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Sustained Viral Suppression After Switch to Bictegravir/Emtricitabine/Tenofovir Alafenamide Among Clinical Trial Participants With Preexisting M184V/I

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Introduction

- M184V and M184I are common NRTI resistance substitutions
  - Confer high-level resistance to lamivudine (3TC) and emtricitabine (FTC), and decrease susceptibility to abacavir (ABC) and didanosine, but increase susceptibility to tenofovir (TFV) and zidovudine[1]
  - Occur in up to 67% of participants after treatment failure[2]
  - In 2019, Monogram Biosciences (South San Francisco, California, USA) reported the detection of M184V/I in 27% of HIV-1 DNA samples using GenoSure Archive®, which was the most frequently observed resistance substitution among >64,000 participant samples[3]
- M184V/I prevalence may be underreported and under-recognized in standard clinical practice
  - M184V/I is detected in ~4% of acute HIV infections and in up to 23% of transmission clusters; plasma detection decreases over time, but mutant virus is archived in the latent reservoir[2,4,5]
  - In virologically suppressed people living with HIV (PLWH), only ~50% of previously documented M184V/I is detected by proviral DNA genotyping using next-generation sequencing, including GenoSure Archive[6,7] and the deepType HIV assay (Seq-IT GmbH & Co. KG, Kaiserslautern, Germany) when mutation detection cutoff is ≥15% of deep-sequence reads[8]
- Proviral DNA genotype can help guide regimen switching and decrease risk of virologic failure[9]
- Bictegravir (BIC)/FTC/TFV alafenamide (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 y[10-13]
- B/F/TAF safety and efficacy have been demonstrated in controlled clinical trials through 144 wk[14-20]
  - No treatment-emergent resistance to B/F/TAF has been detected in clinical trial participants, including those with preexisting NRTI resistance[14-25]

Objectives

- To determine the prevalence of preexisting M184V/I among 2034 virologically suppressed clinical trial participants in Studies 4030, 4580, 1844, 1878, 4449, and 1474, and evaluate the impact of preexisting M184V/I on virologic outcomes after switching to B/F/TAF

Methods

Table 1. Overview of B/F/TAF Switch Studies in Virologically Suppressed PLWH

Study*	Resistance Criteria	M184V/I at Screening	Population Age, y	Baseline ARV Regimen	Participants, n	Study Phase and Treatment: Baseline–Week 48	Study Phase and Treatment: Week 48–End of Study
4030	NRTI-R, NNRTI-R, PI-R allowed; INSTI-R excluded	Allowed	≥18	DTG + either F/TAF or F/TDF	284	B/F/TAF (DTG + F/TAF PBO)	—
					281	DTG + F/TAF (B/F/TAF PBO)	—
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	Allowed	≥18	Any 3rd agent + 2 NRTIs	330	B/F/TAF	—
					165	SBR (through Week 24) / B/F/TAF (Weeks 24–48)	—
1844	FTC-R or TFV-R excluded	Excluded	≥18	DTG + ABC/3TC (either STR or MTR)	282	B/F/TAF (DTG/ABC/3TC PBO)	B/F/TAF
					281	DTG/ABC/3TC (B/F/TAF PBO)	B/F/TAF
1878	FTC-R or TFV-R excluded	Excluded	≥18	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	Excluded	≥65	E/C/F/TAF or any 3rd agent + F/TDF	86	B/F/TAF	B/F/TAF
1474	FTC-R, TFV-R, and INSTI-R excluded	Excluded	6–<18	Any 3rd agent + 2 NRTIs	100	B/F/TAF	—

*ClinicalTrials.gov NCT02603120 (4030), NCT02603107 (4580), NCT03110380 (1844), NCT03631732 (1878), NCT03405935 (4449), and NCT02881320 (1474). ARV, antiretroviral; ATV, atazanavir; C, cobicistat; DRV, darunavir; DTG, dolutegravir; E, elvitegravir; INSTI, integrase (IN) strand transfer inhibitor; MTR, multitablet regimen; PBO, placebo; PI, protease (PR) inhibitor; R, resistance; SBR, stay on baseline regimen; STR, single-tablet regimen; TAMs, thymidine analog mutations; TDF, TFV disoproxil fumarate.

Baseline Genotypic Analyses

- Historical HIV-1 genotype reports were collected if available on enrollment
- HIV-1 proviral DNA genotype testing (GenoSure Archive) 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 IN
- Participants with preexisting resistance detected after enrollment continued on study and were included in all analyses

HIV-1 Primary Drug Resistance Substitutions (based on IAS-USA)[26]

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
	RPV-R: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L
PI-R	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/I/L/S/T, N83D, I84V, N88S, L90M
INSTI-R	T66I/A/K, E92Q/G, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K

RPV, rilpivirine.

