PE1/6

Prevalence and Risk Factors of Preexisting TAMs in Clinical Trial Participants and Sustained Viral Suppression After Switching to Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF)

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Introduction

- Thymidine analog mutations (TAMs)—M41L, D67N, K70R, L210W, T215Y/F, and K219E/N/Q/R in reverse transcriptase (RT)—are selected by the thymidine analogs zidovudine and stavudine, and can confer cross-resistance to abacavir (ABC), tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF), and didanosine
  - Reduced response to TDF is associated with a specific pattern of ≥3 TAMs that include M41L and/or L210W[1]
  - TAF has a higher resistance threshold than TDF and can inhibit viruses with ≤4 TAMs due to higher intracellular concentrations of the active form of tenofovir[2]
- TAMs are among the most commonly transmitted nucleoside RT inhibitor (NRTI) resistance mutations,[3,4] and have been detected in the proviral DNA archive of people with HIV at frequencies of 9–13%, making them the second most frequently detected NRTI resistance mutations and third overall most frequent resistance mutations among >64,000 clinical samples[5]
- Proviral DNA genotype can help guide regimen switching and decrease risk of virologic failure[6,7]
- B/F/TAF is an EACS, IAS-USA, and DHHS guidelines-recommended regimen for the treatment of HIV-1 infection in adults, adolescents, and children aged >6 years[8-11]
  - No treatment-emergent resistance to B/F/TAF has been detected in clinical trial participants, including those with preexisting NRTI resistance[12-14]
- The Phase 3 Studies 4030 (ClinicalTrials.gov NCT02603120), 4580 (NCT02603107), 1844 (NCT03110380), 1878 (NCT03631732), and 4449 (NCT03405935) demonstrated the safety and efficacy of switching to B/F/TAF in adults with suppressed HIV[15-19]
  - High rates of virologic suppression were maintained after switching to B/F/TAF through 116 weeks[20]

Objectives

- To determine the prevalence of preexisting TAMs and associated risk factors in Studies 4030, 4580, 1844, 1878, and 4449
- To evaluate the impact of TAMs on virologic outcomes after switching to B/F/TAF

Methods

Overview of Studies in Adults With Suppressed HIV Switching to B/F/TAF

Study	Resistance Criteria	BL ARV Regimen	Study Regimen: Participants, n	Study Regimen: BL Through Week 48	Study Regimen: Week 48 Through End of Study
4030	NRTI-R, NNRTI-R, PI-R allowed; INSTI-R excluded	DTG + either F/TAF or F/TDF	284	B/F/TAF	—
			281	DTG + F/TAF	—
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	B/F/TAF
			165	SBR (B: Week 24; B/F/TAF (Week 24–48)	B/F/TAF
1844	FTC-R or TFV-R excluded	DTG + ABC/3TC (either STR or MTR)	282	B/F/TAF	B/F/TAF
			281	DTG/ABC/3TC	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
4449	FTC-R, TFV-R, and BIC-R excluded	E/C/F/TAF or any 3rd agent + F/TDF	86	B/F/TAF	B/F/TAF

3TC, lamivudine; ARV, antiretroviral; ATV, atazanavir; BIC, bictegravir; BL, baseline; C, cobicistat; DRV, darunavir; DTG, dolutegravir; E, elvitegravir; FTC, emtricitabine; INSTI, integrase (IN) strand transfer inhibitor; MTR, multitablet regimen; NNRTI, non-NRTI; PI, protease (PR) inhibitor; R, resistance; SBR, stay on BL regimen; STR, single-tablet regimen; TFV, tenofovir.

Baseline Genotypic Analyses

- Historical HIV-1 genotype reports were collected if available after enrollment
- HIV-1 proviral DNA genotype testing (GenoSure Archive®, Monogram Biosciences, South San Francisco, California, USA) was performed on BL samples (hereafter referred to as BL DNA genotype)
  - Bioinformatic filters removed APOBEC-mediated hypermutated deep-sequence reads from GenoSure Archive results to prevent overreporting of E138K, M184I, and M230I in RT and G163R in 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)[21]

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, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K **Secondary:** M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, T97A, G118R, S119P/R/T, F121C, A128T, E138A/K, G140A/C/S, P145S, Q146K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, E170A

RPV, rilpivirine.

