Poster
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Sustained Viral Suppression among Participants with Pre-existing M184V/I Who Switched to Bictegravir/Emtricitabine/Tenofovir Alafenamide

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Background

- M184V/I is a common NRTI resistance substitution
  - Confers high-level resistance to 3TC and FTC and decreases susceptibility to ABC and ddI, but increases susceptibility to tenofovir (TFV) and AZT[1]
  - Occurs in up to 67% of patients after treatment failure[2]
  - Recently, Monogram Biosciences reported the detection of M184V/I in 27% of HIV-1 DNA samples by the GenoSure Archive assay, which was the most frequently observed resistance substitution among >64,000 patient samples[3]
- However, M184V/I prevalence may be under-reported and M184V/I is often under-recognized in standard clinical practice
  - Detected in up to 23% of primary infections, but rarely detected in chronically infected, treatment-naïve patients suggesting high transmission frequency with rapid reversion to wild-type in circulating viruses, but with mutant virus archived in the latent reservoir[2]
  - In virologically suppressed patients, only ~50% of previously documented M184V/I is detected by proviral DNA genotyping using next generation sequencing, including the GenoSure Archive assay[4,5] and the deepType HIV assay when mutation detection cutoff is ≥15% of deep sequence reads[6]
- B/F/TAF (bictegravir/emtricitabine/tenofovir alafenamide) is an EACS, IAS-USA, and DHHS guidelines-recommended regimen for the treatment of HIV-1 infection[7-9]
- B/F/TAF safety and efficacy has been demonstrated in controlled clinical trials through 144 weeks[10-16]
  - No treatment-emergent resistance to B/F/TAF has been detected in clinical trial participants, including those with pre-existing NRTI resistance[10-19]
- Several studies demonstrated that triple therapy regimens containing FTC and TFV in either prodrug form (TDF or TAF) are able to maintain high rates of virologic suppression in the presence of archived M184V/I[4,20-21]

Objectives

- To determine:
  - The prevalence of, and risk factors for, pre-existing M184V/I among virologically suppressed clinical trial participants
  - The impact of pre-existing M184V/I on virologic outcomes after switching to B/F/TAF

Methods

Table 1. Overview of B/F/TAF Switch Studies in Virologically Suppressed People with HIV

Study	Resistance Criteria	M184V/I at Screening	Population Age	Prior ARV Regimen	Number of Participants	Study Phase and Treatment: Randomized Phase	Study Phase and Treatment: Open Label Extension
4030	NRTI, NNRTI, PI resistance allowed, INSTI resistance excluded	Allowed	Adults ≥18 years old	DTG + either F/TAF or F/TDF	284	B/F/TAF (DTG + F/TAF placebo)	–
					281	DTG + F/TAF (B/F/TAF placebo)	–
1844	FTC or TFV resistance excluded	Excluded	Adults ≥18 years old	DTG + ABC/3TC	282	B/F/TAF (DTG/ABC/3TC placebo)	B/F/TAF
					281	DTG/ABC/3TC (B/F/TAF placebo)	B/F/TAF
1878	FTC or TFV resistance excluded	Excluded	Adults ≥18 years old	Boosted DRV or ATV + either F/TDF or ABC/3TC	290	B/F/TAF	B/F/TAF
					287	Stay on baseline regimen	B/F/TAF
4449	FTC, TFV, and BIC resistance excluded	Excluded	Adults ≥65 years old	E/C/F/TAF or Any 3rd Agent + F/TDF	86	B/F/TAF	–
1474	FTC, TFV, and INSTI resistance excluded	Excluded	Adolescents & children 6 to <18 years old	Any 3rd Agent + 2 NRTIs	100	B/F/TAF	–

Baseline Genotypic Analyses

- Historical HIV-1 genotype reports were collected if available upon enrollment
- HIV-1 proviral DNA genotype testing (GenoSure Archive, Monogram Biosciences) was performed on baseline samples
  - Bioinformatics filters removed APOBEC-mediated hypermutated deep sequence reads from GenoSure Archive results to prevent over-reporting of E138K, M184I, and M230I in RT and G163R in IN
- Participants with pre-existing resistance detected after enrollment continued on study and were included in all analyses

Resistance Analysis Population (RAP)

- Resistance testing was performed in participants with HIV-1 RNA ≥200 c/mL at confirmed virologic failure, Week 48, or last visit on study drugs
- Plasma HIV-1 RNA genotype and phenotype (PhenoSenseGT, GeneSeq IN, and PhenoSense IN, Monogram Biosciences)

HIV-1 Drug Resistance Substitutions (based on IAS-USA)[22]

- **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; rilpivirine resistance substitutions (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/S/T, N83D, I84V, N88S, L90M
- **INSTI-R**: T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K

