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Viral suppression and viral rebound among young adults living with HIV in Canada

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Abstract

Describe the prevalence and covariates of viral suppression and subsequent rebound among younger (≤29 years old) compared with older adults.

A retrospective clinical cohort study; eligibility criteria: documented HIV infection; resident of Canada; 18 years and over; first antiretroviral regimen comprised of at least 3 individual agents on or after January 1, 2000.

Viral suppression and rebound were defined by at least 2 consecutive viral load measurements <50 or >50 HIV-1 RNA copies/mL, respectively, at least 30 days apart, in a 1-year period. Time to suppression and rebound were measured using the Kaplan–Meier method and Life Table estimates. Accelerated failure time models were used to determine factors independently associated with suppression and rebound.

Younger adults experienced lower prevalence of viral suppression and shorter time to viral rebound compared with older adults. For younger adults, viral suppression was associated with being male and later era of combination antiretroviral initiation (cART) initiation. Viral rebound was associated with a history of injection drug use, Indigenous ancestry, baseline CD4 cell count >200, and initiating cART with a protease inhibitor (PI) containing regimen.

The influence of age on viral suppression and rebound was modest for this cohort. Our analysis revealed that key covariates of viral suppression and rebound for young adults in Canada are similar to those of known importance to older adults. Women, people who use injection drugs, and people with Indigenous ancestry could be targeted by future health interventions.

Abbreviations: ADI = AIDS-defining illness, AFT = accelerated failure time, aHR = adjusted hazard ratios, AIC = Akaike Information Criterion, AIDS = acquired immune deficiency syndrome, CANOC = Canadian HIV Observational Cohort Collaboration, cART = combination antiretroviral therapy, DOT = directly observed therapy, HCV = hepatitis C, HIV = human immunodeficiency virus, IDU = injection drug use, MAT = maximally assisted therapy, MSM = men who have sex with men, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PLWH = people living with HIV, UK-CHIC = UK Collaborative HIV Cohort Study, UNAIDS = United Nations Programme on HIV/AIDS.

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1. Introduction

For people living with HIV (PLWH), sustained viral suppression is the primary goal of combination antiretroviral treatment (cART).[1,2] Sustained viral suppression dramatically decreases the likelihood of sexual (and perinatal) HIV transmission[3,4] and is important for maintaining good health through immune function reconstitution (reducing risk of illness and decreasing mortality).[5–8] PLWH can now expect life expectancy similar to that of people living without HIV, if they are able to achieve and maintain viral suppression, making HIV a chronic, manageable disease.[5–8]

Historically, subpopulations including younger adults (≤29 years of age) have experienced suboptimal clinical outcomes when compared to older adults living with HIV.[9,10] Considering the high rates of new HIV diagnoses that annually occur among people aged 29 and younger, this population is of interest for research and intervention.[10] Young adults may face different challenges than older adults (e.g., access to developmentally appropriate care) resulting in cART nonadherence, putting younger adults at risk for unsustained viral suppression, and subsequent viral rebound.[9–15] Viral rebound increases vulnerability to illness, treatment failure, cART resistance, and the potential for HIV transmission.[3,6,15–19] With treatment resumption, individuals can usually regain viral suppression.[20,21]

Previous research indicates, that compared with older adults, young adults are less likely to achieve and maintain viral suppression.[10,22] Among those who do reach suppression, they are more likely than older adults to have suboptimal adherence, and poorer retention in care, risking viral rebound.[10,12,13,14] Viral rebound has been associated with younger age, poor adherence and various other behavioral and sociodemographic factors.[23–26] Suboptimal cART adherence is strongly associated with progression to AIDS and mortality.[27,28]

In Canada, young adults comprise nearly one-quarter of all HIV-positive tests annually.[29] Using data from Canada's largest HIV treatment cohort, we measured and compared the prevalence and correlates of viral suppression and subsequent viral rebound among younger and older adults living with HIV in Canada.

2. Methods

2.1. Study methodology

The Canadian HIV Observational Cohort Collaboration (CANOC) is a retrospective cohort study of PLWH. The data used for this analysis was comprised of 8 population or clinic-based cohorts from 3 provinces (British Columbia, Ontario, and Quebec). CANOC eligibility criteria include: documented HIV infection; resident of Canada; aged 18 years and over; initiation of a first antiretroviral regimen comprised of at least 3 individual agents (i.e., antiretroviral-naive prior to initiating cART) on or after January 1, 2000; and at least 1 measurement of HIV-1 RNA viral load and CD4 cell count within 6 months of initiating cART.[30]

Data extraction of a predefined set of demographic, laboratory, and clinical variables is performed bi-annually by the participating sites and submitted to the BC Centre for Excellence in HIV/AIDS (the Data Coordinating Site). All participating cohorts received research ethics board approval to contribute anonymous patient data to CANOC and for aggregate and de-identified results to be disseminated.

The last date of follow-up data for this analysis was December 31, 2014. Reporting was conducted in accordance with the international STROBE guidelines [31]—a set of recommendations to promote complete reporting of cohort data in a systematic manner.

2.2. Study population

For this analysis, in addition to meeting the CANOC eligibility criteria, participants' first antiretroviral treatment date must have been before December 31, 2013 (to ensure a minimum of 1 year follow-up time) and individuals had to have at least 2 viral load measurements after starting cART. There were 477 participants excluded from the analysis based on this criteria; number of people excluded did not vary significantly between younger and older adults (P value = 0.339). Loss to follow-up among patients included in this analysis was defined as no contact (e.g., clinical visits or laboratory tests) for at least 1 year during the study period (January 1, 2000–December 31, 2014).

2.3. Outcomes and covariates

The primary outcomes were viral suppression and viral rebound. Viral suppression was defined as the time to the first of at least 2 consecutive viral load measurements <50 HIV-1 RNA copies/mL, at least 30 days apart, in a one-year period. Viral rebound was defined as the first of at least 2 consecutive viral load measurements >50 HIV-1 RNA copies/mL, at least 30 days apart, after reaching viral suppression. Prevalence of viral suppression and viral rebound were considered as binary variables, did suppression or rebound ever occur (yes versus no). Viral suppression and subsequent rebound were also included as time-varying variables, beginning at baseline.