Statistical Analyses

- Potential risk factors for TAMs 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

B/F/TAF Efficacy Analysis

	Pooled B/F/TAF	Study 4030*	Study 4580		Study 1844		Study 1878		Study 4449*
			Group 1†	Group 2‡	Group 1†	Group 2‡	Group 1†	Group 2‡	
Participants analyzed, n	**1934**	283	327	162	281	264	289	243	85
With BL data	1808	237	312	156	267	255	276	222	83
Analysis visit	—	Week 48	Week 72	Week 48§	OLE median Week 117	OLE median Week 50	OLE median Week 116	OLE median Week 71	Week 96

*Switched to B/F/TAF on Day 1; †Switched to B/F/TAF at Week 24 of randomized phase; ‡Continued BL regimen during randomized phase and switched to B/F/TAF at Week 48 in open-label extension (OLE); §Derived B/F/TAF Week 48 (equivalent to study Week 72).

- Analysis included participants who switched to B/F/TAF during randomized or open-label extension (OLE) phase 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 imputation: <50 copies (c)/mL (success) or ≥50 c/mL (failure)
  - All participants with data, including those with early discontinuation, had virologic outcomes determined

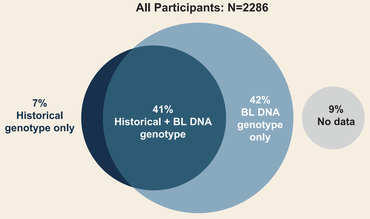
Results

Summary of Resistance Data at Baseline

Participants, % (n or n/N)	All Participants Pooled (Studies 4030, 4580, 1844, 1878, 4449) N=2286
PR/RT data available	**91 (2079)**
Historical genotype*	49 (1118)
BL DNA genotype	84 (1909)
Resistance-associated substitutions present	**37 (762/2079)**
NRTI-R	17 (349/2079)
≥1 TAM	10 (206/2079)
NNRTI-R	22 (461/2079)
PI-R	11 (228/2079)
IN data available	**85 (1944)**
Historical genotype	8 (179)
BL DNA genotype	84 (1909)
Resistance-associated substitutions present	**51 (992/1944)**
Primary INSTI-R	2 (3/1944)
Secondary INSTI-R	50 (975/1944)

*97% of historical genotypes were plasma HIV-1 RNA genotypes and 3% were HIV-1 DNA genotypes.

Baseline RT Genotypic Data Sources



Summary of TAMs at Baseline by Study

Participants, % (n or n/N)	Study 4030		Study 4580		Study 1844		Study 1878		Study 4449
	B/F/TAF n=284	DTG + F/TAF n=281	B/F/TAF n=330	SBR n=165	B/F/TAF n=282	DTG/ABC/3TC n=281	B/F/TAF n=290	SBR n=287	B/F/TAF n=86
RT data available*	84 (238)	83 (232)	95 (315)	96 (158)	95 (268)	93 (260)	96 (277)	86 (247)	84 (84)
NRTI-R	26 (62/238)	24 (55/232)	14 (44/315)	16 (26/158)	10 (26/268)	8 (22/260)	23 (64/277)	17 (41/247)	11 (75/84)
≥1 TAM	13 (32)	15 (34)	6 (20)	10 (16)	7 (18)	7 (18)	11 (31)	11 (28)	11 (9)
M41L	6 (15)	6 (13)	3 (9)	4 (6)	4 (10)	3 (8)	5 (14)	5 (13)	4 (3)
D67N	6 (15)	6 (15)	1 (4)	4 (7)	1 (3)	2 (6)	4 (10)	6 (16)	5 (4)
K70R	8 (18)	9 (21)	2 (6)	5 (8)	2 (5)	3 (7)	5 (15)	5 (12)	6 (5)
L210W	3 (8)	3 (6)	1 (3)	3 (5)	1 (4)	2 (5)	2 (5)	2 (4)	2 (2)
T215F/Y	6 (14)	6 (13)	2 (5)	4 (6)	2 (5)	1 (3)	4 (11)	5 (12)	6 (5)
K219E/N/Q/R	5 (12)	7 (16)	2 (7)	4 (6)	1 (3)	3 (9)	4 (11)	6 (15)	4 (3)
1–2 TAMs	7 (16)	7 (17)	6 (18)	5 (8)	6 (15)	5 (13)	8 (21)	6 (14)	6 (5)
≥3 TAMs	7 (16)	7 (17)	1 (2)	5 (8)	1 (3)	2 (5)	4 (10)	6 (14)	5 (4)
≥3 TAMs, including M41L and/or L210W	5 (11)	4 (9)	<1 (1)	3 (4)	1 (3)	2 (4)	2 (5)	3 (8)	4 (3)

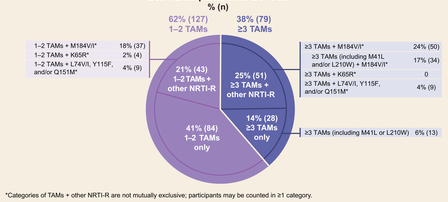
*From cumulative historical and/or BL DNA genotypes.

