HIV and AIDS Research Journal

Research Article

A SCITECHNOL JOURNAL

Impact of Baseline NNRTI Resistance in Antiretroviral-naïve Patients with HIV in A Large Urban Clinic

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Abstract

Background: Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are prone to baseline resistance and potential early treatment failure. We investigated the NNRTI resistance profiles of antiretroviral therapy (ART)–naive patients with HIV in a large urban clinic and assessed their response to initial ART.

Materials and Methods: This was a retrospective cohort study of ART-naive patients, who had baseline genotypes, starting ART prior to July 16, 2015. Cox regression was used to determine the impact on time to viral suppression with baseline NNRTI resistance as the primary covariate of interest. Of those who achieved virologic suppression, Cox regression was used to determine the impact on viral rebound [viral load (VL) ≥ 200 copies/mL or two VLs at least two weeks apart ≥ 50 copies/mL].

Results: Of the 1220 included, 84 (6.9%) had baseline NNRTI resistance (34-103N, 19-138A/G/K, 15-181C, 16-17D/E, and 7-101E/H/P). Of the 84, 7 had 184V, 20 had other NRTI mutations and 6 had PI mutations. Patients without NNRTI mutations were most commonly started on NNRTI-based regimens (41%), followed by PI-based (30%) and then integrase inhibitor (INI)-based regimens (11%). Patients with baseline NNRTI resistance were most commonly started on PI-based regimens (42%), followed by INI-based regimens (19%). Overall 83% with NNRTI mutations achieved viral suppression as compared to 84% without NNRTI mutations. In multivariable analysis, adjusting for age, gender, baseline VL and CD4 count, duration of HIV and baseline PI mutations, the presence of NNRTI mutations did not impact virologic suppression (aHR=0.96; 95%CI=0.74-1.23). For virologic rebound, after adjusting for the same covariates, the presence of NNRTI mutations did not impact virologic rebound (aHR=1.10; 95%CI=0.67-1.81).

Conclusions: Despite having baseline NNRTI mutations, the majority of the patients reached viral suppression and did not experience virologic rebound. It's reassuring to clinicians that those with baseline NNRTI mutations still respond well to ART.

Keywords

HIV; Antiretroviral-naïve; NNRTI resistance; Antiretroviral therapy; Viremia; Mutations

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Received: January 8, 2018 **Accepted:** January 16, 2018 **Published:** January 24, 2018

Abbreviations: HIV-Human Immunodeficiency Virus; NNRTI-Non-Nucleoside Reverse Transcriptase Inhibitor; ART-Antiretroviral Therapy; NRTI-Nucleoside Reverse Transcriptase Inhibitor; PI-Protease Inhibitor

Introduction

Antiretroviral therapy (ART) is highly effective at suppressing HIV and prolonging the lives of those living with the virus. However, there are still issues and barriers in achieving ideal health outcomes. For example, both clinical and psychosocial factors in patients lead to non-adherence, drug resistance, and drug toxicity in patients taking ART, which limits treatment efficacy, compromises virologic suppression and decreases overall health [1,2]. Durable viral suppression is important during the treatment of HIV because it lowers the risk of both AIDS-defining and non-AIDS-defining illnesses and death and improves immune function and overall quality of life [3]. It has been suggested that suboptimal adherence to ART accounts for 28% to 40% of virologic failure and regimen discontinuities [4,5]. Common reasons for non-adherence are mental health conditions, active substance use, chaotic lifestyles, low levels of social support and possible dissatisfaction with the prescribed regimen [5]. Non-adherence to ART and the emergence of drug resistant mutations are largely correlated as non-adherence leads to viral replication in the presence of sub-optimal drug levels and the development of drug-resistant mutations. In addition, loss of virologic control due to non-adherence to ART can result in the transmission of a drug resistant virus. Therefore, it is currently standard practice to do an HIV genotype on the virus in ART-naïve patients. If an ART-naïve patient has baseline drug resistance, it potentially restricts the number of suitable treatment options and may impact the response of ART. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), the most commonly prescribed third ART class worldwide, are particularly prone to treatment failure and drug resistance as high-level drug resistance has been associated with a single point mutation within the binding site of reverse transcriptase [6-8]. The licensed first generation NNRTIs are nevirapine (NVP), efavirenz (EFV), and delavirdine (DLV) and over 40 amino acid substitutions are associated with resistance to theses NNRTIs [9-11]. Specifically, the two most prevalent mutations observed in patients experiencing resistance to NNRTIs are K103N and Y181C, related to EFV and NVP use, respectively, [10-12], and have been reported to result in virologic failure in 50-70 % if present [13]. Previous research suggests that K103N reduces EFV susceptibility 25-fold, and the Y181C mutation confers very high-level resistance (50-100 fold) to NVP and DLV-administered patients [14]. Despite EFV-based regimens being removed as a recommended regimen for ART-naïve patients in many guidelines, it is still one of the most commonly used third agents as it is available in a single tablet regimen and is available worldwide at a lower cost [3]. Second-generation NNRTIs currently include etravirine (ETR) and rilpivarine (RPV), which display a better resistance profile and an increased genetic barrier to the development of resistance. Unfortunately, second generation NNRTIs exhibit their own weaknesses as RPV requires concomitant food intake for its absorption, is contraindicated with the commonly prescribed proton-pump inhibitors and it is not recommended in RT-naïve patients with baseline viral loads ≥ 100,000 copies/mL [15,16]. While an excellent