Covariates of interest included: age; sex; province of residence; ethnicity; Indigenous ancestry; transmission risk category (men who have sex with men (MSM), injection drug use (IDU), and follow-up time (years). Clinical variables including hepatitis C (HCV) co-infection (ever); the presence of an AIDS-defining illness (ADI); era of cART initiation (2000–2003, 2004–2007, 2008–2011, 2012–2013); composition of initial cART regimen (nucleoside reverse transcriptase inhibitor (NRTI) backbone and third drug in the regimen); baseline CD4 cell count (cells/mm^3); and HIV plasma viral load (log10). Baseline was defined as participant entrance into the CANOC cohort (date of cART initiation on or after the latter of January 1, 2000 or 18th birthday).

2.4. Statistical analysis

Sociodemographic and patient characteristics were compared by age (≤29 vs 30+ years old), viral suppression status (yes vs no), and viral rebound after suppression (yes vs no) in bivariate analyses using Chi-square tests for categorical variables and Wilcoxon's Rank Sum test for continuous variables. Viral load measurements were buffered to a minimum of 50 copies/mL and a maximum of 100,000 copies/mL to accommodate temporal changes in viral load assay sensitivities over the study period.

Kaplan–Meier methods and stratified life tables (using Log-rank tests and hazard ratios, respectively) were used to compare time to viral suppression and viral rebound stratified by age group (≤29 vs 30+ years old). Bivariate and unadjusted accelerated failure time (AFT) models with exponential distributions or Weibull distributions were explored before multivariable models were selected to determine the association between covariates and time to viral suppression and viral rebound. AFT models were fit using an exploratory model selection process

based on Akaike Information Criterion (AIC) and Type III *P*-values. Goodness-of-fit was assessed by a log-survivor plot.[32] Based on model diagnosis and the goodness-of-fit tests, we did not use a Cox Proportional Hazard model due to a violation of the proportional hazards assumption. As a sensitivity analysis, Cox Proportional Hazard models were constructed. A 2-sided *P*-value below 0.05 was considered statistically significant. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).[32]

3. Results

3.1. Population characteristics

A total of 9031 individuals were included in this analysis, 1281 were aged 29 and under (14%). A higher proportion of younger adults were female (27% vs 16%), experienced an ADI after initiating cART (87% vs 79%), initiated cART in 2008–2011 (38% vs 36%) or 2012–2013 (21% vs 14%), and had higher baseline CD4 cell counts (Median 280 cells/mm^3 vs 220 cells/mm^3). Younger adults were less likely to be from the province of BC (43% vs 50%), be white (31% vs 37%), have a history of injecting drugs (18% vs 22%) or be HCV co-infected (18% vs 25%) (Table 1). Loss to follow-up at 12, 18, 24, and 36 months was not significantly different between younger and older adults (*P*-values: .213, .820, .906, .736, respectively).

Among the 8358 (93%) CANOC participants who achieved viral suppression, 2,231 (27%) experienced subsequent viral rebound. A lower proportion of young adults achieved viral suppression (90% vs 93%, $P<.001$) compared to older adults, though there were no significant differences in the

Table 1

Demographic comparison of all eligible CANOC participants (n = 9031).

	Overall n (%)	≤29 At first ARV initiation n (%)	>29 At first ARV initiation n (%)
Gender			
Female	1613 (18)	368 (27)	1245 (16)*
Male	7418 (82)	984 (73)	6434 (84)
Age (n (Q1–Q3))	40 (33–47)	26 (24–28)	42 (36–48)*
Province			
British Columbia	4381 (49)	576 (43)	3805 (50)*
Ontario	2782 (31)	486 (36)	2296 (30)
Quebec	1868 (21)	290 (21)	1578 (21)
Ethnicity			
Caucasian	3282 (36)	419 (31)	2863 (37)*
Black	954 (11)	174 (13)	780 (10)
Indigenous	580 (6)	96 (7)	484 (6)
Other	981 (11)	196 (14)	785 (10)
Unknown/Missing	3234 (36)	467 (35)	2767 (36)
Indigenous			
Not Indigenous	5217 (58)	789 (58)	4428 (58)
Indigenous	580 (6)	96 (7)	484 (6)
Unknown/Missing	3234 (36)	467 (35)	2767 (36)
HIV risk IDU			
No	6073 (67)	952 (70)	5121 (67)*
Yes	1893 (21)	239 (18)	1654 (22)
Unknown	1065 (12)	161 (12)	904 (12)
HCV co-infected			
No	6435 (71)	1037 (77)	5398 (70)*
Yes	2161 (24)	250 (18)	1911 (25)
Unknown	435 (5)	65 (5)	370 (5)
Baseline ADI			
No ADI ever	367 (4)	53 (4)	314 (4)*
≥1 ADI after first cART	7243 (71)	1170 (87)	6073 (79)
≥1 before/at first cART	1421 (16)	126 (10)	1292 (17)
Era of cART initiation			
2000–2003	1910 (21)	250 (18)	1660 (22)*
2004–2007	2480 (27)	305 (23)	2175 (28)
2008–2011	3296 (36)	517 (38)	2779 (36)
2012–2013	1345 (15)	280 (21)	1065 (14)
Classes of ARVs in first regimen			
NNRTI	4173 (46)	621 (46)	3552 (46)*
Unboosted PI	584 (6)	124 (9)	460 (6)
Boosted PI	3712 (41)	503 (37)	3206 (42)
Other	562 (6)	104 (8)	458 (6)
Baseline CD4 cell counts (cells/mm^3)	230 (127–345)	280 (180–420)	220 (120–332)*
Baseline viral load (Log10 copies/mL)	5 (4–5)	5 (4–5)	5 (4–5)*
Follow-up time, years	6 (3–9)	5 (3–8)	6 (3–9)*

ADI = AIDS defining illness, ARV = antiretroviral, cART = combination antiretroviral therapy, HCV = hepatitis C virus, IDU = injection drug use, NNRTI = non-nucleotide reverse-transcriptase inhibitors, PI = protease inhibitor, Q = quartile.

* Denotes statistically significant differences at the 0.05 level between ≤29 and >29 years of age.

Table 2

Demographic comparison of all eligible CANOC participants reaching virologic suppression, and demographic characteristics of all participants who experiences virologic rebound after virologic suppression, stratified by age at first ARV initiation.

