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Preexisting Resistance and B/F/TAF Switch Efficacy in African Americans

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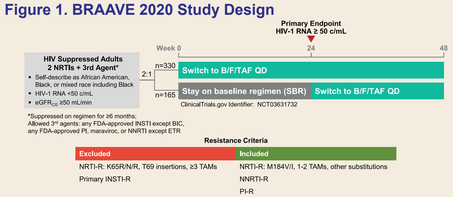
Introduction

- The single-tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a DHHS, IAS–USA, and EACS guidelines-recommended regimen,[1-3] with demonstrated safety and efficacy, and a high barrier to resistance
  - No treatment-emergent resistance to B/F/TAF has been detected in >2000 participants from 8 Phase 3 clinical trials, including in those with preexisting resistance[4-10]
- Black Americans have the highest rates of HIV/AIDS in the U.S. but are under-represented in medical research
  - International Phase 3 studies of B/F/TAF in treatment-naïve participants included 33% who identified as Black or of African descent[4]
- The BRAAVE 2020 Study is evaluating the efficacy and safety of switching to B/F/TAF in HIV-1 infected, virologically suppressed participants who self-identify as African American or Black
- M184V/I is a common NRTI resistance substitution but is often not identified by routine genotyping and prevalence may be under-estimated[10-13]
  - Previously, Black race was associated with preexisting M184V/I in virologically suppressed clinical trial participants[14]
- Here, resistance analyses from BRAAVE 2020 through Week 24 are presented

Methods

Figure 1. BRAAVE 2020 Study Design



BIC, bictegravir; c, copies; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; ETR, etravirine; INSTI, integrase strand transfer inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor, -R, resistance; TAMs, thymidine analog mutations

Baseline Genotypic Analyses

- Historical HIV-1 genotyping reports were collected if available
- HIV-1 proviral DNA genotype testing (GenoSure Archive, Monogram Biosciences) was performed on baseline samples retrospectively; no data due to assay failure or sample unavailability was imputed as wild-type (n=22)
  - Participants with preexisting resistance detected after enrollment continued on study

Resistance Analysis Population

- Resistance testing was performed for participants with confirmed virologic failure (HIV-1 RNA ≥50 c/mL at 2 consecutive visits) and HIV-1 RNA ≥200 c/mL at the confirmation visit or with HIV-1 RNA ≥200 c/mL at Week 24 or last visit, with no resuppression of HIV-1 RNA to <50 c/mL while 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)[15]

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/I/L/S/T, N83D, I84V, N88S, L90M

Primary INSTI-R: T66I/A/K, E92Q/G, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K

Secondary INSTI-R: M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, T97A, 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

Methods (cont'd)

Efficacy Analyses

- Analyses included all participants who had ≥1 on-treatment HIV-1 RNA measurement
  - 2 participants with primary INSTI-R substitutions detected by historical genotype were enrolled in error and were excluded from efficacy analyses
- 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

Results

Table 1. Baseline Resistance Data Sources

	Proportion of Participants, % (n)			
	B/F/TAF n=330		SBR n=165	
	PR/RT	IN	PR/RT	IN
Baseline Data Available	95% (315)	93% (307)	96% (158)	92% (151)
Historical Genotype	48% (157)	10% (32)	48% (80)	11% (18)
Baseline Proviral Genotype	92% (304)	92% (304)	92% (151)	92% (151)
Historical + Proviral Genotype	44% (146)	9% (29)	44% (73)	11% (18)

