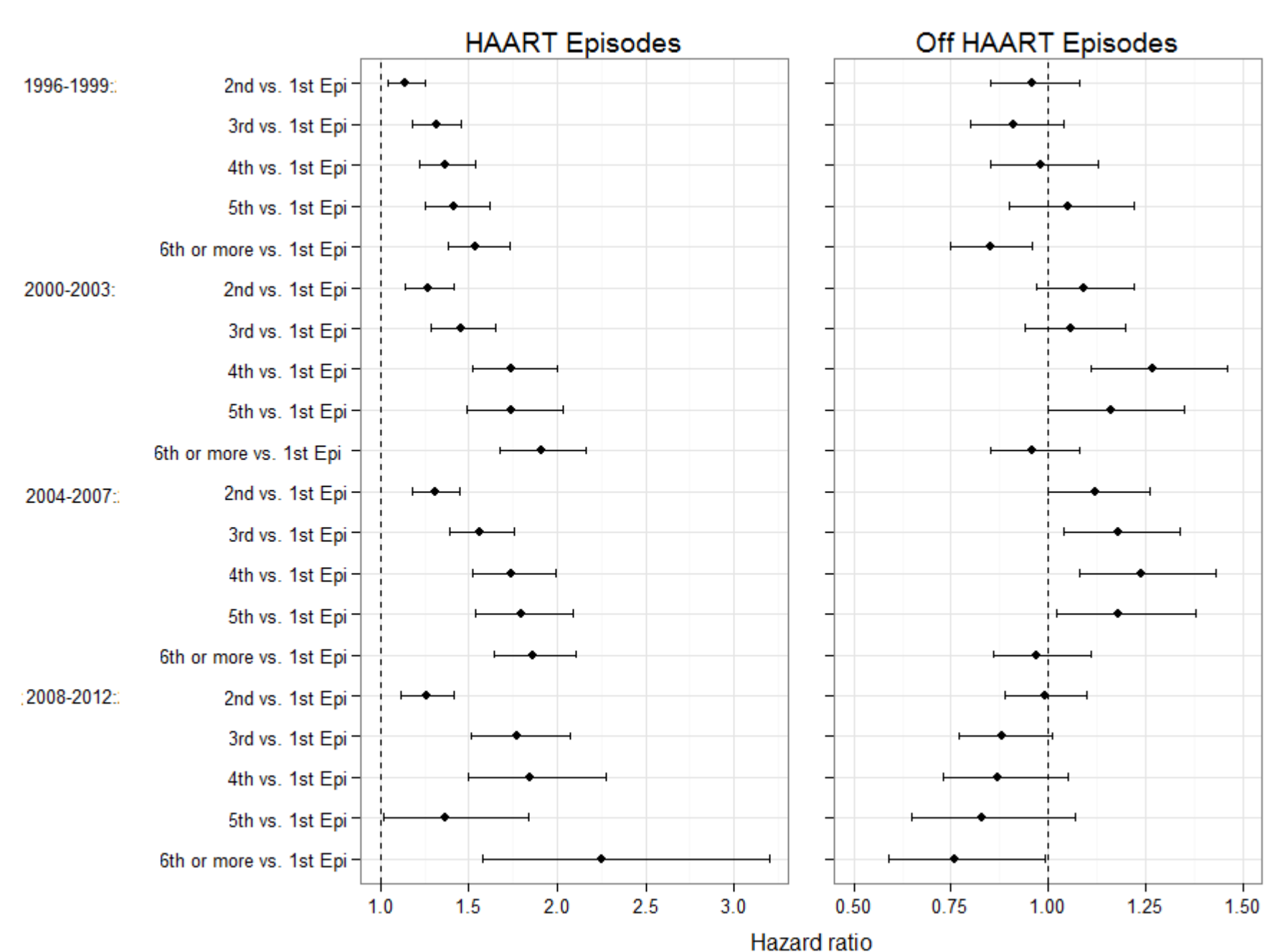
	N	Months in episode, Median (Q1, Q3)	12 months, N (%)	24 months, N (%)	Censored, N (%)
<b>HAART Episodes</b>					
1st Episode	6152	12.7 (3.7, 35.8)	3170 (51.5)	2144 (34.9)	1811 (29.4)
2nd Episode	3556	8.0 (2.8, 22.1)	1419 (39.9)	849 (23.9)	836 (23.5)
3rd Episode	2330	6.1 (2.0, 16.3)	761 (32.7)	399 (17.1)	406 (17.4)
4th Episode	1684	4.9 (2.0, 12.6)	443 (26.3)	224 (13.3)	266 (15.8)
5th Episode	1242	4.8 (2.0, 11.5)	299 (24.1)	129 (10.4)	194 (15.6)
>=6th Episode	3731	4.1 (2.0, 9.1)	686 (18.4)	278 (7.5)	557 (14.9)
All episodes	18695	6.8 (2.3, 19.5)	6778 (36.3)	4023 (21.5)	17 (25.2)
<b>Off HAART Episodes</b>					
1st Episode	4043	2.0 (1.2, 5.8)	669 (16.5)	388 (9.6)	487 (12.0)
2nd Episode	2585	1.9 (1.3, 5.3)	376 (14.5)	180 (7.0)	255 (9.9)
3rd Episode	1853	1.9 (1.3, 5.0)	233 (12.6)	117 (6.3)	168 (9.1)
4th Episode	1374	1.8 (1.2, 3.5)	128 (9.3)	61 (4.4)	132 (9.6)
5th Episode	1013	1.8 (1.3, 3.4)	80 (7.9)	29 (2.9)	97 (9.6)
>=6th Episode	3107	1.9 (1.3, 3.6)	208 (6.7)	99 (0.3)	290 (9.3)
All episodes	13975	1.9 (1.2, 4.5)	1694 (12.1)	874 (6.3)	1429 (10.2)