	Experienced virologic suppression (N = 8358)		Experienced virologic rebound (N = 2231)	
	≤29 at first ARV initiation (n = 1218) (90%)	>29 at first ARV initiation (n = 7140) (93%)*	≤29 at first ARV initiation (n = 344) (28%)	>29 at first ARV initiation (n = 1887) (26%)
Age (median years, Q1–Q3)	26 (24–28)	42 (36–48)	26 (24–28)	41 (36–47)
Female sex	315 (26%)	1111 (16%)*	154 (45%)	405 (21)*
Cohort province				
British Columbia	497 (41%)	3488 (49%)*	174 (51%)	1109 (59%)*
Ontario	451 (37%)	2173 (30%)	119 (35%)	467 (25%)
Quebec	270 (22%)	1479 (21%)	51 (15%)	311 (16%)
Caucasian ethnicity†,‡	390 (32%)	2725 (38%)*	115 (33%)	750 (40%)*
Indigenous ethnicity†	76 (6%)	412 (6%)	42 (12%)	172 (9%)
HIV risk, injection drug use†	196 (16%)	1452 (20%)*	108 (31%)	596 (32%)
Hepatitis C co-infection†	207 (17%)	1675 (23%)*	113 (33%)	683 (36%)
HIV risk, MSM (female, n = 0)†	615 (50%)	3321 (47%)*	117 (34%)	750 (40%)*
ADI, ≥1 before/at first cart	114 (9%)	1181 (17%)*	43 (13%)	352 (19%)*
Median year of ART initiation (Q1–Q3)	2009 (2005–2011)	2008 (2004–2010)*	2006 (2002–2009)	2005 (2002–2008)
Classes of ARVs in first regimen‡				
NNRTI	570 (47%)	3347 (47%)*	139 (40%)	752 (40%)*
Unboosted PI	107 (9%)	404 (6%)	54 (16%)	174 (9%)
Boosted PI	444 (36%)	2966 (42%)	137 (40%)	873 (46%)
Third drug in ARV regimen‡				
Efavirenz	435 (36%)	2561 (36%)*	83 (24%)	500 (26%)*
Atazanavir	267 (22%)	1635 (23%)	70 (20%)	487 (26%)
Lopinavir	147 (12%)	1052 (15%)	64 (19%)	333 (18%)
Baseline CD4 (median, 95% CI)	280 (184–415)	224 (120–340)*	245 (150–380)	180 (90–290)*
Baseline VL (median, 95% CI)	5 (4–5)	5 (4–5)*	5 (4–5)	5 (5–5)*
Follow up time (median years, Q1–Q3)	5 (3–8)	6 (4–9)*	8 (5–11)	8 (6–11)*
Life table estimate of the probability of suppression/rebound				
	n (%)	n (%)	HR (95%CI)	n (%)	n (%)	HR (95%CI)
6 months	0.63 (0.60–0.65)	0.63 (0.62–0.64)	1.01 (0.87, 1.16)	0.05 (0.03–0.06)	0.03 (0.03–0.03)	1.02 (0.79, 1.29)
12 months	0.80 (0.78–0.82)	0.83 (0.82–0.84)	0.85 (0.70, 1.24)	0.11 (0.10–0.13)	0.09 (0.08–0.09)	1.03 (0.75, 1.37)
18 months	0.84 (0.82–0.86)	0.88 (0.88–0.89)	0.75 (0.58, 1.33)	0.16 (0.14–0.19)	0.13 (0.13–0.12)	1.05 (0.71, 1.47)
24 months	0.87 (0.85–0.89)	0.91 (0.90–0.92)	0.68 (0.67, 1.08)	0.20 (0.18–0.22)	0.16 (0.15–0.17)	1.05 (0.85, 1.23)

ADI = AIDS defining illness, ARV = antiretroviral, cART = combination antiretroviral therapy, HR: hazard ratio, MSM = men who have sex with men, NNRTI = non-nucleotide reverse-transcriptase inhibitors, PI = protease inhibitor; CI = confidence interval; CD4 (cells/mm^3), Q = quartile, VL = viral load (Log10 copies/mL).

* Denotes statistically significant differences at the 0.05 level between ≤29 and >29 years of age.

† Overall missing data; ethnicity: 3234 (36%); HIV risk IDU: 1065 (12%); Hepatitis C: 435 (5%), MSM: 1461 (16%).

‡ Overall other classification; Non-Caucasian ethnicity: 2515 (28%); Class of first ARV: 562 (6%), Third Drug in ARV regimen: 2496 (27%).

probability of experiencing viral rebound (28% vs 26%) (Table 2).

3.2. Characteristics of those achieving viral suppression

Among young adults who achieved viral suppression (90%), a significantly higher proportion were: female (26% vs 16%); from Ontario (37% vs 30%) or Quebec (22% vs 21%); started cART with an unboosted PI (9% vs 6%); and initiated cART with a higher baseline CD4 count (cells/mm^3) (median 280 vs 224) compared to older adults who achieved viral suppression. A lower proportion of young adults who achieved viral suppression: reported Caucasian ethnicity (32% vs 38%); had a history of IDU (16% vs 20%); were hepatitis C co-infected (17% vs 23%); and had ADI before or at cART initiation (9% vs 17%) compared to older adults who achieved viral suppression (Table 2).

Life table estimates of the probability of suppression were not significantly different between younger and older adults at 6, 12, 18, and 24 months (Table 2).

Kaplan–Meier curves indicated significant differences ($P < .03$) in viral suppression between younger and older adults (Fig. 1).

3.3. Characteristics of those achieving viral rebound

Among those who experienced viral rebound, a higher proportion of young adults were: female (45% vs 21%); from Ontario (35% vs 25%); Indigenous (12% vs 9%); started cART with an unboosted PI (16% vs 9%); and initiated cART with a higher baseline CD4 count (cells/mm^3) (median 245 vs 180) compared to older adults who experienced viral rebound. Fewer young adults who experienced viral rebound were: Caucasian (33% vs 40%); identified as MSM (34% vs 40%); or had an ADI before or at cART initiation (13% vs 19%) compared to older adults (Table 2).

Life table estimates of the probability of experiencing viral rebound after viral suppression indicated that rebound was not significantly different between younger and older adults at 6, 12, 18, and 24 months (Table 2).