NNRTI, ETR's labeling is limited to patients with drug resistance or who require a second line regimen [17]. A third generation NNRTI, called doravirine (DOR), has just completed its phase 3 trials and its licensing has been submitted to the Federal Drug Agency [18]. This new third generation NNRTI is unique in that it does not have any food restrictions, has a very favourable toxicity profile and is active against NNRTI-resistant virus [19]. With the release of a new NNRTI, we believed that data was warranted with regards to the baseline resistance profiles of ART-naïve patients in a large urban HIV clinic and to determine the virologic response in patients with baseline NNRTI resistance. Therefore, our study investigated the baseline resistance profiles of ART–naïve patients seen at our clinic, most interested in NNRTI resistance and assessed their virologic responses, both viral suppression and rebound, of patients with and without baseline NNRTI resistance after starting ART.

Materials and Methods

Study setting and population

Patient data was collected retrospectively from January 1, 1995 to July 16, 2015 who received care at Maple Leaf Medical Clinic (MLMC) during that time. As of July 2015, MLMC housed 13 doctors and provides HIV primary-care and community-specific specialty care to over 4,000 HIV-positive and approximately 9,000 HIV-negative patients. Among the 4,000 HIV-positive patients ever seen at MLMC, approximately 2,800 are actively receiving care (defined as having at least one doctor visit in the last two years). Of the 2,800 patients in care at MLMC, 2,611 were currently on a ART regimen as of July 2015. Data for this project was collected from the Electronic Medical Record (EMR) system, HSPractice (v3.1.3). The EMR contains baseline demographic and clinical characteristics of HIV-positive patients prospectively collected since January 1, 2005. Retrospective medical information from dates prior to January 1, 2005 were transferred to the EMR from paper charts, creating a complete dataset on all HIV positive patients receiving care at the clinic. Standard Operational Procedures (SOPs) were developed for retrospective data capture by our "Back Data Entry" staff as well as for prospective data capture for Administrative, Clinical and Research staff. Inclusion criteria for this analysis were 1) being HIV positive; 2) being 16 years of age or older at baseline assessment (i.e.at first cART initiation); 3) having a baseline viral load result available prior to the start of ART; 4) having a baseline genotype testing done (any time before and up to 3 weeks after the start of ART); and 5) initiating combination ART from January 1, 1995 to July 16, 2015. Patients were excluded from this analysis if any viral load prior to baseline was <200 copies/mL (as some patients could have been transferred from other clinics on ART). Baseline assessment of variables took place at the onset of the initial ART regimen. In order to fully characterize the specific populations, we divided the study population into two groups: 1) those with baseline NNRTI mutations and 2) those with no baseline NNRTI mutations.

