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Viral Suppression and Discontinuation Rates have Improved in HIV Patients with Modern Antiretroviral Therapies

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Abstract

Objective: Rates and determinants of first-line antiretroviral (ARV) discontinuation or change in prescribed regimen were assessed between old (pre-2006) and modern (post-2006) era stratified by dosing frequency [(once daily (QD) versus twice or more daily (BID+)].

Methods: A single-center retrospective cohort study was conducted. All adult HIV patients initiating ARVs from January 1995-November 2015 were included. Patients were stratified by old- or modern-era and by dosing frequency. The primary outcome was rate of ARV therapy discontinuation or change in initial regimen. The secondary outcome was reason for discontinuation.

Results: 1,127 patients were included from the old (n=621) and modern era (n=506). Modern-era patients were more likely to receive QD regimens (p<0.001) and had increased viral suppression at the last recorded testing than old-era patients (70.9% vs. 43.2%, p<0.001). Modern-era and QD patients had better adherence and treatment duration. Patients on integrase inhibitor (INSTI)- and NNRTI-based therapy had longer treatment durations and better ARV adherence. Risk factors for treatment switch or discontinuation included old-era therapy, IDU and PI+NRTI treatment. Older ages and immigrants were less likely to discontinue therapy. Common reasons for treatment discontinuation included changing treatments to improve regimen profile, gastrointestinal side effects, and neuropsychological issues.

Conclusion: In patients initiating first-line ARV, risk of discontinuation or regimen changes has diminished in the modern-era with QD, INSTI- or NNRTI-based regimens. More attention to high risk patients including IDU is advised in attempts to improve outcomes. These findings provide 'real world' support for current clinical practice guidelines.

Keywords: HIV; Antiretrovirals; Adherence; QD dosing

Introduction

Since July 1996, highly active antiretroviral treatments (HAART) has represented standard of care for HIV management [1-3]. HAART has substantially reduced disease progression to AIDS, opportunistic infections, hospitalizations, and death [2]. However, the proportion of those diagnosed with HIV initiating antiretroviral therapy (ARV) is far from ideal [4,5]. Further, of those patients that do initiate therapy, high pill burdens, frequent dosing, and difficult side effects may contribute to poor treatment adherence [6,7].

It is estimated that 15-38% of HIV patients are non-adherent [2,4,8]. Barriers to ARV adherence include issues with scheduling, ARV safety concerns, stigma, and family responsibilities [9]. Identified risk factors for treatment discontinuation include young age (<40 years), higher HIV viral levels, AIDS, depression, injection drug use, African American ethnicity, higher burden of HIV symptoms, and diminished CD4 T cell counts response with ARV therapy [10-13].

Frequent dosing regimens for old-era HAART were major impediments to adherence. The development of single-tablet regimens, beginning in October 2006 with the regulatory approval of Atripla™, marked an important milestone in HIV therapy. Approval of Raltegravir in 2007 [14], Stribild™ in 2012 [15] and Triumeq™ in 2014 [16], allowed for utilization of low pill count regimens with reduced dosing frequencies and fewer side effects. Despite these advances, poor drug adherence remains an issue. Furthermore, little is known regarding risk factors for discontinuation of single dose ARV. Since many contributing factors affect patient and physician decisions to discontinue ARV, it remains uncertain as to whether the single dose, modern-era regimens have resulted in improved adherence and reduced ARV discontinuation compared to more complex regimens of the past.

We evaluated ARV discontinuation rates in old and modern-era first-line HIV regimens. Specifically, once daily (QD) and twice or more daily (BID+) dosing regimens were evaluated. We also assessed risk factors for discontinuation of the first prescribed ARV regimen in QD recipients.

Methods

A single-center retrospective non-concurrent cohort study of adult HIV patients was conducted at The Ottawa Hospital Immunodeficiency Clinic in Ottawa, Canada. Institutional Review Boards/Ethics Committees at the study site approved the performed study procedures prior to study initiation (REB 2004-032).