Kaplan–Meier curves indicated significant differences ($P < .001$) in viral rebound between younger and older adults (Fig. 1).

3.4. AFT models of younger and older adults

The overall adjusted AFT model, including older and younger adults, indicated that per 1-year increase in age, there was a 1%

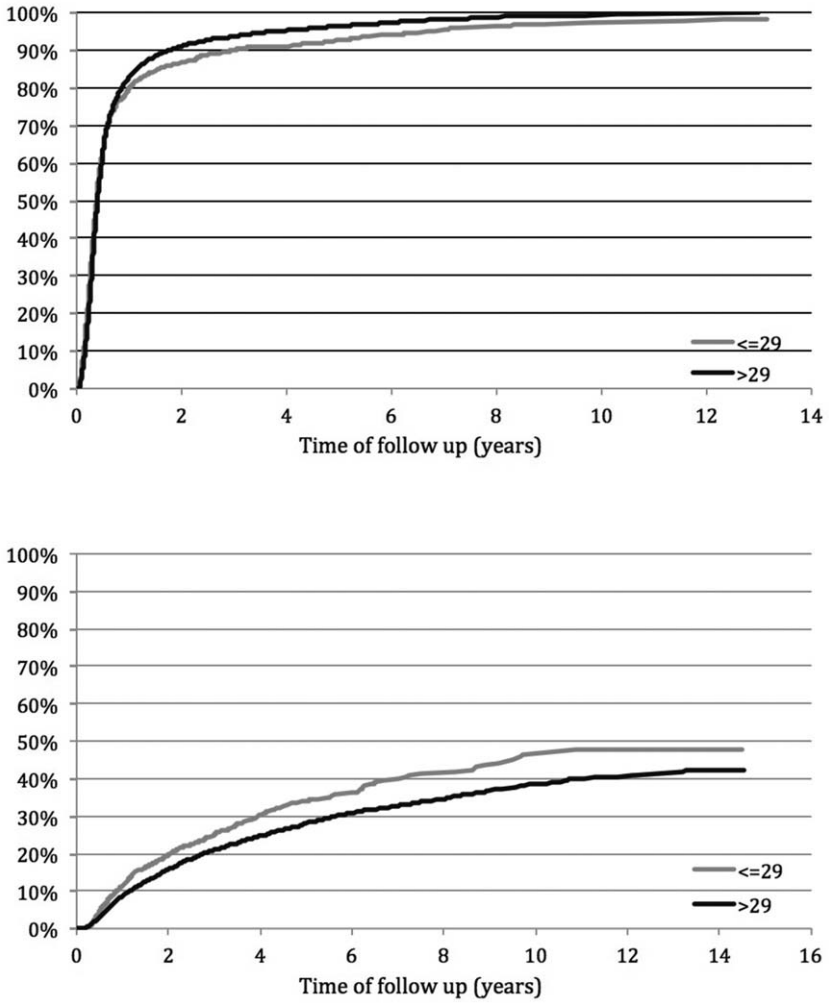

Figure 1. Kaplan–Meier plots of the probability of achieving viral suppression (top) and experiencing viral rebound (bottom) for young adults (≤29) compared to older adults (>29).

increase in the rate of viral suppression. Viral suppression was also positively associated with: being male (adjusted hazard ratios [aHR] 1.27 95% confidence intervals (CI): 1.19, 1.35); having a baseline CD4 cell count above 200 cells/mm^3 (aHR 1.09, 95%CI: 1.04, 1.14); later era of cART initiation; and Quebec province of residence (aHR 1.08, 95% CI: 1.01–1.15) compared to British Columbia. Viral suppression was negatively associated with: having a history of IDU (aHR 0.58, 95%CI: 0.54, 0.61); initial cART regimen containing an unboosted PI (aHR 0.59, 95% CI: 0.48–0.72) or a boosted PI (aHR 0.78, 95%CI: 0.67–0.91) compared to (non-nucleoside reverse-transcriptase inhibitors) NNRTI; and higher viral load at baseline (aHR 0.73, 95% CI: 0.70, 0.76) (Table 3).

Adjusted AFT models indicated that per 1-year increase in age, there was a 1% decrease in the likelihood of viral rebound. Viral rebound was also less likely to occur among males (aHR 0.65, 95% CI: 0.59, 0.72), participants who experienced an ADI, either before (aHR 0.73, 95% CI: 0.56–0.94) or after initiating cART (aHR 0.72, 95% CI: 0.54–0.90) compared with never experiencing an ADI, later era of treatment initiation and province of residence. Overall, those with a history of IDU (aHR 1.64, 95%CI: 1.48, 1.82), and Indigenous heritage (aHR 1.44, 95%CI: 1.23, 1.68) were more likely to experience viral rebound (Table 3).

Results from the sensitivity analysis indicate that the associates and direction of association were the same for AFT models and for Cox Proportional Hazard models.

3.5. AFT models of younger adults

Among younger adults, adjusted AFT models indicated that, being male (aHR 1.45, 95%CI: 1.25, 1.67), and initiating cART in 2004 to 2013 (compared with 2000–2003) was associated with a higher probability of achieving viral suppression. A history of IDU (aHR 0.59, 95%CI: 0.50, 0.71), initiating cART with an unboosted PI (aHR 0.62, 95%CI: 0.50, 0.78) compared to an NNRTI and higher viral load (aHR 0.72, 95%CI: 0.65, 0.79) were associated with a decreased probability of experiencing viral suppression (Table 4).

Decreased probability of experiencing viral rebound was associated with being male (aHR 0.51, 95%CI: 0.41, 0.64), initiating cART between 2008 and 2011 (aHR 0.72, 95%CI: 0.53, 0.97) compared with 2000 to 2003 and having a higher viral load (aHR 0.80 95%CI: 0.67, 0.96). Increased probability of experiencing viral rebound was associated with having a history of IDU (aHR 2.21 95%CI: 1.68, 2.91), being Indigenous (aHR 1.60 CI: 1.11, 2.32), having a CD4 cell count ≥200 cells/mm^3 (aHR

Table 3

Adjusted and unadjusted accelerated failure time models for time to suppression and time to rebound for all eligible CANOC participants (n = 9031).