Outcomes, exposures of interest and other variables

The primary outcome of this study was to determine the time to virologic suppression in ART-naïve patients with or without NNRTI resistance initiating ART and the secondary outcome was to determine time to virologic rebound in those ART-naïve patients who achieved suppression. Virologic suppression was defined as a viral load < 50 copies/mL or < 40 copies/mL (after January 1, 2011 due to a change in vial load testing assay) by six months after initiating ART. Virologic rebound was defined as a viral load ≥ 200 copies/ or two 2 consecutive viral loads > 50 copies/mL after virologic suppression. The primary exposure of interest was the presence of baseline NNRTI mutations. We also reported on nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) mutations. Resistance testing at MLMC is carried out at the British Columbia Centre for Excellence in HIV/AIDS (Vancouver, British Columbia, Canada) using validated "in-house" methods [20]. Pre-treatment resistance testing has become standard for patients prior to starting ART; however, some were missed due to being transferred from another clinic. Follow-up resistance testing is conducted on any sample with a viral load ≥ 200 copies/mL. The resistance profiles were described for each ART class and further classified by drugs within the classes**.** Other independent variables included demographic data: age, gender, ethnicity, HIV risk factors *[men who have sex with men (MSM), being heterosexual, injection drug use (IDU), having multiple partners, coming from an endemic region, having an HIV-positive partner, accidental exposure, blood transfusion, other and no risk factor)]*, and ethnicity *(Caucasian, Black, East Asian, South Asian, Hispanic, Aboriginal, mixed, other, missing, and unknown)*; and clinical data: years from HIV diagnosis prior to baseline genotype, years from HIV diagnosis prior to initiating cART, baseline HIV viral load, baseline CD4+ count, hepatitis C (HCV) and hepatitis B (HBV) status, ART regimen, follow-up genotype tests if available, baseline NNRTI mutations, baseline 184V mutation, baseline 65R mutation, other baseline NRTI mutations, baseline PI mutations, and frequency of viral load testing per year. At MLMC, the general practice is to see patients monthly after the start of ART monthly until virologic suppression is achieved and then every 3-4 months thereafter. Viral load testing in Ontario is done using Abbott's *m*2000 RealTi*me*™ System and RealTi*me*™ HIV-1 assay (Abbott Molecular Inc., Mississauga, Ontario, Canada) as of August 16, 2010 and Siemens' Versant® HIV-1 bDNA 3.0 Assay (Siemens, Oakville, Ontario, Canada) prior to this date.

Statistical analyses

Demographic and clinical data were summarized using frequencies and proportions for categorical variables and compared using the Chi-square test and medians and interquartile ranges (IQRs) for continuous variables and compared using the Wilcoxon rank sum test. Cox proportional hazard models were used to assess if the presence of baseline NNRTI resistance was associated with time to virologic suppression adjusting for other covariates. Assumptions for the proportional hazard models were checked and met. Censoring occurred if a patient died, was transferred to another clinic, was lost to follow up for two years, or if the end of follow up was reached at July 16, 2015. Covariates associated with time to suppression in the univariate analyses with a $p<0.10$ were included in the multivariable model and backwards selection method was used to develop the final model. A stepwise multivariable Cox proportional hazard models were also used to assess if the presence of baseline NNRTI resistance was associated with time to virologic rebound in patients who achieved viral suppression adjusting for other covariates. Assumptions for the proportional hazard models were checked and met. The same censoring and methods to develop the multivariable model was used.

Results

Study population

Of the 1,220 that fit the inclusion criteria, 95 % were male and the mean age was 38 years (IQR=31-44). 77.7 % of patients were

MSM and 69.7% of our total population was Caucasian. The median baseline log_{10}VL of the total cohort was 4.74 copies/mL (IQR=4.18-5.23) and baseline CD4+ count was 290 cells/μL (IQR=190-410). The median duration from HIV diagnosis prior to baseline genotype was 0.1 years (IQR=0-0.7). The median duration of HIV prior to ART initiation was 1.8 years (IQR=0.3-4.6); 0.9 (IQR-0.2-2.8) for those with baseline NNRTI resistance mutations and 1.9 (IQR-0.3-4.7) for those without baseline NNRTI resistance mutations (p=0.01). Baseline characteristics are summarized in more detail in Table 1.