Efficacy Analyses

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

Methods, cont'd

Statistical Analyses

- We assessed risk factors for M184V/I using a multivariate logistic regression model with stepwise selection significance level for entry (SLE) α = 0.20 and significance level for stay (SLS) α = 0.05 and adjusted for study specific effects
  - **Analysis included**: all participants from the B/F/TAF and comparator treatment groups with baseline genotypic data from Studies 4030 (n=470), 1844 (n=528), and 1878 (n=524)
    - Participants from Studies 4449 and 1474 were excluded due to possible confounding effects of study age requirements
  - **Intrinsic predictors**: groups of age, sex, race, ethnicity, BMI, CKD stage, region
  - **HIV specific variables at baseline**: CD4, HIV RNA, HIV acquisition risk factor, HIV disease status, time since ART start, prior treatment with any PI, NNRTI, INSTI, or non-DTG INSTI (RAL or EVG), number of prior 3rd agents, number of prior 3rd agent classes, duration of baseline ARV regimen
  - **HIV resistance variables**: NRTI-R (other than M184V/I), TAMs, PI-R, NNRTI-R, RPV-R, INSTI-R

3TC = lamivudine; ABC = abacavir; ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir; BMI = body mass index, C = cobicistat; CKD = chronic kidney disease, DRV = darunavir; DTG = dolutegravir, EVG or E = elvitegravir, FTC or F = emtricitabine; INSTI = integrase strand transfer inhibitor, NNRTI = nonnucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor, -R = resistance, RAL = raltegravir, RPV = rilpivirine, TAF = tenofovir alafenamide; TAMs = thymidine analog mutations; TDF = tenofovir disoproxil fumarate

Results
Section 1: Studies 4030, 1844, 1878, 4449, and 1474 (B/F/TAF Groups)

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

	Pooled B/F/TAF	B/F/TAF Group by Study: Study 4030	Study 1844: Group 1[a]	Study 1844: Group 2[b]	Study 1878: Group 1[a]	Study 1878: Group 2[b]	Study 4449	Study 1474
Number of Participants Analyzed, n	**1545**	283	281	264	289	243	85	100
Analysis Time point	–	Week 48	OLE Median Week 117	OLE Median Week 50	OLE Median Week 116	OLE Median Week 71	Week 48	Week 24 or Week 48[c]
HIV-1 RNA <50 c/mL, % (n)	**98.9% (1528)**	99.6% (282)	98.2% (276)	98.9% (261)	98.6% (285)	98.8% (240)	100% (85)	99.0% (99)
HIV-1 RNA ≥50 c/mL, % (n)	**1.1% (17)**	0.4% (1)	1.8% (5)	1.1% (3)	1.4% (4)	1.2% (3)	0	1.0% (1)
Emergent Resistance, n	**0**	0	0	0	0	0	0	0

a. Group 1 participants switched to B/F/TAF on Day 1 of study randomized phase
b. Group 2 participants continued baseline regimen during randomized phase and switched to B/F/TAF in open-label extension (OLE)
c. 75 participants completed 48 weeks of B/F/TAF treatment and 25 participants completed 24 weeks 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 in the Pooled B/F/TAF Treatment Group

Baseline Genotype	Proportion of Participants, % (n or n/N): Pooled B/F/TAF (n=1545)
PR/RT Data Available (Historical and/or Proviral)	88% (1356)
NRTI-R	**16% (220/1356)**
M184V/I	9.7% (132)
V only substitution	8.6% (116)
I only substitution	0.7% (10)
V and I substitutions	0.4% (6)
K65R/E/N	1.0% (14)
Any TAM	9.7% (132)
NNRTI-R	**22% (295/1356)**
RPV-R	10% (135)
K103N/S	11% (152)
PI-R	**10% (135/1356)**
IN Data Available (Historical and/or Proviral)	83% (1272)
INSTI-R	**3.7% (47/1278)**
T97A	2.2% (28)

Table 4. Frequency of Pre-existing M184V/I by Study

Baseline Genotype	Proportion of Participants, % (n or n/N): Study 4030 (n=283)	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[a]	84% (237)	95% (267)	97% (255)	96% (276)	91% (222)	96% (82)	17% (17)
M184V/I	20% (47/237)	3.7% (10/267)	2.7% (7/255)	16% (44/276)	8.1% (18/222)	3.7% (3/82)	18% (3/17)
V only substitution	18% (43)	2.6% (7)	2.4% (6)	19% (39)	6.8% (15)	3.7% (3)	18% (3)
I only substitution	0.8% (2)	0.7% (2)	0.4% (1)	1.4% (3)	0.9% (2)	0	0
V and I substitutions	0.8% (2)	0.5% (1)	0	1.0% (2)	0.5% (1)	0	0

a. From cumulative historical and/or proviral genotypes

- M184V/I was detected in 132 suppressed participants enrolled across 5 studies, including 85 that would have been excluded if known prior to randomization

Results, cont'd
Section 1: Studies 4030, 1844, 1878, 4449, and 1474 (B/F/TAF Groups)

Figure 1. M184V/I Detection by Historical and Baseline Proviral Genotypes

- Pre-existing M184V/I was detected in 10% (132/1356) of participants switched to B/F/TAF
  - Most M184V/I was identified by baseline proviral DNA genotyping