	Viral suppression		Viral rebound	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age at first ARV initiation (per 1 years)	1.01 (1.01,1.02)	1.01 (1.01,1.01)	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)
Gender				
Female	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Male	1.61 (1.52,1.71)	1.27 (1.19,1.35)	0.53 (0.48,0.58)	0.65 (0.59,0.72)
HIV risk IDU				
No	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Yes	0.47 (0.45, 0.5)	0.58 (0.54,0.61)	2.19 (2.00,2.40)	1.64 (1.48,1.82)
Unknown	1.00 (0.93, 1.07)	1.03 (0.96,1.12)	0.92 (0.78,1.08)	0.90 (0.76,1.08)
Indigenous				
Not Indigenous	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Indigenous	0.49 (0.44,0.53)	0.68 (0.62,0.75)	2.31 (2.00,2.66)	1.44 (1.23,1.68)
Unknown/Missing	1.02 (0.98,1.07)	0.97 (0.92,1.03)	0.88 (0.80,0.97)	0.89 (0.79,0.99)
Baseline ADI				
No ADI ever	1.00 (–)	Not selected	1.00 (–)	1.00 (–)
≥1 ADI after first cart	0.94 (0.84,1.04)		0.91 (0.75,1.10)	0.72 (0.57,0.90)
≥1 before/at first cart	0.86 (0.76,0.97)		0.95 (0.77,1.17)	0.73 (0.56,0.94)
Baseline CD4 cell counts (cells/mm^3)				
<200	1.00 (–)	1.00 (–)	1.00 (–)	Not selected
≥200	1.34 (1.28,1.4)	1.09 (1.04,1.14)	0.80 (0.74,0.87)	
Classes of ARVs in first regimen				
NNRTI	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Unboosted PI	0.44 (0.4,0.48)	0.59 (0.48,0.72)	1.92 (1.66,2.22)	1.11 (0.70,1.76)
Boosted PI	0.84 (0.8,0.88)	0.78 (0.67,0.91)	1.40 (1.28,1.53)	0.84 (0.55,1.28)
Other	1.19 (1.08,1.3)	1.08 (0.92,1.26)	1.17 (0.95,1.43)	0.84 (0.55,1.29)
Era of cART initiation				
2000–2003	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
2004–2007	1.46 (1.37,1.55)	1.35 (1.26,1.45)	0.87 (0.79,0.96)	0.89 (0.79,1.00)
2008–2011	1.92 (1.81,2.04)	1.45 (1.35,1.56)	0.71 (0.64,0.79)	0.81 (0.71,0.92)
2012–2013	2.26 (2.10,2.43)	1.57 (1.45,1.71)	0.40 (0.30,0.52)	0.45 (0.34,0.59)
Province				
British Columbia	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Ontario	1.30 (1.24,1.37)	1.06 (0.99,1.12)	0.63 (0.57,0.69)	0.68 (0.61,0.77)
Quebec	1.39 (1.32,1.47)	1.08 (1.01,1.15)	0.57 (0.51,0.65)	0.61 (0.53,0.71)
Baseline viral load (Log10 copies/mL)	0.78 (0.75,0.81)	0.73 (0.70,0.76)	1.07 (0.98,1.16)	1.08 (0.98,1.17)

ADI = AIDS defining illness, ARV = antiretroviral, cART = combination antiretroviral therapy, HR = hazard ratio, IDU = injection drug use.

1.30 95%CI: 1.02, 1.66), and initiating cART with an unboosted PI (aHR 1.59 95%CI: 1.14, 2.22) or a boosted PI (aHR 1.48 95% CI: 1.15, 1.90) compared to an NNRTI (Table 4).

4. Discussion

In a large Canadian HIV treatment cohort, we found that younger adults were less likely to achieve viral suppression compared with older adults. We observed no differences in prevalence of viral rebound after suppression between the two groups. However, all measured differences between younger and older adults were moderate, and may not be clinically significant. Among younger and older adults, the rate of viral suppression was 93%, surpassing the United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets. Among younger adults, sex, era of cART initiation, history of IDU, composition of first cART regimen and viral load were independently associated with viral suppression, in addition to the aforementioned characteristics, being Indigenous and CD4 cell count at cART initiation were associated with viral rebound.

Youth in our study had better outcomes compared with other large cohort studies. The UK Collaborative HIV Cohort Study (UK-CHIC) found that for every 10-year increase in age, the rate of viral rebound decreased by 28%,[14] compared to a 1% decrease per year in our analysis. A large adolescent and young adult cohort in the United States (REACH) found that only 51% of young people maintained a suppressed viral load for a year;[23] in contrast our study indicated that only 11% of youth experienced viral rebound at 12 months post suppression. Though, differences may be explained by systematic differences between the health systems in the UK, USA, and Canada.

Our results align with previous research indicating that young women are at greater risk of viral rebound compared to young men, which may be partially explained by lower levels of adherence among women.[33,34] Many women with HIV contend with complex, competing priorities, such as childcare, employment, and housing as well as competing comorbidities such as depressive symptoms and substance use disorders, which create barriers and challenges to optimal cART adherence.[35–38] Access to women-centred HIV care, cART adherence support, transportation support, and onsite childcare may result in improved treatment outcomes.[39,40] In addition, gender sensitivity training is recommended for all health care workers to ensure that positive women receive comprehensive care in a holistic, comfortable and respectful clinic environment.[39,40]

Table 4

Adjusted and unadjusted accelerated failure time models for time to suppression and time to rebound for all eligible CANOC participants aged 29 and younger.