Summary of baseline NNRTI resistance

Of the total study population, 84 (6.9 %) had baseline NNRTI resistance and 1136 (93.1%) did not. Patients without NNRTI mutations were most commonly started on NNRTI-based regimens (41%), followed by PI-based (30%) and finally, an integrase inhibitor (INI)-based regimens (11%). Patients with baseline NNRTI resistance were most commonly started on PI-based regimens (42%), followed by INI-based regimens (19%). Of the 84 with baseline NNRTI mutations, 7 (8%) had 184V, 20 (24%) had other NRTI mutations and 6 (7%) had PI mutations. Of the 1136 without baseline NNRTI mutations, 5 (0.4%) had 184V (p<0.0001), 49 (4%) had other NRTI mutations (p<0.0001) and 24 (2%) had PI mutations (p=0.004). On average, those with baseline NNRTI mutations experienced more frequent viral load testing [median=4.1 years; (IQR=3.2-5.1)] than those without baseline NNRTI mutations [3.7 years; (IQR=2.9-4.6)] (p=0.02). As seen in Table 2, all resistance mutations were reported and divided by classes. Of the 84 patients with baseline NNRTI mutations, 34 had a 103N substitution, 19 had 138A/G/K, 15 had 181C, 16 had 17D/E and 7 had 101E/H/P. In addition, 6 patients had 190A, and 100I, 103S, 106A, 106M, 188L, and 190S mutations were all found in one patient each. In descending order, the most prevalent baseline NRTI mutations were 41L, 67N, 219Q, 184V, 210W, 70R, which were experienced in 49, 15, 13, 12, 12, and 8 patients, respectively. Minor NRTI mutations included 6 with 215F/Y, 2 with 219E, 1 with 70E, and 6 with 74I/V. Lastly, out of the 65 baseline PI resistance mutations that were found, 15 had 90M, 13 had 82A/V, 9 had 46/I/L, 14 had 54 L/T/V, and 6 had 48V. PI mutations that occurred less frequently include 2 with 24I, 3 with 32I, 1 with 47V, 1 with 76V, and 2 with 84V. No baseline INI resistance mutations were observed; however, it is important to note that it was not routine to do baseline INI resistance testing during the time period of this analysis.

Virologic response of those with versus without baseline NNRTI resistance

Viral suppression was observed for 1028 out of 1220 (84%) individuals included in this analysis (84%); 83% (70/84) and 84% (958/1136) of patients with and without NNRTI mutations achieved suppression, respectively (p=0.81). In univariate Cox regression, the presence of baseline NNRTI resistance did not impact viral suppression (HR=0.98; 95%CI=0.77-1.25) (Table 3). In multivariable analysis, adjusting for age, gender, baseline VL and CD4 count, duration of HIV and baseline PI mutations, the presence of NNRTI mutations still did not impact viral suppression (aHR=0.96; 95%CI=0.74-1.23) (Table 3). For viral rebound, the presence of baseline NNRTI resistance also did not impact its occurrence in the univariate analysis (HR=1.11; 95% CI=0.68-1.81) (Table 4). In multivariable analysis, after adjusting for age, gender, baseline VL and CD4 count, duration of HIV and baseline PI mutations, the presence of NNRTI mutations also did not impact viral rebound (aHR=1.10; 95%CI=0.67-1.81) (Table 4).