Table 2. Preexisting Resistance Substitutions

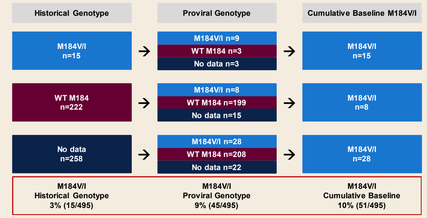
	Proportion of Participants, % (n)	
Resistance Category	**B/F/TAF n=330**	**SBR n=165**
NRTI-R	**13% (44)**	**16% (26)**
K65R	1% (2)[a]	1% (1)[a]
M184V/I	9% (31)	12% (20)
Any TAM	6% (20)	8% (14)
1-2 TAMs	5% (18)	5% (8)
≥3 TAMs	1% (2)	4% (6)
Other (K70E, L74I/V, Y115F, Q151M)	2% (7)	3% (5)
NNRTI-R	**21% (70)**	**19% (32)**
K103N/S	10% (33)	12% (20)
Rilpivirine associated[b]	9% (29)	7% (12)
PI-R	**11% (36)**	**15% (25)**
Atazanavir or darunavir associated[c]	2% (6)	3% (5)
Primary INSTI-R	**2% (8)**	**2% (3)**
T66A	0	1% (1)
E92G	1% (2)	1% (1)
Y143C/H	1% (3)[d]	0.7% (1)
Q148H/K/R	1% (3)[d]	0
Secondary INSTI-R	45% (149)	47% (78)
M50I	21% (69)	22% (36)
T97A	3% (10)	1% (1)
S119P/R/T	21% (70)	20% (33)
E157K/Q	8% (26)	10% (16)

a. K65R was detected only by proviral genotype in 3 participants
b. Rilpivirine associated substitutions are L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, and M230I/L
c. Atazanavir or darunavir associated substitutions are I47V, I50L/V, I54M/L, L76V, I84V, and N88S
d. Y143C and Q148K were detected by historical genotype in 1 participant each; both participants were excluded from efficacy analyses but maintained virologic suppression at all study visits through Week 24

Results (cont'd)

- Preexisting resistance to NRTIs, NNRTIs, and PIs was frequently detected
  - Among all participants: NRTI-R 14% (70/495), NNRTI-R 21% (102/495), and PI-R 12% (61/495)

Figure 2. Detection of Preexisting M184V/I



- Preexisting M184V/I was detected in 10% (51/495) of participants; most M184V/I was identified by baseline proviral DNA genotyping (71%, 36/51)

Figure 3. Participants with ≥1 Resistance Substitution Per ARV Class

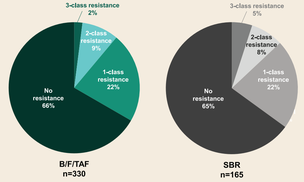
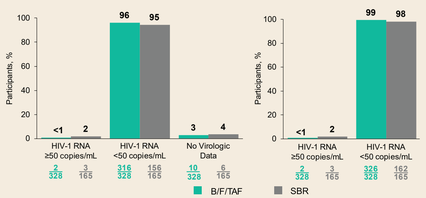


Table 3. Preexisting Primary Resistance by ARV Class

	Proportion of Participants, % (n)	
Resistance Category	**B/F/TAF n=330**	**SBR n=165**
No Primary Resistance (PR, RT, IN)	**66% (218)**	**65% (107)**
Any Primary Resistance (PR, RT, IN)	**34% (112)**	**35% (58)**
1-class resistance	22% (74)	22% (37)
NNRTI-R	12% (40)	10% (16)
PI-R	5% (17)	7% (11)
NRTI-R	4% (14)	4% (7)
INSTI-R	1% (3)	2% (3)
2-class resistance	9% (30)	8% (13)
NRTI-R + NNRTI-R	5% (16)	4% (6)
NRTI-R + PI-R	2% (6)	3% (5)
NNRTI-R + PI-R	1% (4)	1% (2)
NRTI-R or NNRTI-R or PI-R + INSTI-R	1% (4)	0
3-class resistance	2% (8)	5% (8%)
NRTI-R + NNRTI-R + PI-R	2% (7)	5% (8%)
NNRTI-R + PI-R + INSTI-R	<1% (1)	0

- ≥1 preexisting primary resistance substitution was detected in 34% (170/495) of participants; most had resistance to 1 ARV class