	CANOC population ≤29 years of age			
	Viral suppression		Viral rebound	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Gender				
Female	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Male	2.2 (1.94, 2.51)	1.45 (1.25, 1.67)	0.4 (0.32, 0.49)	0.51 (0.41, 0.64)
HIV risk IDU				
No	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Yes	0.38 (0.33, 0.44)	0.59 (0.50, 0.71)	2.96 (2.35, 3.72)	2.21 (1.68, 2.91)
Unknown	0.76 (0.63, 0.91)	0.96 (0.79, 1.18)	0.84 (0.53, 1.33)	0.84 (0.51, 1.38)
Indigenous				
Not Indigenous	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Indigenous	0.39 (0.31, 0.5)	0.95 (0.73, 1.25)	3.12 (2.24, 4.35)	1.6 (1.11, 2.32)
Unknown/Missing	1.07 (0.95, 1.21)	1.05 (0.9, 1.22)	0.93 (0.73, 1.19)	1.02 (0.76, 1.37)
Baseline ADI				
No ADI ever	1.00 (–)	Not selected	1.00 (–)	1.00 (–)
≥1 ADI after first cart	0.97 (0.72, 1.3)		1.25 (0.74, 2.1)	1.02 (0.54, 1.91)
≥1 before/at first cart	0.88 (0.63, 1.23)		1.64 (0.91, 2.96)	1.54 (0.76, 3.09)
Baseline CD4 cell counts (cells/mm3)				
<200	1.00 (–)	Not selected	1.00 (–)	1.00 (–)
≥200	1.47 (1.3, 1.66)		1.05 (0.85, 1.31)	1.30 (1.02, 1.66)
Classes of ARVs in first regimen				
NNRTI	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Unboosted PI	0.45 (0.37, 0.56)	0.62 (0.50, 0.78)	2.06 (1.5, 2.82)	1.59 (1.14, 2.22)
Boosted PI	0.92 (0.81, 1.04)	0.91 (0.8, 1.04)	1.43 (1.13, 1.81)	1.48 (1.15, 1.90)
Other	1.59 (1.28, 1.97)	1.22 (0.98, 1.53)	0.74 (0.43, 1.28)	0.74 (0.42, 1.30)
Era of cART initiation				
2000–2003	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
2004–2007	1.31 (1.09, 1.56)	1.41 (1.16, 1.7)	0.81 (0.62, 1.06)	0.76 (0.57, 1.01)
2008–2011	2.64 (2.25, 3.1)	1.77 (1.48, 2.12)	0.72 (0.55, 0.93)	0.72 (0.53, 0.97)
2012–2013	3.32 (2.76, 3.98)	2.26 (1.85, 2.78)	0.56 (0.34, 0.93)	0.63 (0.37, 1.09)
Province				
British Columbia	1.00 (–)	1.00 (–)	1.00 (–)	1.00 (–)
Ontario	1.5 (1.32, 1.7)	0.89 (0.76, 1.05)	0.68 (0.54, 0.86)	0.89 (0.65, 1.2)
Quebec	1.89 (1.63, 2.19)	1.13 (0.96, 1.34)	0.47 (0.34, 0.64)	0.66 (0.45, 0.98)
Baseline viral load (Log10 copies/mL)	0.8 (0.73, 0.87)	0.72 (0.65, 0.79)	0.73 (0.62, 0.86)	0.80 (0.67, 0.96)

ADI = AIDS defining illness, ARV = antiretroviral, cART = combination antiretroviral therapy, HR = hazard ratio, IDU = injection drug use.

We found that unboosted PIs were associated with a reduced likelihood of achieving viral suppression and increased risk for viral rebound. This may be due to unboosted PI regimens being more complex compared to NNRTI. Beyond adherence, women and youth have historically been excluded from clinical trials, minimizing knowledge about the effectiveness of cART on disease progression for young women living with HIV.[41] Given that complex drug regimens are related to poor adherence the effects of regimen and era of cART initiation may be directly related to the increasing availability of once-daily regimens increasing adherence.[42,43] We found that initiating cART later was associated with increased suppression and reduced likelihood of viral rebound.

Young adults with a history of IDU often have significant difficulties in maintaining cART adherence.[37,44,45] Treating their HIV may not be their first priority in the face of other competing necessities such as food, housing, and addiction services.[37,44,45] Many young adults with a history of IDU have also tested positive for HCV co-infection. Those who are co-infected with HCV may stop cART due to toxicities or competing treatment priorities.[46] Many young people who inject drugs report facing stigma when attending health clinics, making them reluctant to follow-up on their care.[47–49] Low-threshold support programs such as directly observed therapy (DOT) and maximally assisted therapy (MAT) programs have been shown to improve adherence for people on cART who use drugs.[50] The development of such programs for young adults living with HIV could assist those who are in need of low-threshold health care and support to remain on treatment as well as access other services that may be linked. Treatment partnerships in which health providers work directly with the patient to tailor health care to the individual's needs can increase feelings of support and levels of comfort when communicating with health providers increasing the likelihood of the individuals being retained in care.[51,52]

Our finding that younger adults who identify as Indigenous are more likely than non-Indigenous people to experience viral rebound suggests the importance of retention in care and follow-up while on treatment. For many young Indigenous people in Canada, especially women, remaining in care can be a difficult, in part due to complex historical relationships relating to colonialism and trauma.[36] The lack of culturally safe health services can hinder young peoples' willingness to remain in care. Young people of Indigenous ancestry have voiced their frustration with

the lack of youth friendly messaging and language, and services available to them.[53]

Pharmacological responses to issues with adherence to combat viral rebound are extremely valuable; however, the best clinical practice must incorporate comprehensive, multidisciplinary approaches to promote retention and adherence.[52] A recent study from a large North American HIV cohort (NA-ACCORD) showed that young people retained in care were more likely to maintain viral suppression.[54] The most promising strategies for improving retention among young people use holistic approaches involving patient and caregiver education, self-monitoring, peer support, and follow-up.[55–58] Given that health literacy is often a barrier to adherence, education sessions and mentorship programs can provide a safe environment to discuss HIV treatment with young people and to answer any questions they may have.[59,60] Young people may not completely understand the gravity of staying on treatment and remaining adherent.[61] It is up to the health care and social service providers to meet young people where they are at, in a respectful, culturally appropriate, gender-sensitive and compassionate manner, in order to improve retention in care.

