PEB0254

Prevalence and Risk Factors of Preexisting NNRTI Resistance Among Suppressed PLWH in B/F/TAF Switch Studies

Kristen Andreatta, Rima Acosta, Michelle L. D'Antoni, Madeleine Willkom, Hui Liu, Ross Martin, Silvia Chang, Lilian Wei, Sean Collins, Hal Martin, Kirsten L. White — Gilead Sciences, Inc., Foster City, California, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

- There is a high prevalence of NNRTI resistance (-R) substitutions in people living with HIV (PLWH)
  - NNRTIs were widely prescribed 3rd agents in ARV regimens before the era of INSTIs
  - Recent approval of the INSTI dolutegravir (DTG) and NNRTI rilpivirine (RPV) as a 2-drug regimen renew the importance of assessing preexisting NNRTI-R
  - Many NNRTIs have low genetic barriers to resistance; NNRTI-R linked with NRTI-R is common after virologic failure on an NNRTI-based regimen[1-3]
  - NNRTI-resistant viruses are relatively fit, leading to persistence in circulating and archived viral genomes, with high rates of transmission[3-5]
- Resistance to early NNRTIs (efavirenz and nevirapine) occurs primarily through the K103N/S or Y181C pathway; resistance to later NNRTIs, such as RPV, occurs through additional pathways that are often cross-resistant to multiple NNRTIs[6]
- Complete ARV history and drug resistance data are critical when considering an ARV regimen switch; however, medical records are often incomplete or missing
  - Routine resistance testing is not possible in virologically suppressed PLWH; proviral DNA genotyping is an option, but lacks sensitivity[7-9]
- The bictegravir/emtricitabine (FTC)/tenofovir alafenamide (B/F/TAF) single-tablet regimen is a DHHS, IAS-USA, and EACS guidelines-recommended regimen for the treatment of HIV infection[10-12]
  - Bictegravir is an INSTI; FTC and TAF are NRTIs
- No treatment-emergent resistance to B/F/TAF has been detected to date in clinical trials
  - Treatment-naïve adults: 2 Phase 3 studies of 634 participants through 144 wk[13]
  - Suppressed switch adults: 6 Phase 3/3b studies of 1781 participants through 116 wk[14-23]
  - Suppressed switch adolescents and children: 1 Phase 2/3 study of 100 participants through 48 wk[24]
- High rates of virologic suppression were maintained in participants with preexisting NNRTI-R who switched to B/F/TAF[14-17,25]
  - Preexisting NNRTI-R was observed in ~15% of virologically suppressed participants, including ~10% with M184V/I
- The Phase 3 studies 1844, 1878, 4030, and 4580 demonstrated the safety and noninferior efficacy of switching to B/F/TAF in virologically suppressed HIV-1–infected adults (aged ≥18 years)[18,19,22,23]
  - High rates of virologic suppression were maintained after switching to B/F/TAF through 116 wk[14-17]

Objective

- To determine the prevalence of preexisting NNRTI resistance and associated risk factors among 2200 virologically suppressed clinical trial participants in Studies 1844, 1878, 4030, and 4580

Methods

Overview of B/F/TAF Switch Studies in Virologically Suppressed Adults*

Study	Resistance Criteria	Baseline ARV Regimen	Participants, n	Study Phase and Treatment: Randomized Phase Through Week 48	Study Phase and Treatment: Open-label Extension
1844	FTC-R or TFV-R excluded	DTG + ABC/3TC (either STR or MTR)	282	B/F/TAF (DTG/ABC/3TC placebo)	B/F/TAF
			281	DTG/ABC/3TC (B/F/TAF placebo)	B/F/TAF
1878	FTC-R or TFV-R excluded	Boosted DRV or ATV + either F/TDF or ABC/3TC	290	B/F/TAF	B/F/TAF
			287	SBR	B/F/TAF
4030	NRTI-R, NNRTI-R, PI-R allowed; INSTI-R excluded	DTG + either F/TAF or F/TDF	284	B/F/TAF (DTG + F/TAF placebo)	—
			281	DTG + F/TAF (B/F/TAF placebo)	—
4580	NNRTI-R or PI-R allowed; INSTI-R excluded; NRTI-R: M184V/I, <2 TAMs allowed, K65R/E/N, T69 insertions, ≥3 TAMs excluded	Any 3rd agent + 2 NRTIs	330	B/F/TAF	—
			165	SBR (through Week 24)	B/F/TAF (Weeks 24–48) —