Discussion

Non-nucleoside reverse transcriptase inhibitors have historically the most commonly prescribed third antiretroviral agent as part of combination ART for patients with HIV. Due to multiple limitations, this could change worldwide such that INI could become the class mostly used as the anchor or ART regimens. Recently a third generation NNRTI has been released, DOR, with minimal limitations, which could contribute the NNRTI class still playing an important role as a third agent. We determined in our large urban practice that baseline NNRTI resistance was only moderately common with 84 of 1,220 (6.9 %) of ART-naïve patients having such a mutation. The presence of a baseline NNRTI mutation did not impact the time to virologic suppression nor the time to virologic rebound in those who did achieve suppression. Therefore, we conclude that the presence of baseline NNRTI resistance is of minimal significance. The prevalence of baseline NNRTI resistance was higher in our cohort than reported internationally [21-23]; however, comparable to high prevalence areas of Canada [20]. Previous studies in western societies describe a large range of baseline NNRTI resistance mutation levels, as the rates largely depend on the demographic characteristics of the cohort and the epidemiologic situation in the geographic area [20-23]. For example, a survey of treatment-naïve patients conducted in the United States (US), from the Centers for Disease and Prevention, reported a baseline NNRTI resistance prevalence of 1.7% [21]. In this study, efficacy of first-line therapy ranged from a high of 75% viral suppression at 48 weeks in patients with no PI or NRTI resistance who start receiving a lopinavir/ritonavir-based initial regimen to 19% viral suppression at 48 weeks in patients with baseline NNRTI resistance who start receiving an EFV-based initial regimen [21,22]. Similarly, the Terry Beirn Community Program for Clinical Research on AIDS (CPCRA), a multicenter network encompassing 25 US cities, found an overall prevalence of resistance of 3% in their cohort of antiretroviral-naïve HIV-positive patients [23]. In contrast, within Canada, a previous cohort study in British Columbia (1996-1999) detected NNRTI resistance mutations in approximately 10% (n= 120/1191) of their cohort in which the majority of patients were administered NVP (n= 288, 96.6%) followed by EFV (n= 8, 2.7%) [20]. Interestingly, our results show that the clinical significance of NNRTI resistance may not be as large as previously believed. In our analysis, those with NNRTI resistance mutations experienced similar virologic responses to those without NNRTI resistance mutations. We found that HIV-positive patients with NNRTI resistance mutations were most regularly administered PI-based regimens; however, this may not be the most beneficial option for all patients due to the metabolic and cardiovascular toxicities linked to the PI class [24]. Therefore, there could be a role for a third generation NNRTI, DOR, in such patients. There are several limitations that exist within our study. First, selection bias and generalizability issues may be relevant because the primary HIV clinic is in Toronto, a highly populated, urban centre. Toronto represents the residence of most our cohort; however, it differs demographically to less dense areas of Canada and the rest of the world as most of our cohort were MSM. In addition, our investigation was retrospective and data was obtained from EMRs, leading to inevitable channeling bias, attrition bias, and unmeasured confounding variables. Common confounding variables that were demonstrated in similar studies were lacking such as ART adherence and detailed substance use. Finally, missing data is always an important limitation of retrospective chart reviews. In summary, our retrospective clinical chart review demonstrates a baseline NNRTI resistance prevalence of 6.9 % in ART-naive patients beginning combination ART in our clinic. Despite having baseline NNRTI mutations, most patients (83 %) achieved viral suppression

Table 1: Demographic and baseline characteristics of the study population.