Resistance Analysis Population

- Resistance testing was performed in participants with HIV-1 RNA ≥200 copies/mL at confirmed virologic failure, Week 48, or last visit on study drugs
- Plasma HIV-1 RNA genotype and phenotype (PhenoSense® GT, Genosure® MG, and PhenoSense®, Monogram)

Efficacy Analysis

- Analysis included participants who switched to B/F/TAF during the study 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 (success) or ≥50 (failure) copies/mL
  - All participants with data, including those with early discontinuation, had virologic outcomes determined
- A population size of 182 with 3 failures has a failure rate detection limit of 4.7%
  - For comparison, a population size of 4 with 0 failures has a failure rate detection limit of 49%[27]

Results

Table 2. Virologic Outcomes (LOCF) of Participants Switched to B/F/TAF

	Pooled B/F/TAF	B/F/TAF Group by Study								
		Study 4030	Study 4580 Group 1*	Study 4580 Group 2†	Study 1844 Group 1*	Study 1844 Group 2†	Study 1878 Group 1*	Study 1878 Group 2†	Study 4449	Study 1474
Participants analyzed, n	2034	283	327	162	281	264	289	243	85	100
Analysis time point	–	Week 48	Week 48	Week 24	End of study	End of study	End of study	End of study	Week 96	Week 24 or 48‡
Median B/F/TAF treatment duration, wk	48	48	48	24	119	50	120	72	72	48
HIV-1 RNA <50 copies/mL, % (n)	99% (2012)	>99% (282)	99% (324)	100% (162)	98% (276)	98% (259)	99% (285)	99% (240)	100% (85)	99% (99)
HIV-1 RNA ≥50 copies/mL, % (n)	1% (22)	<1% (1)	1% (3)	0%	2% (5)	2% (5)	1% (4)	1% (3)	0%	1% (1)
Emergent resistance, n	0	0	0	0	0	0	0	0	0	0

*Participants switched to B/F/TAF at baseline; †Participants continued baseline regimen and switched to B/F/TAF at Week 24 (Study 4580) or 48 (Studies 1844 and 1878); ‡75 participants completed 48 wk and 25 participants completed 24 wk of B/F/TAF treatment.

- B/F/TAF maintained high rates of virologic suppression with no treatment-emergent resistance

Table 3. Frequency of Baseline Resistance-Associated Substitutions: Pooled B/F/TAF Group

Baseline Genotype, % (n/N)	Pooled B/F/TAF n=2034
PR/RT data available (historical and/or proviral)	90% (1825/2034)
NRTI-R	**16% (288/1825)**
M184V/I	**10% (182/1825)**
V only substitution	**9% (161/1825)**
I only substitution	**1% (11/1825)**
V and I substitutions	**1% (10/1825)**
K65R/N	1% (18/1825)
Any TAM	9% (167/1825)
NNRTI-R	**22% (397/1825)**
RPV-R	9% (170/1825)
K103N/S	11% (205/1825)
PI-R	**11% (201/1825)**
IN data available (historical and/or proviral)	85% (1731/2034)
INSTI-R	**2% (30/1731)**

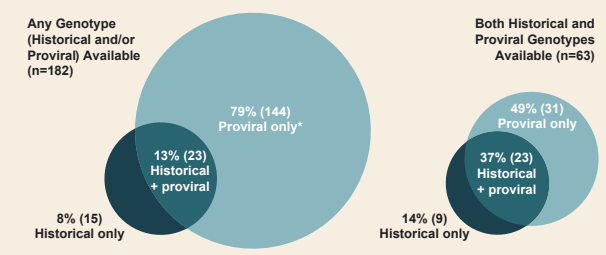
Table 4. Frequency of Preexisting M184V/I by Study

Baseline Genotype, % (n or n/N)	Study 4030 n=283	Study 4580 Group 1* n=327	Study 4580 Group 2† n=162	Study 1844 Group 1* n=281	Study 1844 Group 2† n=264	Study 1878 Group 1* n=289	Study 1878 Group 2† n=243	Study 4449 n=85	Study 1474 n=100
RT data available‡	84% (237)	95% (312)	96% (156)	95% (267)	97% (255)	96% (276)	91% (222)	96% (82)	17% (17)
M184V/I	20% (47/237)	10% (30/312)	13% (20/156)	4% (10/267)	3% (7/255)	16% (44/276)	8% (18/222)	4% (3/82)	18% (3/17)
V only substitution	18% (43)	9% (27)	12% (19)	3% (7)	2% (6)	19% (39)	7% (15)	4% (3)	18% (3)
I only substitution	1% (2)	<1% (1)	0%	1% (2)	<1% (1)	1% (3)	1% (2)	0%	0%
V and I substitutions	1% (2)	1% (2)	1% (1)	<1% (1)	0%	1% (2)	<1% (1)	0%	0%

*Participants switched to B/F/TAF at baseline; †Participants continued baseline regimen with delayed switch to B/F/TAF; ‡From cumulative historical and/or proviral genotypes.