Frequency and Detection of TAMs at Baseline: All Participants Pooled

Participants, % (n)	BL Data Available (cumulative historical and/or BL DNA) n=2079	Historical Genotype n=1118	BL DNA Genotype n=1909
≥1 TAM	10 (206)	5 (57)	10 (186)
M41L	4 (91)	2 (27)	4 (83)
D67N	4 (80)	2 (21)	4 (69)
K70R	5 (97)	2 (19)	4 (85)
L210W	2 (42)	1 (10)	2 (37)
T215F/Y	4 (74)	2 (17)	3 (65)
K219E/N/Q/R	4 (82)	2 (24)	4 (71)
1–2 TAMs	6 (127)	4 (41)	6 (117)
≥3 TAMs	4 (79)	1 (16)	4 (69)
≥3 TAMs, including M41L and/or L210W	2 (48)	1 (7)	2 (43)
≥1 TAM only NRTI-R (no other NRTI-R)	5 (112)	3 (37)	5 (102)
≥1 TAM + other NRTI-R	5 (94)	2 (20)	4 (84)
≥1 TAM + M184V/I	4 (87)	2 (19)	4 (78)
≥1 TAM + K65R	<1 (4)*	<1 (1)	<1 (4)
≥1 TAM + L74V/I, Y115F, and/or Q151M	2 (18)	<1 (4)	1 (17)

*TAMs present with K65R: M41L (n=1), K70R+K219Q (n=1), and D67N (n=2).

No. of TAMs and Presence With Other NRTI-R Substitutions at Baseline



*Categories of TAMs + other NRTI-R are not mutually exclusive; participants may be counted in ≥1 category.

- The most frequent pattern of TAMs observed was 1–2 TAMs with no other NRTI-R

No. of Preexisting TAMs and Comparison of Detection Type

	Participants With ≥1 TAM: Any Genotype (cumulative historical and/or BL DNA) n=206	Historical Genotype n=57	BL DNA Genotype n=186	Both Genotypes (cumulative historical and BL DNA) n=36
Mean no. of TAMs (range)	2.3 (1–6)	2.1 (1–5)	2.2 (1–6)	2.2 (1–5)
Participants with ≥1 TAM, % (n)				
1 TAM	45 (92)	44 (25)	47 (87)	36 (13)
2 TAMs	17 (35)	28 (16)	16 (30)	31 (11)
3 TAMs	17 (36)	12 (7)	18 (33)	14 (5)
4 TAMs	10 (20)	9 (5)	9 (17)	14 (5)
5 TAMs	11 (22)	7 (4)	10 (18)	6 (2)
6 TAMs	<1 (1)	0	1 (1)	0
Comparison of no. of TAMs, % (n)				
Historical > BL DNA	11 (23)*	—	—	6 (2)
Historical = BL DNA	13 (26)*	—	—	72 (26)
Historical < BL DNA	76 (157)*	—	—	22 (8)

*116 and 9 participants had no historical and BL DNA genotypes, respectively.

- Most participants with TAMs had only 1 TAM (45% [92/206])
- Previously undocumented TAMs were detected by BL DNA genotyping in 8% of participants (157/2079)
  - Most had no historical genotype available

Baseline Resistance by Preexisting TAM Status

BL Genotype, %	≥1 TAM n=206	No TAMs n=1873	p-Value*
NRTI-R other than TAMs	46	8	<0.001
M184V/I	42	7	<0.001
NNRTI-R	44	20	<0.001
RPV-R	22	8	<0.001
PI-R	29	9	<0.001
Primary INSTI-R†	1	2	0.92
Secondary INSTI-R†	43	51	0.037

*Determined by Cochran-Mantel-Haenszel test; †IN data not available for 135 participants (≥1 TAM: n=7; no TAMs: n=128).

- Participants with TAMs were also more likely to have other NRTI-R (including M184V/I), NNRTI-R (including RPV-R), and PI-R by univariate analysis

Baseline Characteristics by Preexisting TAM Status

	≥1 TAM n=206	No TAMs n=1873	p-Value*
Demographics, %			
Age ≥50 years	68	45	<0.001†
Black race or African descent	34	38	0.27†
ARV treatment history			
Prior NNRTI treatment, %	49	38	0.003†
Prior PI treatment, %	77	53	<0.001†
Prior INSTI treatment, %	66	66	0.80†
Median no. of prior third agents (IQR)	2.0 (2.0, 4.0)	2.0 (1.0, 2.0)	<0.001
Median time since ARV start, years (IQR)	19.5 (8.9, 23.5)	7.5 (4.0, 14.0)	<0.001

*Determined by Cochran-Mantel-Haenszel test for categorical data and 2-sided Wilcoxon rank-sum test for continuous data; †vs age <50 years, non-Black race, and no prior NNRTI, PI, or INSTI treatment. IQR, interquartile range.

