Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) shows high efficacy in clinical study participants infected with HIV-1 subtype F

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Introduction

- HIV-1 subtype F (F1 and F2) accounts for less than 1% of all HIV-1 infections globally, and is mostly present in Africa and South America[1]
  - In the past 10-15 years, there has been a rise of subtype F infections in MSM in Western Europe
  - Subtype F has been identified in up to 26% of newly diagnosed patients in some parts of Spain[2]
- Some reports have suggested that nonnucleoside reverse transcriptase inhibitor- (NNRTI-), protease inhibitor- (PI-), and integrase strand transfer inhibitor- (INSTI-) based ART response may be worse for those infected with subtype F vs. subtype B[3,4]
  - In a Spanish cohort, virologic suppression rates using INSTI-based regimens were lower at Week 24 in those with subtype F vs. subtype B; however, results might be confounded by differences in baseline characteristics, such as lower CD4 cell count in the subtype F group[5]
- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a potent, once-daily, INSTI-containing single tablet regimen for treatment of HIV-1 infection, with in vitro activity against all B and non-B subtypes, including subtype F[6,7]
  - 48 weeks of B/F/TAF treatment had high efficacy in participants (n=6 with subtype F)[8]

Objective

- To assess the efficacy of B/F/TAF and other INSTI-containing regimens against HIV-1 subtype F in treatment-naïve and virologically suppressed clinical trial participants

Methods

- Participants from 5 phase 3 B/F/TAF studies were included in this analysis
  - Treatment-naïve (N=1274): Studies 1489 and 1490 (NCT02607930 and NCT02607956)
  - Virologically suppressed switch (N=1226): Studies 1844, 1878, and 4449 (NCT02603120, NCT02603107, and NCT03405935)
  - Studies 1474, 1961, 4030, and 4580 were not included in this analysis as these studies did not enroll any participants with subtype F
- Genotype and Subtype Determination:
  - Treatment-naïve studies: HIV-1 genotype and subtype were determined at screening using population genotyping of reverse transcriptase (RT) and protease (PR) (Monogram Biosciences) and at baseline using next generation sequencing (NGS) (Seq-IT) of integrase (IN) with a mutation frequency cutoff of ≥15%
  - Virologically suppressed switch studies: Historical HIV-1 genotypes and subtypes were collected if available but were not required for study entry. Baseline proviral DNA genotyping of PR, RT, and IN (GenoSure Archive, Monogram Biosciences) was conducted retrospectively on a subset of participants
- Treatment response was assessed by last on-treatment observation carried forward (LOCF: HIV-1 RNA <50 copies/mL or HIV-1 RNA ≥50 copies/mL) at the latest timepoint of each participant's follow-up

Table 1: B/F/TAF Clinical Studies with HIV-1 Subtype F Participants

Study	Baseline ART Status	Participants, n	Study Phase and Treatment		HIV-1 Subtype F Participants, n	Timepoint in Subtype F Analysis
			Baseline-Week 48	Weeks 48-96/144/End of study		
Study 1489	ART-naïve adults	314	B/F/TAF (DTG/ABC/3TC placebo)	B/F/TAF (DTG/ABC/3TC placebo)	1	Week 144
		315	DTG/ABC/3TC (B/F/TAF placebo)	DTG/ABC/3TC (B/F/TAF placebo)	5	Week 144
Study 1490	ART-naïve adults	320	B/F/TAF (DTG+F/TAF placebo)	B/F/TAF (DTG+F/TAF placebo)	5	Week 144
		325	DTG+F/TAF (B/F/TAF placebo)	DTG+F/TAF (B/F/TAF placebo)	3	Week 144
Study 1844	Virologically suppressed adults	282	B/F/TAF (DTG/ABC/3TC placebo)	B/F/TAF	1	End of study (Week 156)
		281	DTG/ABC/3TC (B/F/TAF placebo)	B/F/TAF	1[a]	DTG/ABC/3TC: Week 48 B/F/TAF: End of study (Week 108)
Study 1878	Virologically suppressed adults	290	B/F/TAF	B/F/TAF	1	End of study (Week 108)
		287	SBR (PI-containing regimen)	B/F/TAF	0	-
Study 4449	Virologically suppressed adults ≥65 years	86	B/F/TAF	B/F/TAF	3	Week 48