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All treatment-naïve HIV positive patients initiating a first round of HAART from January 1995 to November 2015 were included assuming at least one month of medication was completed. Exclusion criteria included ARV post-exposure prophylaxis or atypical regimens (i.e., Fuzeon, hydrozyurea-based) or those with missing/anecdotal records. Patients were stratified by old and modern-era therapies, and by QD or BID+ dosing regimens. Old-era patients were defined as those initiating HAART before October 2006 and modern-era patients were those initiating HIV therapy after this date.

The primary outcome focused on rates of ARV discontinuation and reasons for treatment interruption or switch as a function of treatment era. Secondary outcomes focused on the influence of dosing frequencies on these outcomes. The clinic database contained information on patient demographics, HIV exposure risk factors, alcohol and drug abuse history, country of origin, laboratory measures, therapy initiation and discontinuation dates as well as treatment adherence information. Reasons for discontinuing HAART were collected (Appendix 1). Blood work including HIV RNA and CD4 T cell counts were recorded at baseline/start of treatment and at 3, 6, 9, 12 and at 6 month intervals thereafter. ARV classes included, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (INSTIs) and CCR5 antagonists [3].

Chi-Squared statistics were used for categorical variables, the T-test statistic for dates, and the Wilcoxon-Mann-Whitney test for laboratory measurements. Survival analysis methods were used to assess the risk of treatment discontinuation and HAART outcomes. Patients who died or discontinued therapy were treated as failure events while those continuing therapy were censored on the date of their most recent follow-up visit. Patients contributed person-time at risk for treatment discontinuation from the start of treatment until the time of discontinuation, last visit, death, or lost to follow-up. A sensitivity analysis was conducted where all lost to follow-up patients were considered to have discontinued treatment. Cox's proportional hazard model was used to calculate hazard ratios (HR) for the multivariate analysis using SAS® statistics software (SAS Institute, Cary, NC). Tied data were taken into account using Breslow's method. The proportional hazard assumption was confirmed with the Kaplan-Meier and the Cox's proportional hazard curve, and absence of interactions.

Results

A total of 1,127 patients receiving first-line HIV therapy were included in this analysis (Table 1). In both the old- and modern-era, the majority of patients were male (73%). By the later era the age distribution was older and more patients were non-White with increases in Black (28% to 36%) and Asian (1% to 4%) races indicating a change in patient demographics over time. More than 20% were HBV and/or HCV co-infected with a higher proportion of HIV mono-infection in the later era. Higher rates of IDU/crack cocaine use history were noted in the pre-2006 era ($p<0.001$); HIV risk factors differed by era ($p<0.001$) and baseline CD4 cell counts >200 cells/μL were more prevalent in the post-2006 era (67% vs. 56%, $p<0.001$).

Treatment regimens and adherence status were stratified by era (Table 2). QD regimens were infrequently prescribed in the old-era (8%) compared to the modern-era (75%). The most frequently prescribed ARV regimen in the older era consisted of a PI+NRTI (56%); changing to a NRTI+NNRTI-based regimen in the modern era (46%), with a difference in class of ARV drug regimens across eras ($p<0.001$). Forty-two percent of modern-era patients remained on the initially prescribed regimen at most recent visit compared to 3% during the older-era. Adherence to treatment regimen was improved in the modern era (91% vs 79%). Viral suppression surpassed 77% at last testing in the modern-era compared to 58% in the previous era.