Readers should be cautious when interpreting these data. We did not consider antiretroviral adherence, an important predictor of viral suppression and rebound, as adherence data were not available from all cohorts.[17] The data were obtained from only 3 provinces and thus the findings cannot be generalized to all PLWH in Canada. However, the majority of PLWH in Canada receive care in these 3 provinces. In fact, CANOC contains over one-third of all patients on therapy and a much larger proportion of those who initiated treatment since 2000. It is possible that some women in the study may have experienced viral rebound after halting therapy that was initiated solely for purposes of prevention of perinatal HIV transmission; however, pregnancy data are not available in the CANOC database. Perinatal versus behavioral infection was not documented in CANOC; however, the inclusion criteria of being cART naïve on or after 18 years of age may reduce the number of PLWH who were perinatally infected. Additionally, the differences between provinces in viral suppression may be due to the fact that the sample of participants in British Columbia is population based, while the sample from Ontario and Quebec is based on a selection of clinics. Variances may also reflect differences in access to cART between provinces. Some variables had a high proportion of missing or unknown data included, which may introduce bias.[62] Despite these limitations, important information regarding factors associated with viral suppression and viral rebound for young adults were identified. This information is of value in identifying young people at risk for suboptimal therapeutic outcomes.

In conclusion, our results indicate that difference in the likelihood, as well as time to viral suppression and subsequent rebound are modestly different between younger and older adults living with HIV in Canada. The independent associates of viral suppression and rebound for younger adults are similar to those known to affect older adults (e.g., history of IDU), highlighting at-risk populations for future research and intervention. Tailored approaches to engage young people including, women, people who use drugs and Indigenous people, should be developed to assist these populations to reach their optimal health. Antiretroviral therapy adherence and retention in care are important issues for all people living with HIV and should be considered in the context of Treatment as Prevention and reaching the UNAIDS 90-90-90 targets. Reducing barriers to care for important key populations will assist in reaching these targets by 2030.

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References

[1] Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493–505.
[2] Lima VD, Johnston K, Hogg RS, et al. Expanded access to highly active antiretroviral therapy: a potentially powerful strategy to curb the growth of the HIV epidemic. J Infect Dis 2008;198:59–67.
[3] Montaner JSG. Treatment as prevention—a double hat-trick. Lancet 2011;378:208–9.
[4] Montaner JSG, Lima VD, Barrios R, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet 2010;376:532–9.
[5] Gortmaker SL, Hughes M, Cervia J, et al. Effect of combination therapy including protease inhibitors on mortality among children and adolescents infected with HIV-1. N Engl J Med 2001;345:1522–8.
[6] Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA 1998;279:450–4.
[7] Lima VD, Hogg RS, Harrigan PR, et al. Continued improvement in survival among HIV-infected individuals with newer forms of highly active antiretroviral therapy. AIDS 2007;21:685–92.
[8] Van Sighem AI, van de Wiel MA, Ghani AC, et al. Mortality and progression to AIDS after starting highly active antiretroviral therapy. AIDS 2003;17:2227–36.
[9] Agwu AL, Fleishman JA, Korthuis PT, et al. Disparities in antiretroviral treatment: a comparison of behaviorally HIV-infected youth and adults in the HIV Research Network. J Acquir Immune Defic Syndr 2011;58:100–7.
[10] Ryscavage P, Anderson EJ, Sutton SH, et al. Clinical outcomes of adolescents and young adults in adult HIV care. J Acquir Immune Defic Syndr 2011;58:193–7.
[11] Kahana SY, Fernandez MI, Wilson PA, et al. Rates and correlates of antiretroviral therapy use and virologic suppression among perinatally and behaviorally HIV-infected youth linked to care in the United States. J Acquir Immune Defic Syndr 2015;68:169–77.
[12] Becker SL, Dezii CM, Burtcel B, et al. Young HIV-infected adults are at greater risk for medication nonadherence. MedGenMed 2002;4:21.
[13] Zanoni BC, Mayer KH. The adolescent and young adult HIV cascade of care in the United States: exaggerated health disparities. AIDS Patient Care STDS 2014;28:128–35.
[14] Smith CJ, Phillips AN, Hill T, et al. The rate of viral rebound after attainment of an HIV load <50 copies/mL according to specific antiretroviral drugs in use: results from a multicenter cohort study. J Infect Dis 2005;192:1387–97.
[15] Ho DD, Zhang L. HIV-1 rebound after anti-retroviral therapy. Nat Med 2000;6:736–7.
[16] Wainberg MA, Zaharatos GJ, Brenner BG. Development of antiretroviral drug resistance. N Engl J Med 2011;365:637–46.
[17] Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. AIDS 2001;15:1181–3.
[18] Martinez-Picado J, DePasquale MP, Kartsonis N, et al. Antiretroviral resistance during successful therapy of HIV type 1 infection. Proc Natl Acad Sci U S A 2000;97:10948–53.
[19] Sherr L, Lampe FC, Clucas C, et al. Self-reported non-adherence to ART and virological outcome in a multiclinic UK study. AIDS Care 2010;22:939–45.
[20] Kaufmann GR, Elzi L, Weber R, et al. Interruptions of cART limits CD4 T-cell recovery and increases the risk for opportunistic complications and death. AIDS 2011;25:441–51.
[21] Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. Trop Med Int Health 2011;16:1297–313.
[22] Rudy BJ, Lindsey JC, Flynn PM, et al. Immune reconstitution and predictors of virologic failure in adolescents infected through risk behaviors and initiating HAART: week 60 results from the PACTG 381 cohort. AIDS Res Hum Retroviruses 2006;22:213–21.
[23] Murphy DA, Belzer M, Durako SJ, et al. Longitudinal antiretroviral adherence among adolescents infected with human immunodeficiency virus. Arch Pediatr Adolesc Med 2005;159:764–70.
[24] Le Moing V, Chêne G, Carrieri MP, et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. AIDS 2002;16:21–9.
[25] Moore DM, Zhang W, Yip B, et al. Non-medically supervised treatment interruptions among participants in a universally accessible antiretroviral therapy programme. HIV Med 2010;11:299–307.
[26] Kavasery R, Galai N, Astemborski J, et al. Nonstructured treatment interruptions among injection drug users in Baltimore, MD. J Acquir Immune Defic Syndr 2009;50:360–6.
[27] Lima VD, Harrigan R, Bangsberg DR, et al. The combined effect of modern highly active antiretroviral therapy regimens and adherence on mortality over time. J Acquir Immune Defic Syndr 2009;50:529–36.
[28] Hogg RS, Heath K, Bangsberg D, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. AIDS 2002;16:1051–8.
[29] Public Health Agency of Canada. HIV and AIDS in Canada: Surveillance Report to December 31st, 2013. Ottawa; 2013. Available at: http://www.catie.ca/sites/default/files/HIV-and-AIDS-in-Canada-2013.pdf.
[30] Palmer AK, Klein MB, Raboud J, et al. Cohort profile: The Canadian Observational Cohort collaboration. Int J Epidemiol 2010;40:25–32.
[31] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg 2014;12:1495–9.
[32] Allison PD. Survival Analysis Using SAS: A Practical Guide [Internet]. 2nd ed.2010;SAS Institute,
[33] Puskas CM, Forrest JI, Parashar S, et al. Women and vulnerability to HAART non-adherence: a literature review of treatment adherence by gender from 2000 to 2011. Curr HIV/AIDS Rep 2011;8:277–87.
[34] Howard AA, Arnsten JH, Lo Y, et al. A prospective study of adherence and viral load in a large multi-center cohort of HIV-infected women. AIDS 2002;16:2175–82.
[35] Merenstein DJ, Schneider MF, Cox C, et al. Association between living with children and adherence to highly active antiretroviral therapy in the Women's Interagency HIV Study. Pediatrics 2008;121:e787–93.