Description		All	Baseline NNTRI Mutations	No Baseline NNTRI Mutations	P-value
Total Population (All patients with BL genotype & started ARV), **n%**		1220 (100%)	84 (6.9%)	1136 (93.1%)	
Age, Median (IQR)		38 (31,44)	38 (31,46)	38 (31,44)	0.8362
Gender, n (%)	Males	1158 (94.9%)	76 (90.5%)	1082 (95.2%)	0.0547
	Females	62 (5.1%)	8 (9.5%)	54 (4.8%)	
Risk factors, n (%)	MSM	654/842 (77.7%)	35/48 (72.9%)	619/794 (78.0%)	0.4152
	Heterosexual	64/842 (7.6%)	4/48 (8.3%)	60/794 (7.6%)	0.7789
	IDU	21/842 (2.5%)	1/48 (2.1%)	20/794 (2.5%)	1.0000
	Endemic region	20/842 (2.4%)	2/48 (4.2%)	18/794 (2.3%)	0.3174
	Other risk factor	83/842 (9.9%)	6/48 (12.5%)	77/794 (9.7%)	0.5271
Ethnicity, n (%)	Caucasian	749/1075 (69.7%)	45/73 (61.6%)	704/1002 (70.3%)	0.1221
	Black	93/1075 (8.7%)	8/73 (11.0%)	85/1002 (8.5%)	0.4675
	Asian	72/1075 (6.7%)	8/73 (11.0%)	64/1002 (6.4%)	0.1314
	Hispanic	71/1075 (6.6%)	4/73 (5.5%)	67/1002 (6.7%)	1.0000
	Aboriginal	10/1075 (0.9%)	0/73 (0.0%)	10/1002 (1.0%)	1.0000
	Other	80/1075 (7.4%)	8/73 (11.0%)	72/1002 (7.2%)	0.2356
Years from HIV diagnosis prior to BL genotype, Median (IQR)		0.1 (0,0.7)	0.1 (0,0.2)	0.1 (0,0.8)	0.0494
BL CD4 count, Median (IQR)		290 (190,410)	333 (200,435)	290 (190,407)	0.2778
BL CD4 count, n (%)	<200 cells/mm^3	308 (25.8%)	18 (22.5%)	290 (26.1%)	0.4827
	>=200 cells/mm^3	885 (74.2%)	62 (77.5%)	823 (73.9%)	
BL $\log_{10}$ HIV viral load, Median (IQR)		4.74 (4.18,5.23)	4.63 (4.05,5.28)	4.74 (4.19,5.23)	0.5582
BL viral load, n (%)	<100,000 copies/mL	782 (64.1%)	56 (66.7%)	726 (63.9%)	0.6111
	>=100,000 copies/mL	438 (35.9%)	28 (33.3%)	410 (36.1%)	
HCV status, n (%)	missing	1151 (94.3%)	80 (95.2%)	1071 (94.3%)	0.5664
	no	18 (1.5%)		18 (1.6%)	
	yes	51 (4.2%)	4 (4.8%)	47 (4.1%)	
HBV status, n (%)	missing	346 (28.4%)	27 (32.1%)	319 (28.1%)	0.4381
	no	844 (69.2%)	54 (64.3%)	790 (69.5%)	
	yes	30 (2.5%)	3 (3.6%)	27 (2.4%)	
Started ART, n (%)	Started ART	1220 (100.0%)	84 (100.0%)	1136 (100.0%)	
Years from HIV diagnosis to ART, Median (IQR)		1.8 (0.3,4.6)	0.85 (0.2,2.8)	1.9 (0.3,4.7)	0.0077
Years of ART (if started), Median (IQR)		4.9 (2.8,7.75)	3.65 (1.5,6.85)	5 (2.8,7.85)	0.0080
ART regimen, n(%)	NNRTI	16/1220 (1.3%)	0/84 (0.0%)	16/1136 (1.4%)	0.6199
	NRTI	16/1220 (1.3%)	1/84 (1.2%)	15/1136 (1.3%)	1.0000
	NRTI+INI	144/1220 (11.8%)	16/84 (19.0%)	128/1136 (11.3%)	0.0330
	NRTI+NNRTI	469/1220 (38.4%)	9/84 (10.7%)	460/1136 (40.5%)	<.0001
	NRTI+NNRTI+INI	16/1220 (1.3%)	2/84 (2.4%)	14/1136 (1.2%)	0.3029
	NRTI+NNRTI+PI	25/1220 (2.0%)	0/84 (0.0%)	25/1136 (2.2%)	0.4096
	NRTI+PI	372/1220 (30.5%)	35/84 (41.7%)	337/1136 (29.7%)	0.0211
	NRTI+PI+INI	26/1220 (2.1%)	6/84 (7.1%)	20/1136 (1.8%)	0.0010
	NRTI+PI+INI+EI	13/1220 (1.1%)	3/84 (3.6%)	10/1136 (0.9%)	0.0545
	PI	13/1220 (1.1%)	0/84 (0.0%)	13/1136 (1.1%)	1.0000
	Other	110/1220 (9.0%)	12/84 (14.3%)	98/1136 (8.6%)	0.0806
Follow-up genotype tests available, n (%)	no	1077 (88.3%)	74 (88.1%)	1003 (88.3%)	0.9568
	yes	143 (11.7%)	10 (11.9%)	133 (11.7%)	
BL 184V mutation, n (%)	no	1208 (99.0%)	77 (91.7%)	1131 (99.6%)	<.0001
	yes	12 (1.0%)	7 (8.3%)	5 (0.4%)	
BL 65R mutation, n (%)	no	1220 (100.0%)	84 (100.0%)	1136 (100.0%)	
BL NRTI mutations, n (%)	no	1151 (94.3%)	64 (76.2%)	1087 (95.7%)	<.0001
	yes	69 (5.7%)	20 (23.8%)	49 (4.3%)	
BL PI mutations, n (%)	no	1190 (97.5%)	78 (92.9%)	1112 (97.9%)	0.0041
	yes	30 (2.5%)	6 (7.1%)	24 (2.1%)	
Frequency of viral load testing per year, Median (IQR)		3.65 (2.89,4.62)	4.06 (3.19,5.10)	3.62 (2.88,4.59)	0.0188
Last viral load available, Median (IQR)		0 (0,<40)	0 (0,<40)	0 (0,<40)	0.4251

NNRTI, non-nucleoside reverse transcriptase inhibitor; IQR, interquartile range; MSM, men who have sex with men; BL, baseline; HCV, hepatitis C; HBV, hepatitis B; ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; INI, integrase inhibitor; PI, protease inhibitor

Table 2: Baseline resistance profile.