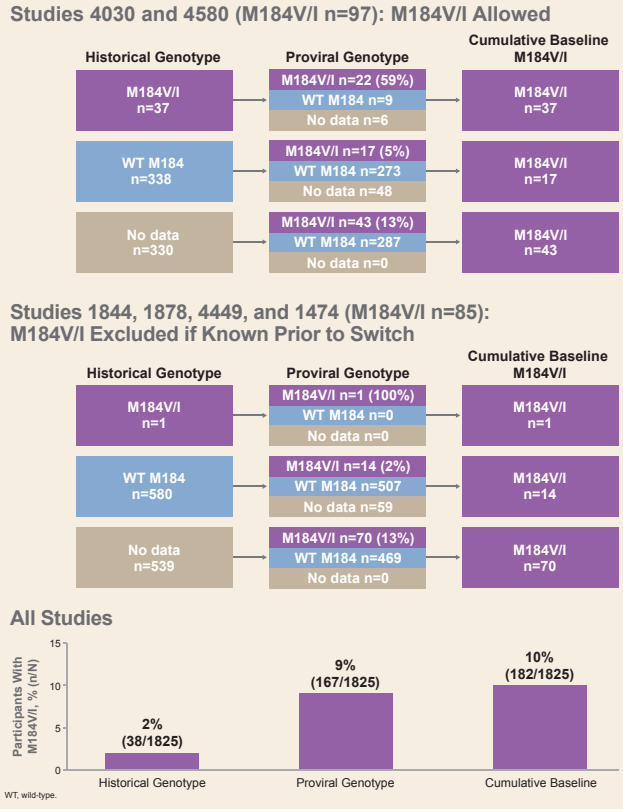
- M184V/I was detected in 182 virologically suppressed participants enrolled across 6 studies
- M184V/I frequency ranged from 3% to 20% based on study population
- The most commonly detected M184 substitution was M184V (94% [171/182])

Figure 1. M184V/I Detection by Historical and/or Proviral Genotype



*113/144 participants had no historical genotype available.

Figure 2. Discovery of M184V/I by Retrospective Baseline Proviral Genotyping



WT, wild-type.

- M184V/I was detected in 10% of participants switched to B/F/TAF
  - Most M184V/I was identified by baseline proviral DNA genotyping
  - M184V/I was detected by proviral genotyping in 3% (31/918) with WT M184 by historical genotype vs 13% (113/869) with no historical data

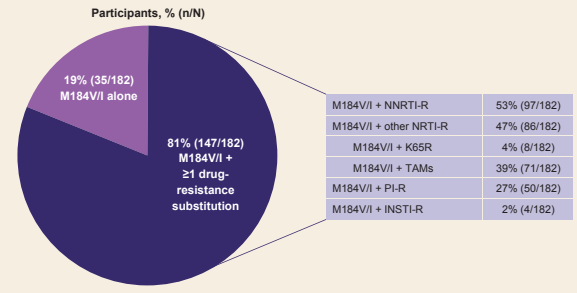
Table 5. Baseline Characteristics by Preexisting M184V/I

	M184V/I n=182	WT M184 n=1644	p-Value
Mean age, y (range)	52 (15–78)	47 (8–80)	<0.001*
From USA, % (n)	81% (148)	69% (1138)	0.001†
Male sex at birth, % (n)	77% (140)	81% (1338)	0.16†
Black or African-American race, % (n)	50% (91)	39% (639)	0.004†
Baseline CD4 cell count <500 cells/μL, % (n)	31% (57)	24% (402)	0.048†
Drug resistance substitutions other than M184V/I, % (n)	81% (147)	30% (486)	<0.001†

*Determined by t-test; †Determined by Fisher's exact test vs ex-USA, female sex at birth, non-Black race, and baseline CD4 cell count ≥500 cells/μL.