**Table 2. 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	ref			ref		
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
Age: 30-39	1.27	1.19	1.35	0.77	0.72	0.82
Age: 40-49	1.11	1.04	1.17	0.89	0.84	0.95
Age: ≥ 50	ref			ref		
MSM*	ref			ref		
PWID*	1.98	1.85	2.13	0.90	0.84	0.97
MSM/PWID*	1.72	1.56	1.89	0.91	0.83	1.00
Heterosexual*	1.43	1.31	1.57	1.12	1.02	1.23
Other/Unknown*	1.58	1.45	1.73	0.89	0.82	0.98
Year of HAART initiation:						
1996-1999*	ref			ref		
2000-2003*	0.90	0.84	0.97	1.01	0.95	1.08
2004-2007*	0.86	0.80	0.93	1.26	1.18	1.36
2008-2012*	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	ref			ref		
CD4: 200-349	1.10	1.05	1.16	0.91	0.85	0.96
CD4: 350-499	1.14	1.08	1.21	0.89	0.84	0.95
CD4≥500	1.22	1.15	1.30	0.86	0.81	0.92
Specialist visits, past 12m: 0	1.27	1.20	1.34	0.92	0.87	0.97
Specialist visits, past 12m: 1-3	1.16	1.10	1.22	0.92	0.87	0.97
Specialist visits, past 12m: >3	ref			ref		
HIV-related visit: 0 vs >0	1.18	1.12	1.24	0.94	0.89	0.99

\*indicates fixed (non-time-varying) covariates. HAART: highly active antiretroviral therapy; AHR: adjusted hazard ratio; 95% CI: 95% confidence interval; PWID: person who injects drugs; MSM: men who have sex with men

**Figure 1. Adjusted hazards of time to HAART and off-HAART episode discontinuation (95% Confidence Interval)**



## Conclusion

- We found extensive evidence of churn among those on HAART in a setting with universal access to treatment and care.
- Nonetheless, we observed increasing duration of HAART episodes (and diminishing durations off off-HAART episodes) over time.
- Clinical and public health strategies are urgently needed to improve HAART persistence, particularly among those at earlier stages of disease progression, the young, and people who inject drugs.

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