Reasons for discontinuation stratified by treatment era and

	Old-Era* (n=621)		Modern-Era* (n=506)		Total (N=1127)		P-value**
	n***	%	n	%	N	%	
Gender							0.12
Male	466	75.0	352	69.6	818	72.6	
Female	154	24.8	153	30.2	307	27.2	
Transgender	1	0.2	1	0.2	2	0.2	
Age							<0.001
18-24 years	24	3.9	42	8.3	66	5.9	
25-34 years	199	32.0	126	24.9	325	28.8	
35-44 years	258	41.5	174	34.4	432	38.3	
45+ years	140	22.5	164	32.4	304	27.0	
Race (n=861)							<0.001
White	345	55.6	249	49.2	594	52.7	
Black	176	28.3	184	36.4	360	31.9	
Asian	8	1.3	20	4.0	28	2.5	
Aboriginal	15	2.4	8	1.6	23	2.0	
Hispanic	13	2.1	13	2.6	26	2.3	
Unknown	64	10.3	32	6.3	96	8.5	
Country of Birth							<0.001
Canada	209	33.7	238	47.0	447	39.7	
Immigrant	314	50.6	255	50.4	569	50.5	
Unknown	98	15.8	13	2.6	111	9.8	
Co-infection Status							0.005
HIV only	468	75.5	421	83.2	889	79.0	
HCV+	114	18.4	55	10.9	169	15.0	
HBV+	32	5.2	26	5.1	58	5.2	
HCV+/HBV+	6	1.0	4	0.8	10	0.9	
History of Substance Abuse	233	37.5	110	21.7	343	30.4	<0.001
HIV Risk Factors							<0.001
MSM	181	29.1	201	39.7	382	33.9	
IDU/Crack Cocaine	126	20.3	58	11.5	184	16.3	
Transfusions/ Surgery	32	5.2	30	5.9	62	5.5	
Origin from High Prevalence Area	115	18.5	72	14.2	187	16.6	
Tattoo/Piercings/ Prison	15	2.4	22	4.3	37	3.3	
Heterosexual sex	30	4.8	6	1.2	36	3.2	
Other risk factor	73	11.8	92	18.2	165	14.6	
Baseline RNA (n=941)							0.82
HIV RNA ≤ 100,000 copies/mL	334	72.5	346	71.8	680	72.1	
HIV RNA >100,000 copies/mL	127	27.5	136	28.2	263	27.9	
CD4 (n=994)							<0.0001
≤ 200 cells/μL	224	44.4	164	33.3	388	38.9	
>200 cells/μL	281	55.6	329	66.7	610	61.1	

HBV=Hepatitis B, HCV=Hepatitis C; IDU=Intravenous drug use; MSM=Men who have sex with men
*Old Era – Prior to October 2006; Modern-Era – after October 2006
**P-values calculated from the Chi-square statistic
***n's less than the total sample size reflect missing data

Table 1: Baseline characteristics of patients included for analysis.

	Old-Era* (n=621)		Modern-Era* (n=506)		Total (N=1127)		p-value
	n***	(%)	n	(%)	N	(%)	
Dosing Frequency							<0.0001
QD	52	8.4	379	74.9	431	38.2	
BID+	562	90.5	118	23.3	680	60.3	
Not recorded	7	1.1	9	1.8	16	1.4	
Drug Groups							<0.0001
NRTI+PI	348	56.0	146	28.9	494	43.8	
NRTI+NNRTI	135	21.7	235	46.4	370	32.8	
NRTI+INSTI	0	0.0	91	18.0	91	8.1	
Combination NRTI	69	11.1	17	3.4	86	7.6	
NNRTI+PI	36	5.8	1	0.2	37	3.3	
Others/CCR5+NRTI/PI+INSTI	14	2.3	5	1.0	19	1.7	
PI Monotherapy	16	2.6	3	0.6	19	1.7	
Not recorded	3	0.5	8	1.6	11	1	
Treatment Status							<0.0001
On original regimen at last assessment	20	3.2	214	42.3	234	20.8	
LTFU/death	50	8.1	27	5.3	77	6.8	
Changed initial ARV regimen	533	85.8	254	50.2	787	69.8	
Stopped ARV entirely	18	2.9	11	2.2	29	2.6	
Viral Load while on therapy (n=923)							<0.0001
Viral Suppression**	268	58.3	358	77.7	626	67.8	
Viral failure	192	41.7	103	22.4	295	32.0	

QD: Once Daily Regimen; BID+: Twice or More Daily, PI: Protease Inhibitors; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; INSTI: Integrase Inhibitors; CCR5: Antagonist-Containing Regimens; LTFU: Lost to Follow-Up
*Old Era – Prior to October 2006; Modern-Era – after October 2006
**VL<50 copies/mL (prior to 1998 assay sensitivity for suppression was <499 copies/mL)
***n's less than the total sample size reflect missing data