Figure 4. Virologic Outcome at Week 24, Full Analysis Set[a]



a. 2 participants were excluded from the full analysis set due to primary INSTI-R substitutions detected by historical genotype, but maintained suppression through Week 24 on B/F/TAF
b. LOCF (last observation carried forward) analysis used the last available on-treatment HIV-1 RNA through Week 24

Participants with HIV-1 RNA ≥ 50 c/mL at Week 24

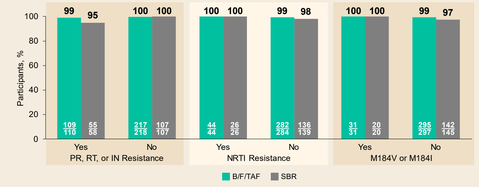
B/F/TAF (n=2)

- 1 with HIV-1 RNA 80 c/mL at Week 24 resuppressed to HIV-1 RNA <50 c/mL
- 1 with HIV-1 RNA 248 c/mL at Week 24 had no resistance development and was lost to follow-up (Table 4)

SBR (n=3)

- 2 with HIV-1 RNA 103 c/mL and 91 c/mL at Week 24
- 1 with HIV-1 RNA 23,100 c/mL at Week 24 and no resistance development (Table 4)
- All 3 switched to B/F/TAF at Week 24 and resuppressed to HIV-1 RNA <50 c/mL by their next study visits

Figure 5. Virologic Suppression at Week 24 by Baseline Resistance, Full Analysis Set



- Participants with preexisting resistance including NRTI-R and M184V/I maintained virologic suppression when switched to B/F/TAF

Table 4. Resistance Analysis Population

Participants, n	B/F/TAF n=328	SBR n=165
Analyzed for Resistance (PR, RT, IN)	1	1
Any Emergent Resistance	0	0

Conclusions

- Preexisting resistance was common among virologically suppressed Black participants in the US
  - ≥1 primary preexisting resistance substitution in PR, RT, or IN detected in 34% (170/495)
  - NNRTI-R (21%, 102/495), NRTI-R (14%, 70/495), and PI-R (12%, 61/495) frequently detected
  - M184V/I detected in 10% (51/495), most of which was previously undocumented
- High rates of virologic suppression were maintained on B/F/TAF
  - 99% overall and 99% with preexisting resistance had HIV-1 RNA < 50 c/mL at last study visit through Week 24
- There was no treatment emergent resistance in either group
- 31 participants who switched to B/F/TAF had preexisting M184V/I; 100% maintained suppression through 24 weeks
  - In all Phase 3 B/F/TAF studies including BRAAVE 2020, a total of 163 participants with preexisting M184V/I switched to B/F/TAF; 98% (160/163) maintained virologic suppression on B/F/TAF treatment with no emergence of new resistance[14]
- B/F/TAF is an effective treatment option for virologically suppressed Black PWH with or without preexisting resistance to NNRTIs, PIs, or most NRTIs including M184V/I

References: **1.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV, DHHS, http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. **2.** European AIDS Clinical Society Guidelines Version 10, November 2019. **3.** Saag MS, et al., JAMA 2018; 320: 379-96. **4.** Orkin C, et al., EACS 2019; Poster #PE3/14. **5.** Kityo C, et al., IAS 2019; Presentation #MOAB0106. **6.** Maggiolo F, et al., EACS 2019; Poster #PE9/49. **7.** Gaur AH, et al., CROI 2019);Presentation #46. **8.** Andreatta K, et al., CROI 2019; Poster #552. **9.** Andreatta K, et al., IAS 2019; Poster #MOPEB243. **10.** Acosta R, et al., IAS 2019; Poster #MOPEB241. **11.** Wainberg, MA et al., JAC 2011; 66: 2346-49. **12.** Yang D et al., CROI 2019; Poster #543. **13.** Perez-Valero I et al., IAS 2018; Presentation #TUAB0104. **14.** Andreatta K et al., EACS 2019; Poster #PE13/21. **15.** Wensing AM, et al., Top Antivir Med 2017; 24: 132-41.

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