*ClinicalTrials.gov NCT02603120, NCT02603107, NCT03110360, and NCT03631732. 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; DRV, darunavir; MTR, multitablet regimen; PI, protease (PR) inhibitor; -R, resistance; SBR, stay on baseline regimen; STR, single-tablet regimen; TAMs, thymidine analog mutations; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Baseline Genotypic Analyses

- Historical HIV-1 genotype reports were collected if available on enrollment
- HIV-1 proviral DNA genotype testing (GenoSure Archive®, Monogram Biosciences, South San Francisco, California, USA) was performed on baseline samples
  - Bioinformatic filters removed APOBEC–mediated hypermutated deep-sequence reads from GenoSure Archive results to prevent overreporting of E138K, M184I, and M230I in reverse transcriptase (RT) and G163R in integrase (IN)
- Participants with preexisting resistance detected after enrollment continued on study and were included in all analyses

HIV-1 Drug-Resistance Substitutions (based on IAS-USA)[6]

NRTI-R	K65R/E/N, T69 insertions, K70E, L74V/I, Y115F, Q151M, M184V/I, TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R)
NNRTI-R	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L
PI-R	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
INSTI-R	**Primary:** T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K **Secondary:** M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A

Statistical Analyses

- Potential risk factors for NNRTI-R or RPV-R were assessed using a multivariate logistic-regression model, with stepwise selection significance level for entry α=0.20 and significance level for stay α=0.05, and adjusted for study-specific effects

Intrinsic predictors	Groups of age, sex, race, ethnicity, BMI, CKD stage
HIV-specific variables at baseline	CD4, HIV RNA, HIV disease status, time since ARV start, prior treatment with any NNRTI, RPV, NNRTI other than RPV, PI, INSTI, or non-DTG INSTI (RAL, EVG), number of prior 3rd agents, number of prior 3rd agent classes, duration of baseline ARV regimen
HIV resistance variables	Any NRTI-R, M184V/I, NRTI-R other than M184V/I, TAMs, PI-R, primary INSTI-R, secondary INSTI-R

BMI, body mass index, CD4, cluster of differentiation-4; CKD, chronic kidney disease; EVG, elvitegravir; RAL, raltegravir.

B/F/TAF Efficacy Analysis

	Pooled B/F/TAF	Study 1844		Study 1878		Study 4030	Study 4580	
		Group 1*	Group 2†	Group 1*	Group 2†		Group 1*	Group 2‡
Participants analyzed, n	**1849**	281	264	289	243	283	327	162
Analysis time point	–	OLE median Week 117	OLE median Week 50	OLE median Week 116	OLE median Week 71	Week 48	Week 48	Week 24§

*Switched to B/F/TAF on Day 1 of randomized phase; †Continued baseline regimen during randomized phase and switched to B/F/TAF in open-label extension (OLE); ‡Switched to B/F/TAF at Week 24 of randomized phase; §Over the B/F/TAF Week 24 (equivalent to study Week 48).

- Analysis included participants who switched to B/F/TAF during randomized or OLE phases and had ≥1 on-treatment HIV-1 RNA measurement
- Virologic outcomes based on last available on-treatment HIV-1 RNA using last observation carried forward (LOCF) imputation: <50 copies/mL (success) or ≥50 copies/mL (failure)
  - All participants with data, including those with early discontinuation, had virologic outcomes determined

Results

Table 1: Frequency of Baseline Resistance-Associated Substitutions in B/F/TAF Switch Studies