Table 2: Treatment and regimen status stratified by ARV era.

dosing frequency are presented in Table 3. Most reasons for change or discontinuing the first prescribed regimen were similar in proportion between QD and BID+ regimens, although gastrointestinal symptoms and metabolic concerns were higher in the BID+ group. Overall discontinuation rates of initially prescribed HAART were greater in the early (89%) compared to the later era (53%, p<0.001). The most common reasons for treatment discontinuation/change in the entire cohort included intent to improve dosing regimens (17%), gastrointestinal side effects (9%), and neuropsychological side effects (7%). There were several differences observed between old-era and modern-era therapy discontinuation reasons including gastrointestinal disorders (p<0.001), viral breakthrough (p<0.001), metabolic disorder (p<0.001), and end of clinic study (p=0.007). When stratified by dosing frequency, there was a difference between total discontinuation rate between QD and BID+ regimens (p<0.001). There were differences between QD and BID+ treatment regimen discontinuation for reasons of gastrointestinal side effects (p<0.001), metabolic concerns (p<0.001), end of clinical study (p=0.04), viral breakthrough (p=0.003) and abnormal hematology results (p=0.04).

Adherence was improved in the QD group (91%) compared to the BID+ strata (79%) (p<0.001) (Table 4). Viral suppression was achieved in a greater frequency with QD dosing (76%) compared to BID+ (62%). Viral failure was lower among patients with QD dosing (24%) compared to BID+ (38%) (p<0.001); across both groups.

Survival analysis

The median treatment durations were shorter during the old-era [21 months (18-24) versus 37 (34-46), log-rank p<0.0001] and with BID+ dosing [24 months (20-26) versus 37 (30-48), log-rank p<0.0001] (Figure 1). Across ARV regimens, INSTI+NRTI [36 months (34-53)] and NNRTI + NRTI [35 months (29-46)] regimen recipients were observed to have longer treatment durations compared to PI + NRTI-containing regimen recipients [21months (18-26), log-rank p<0.0001]. Crude analyses of several risk factors associated with HIV exposure (MSM, IDU, origin from a high-prevalence area) did not indicate a statistical difference in the likelihood of remaining on the initially prescribed ARV regimen (Log rank χ^2=3.99 (2 d.f.); p=0.14), although the median duration of initial therapy was 17 months in IDU compared to 26 and 27 months in MSM and those having HIV originating from a high prevalence region, respectively.

Correlates of time to treatment discontinuation

In unadjusted analyses of time to treatment discontinuation, patients starting therapy in the old-era had an increased risk of discontinuing first line ARV compared with those starting after October 2006 [HR 1.5 (95% CI: 1.29, 1.74)], this attenuated but remained significant after adjusting for confounders [HR 1.35 (95% CI: 1.11, 1.63)] (Table 5). The risk of ARV discontinuation was also higher in those on BID+ regimens in unadjusted analyses (HR 1.4), although this effect was attenuated after multivariable adjustment and was not statistically significant at conventional levels (HR 1.04, (95% CI: 0.85,1.27), p=0.72) in the final model. Patients initiating INSTI+NRTI and NNRTI+NRTI regimens were less likely to discontinue first line therapy compared to patients on PI+NRTI regimens in unadjusted models. The effect of PI+NRTI (HR 1.19, (95% CI: 1.00-1.42) remained significant after adjustment for a series of covariates including age, sex, risk factors, viral co-infection, baseline laboratory data, race and immigrant status. The final multivariable model indicated that IDU/crack cocaine usage was associated with a 1.30 HR for discontinuation/switch (95% CI:

	Old-Era* (n=621)		Modern-Era* (n=506)		p-value	BID+ (n=680)**		QD (n=431)**		p-value
	n	%	n	%		n	%	n	%	
Total Discontinued/Changed from First Prescribed	553	(89.0)	269	(53.2)	<0.001	581	(85.4)	232	(53.8)	<0.001
Reasons for Discontinuation										
Attempt to Improve Regimen	105	(16.9)	86	(17.0)	0.969	119	(17.5)	72	(16.7)	0.180
Gastrointestinal Complication	76	(12.2)	28	(5.5)	<0.001	87	(12.8)	17	(3.9)	<0.001
Neuropsychological Disorder	51	(8.2)	33	(6.5)	0.282	48	(7.1)	34	(7.9)	0.650
End of Clinical Trial	40	(6.4)	15	(3.0)	0.007	42	(6.2)	12	(2.8)	0.037
HIV Viral Breakthrough	39	(6.3)	6	(1.2)	<0.001	38	(5.6)	7	(1.6)	0.003
Adherence / Social Issue	38	(6.1)	19	(3.8)	0.072	37	(5.4)	19	(4.4)	0.728
Metabolic Complication	37	(6.0)	6	(1.2)	<0.001	38	(5.6)	4	(0.9)	<0.001
Drug Interaction	22	(3.5)	16	(3.2)	0.725	22	(3.2)	14	(3.2)	0.125
Financial Constraints	20	(3.2)	15	(3.0)	0.805	21	(3.1)	14	(3.2)	0.762
Pregnancy Related	16	(2.6)	7	(1.4)	0.159	16	(2.4)	6	(1.4)	0.265
Liver Toxicity	14	(2.3)	5	(1.0)	0.101	13	(1.9)	6	(1.4)	0.702
Dermatology Complication	14	(2.3)	4	(0.8)	0.051	14	(2.1)	4	(0.9)	0.300
Hematology Complication	12	(1.9)	2	(0.4)	0.020	13	(1.9)	1	(0.2)	0.043
ETOH / Substance Abuse	10	(1.6)	3	(0.6)	0.112	11	(1.6)	2	(0.5)	0.195
Fatigue	8	(1.3)	2	(0.4)	0.112	9	(1.3)	1	(0.2)	0.156
Kidney Complications	5	(0.8)	7	(1.4)	0.347	6	(0.9)	6	(1.4)	0.662
Other / Not Captured	46	(7.4)	15	(3.0)	<0.001	47	(6.9)	13	(3.0)	0.003

*Old Era – Prior to October 2006; Modern-Era – after October 2006.
**16 patients (1.4%) did not have dosing frequency recorded and were excluded

Table 3: Reported reasons for discontinuation of initially prescribed ARV regimen**

	BID+ (n=680)		QD (n=431)		Total (n=1111)		p-value
	n***	%	n	%	N	%	
Adherence Status							<0.001
Adherent	538	79.1	390	90.5	928	83.5	
Non-adherent	138	20.3	40	9.3	178	16.0	
Not reported	4	0.6	1	0.2	5	0.5	
Viral Load (n=914)**							<0.001
Viral Suppression	319	61.7	302	76.1	621	67.9	
Viral Failure	198	38.3	95	23.9	293	32.1	

*16 patients (1.4%) did not have dosing frequency recorded and were excluded
**defined as <40 copies/mL (prior to 1998 assay sensitivity for suppression was <499 copies/mL)
***n's less than the total sample size reflect missing data

Table 4: Adherence to treatment stratified by dosing frequency*.