Baseline mutations		Frequency
ART class	Resistance mutation	
NNRTI	100I	1
	101E	4
	101H	1
	101P	2
	103N	34
	103S	1
	106A	1
	106M	1
	138A	16
	138G	2
	138K	1
	179D	11
	179E	5
	181C	15
	188L	1
	190A	6
	190S	1
NRTI	184V	12
	210W	12
	215F	2
	215Y	4
	219E	2
	219Q	13
	41L	49
	67N	15
	70E	1
	70R	8
	74I	3
	74V	3
PI	24I	2
	32I	3
	46I	8
	46L	1
	47V	1
	48V	6
	54L	2
	54T	9
	54V	3
	76V	1
	82A	12
	82V	1
	84V	1
	90M	15

NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor

Table 3: Unadjusted and adjusted cox proportional hazard models: viral suppression.

	Unadjusted Proportional Hazard Model				Adjusted Proportional Hazard Model			
Label	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**P-value**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**P-value**
Age	1.00	1.00	1.01	0.27	1.00	1.00	1.01	0.57
Gender (Male vs. Female)	1.26	1.01	1.58	0.04	1.07	0.79	1.46	0.65
Baseline NNRTI mutations (yes vs. no)	1.03	0.80	1.31	0.85	1.05	0.81	1.35	0.72
Baseline PI mutations (yes *vs.* no)	1.05	0.68	1.62	0.82	0.99	0.63	1.55	0.96
Baseline $\log_{10}$ HIV viral load (per one unit of $\log_{10}$ (VL))	0.79	0.75	0.84	<.0001	0.66	0.61	0.72	<.0001
Baseline CD4+ count (per one cell/mm^3)	1.00	1.00	1.00	0.09	1.00	1.00	1.00	0.05
Years from HIV diagnosis to start of ART (per one year)	0.99	0.98	1.01	0.23	0.99	0.97	1.01	0.16

ART, antiretroviral therapy

Table 4: Unadjusted and adjusted proportional hazard models: viral rebound.

	Unadjusted Proportional Hazard Model				Adjusted Proportional Hazard Model			
Label	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**P-value**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**P-value**
Age	1.00	0.99	1.01	0.30	1.00	0.98	1.01	0.67
Gender (Male *vs.* Female)	1.08	0.73	1.59	0.72	1.23	0.73	2.05	0.44
Baseline NNRTI mutations (yes *vs.* no)	0.92	0.56	1.50	0.72	0.91	0.55	1.49	0.69
Baseline PI mutations (yes *vs.* no)	0.80	0.38	1.69	0.55	0.83	0.37	1.89	0.66
Baseline $\log_{10}$ HIV viral load (per one unit of $\log_{10}$ (VL))	1.03	0.92	1.17	0.60	1.18	1.00	1.38	0.05
Baseline CD4+ count (per cell/mm^3)	1.00	2.00	1.00	0.98	1.00	1.00	1.00	0.12
Years from HIV diagnosis to start of ART (per one year)	1.01	0.99	1.03	0.31	1.00	0.97	1.03	0.87

and did not experience increased risk of viral rebound; similarly to those without baseline NNRTI resistance. It is likely that baseline NNRTI resistance prevalence will decrease further over time with better third agents and will make the phenomenon even less clinically relevant than we have found.

Acknowledgements

We would like to thank the patients and research staff at the Maple Leaf Medical Clinic for making this work possible.

Disclosures and Funding

Fred Crouzat, Graham Smith, Colin Kovacs, David Fletcher, David Knox, Barry Merkley and Mona Loutfy have acted as Advisory Board members for Gilead Science Canada, Merck Frosst Canada and ViiV Healthcare. Funding was provided by Merck Frosst Canada for the analysis. Funders were not involved in protocol, statistical plan or manuscript writing in any form.

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