Baseline Genotype, % (n or n/N)	All Participants N=2200	Study 1844		Study 1878		Study 4030		Study 4580	
		B/F/TAF n=282	DTG/ABC/3TC n=281	B/F/TAF n=290	SBR n=287	B/F/TAF n=284	DTG + F/TAF n=281	B/F/TAF n=330	SBR n=165
PR/RT data available (historical and/or proviral)	91 (1995)	95 (268)	93 (260)	96 (277)	86 (247)	84 (238)	83 (232)	95 (315)	96 (158)
NNRTI-R	22 (448/1995)	17 (45/268)	17 (44/260)	29 (80/277)	24 (59/247)	26 (61/238)	25 (57/232)	22 (70/315)	20 (32/158)
NRTI-R	17 (339/1995)	10 (26/268)	8 (22/260)	23 (64/277)	17 (41/247)	26 (62/238)	23 (54/232)	14 (44/315)	16 (26/158)
PI-R	10 (208/1995)	10 (26/268)	11 (28/260)	10 (29/277)	10 (25/247)	6 (15/238)	10 (23/232)	11 (36/315)	16 (26/158)
IN data available (historical and/or proviral)	85 (1861)	92 (260)	86 (243)	90 (260)	79 (227)	75 (213)	71 (200)	93 (307)	92 (151)
Primary INSTI-R	4 (73/1861)	3 (7/260)	4 (10/243)	2 (6/260)	4 (8/227)	7 (15/213)	3 (5/200)	6 (18/307)	3 (4/151)
Secondary INSTI-R	49 (918/1861)	51 (133/260)	53 (130/243)	52 (134/260)	42 (96/227)	50 (107/213)	48 (95/200)	47 (145/307)	52 (78/151)

Figure 1: Baseline RT Genotypic Data Sources: % (n)

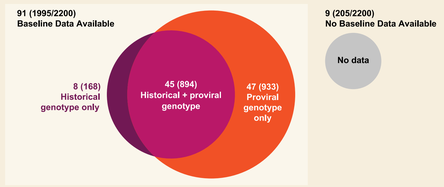


Table 2: Frequency and Detection of Preexisting NNRTI Resistance

Participants, % (n)	Cumulative Baseline Genotype n=1995	Detection Method: Historical Genotype n=1063	Detection Method: Proviral Genotype n=1827
NNRTI-R	22 (448)	17 (176)	21 (390)
K103N/S	12 (232)	10 (110)	11 (196)
RPV-R	10 (196)	6 (67)	9 (170)
L100I	<1 (4)	<1 (1)	<1 (3)
K101E/P	2 (44)	1 (12)	2 (41)
E138A/G/K/Q/R	4 (83)	3 (33)	4 (71)
V179L	<1 (1)	<1 (1)	0
Y181C/I/V	3 (53)	1 (13)	3 (47)
Y188L	1 (16)	1 (8)	1 (12)
H221Y	1 (27)	1 (7)	1 (22)
F227C	<1 (1)	0	<1 (1)
M230I/L	1 (10)	<1 (3)	<1 (8)
Other*	8 (151)	4 (42)	7 (132)
V106A/M	<1 (7)	<1 (2)	<1 (5)
V108I	3 (54)	1 (10)	3 (48)
Y188C/H	1 (14)	<1 (4)	1 (12)
G190A/E/Q/S	3 (61)	2 (20)	3 (53)
P225H	1 (27)	1 (8)	1 (24)

*Doravirine-R substitutions are V106A/M and Y188L.

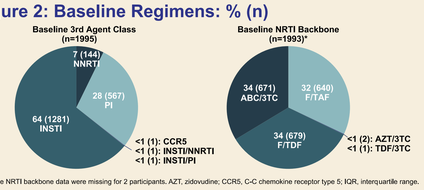
Table 3: Number of Preexisting NNRTI-R Substitutions/Participant

		Cumulative Baseline Genotype With NNRTI-R n=448	Detection Method: Historical Genotype With NNRTI-R n=176	Detection Method: Proviral Genotype With NNRTI-R n=390
Mean NNRTI-R substitutions (range)		1.4 (1–5)	1.3 (1–3)	1.4 (1–5)
Participants with NNRTI-R, % (n)	1 substitution	71 (317)	73 (128)	73 (285)
	2 substitutions	20 (89)	24 (42)	17 (68)
	≥3 substitutions	9 (42)	3 (6)	9 (37)
Comparison of numbers of NNRTI-R substitutions, % (n)*	Historical > proviral	15 (68)	—	—
	Historical = proviral	21 (95)	—	—
	Historical < proviral	64 (285)	—	—

*No genotype was imputed as 0 substitutions (n=272 for historical genotypes and 58 for proviral genotypes).

- Among all participants with baseline NNRTI-R (n=448):
  - Most had a single NNRTI-R substitution (71% [317/448])
  - Previously undocumented NNRTI-R was detected by proviral genotyping in 14% of participants (285/1995)

Figure 2: Baseline Regimens: % (n)



*Baseline NRTI backbone data were missing for 2 participants. AZT, zidovudine; CCR5, C-C chemokine receptor type 5; IQR, interquartile range.