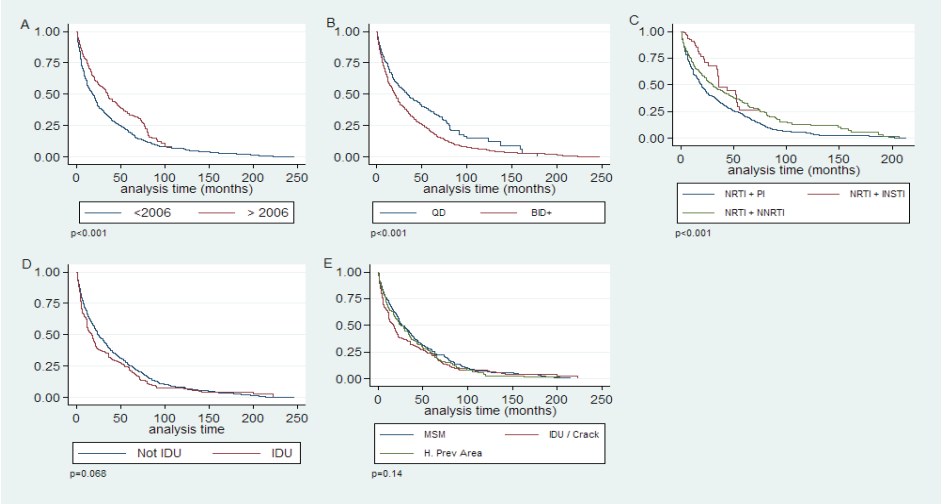
1.00-1.68, p=0.046) compared to other risk factors. IDU users were less likely to remain on their initially prescribed regimen (5.2% vs 11.4%, p=0.007) or switch in an attempt to improve their regimen (14.7% vs. 28.8%, p=0.002) compared to MSM. Immigrants were less likely to discontinue treatment compared to Canadian-born. Those greater than 35 years of age were less likely to discontinue therapy compared to those aged 18-24 years.

Sensitivity analysis

A sensitivity analysis was conducted with all lost to follow-up patients (n=71) coded as discontinuing treatment rather than being censored. The same patterns of discontinuation were observed. The effects for era of starting therapy, dosing frequency, regimen type were diminished but remained statistically significant and clinically relevant. The median time to when half of the patients discontinued treatment was shorter in the old-era group with a HR of 1.5 (p<0.001). Compared with OD regimens, more frequently dosed regimens were associated with a HR of 1.4 (p<0.001). PI+NRTI regimens were associated with a HR of 1.3 (p<0.001) compared to other regimes.

Discussion

Our analysis identified that prescription of modern regimens has resulted in increased HIV viral suppression and lower HIV viral failure rates. Patients on QD regimens were significantly more adherent. Our observations indicate that ARV side effects and regimen improvements remain major reasons driving patient discontinuation of first-round therapy in the modern HAART era and are consistent with the findings of other groups [17-19]. The most common reasons for treatment switch or discontinuation were consistent over time and included change in regimen with the aim of improving the ARV regimen, gastrointestinal side effects, or neuropsychological complications. These results suggest that treatment discontinuation in the modern-era of ARV and challenges to drug adherence remain key clinical issues [20-23]. Nevertheless, the benefits of less frequent treatment dosing was demonstrated in this analysis as QD patients were more adherent than BID+ patients, were more likely to achieve viral suppression, and less likely to discontinue or switch their initially prescribed regimen due to viral failure [18,24-29]. These findings are highly relevant to informing clinicians in their attempts to retain patients on effective antiretroviral



A) starting before or after Oct. 2006; B) QD (once daily) and BID+ twice or more daily dosing frequencies; C) on different regimen types (NRTI + either INSTI, NNRTI or PI); D) for histories of IDU, crack vs. other risk factors; E) different HIV risk factors (MSM, IDU,HIV endemic/high prevalence region)
The p-value is included below each panel.

Figure 1: Kaplan-Meier estimates for probability of remaining on first prescribed ARV treatment.