ART=antiretroviral therapy. B/F/TAF=bictegravir, emtricitabine, and tenofovir alafenamide. DTG+F/TAF=dolutegravir, emtricitabine, and tenofovir alafenamide. DTG/ABC/3TC=dolutegravir, abacavir, and lamivudine. PI=protease inhibitor. SBR=stay on background regimen.
a. One participant with HIV-1 subtype F in Study 1844 started the study on DTG/ABC/3TC and switched to B/F/TAF after Week 48. This participant is counted twice in subsequent analyses, once when assessing viral suppression on DTG/ABC/3TC and once when assessing suppression on B/F/TAF.

Results

Table 2: Baseline Characteristics of Subtype F Participants

	B/F/TAF		DTG+2 NRTIs	
	Naïve (n=6)	Switch (n=6)	Naïve (n=8)	Switch (n=1)
Median age, years (range)	36 (26-58)	60 (38-74)	28 (22-41)	41
Male, %	83	67	88	100
White race, %	67	100	75	100
Hispanic/Latino ethnicity, %	17	17	25	0
HIV-1 RNA copies/mL, %				
≤100,000	83	-	100	-
>500,000	17	-	0	-
<50	-	100	-	100
CD4 cell count cells/µL, %				
≥200 to <350	33	0	12	0
≥350 to <500	0	0	50	0
≥500	67	100	38	100
Country, %				
Western Europe	100	100	88	100
Dominican Republic	0	0	12	0

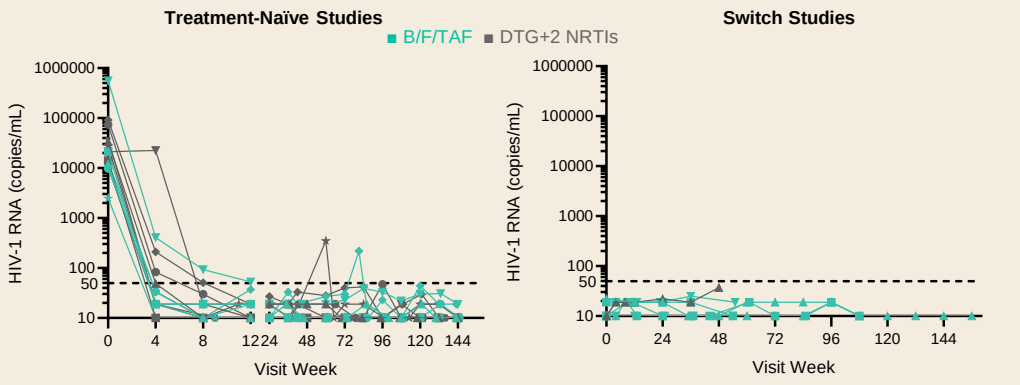
Results, cont'd.

Table 3: Frequency of Baseline Resistance Associated-Substitutions in Subtype F Participants

Resistance Substitutions (-R), n/N (%)[a]	B/F/TAF		DTG+2 NRTIs	
	Naïve (n=6)	Switch (n=6)	Naïve (n=8)	Switch (n=1)
Primary INSTI-R	0	0	0	0
Secondary INSTI-R	3/6 (50)	3/6 (50)	4/8 (50)	1/1 (100)
M50I	1 (17)	1 (17)	1 (13)	0
S119P/R/T	2 (33)	3 (50)	3 (38)	1 (100)
G163R	1 (17)	1 (17)	0	0
Primary NRTI-R	0	0	0	0
Primary NNRTI-R	0	2/6 (33)	1/8 (13)	0
K101E/Q	0	1 (17)	0	0
K103N	0	1 (17)	0	0
V106I	0	0	1 (13)	0
E138A	0	2 (33)	0	0
Primary PI-R (M46I)	1/6 (17)	0	0	0