Table 5. Association of M184V/I with Other Resistance Substitutions

	Proportion of Participants, % (n/N): Pooled B/F/TAF With Pre-existing M184V/I (n=132)	HIV-1 RNA <50 c/mL at Last Visit
M184V/I alone	**23% (31/132)**	**97% (30/31)**
M184V/I + ≥1 primary resistance substitution	**77% (101/132)**	**98% (99/101)**
M184V/I + NNRTI-R	52% (68/132)	99% (67/68)
M184V/I + Other NRTI-R	47% (62/132)	98% (61/62)
M184V/I + TAMs	40% (53/132)	98% (52/53)
M184V/I + PI-R	20% (27/132)	100% (27/27)
M184V/I + Primary INSTI-R	4% (5/132)[a]	100% (5/5)

a. Primary INSTI-R substitutions observed with M184V/I: T97A (n=2) and Y143H, Q148R, and N155H (n=1 each).

- M184V/I was frequently detected with other primary resistance substitutions, but was the only resistance substitution detected in 23% of participants

Figure 2. Virologic Outcomes by Pre-existing Resistance, Pooled B/F/TAF Analysis

a. One participant was off study drug at the time of virologic failure (plasma BIC concentration was BLQ) and had no new resistance development, one participant with poor adherence (71% by pill count) discontinued with HIV-1 RNA 61 c/mL, and one participant had a HIV-1 RNA 87 c/mL at their last study visit then switched to commercial B/F/TAF and resuppressed at their follow-up visit

- B/F/TAF efficacy was not affected by resistance at baseline

Figure 3. Virologic Suppression at Last On-treatment Visit Stratified by Study and Pre-existing M184V/I (n=132)

- No difference in the rates of virologic suppression between participants with or without pre-existing M184V/I

Results
Section 2: Studies 4030, 1844, and 1878 (All Treatment Groups)

Table 6. Baseline Characteristics Stratified by M184V/I Detection in Studies of Suppressed Adults

	Participants with Baseline Data Pooled Studies 1844, 1878, & 4030: M184V/I (n=162)	Wild-type M184 (n=1360)
Race/Ethnicity, % (n)		
Non-Black	64% (101)	78% (1058)
Black or African American	36% (58)	22% (299)
Hispanic/Latino	25% (39)	17% (237)
Mean time since ART start, years (range)	16.2 (0.8–32.2)	8.5 (0.3–31.8)
Mean CD4 count, cells/µL (range)	633 (173–1515)	697 (18–2582)
CD4 <500 cells/µL , % (n)	36% (59)	27% (370)
CD4 ≥500 cells/µL, % (n)	64% (103)	73% (990)
HIV status, % (n)		
Symptomatic or AIDS	25% (40)	16% (217)
Asymptomatic	75% (122)	84% (1143)
Resistance substitutions present, % (n)		
NRTI-R (other than M184V/I)	48% (77)	8% (107)
NNRTI-R	51% (83)	19% (263)
PI-R	20% (33)	8% (113)

Table 7. Risk Factors Associated with Pre-existing M184V/I by Multivariate Logistic Regression Model

Variables Associated with Pre-existing M184V/I	OR (95% CI)	p-value
Black race (vs non-Black)	2.57 (1.67, 3.97)	< 0.001
Hispanic/Latino ethnicity (vs not Hispanic/Latino)	1.84 (1.13, 3.00)	0.014
Time since ART start (per year)	1.09 (1.06, 1.12)	< 0.001
CD4 <500 cells/µL (vs ≥500 cells/µL)	1.57 (1.03, 2.40)	0.035
HIV status: symptomatic or AIDS (vs asymptomatic)	1.74 (1.08, 2.82)	0.024
History of NRTI resistance (other than M184V/I)	4.56 (2.87, 7.25)	< 0.001
History of NNRTI resistance	2.80 (1.87, 4.19)	< 0.001
History of PI resistance	1.86 (1.07, 3.25)	0.029

The results are adjusted by study effect

- Risk factors associated with M184V/I include Black race, Hispanic/Latino ethnicity, longer time since ART treatment started (10% per year), CD4 cell count <500 cells/µL, symptomatic HIV status or AIDS, and NRTI-R (other than M184V/I), NNRTI-R, or PI-R

Conclusions

- Virologically suppressed participants who switched to B/F/TAF in Studies 1844, 1878, 4030, 4449, and 1474 maintained viral suppression with no treatment emergent resistance
  - 99% had HIV-1 RNA <50 c/mL at their last study visit
- M184V/I was detected in 132/1356 (10%) of participants, most of which was previously undocumented
- High efficacy was observed among participants with pre-existing M184V/I who switched to B/F/TAF
  - 98% with M184V/I an had HIV-1 RNA <50 c/mL at their last study visit
  - No treatment-emergent resistance was detected
- M184V/I at baseline was associated with Black race, Hispanic/Latino ethnicity, a longer duration of ART, CD4 cell count <500 cells/µL, symptomatic HIV or AIDS, and other NRTI, NNRTI, or PI resistance
- A triple therapy regimen of B/F/TAF is an effective treatment option for suppressed PLWH, including those with known or unidentified M184V/I

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