	Unadjusted HR	95% CI	p-value	Adjusted HR	95% CI	p-value
Era of therapy						
Old-era	1.50	(1.29-1.74)	<0.001	1.35	(1.11-1.63)	<0.001
Dosing frequency						
BID+	1.43	(1.23-1.67)	<0.001	1.04	(0.85-1.27)	0.72
Regimen type						
NNRTI+NRTI	0.76	(0.65-0.89)	<0.001	0.94	(0.77-1.15)	0.55
PI+NRTI	1.33	(1.16-1.52)	<0.001	1.19	(1.00-1.42)	0.048
Risk factors						
MSM	0.94	(0.82-1.09)	0.41	1.21	(0.96-1.52)	0.11
IVDU/crack	1.13	(0.92-1.39)	0.25	1.30	(1.00-1.68)	0.046
Transfusion, surgery	1.00	(0.74-1.35)	0.98			
High prevalence region	1.05	(0.88-1.26)	0.58	1.29	(1.01-1.66)	0.045
Tattoo/Piercings/Prison	0.88	(0.60-1.30)	0.52			
Heterosexual sex	1.03	(0.85-1.24)	0.80			
Other/multiple risk factors	0.82	(0.62-1.09)	0.18			
Age and Gender						
Gender (female)	0.96	(0.82-1.12)	0.60	0.92	(0.77-1.10)	0.359
Age 25-34y	1.17	(1.01-1.36)	0.04	0.84	(0.62-1.15)	0.277
Age 35-44 y	0.83	(0.72-0.95)	0.01	0.71	(0.52-0.96)	0.026
Age 45+	1.03	(0.88-1.21)	0.72	0.82	(0.60-1.13)	0.228
Viral co-infection						
HIV/HCV+	1.02	(0.85-1.24)	0.81			
HIV/HBV+	1.10	(0.80-1.51)	0.55			
HIV/HBV/HCV+	1.11	(0.58-.14)	0.75			
Baseline viral load (>100,000 cp/mL)	1.07	(0.91-1.27)	0.41			
Baseline CD4 (>200 cells/µL)	0.87	(0.75-1.01)	0.07			
Race/ethnicity (ref. White)						
Black	1.04	(0.90-1.20)	0.62	0.96	(0.71-1.29)	0.769
Asian	0.84	(0.52-1.36)	0.49	0.75	(0.44-1.27)	0.280
Aboriginal	0.81	(0.49-1.36)	0.43	0.98	(0.61-1.58)	0.946
Hispanic	1.12	(0.73-1.73)	0.61	0.88	(0.53-1.46)	0.620
Country of Birth						
Immigrant	0.82	(0.71-0.94)	<0.001	0.67	(0.50-0.90)	0.008
Unknown	1.59	(1.27-2.00)	<0.001	1.23	(0.88-1.70)	0.224

Table 5: Unadjusted and adjusted hazard ratios and 95% confidence intervals from Cox proportional hazards model of correlates of treatment discontinuation.

therapy and are a critical component of the HIV cascade of care [30,31]. At a public health level, sustained HIV RNA suppression in individuals translates into reduced transmission within populations at risk for acute HIV infection [32].

Patient characteristics, coupled with the HIV drug composition create a complex decision tree for selecting a regimen that is likely to facilitate adherence and that is clinically effective. INSTI- and NNRTI-containing regimens are characterized by lower rates of discontinuation of first-line therapy thereby supporting the use of this ARV class as first line therapy [33]. Those on INSTI+NRTI and NNRTI+NRTI regimens in our clinic were adherent to treatment longer than those on PI+NRTI therapies (Table 5 and Figure 1). This likely explains much of our findings pertaining to therapeutic success with INSTI- and NNRTI-based treatment.

Now that efficient drug components are available, the challenge is to improve adherence, reduce therapy discontinuation and maintain viral suppression over the long term by focusing on patient-specific characteristics associated with negative outcome. To this end, multiple risk factors for ARV discontinuation were evaluated. In our cohort, past or present injection drug users remained on initially prescribed therapy for a shorter period of time compared to all other HIV risk factor groups (Table 5) [20].

Several limitations related to this analysis are acknowledged. At the study design level, the retrospective nature of the analysis meant that not all variables of interest were available. Although effect modifiers and confounders were considered, missing data could have introduced bias into our multivariate analysis. There was a potential risk of bias since the baseline characteristics between old-era and modern-era strata were imbalanced in terms of race, country of origin, substance abuse history and HIV risk factors. Although both eras covered approximately the same duration of time, it is possible that a time bias may exist whereby patients in the modern-era group have yet to discontinue treatment. Prospective evaluations with close clinical and laboratory monitoring of new ARV for first and subsequent lines of therapies are important to provide further insights into the reasons for suboptimal adherence and treatment discontinuation, and predict long-term outcomes. Prospective clinical investigations in other HIV-infected groups, such as children, elderly, pregnant women and marginalized populations, would also provide relevant knowledge.

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