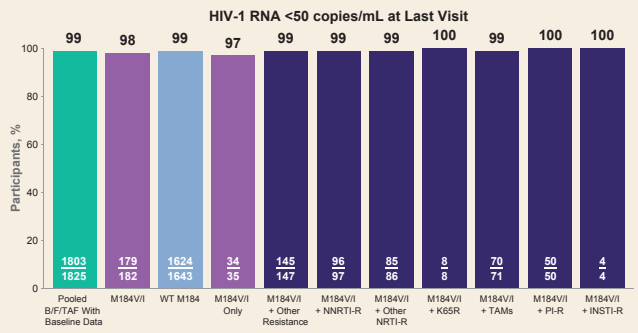
- Preexisting M184V/I was associated with presence of other resistance substitutions, older age, being from the USA, and Black race

Figure 3. Presence of M184V/I With Other Resistance Substitutions



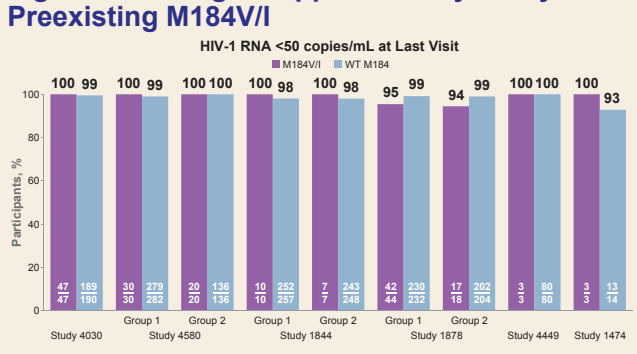
- M184V/I was frequently detected with other resistance substitutions, but was the only resistance in 19% of participants

Figure 4. Virologic Suppression by Preexisting M184V/I: Pooled B/F/TAF Group



- High rates of HIV-1 RNA <50 copies/mL were maintained regardless of presence of M184V/I at baseline
- 3 participants with M184V/I had HIV-1 RNA ≥50 copies/mL at their last visit
  - 2 with HIV-1 RNA <100 copies/mL: 1 resuppressed on commercial B/F/TAF and 1 resuppressed on ATV/r + F/TDF
  - 1 with HIV-1 RNA 2860 copies/mL, documented poor adherence, and undetectable BIC plasma concentrations had no treatment-emergent resistance

Figure 5. Virologic Suppression by Study and Preexisting M184V/I



- B/F/TAF efficacy was not affected by presence of M184V/I at baseline

Conclusions

- M184V/I was detected in 182/1825 virologically suppressed participants (10%), most of which was previously undocumented by historical genotype
- High rates of virologic suppression were maintained in participants with or without preexisting M184V/I who switched to B/F/TAF
  - 98% (179/182) with M184V/I and 99% (1624/1643) without M184V/I had HIV-1 RNA <50 copies/mL at their last study visit
- No treatment-emergent resistance to B/F/TAF was observed
- Preexisting M184V/I was associated with presence of other resistance substitutions, older age, being from the USA, and Black race
- B/F/TAF is an effective and durable regimen for virologically suppressed PLWH, including those with known or unidentified M184V/I

References: **1.** Miller MD, et al. Antivir Ther 2012;17:993-9; **2.** Wainberg MA, et al. J Antimicrob Chemother 2011;66:2346-9; **3.** Yang D, et al. CROI 2019, poster 543; **4.** Little SJ, et al. N Engl J Med 2002;347:385-94; **5.** Metzner KJ, et al. J Infect Dis 2013;208:1102-12; **6.** Acosta R, et al. CROI 2019, poster 551; **7.** Perez-Valero I, et al. IAS 2018, presentation TUAB0104; **8.** Thielen A, et al. European Meeting on HIV & Hepatitis 2018, presentation 5; **9.** Armenia D, et al. J Clin Virol 2018;104:61-4; **10.** European AIDS Clinical Society Guidelines Version 9.1, Oct 2018; **11.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Dept of Health and Human Services, 2019; **12.** Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV. Dept of Health and Human Services, 2020; **13.** Saag MS, et al. JAMA 2018;320:379-96; **14.** Daar ES, et al. Lancet HIV 2018;5:e347-56; **15.** Gaur AH, et al. CROI 2019, presentation 46; **16.** Kityo C, et al. J Acquir Immune Defic Syndr 2019;82:321-8; **17.** Maggiolo F, et al. EACS 2019, poster PE9/49; **18.** Molina JM, et al. Lancet HIV 2018;5:e357-65; **19.** Orkin C, et al. Lancet HIV 2020;7:e389-400; **20.** Sax PE, et al. Clin Infect Dis 2020 Jul 15:ciaa988; **21.** Acosta R, et al. J Acquir Immune Defic Syndr 2020 Jul 21 [online ahead of print]; **22.** Andreatta K, et al. CROI 2019, poster 552; **23.** Andreatta K, et al. CROI 2020, poster 509; **24.** Andreatta K, et al. IAS 2019, presentation MOPEB243; **25.** Andreatta K, et al. J Acquir Immune Defic Syndr 2018;79:e47-50; **26.** Wensing AM, et al. Top Antivir Med 2017;24:132-41; **27.** van Wyk J, et al. Clin Infect Dis 2020 Jan 6;ciz1243.

Acknowledgments: We extend our thanks to the participants, their families, and all participating investigators. These studies were funded by Gilead Sciences, Inc.