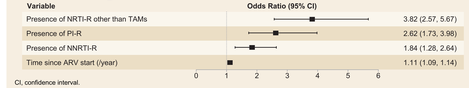
- Older age, prior NNRTI or PI treatment, higher no. of prior 3rd agents, and longer duration of ARV therapy were associated with TAMs by univariate analysis

Potential Factors Assessed for Association With Preexisting TAMs

Intrinsic predictors	Age groups, sex at birth, race, ethnicity, region, BMI, and CKD stage
HIV-specific variables at BL	CD4 group, HIV-1 RNA group, HIV disease status, HIV risk factor, time since ARV start, prior treatment with PI, NNRTI, or INSTI, no. of prior 3rd agents and prior 3rd-agent classes, and duration of BL ARV regimen
HIV resistance variables	Any NRTI-R other than TAMs, M184V/I, PI-R, NNRTI-R, RPV-R, primary INSTI-R, and secondary INSTI-R

BMI, body mass index; CKD, chronic kidney disease.

Risk Factors Significantly Associated With Preexisting TAMs



CI, confidence interval.

- Factors independently associated with TAMs included NRTI-R other than TAMs, PI-R, NNRTI-R, and longer duration of ARV (11% increase in odds/year) by multivariate logistic regression model

Virologic Suppression at Last On-Treatment Study Visit by Preexisting TAMs: Pooled B/F/TAF-Treated Analysis

	n	Participants With HIV-1 RNA <50 c/mL at Last Visit, n/n	%	Median B/F/TAF Duration, Weeks
Pooled B/F/TAF with BL data	100	1787/1808	99	72
≥1 TAM	9	163/166	98	71
1–2 TAMs	6	106/108	98	72
≥3 TAMs	3	57/58	100	63
≥3 TAMs (M41L and/or L210W)	2	36/37	100	62
≥3 TAMs (M41L or L210W) + M184V/I	1	26/26	100	60
≥1 TAM only NRTI-R	5	88/90	99	72
≥1 TAM + other NRTI-R	4	75/76	99	63
≥1 TAM + M184V/I	4	69/70	99	63
≥1 TAM + K65R	<1	4/4	100	73
≥1 TAM + NNRTI-R	4	71/72	99	64
≥1 TAM + PI-R	3	47/48	98	64
≥1 TAM + secondary INSTI-R*	4	68/68	100	69

0 20 40 60 80 100

% with HIV-1 RNA <50 c/mL, including participants with resuppression on commercial B/F/TAF (no change in regimen)

*No participants with ≥1 TAM and primary INSTI-R received B/F/TAF.

- High levels of virologic suppression were observed at last on-treatment visit, regardless of preexisting TAMs
  - Median B/F/TAF treatment duration: 72 weeks
  - No treatment-emergent resistance to B/F/TAF
- 3 participants with TAMs had HIV-1 RNA >50 c/mL at last visit:
  - 1 with K70R and M184V experienced confirmed virologic failure with HIV-1 RNA of 2860 c/mL, documented poor adherence, undetectable BIC plasma concentrations, and no treatment-emergent resistance, and discontinued at the following visit with HIV-1 RNA of 1510 c/mL
  - 1 with M41L, D67N, L210W, and K219E completed the study with HIV-1 RNA of 56 c/mL, and resuppressed on commercial B/F/TAF
  - 1 with K219R discontinued with HIV-1 RNA of 65 c/mL

Conclusions

- TAMs were frequently observed in virologically suppressed adults who enrolled in B/F/TAF switch studies 4030, 4580, 1844, 1878, and 4449: 10% (206/2079) of participants had ≥1 TAM, and 2% (48/2079) had ≥3 TAMs that included M41L and/or L210W, the pattern associated with TFV-R
- BL DNA genotyping uncovered previously undocumented TAMs in 8% of participants (157/2079): most had no historical genotype available
- Preexisting TAMs were associated with the presence of other NRTI-R, PI-R, and NNRTI-R substitutions, and longer duration of ARV therapy
- High levels of virologic suppression were maintained on B/F/TAF through 72 weeks of follow-up
  - 98% with ≥1 TAM had HIV-1 RNA <50 c/mL at their last on-treatment study visit
  - 97% with ≥3 TAMs that included M41L and/or L210W had HIV-1 RNA <50 c/mL at their last on-treatment study visit
  - No treatment-emergent resistance was detected
- For adults with suppressed HIV, switching to B/F/TAF was highly effective regardless of preexisting TAMs

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