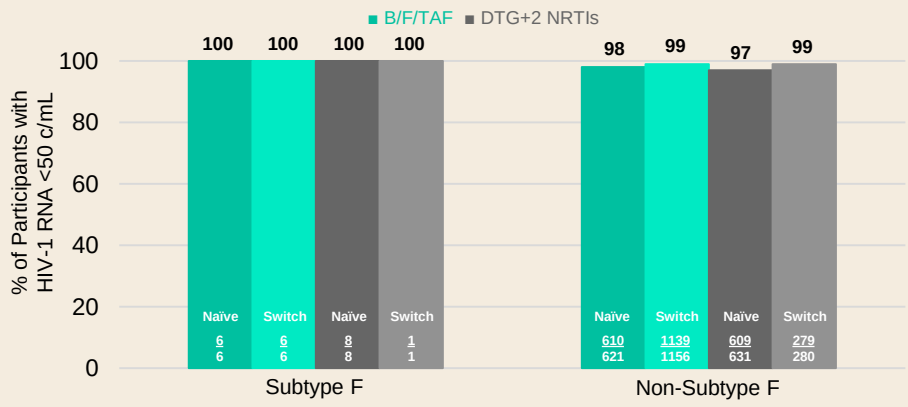
a. Resistance substitutions were detected by HIV-1 plasma RNA genotyping or by proviral DNA genotyping.

Figure 1: HIV-1 RNA Results of Subtype F Participants



- In the treatment-naïve studies, 5 of 6 B/F/TAF and 5 of 8 DTG+2 NRTIs participants suppressed HIV-1 RNA to <50 copies/mL by Week 4; all were suppressed at Week 24
  - One B/F/TAF participant with baseline HIV-1 RNA 562,000 copies/mL had HIV-1 RNA 53 copies/mL at Week 12 and was fully suppressed by Week 24
  - One participant each in the B/F/TAF and DTG/ABC/3TC groups experienced a single blip but had HIV-1 RNA <50 copies/mL at Week 144
- In the virologically suppressed switch studies, all 6 B/F/TAF and 1 DTG/ABC/3TC participants maintained suppression through their latest endpoints, with no blips

Figure 2: Virologic Outcomes (LOCF) of Subtype F Participants



- All 12 B/F/TAF subtype F participants had HIV-1 RNA <50 c/mL by LOCF at their last study visit (through Week 144 for treatment-naïve, through Weeks 48-156 for switch)
- All 9 DTG/ABC/3TC or DTG+F/TAF subtype F participants had HIV-1 RNA <50 c/mL at their last study visit (through Week 144 for treatment-naïve, through Week 48 for switch)
- None of the subtype F participants had virologic failure or qualified for resistance analysis

Conclusions

- There was no evidence of lower virologic response rates in those with HIV-1 subtype F to INSTI-based 3-drug regimens using bictegravir or dolutegravir, although the sample size was small
- B/F/TAF showed high efficacy in participants infected with HIV-1 subtype F in treatment-naïve and virologically suppressed switch studies
  - No participant with HIV-1 subtype F experienced virologic failure or developed resistance to B/F/TAF or DTG+2 NRTIs

References: **1.** Hemelaar J, et al. Lancet Infect Dis 2019 Feb;19(2):143-155; **2.** Paraskevis D, et al. Infection, Gen and Evol 2015;30:96-101; **3**. Pernas B, et al. AIDS 2014 Jul 31;28(12):1837-40; **4.** Ahagon CM, et al. AIDS 2020 23rd International AIDS Conference. Poster PEB0090; **5**. Cid-Silva P, et al. AIDS 2018 Jan 2;32(1):121-125; **6.** Tsiang M, et al. AAC 2016 Nov 21;60(12):7086-7097; **7**. Smith RA, et al. AAC 2019 Apr 25;63(5):e00014-19; **8.** Acosta RK, et al. AAC 2019 May;63(5):e02533-18.
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