- Median duration of baseline ARV regimen: 1.8 years (IQR 1.0, 3.6)
- 7% (145/1995) of participants were on an NNRTI at study baseline

Table 4: Baseline Characteristics by Preexisting NNRTI-Resistance Status

Participants, % (n)		With NNRTI-R n=448	No NNRTI-R n=1547	p-Value*
Age group	<50 years	56 (251)	54 (839)	0.50
	≥50 years	44 (197)	46 (708)	
Race	Black or African-American	45 (203)	37 (574)	0.002
	Nonblack	55 (244)	63 (968)	
ARV treatment history	NNRTI	39 (173)	38 (581)	0.68†
	PI	68 (306)	51 (793)	<0.001†
	RAL	16 (70)	9 (143)	<0.001†

*Determined by Cochran–Mantel–Haenszel (CMH) test; †vs no prior NNRTI, PI, or RAL treatment.

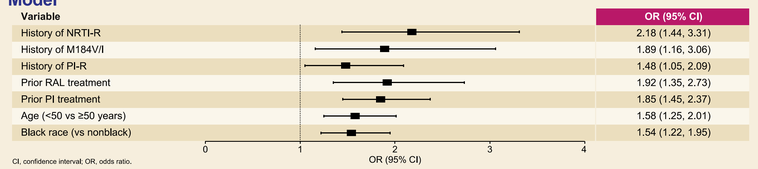
Table 5: Association of NNRTI Resistance With Other Resistance Substitutions: Univariate Analysis

Participants With Baseline Resistance, % (n)		With NNRTI-R n=448	No NNRTI-R n=1547	p-Value*
NRTI-R		35 (156)	12 (183)	<0.001
M184V/I		25 (112)	7 (101)	<0.001
NRTI-R other than M184V/I		23 (102)	8 (123)	<0.001
TAMs		19 (85)	7 (109)	<0.001
PI-R		16 (72)	9 (136)	<0.001
INSTI-R	Primary	5 (20)	4 (53)	0.31
	Secondary	47 (198)	50 (720)	0.31

*Determined by CMH test.

- Participants with NNRTI-R were more likely to also have NRTI-R (including M184V/I and TAMs) and PI-R

Figure 3: Risk Factors Associated With Preexisting NNRTI-R: Multivariate Logistic-Regression Model



CI, confidence interval; OR, odds ratio.

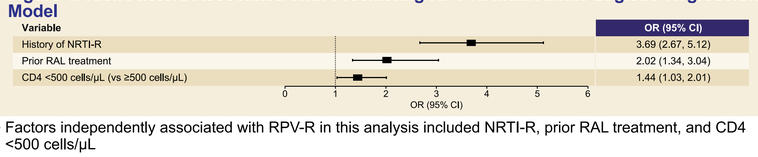
- Factors independently associated with NNRTI-R in this analysis included NRTI-R, M184V/I, and PI-R, prior RAL or PI treatment, age <50 years, and black race
- Prior NNRTI treatment was not associated with preexisting NNRTI-R, potentially due to transmitted resistance or incomplete medical history

Table 6: Baseline Characteristics by Preexisting RPV-Resistance Status

Resistance, % (n)		With RPV-R n=196	No RPV-R n=1799	p-Value*
Baseline NRTI-R substitutions		40 (79)	14 (260)	<0.001†
Baseline CD4 cell count category	<500 cells/μL	33 (65)	26 (463)	0.025
	≥500 cells/μL	67 (131)	74 (1336)	
ARV treatment history	Prior RPV treatment	10 (20)	9 (158)	0.51‡
	Prior RAL treatment	19 (38)	10 (175)	<0.001‡

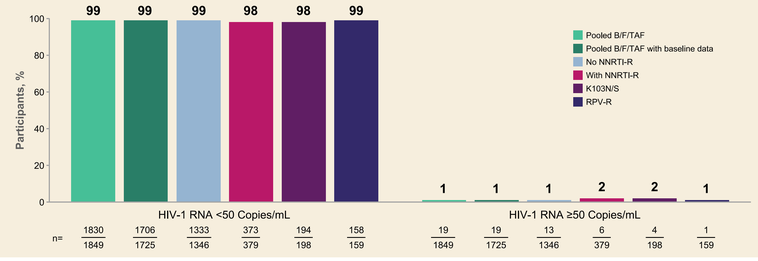
*Determined by CMH test; †vs no NRTI-R substitutions at baseline; ‡vs no prior RPV or RAL treatment.