[36] McCall J, Browne AJ, Reimer-Kirkham S. Struggling to survive: the difficult reality of Aboriginal women living with HIV/AIDS. Qual Health Res 2009;19:1769–82.
[37] Milloy M-J, Kerr T, Bangsberg DR, et al. Homelessness as a structural barrier to effective antiretroviral therapy among HIV-seropositive illicit drug users in a Canadian setting. AIDS Patient Care STDS 2012;26:60–7.
[38] Kacanek D, Jacobson DL, Spiegelman D, et al. Incident depression symptoms are associated with poorer HAART adherence: a longitudinal analysis from the Nutrition for Healthy Living study. J Acquir Immune Defic Syndr 2010;53:266–72.
[39] Carter AJ, Bourgeois S, O'Brien N, et al. Women-specific HIV/AIDS services: identifying and defining the components of holistic service delivery for women living with HIV/AIDS. J Int AIDS Soc 2013;16:17433.
[40] Ehrhardt AA, Exner TM, Hoffman S, et al. A gender-specific HIV/STD risk reduction intervention for women in a health care setting: short- and long-term results of a randomized clinical trial. AIDS Care 2002;14:147–61.
[41] Curno MJ, Rossi S, Hodges-Mameletzis I, et al. A systematic review of the inclusion (or exclusion) of women in HIV research: from clinical studies of antiretrovirals and vaccines to cure strategies. JAIDS 2016;71:181–8.
[42] McKinney RE, Rodman J, Hu C, et al. Long-term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents: Pediatric AIDS Clinical Trials Group Protocol P1021. Pediatrics 2007;120:e416–23.
[43] Belzer M, Fuchs D, Luftman G, et al. Antiretroviral adherence issues among HIV-positive adolescents and young adults. J Adolesc Heal 1999;25:316–9.
[44] Anema A, Chan K, Chen Y, et al. Relationship between food insecurity and mortality among HIV-positive injection drug users receiving antiretroviral therapy in British Columbia, Canada. PLoS One 2013;8:e61277.
[45] Nolan S, Milloy M-J, Zhang R, et al. Adherence and plasma HIV RNA response to antiretroviral therapy among HIV-seropositive injection drug users in a Canadian setting. AIDS Care 2011;23:980–7.
[46] Mocroft A, Phillips AN, Soriano V, et al. Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection. AIDS Res Hum Retroviruses 2005;21:743–52.
[47] Ding L, Landon BE, Wilson IB, et al. Predictors and consequences of negative physician attitudes toward HIV-infected injection drug users. Arch Intern Med 2005;165:618–23.
[48] Wood E, Kerr T, Tyndall MW, et al. A review of barriers and facilitators of HIV treatment among injection drug users. AIDS 2008;22:1247–56.
[49] Kinsler JJ, Wong MD, Sayles JN, et al. The effect of perceived stigma from a health care provider on access to care among a low-income HIV-positive population. AIDS Patient Care STDS 2007;21:584–92.
[50] Tyndall MW, McNally M, Lai C, et al. Directly observed therapy programmes for anti-retroviral treatment amongst injection drug users in Vancouver: access, adherence and outcomes. Int J Drug Policy 2007;18:281–7.
[51] Altice FL, Mezger JA, Hodges J, et al. Developing a directly administered antiretroviral therapy intervention for HIV-infected drug users: implications for program replication. Clin Infect Dis 2004;38(suppl 5):S376–87.
[52] Simoni JM, Amico KR, Pearson CR, et al. Strategies for promoting adherence to antiretroviral therapy: a review of the literature. Curr Infect Dis Rep 2008;10:515–21.
[53] Flicker S, Goldberg E, Read S, et al. HIV-positive youth's perspectives on the Internet and e-health. J Med Internet Res 2004;6:e32.
[54] Yehia BR, Rebeiro P, Althoff KN, et al. Impact of age on retention in care and viral suppression. J Acquir Immune Defic Syndr 2015;68:413–9.
[55] Dodds S, Blakley T, Lizzotte J, et al. Retention, adherence, and compliance: special needs of HIV-infected adolescent girls and young women. J Adolesc Heal 2003;33:39–45.
[56] Johnson RL, Botwinick G, Sell RL, et al. The utilization of treatment and case management services by HIV-infected youth. J Adolesc Heal 2003;33:31–8.
[57] Lyon ME, Trexler C, Akpan-Townsend C, et al. A family group approach to increasing adherence to therapy in HIV-infected youths: results of a pilot project. AIDS Patient Care STDS 2003;17:299–308.
[58] Reisner SL, Mimiaga MJ, Skeer M, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. Top HIV Med 2008;17:14–25.
[59] Hanchak NA, Patel MB, Berlin JA, et al. Patient misunderstanding of dosing instructions. J Gen Intern Med 1996;11:325–8.
[60] Kalichman SC, Benotsch E, Suarez T, et al. Health literacy and health-related knowledge among persons living with HIV/AIDS. Am J Prev Med 2000;18:325–31.
[61] Veinot TC, Flicker SE, Skinner HA, et al. Supposed to make you better but it doesn't really": HIV-positive youths' perceptions of HIV treatment. J Adolesc Health 2006;38:261–7.
[62] Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. AJE 1995;142:1255–64.