Figure 4: Risk Factors Associated With Preexisting RPV-R: Multivariate Logistic-Regression Model



- Factors independently associated with RPV-R in this analysis included NRTI-R, prior RAL treatment, and CD4 <500 cells/μL
- Prior RPV treatment was not associated with preexisting RPV-R potentially due to transmitted resistance or incomplete medical history

Figure 5: Virologic Suppression at Last On-Treatment Study Visit by Preexisting NNRTI-R: Pooled B/F/TAF-Treated Analysis



- High rates of virologic suppression were maintained on B/F/TAF regardless of preexisting NNRTI-R
  - Median B/F/TAF treatment duration was 48 wk (IQR 48, 105) across all 4 studies
- No treatment-emergent resistance to B/F/TAF was detected

Conclusions

- NNRTI-R was the most frequently observed class of preexisting drug resistance in virologically suppressed adults who enrolled in B/F/TAF switch studies 1844, 1878, 4030, and 4580
  - 22% (448/1995) of participants had NNRTI-R and 10% (196/1995) had RPV-R at baseline
- Proviral genotyping uncovered previously undocumented NNRTI-R in 14% of participants (289/1995)
- Preexisting NNRTI-R was associated with NRTI-R, M184V, and PI-R, prior RAL or PI treatment, age <50 years, and black race; preexisting RPV-R was associated with NRTI-R, prior RAL treatment, and CD4 count <500 cells/μL
- High efficacy was observed in participants with preexisting NNRTI-R who switched to B/F/TAF
  - 99% with NNRTI-R had HIV-1 RNA <50 copies/mL at their last on-treatment study visit
  - No treatment-emergent resistance was detected
- High prevalence of NNRTI-R among suppressed PLWH and risk factors associated with NNRTI-R underscore the importance of comprehensively reviewing treatment history and cumulative resistance data prior to switching to RPV or other NNRTI-containing regimens

References: **1.** Kagan R, et al. AIDS Res Hum Retroviruses 2004;20:1-9; **2.** Bladek KM, Richman DD. Antivir Ther 2013;18:115-23; **3.** World Health Organization. HIV drug resistance report 2019. WHO/CDS/HIV/19.21; **4.** Pingen M, et al. J Antimicrob Chemother 2011;66:1467-80; **5.** Rhee S-Y, et al. Clin Infect Dis 2019;68:213-21; **6.** Wensing AM, et al. Top Antivir Med 2019;27:111-21; **7.** Acosta R, et al. CROI 2018, poster 551; **8.** Perez-Valero I, et al. AIDS 2018, abstr TUAB0104; **9.** Thielen A, et al. 16th European Meeting on HIV & Hepatitis 2018, abstr 5; **10.** European AIDS Clinical Society Guidelines Version 10, November 2019; **11.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. DHHS; rev 12/18/19; **12.** Saag MS, et al. JAMA 2018;320:379-96; **13.** Orkin C, et al. EACS 2019, poster PE3/14; **14.** Acosta R, et al. IAS 2019, poster MOPEB242; **15.** Andreatta K, et al. CROI 2019, poster 552; **16.** Andreatta K, et al. CROI 2020, poster 509; **17.** Andreatta K, et al. IAS 2019, poster MOPEB243; **18.** Daar ES, et al. Lancet HIV 2018;5:e347-56; **19.** Hagins D, et al. CROI 2020, abstr 36; **20.** Kityo C, et al. IAS 2019, abstr MOAB0106; **21.** Maggiolo F, et al. EACS 2019, poster PE5/49; **22.** Molina JM, et al. Lancet HIV 2018;5:e357-65; **23.** Sax PE, et al. IAS 2019, abstr MOAB0105; **24.** Gaur AH, et al. CROI 2019, abstr 46; **25.** Andreatta K, et al. EACS 2019, abstr PE13/21.

Disclosures: **K. Andreatta, R. Acosta, M.L. D'Antoni, M. Willkom, H. Liu, R. Martin, S. Chang, L. Wei, S. Collins, H. Martin,** and **K.L. White:** Gilead. **Acknowledgments:** We extend our thanks to the participants, their families, and all study investigators. These studies were funded by Gilead Sciences, Inc.