PEB0257

Baseline NRTI Resistance in Suppressed Participants Did Not Lead to Viral Blips on Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) or Dolutegravir (DTG) + F/TAF Through Week 48 in Study 380-4030

Rima K. Acosta, Hui Liu, Sean E. Collins, Hal Martin, Kirsten L. White — Gilead Sciences, Inc., Foster City, California, USA

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
800-445-3235

Introduction

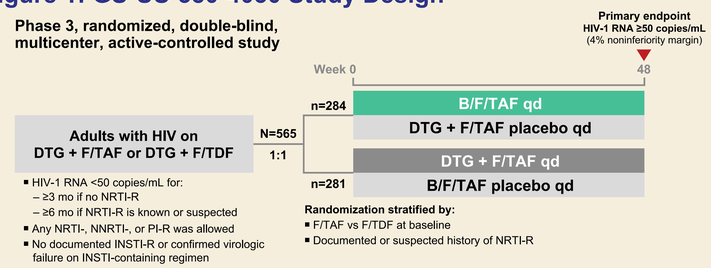
- The single-tablet regimen bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a guidelines-recommended regimen with demonstrated safety and efficacy, and a high barrier to resistance[1-5]
- Study 4030 was the first study to prospectively investigate switching to B/F/TAF in virologically suppressed participants with history of treatment failure or preexisting nucleoside reverse transcriptase inhibitor resistance (NRTI-R)
  - Switching to B/F/TAF was noninferior to dolutegravir (DTG) + F/TAF, with high, durable rates of virologic suppression and no treatment-emergent resistance through 48 wk of treatment[6]
- Viral blips are transient elevated viral load values
  - Most blips are not associated with long-term clinical failure[7,8]
  - However, some blips may be associated with increased viral replication, leading to development of drug resistance[9,10]
- The variability of HIV-1 RNA assays is high at lower viral loads; many blips that are <200 copies/mL may be due to assay fluctuation[11]
  - DHHS guidelines use threshold of ≥200 copies/mL as evidence of virologic failure[1]

Objective

- To investigate viral blips in suppressed participants with or without baseline NRTI-R through 48 wk of treatment on B/F/TAF or DTG + F/TAF

Methods

Figure 1: GS-US-380-4030 Study Design*



*ClinicalTrials.gov NCT03110380. INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

Table 1: NRTI Resistance Categories

Category	NRTI-R Mutation	Resistance
1	K65R/E/N, ≥3 TAMs* that include M41L or L210W, or T69 insertions	High
2	M184V/I, K70E/G/M/Q/S/T, L74V/I, V75A/S/M/T, Y115F, T69D, Q151M, or other TAM* patterns	Low
3	No NRTI-R–associated mutations	None

*Thymidine analog mutations (TAMs) are M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N.

- NRTI-R was classified into 3 categories for stratification at randomization; for participants who qualified for >1 resistance category, the higher resistance category was prioritized: 1, then 2, and then 3
- Stratification category: assigned by investigator at randomization based on review of HIV-1 historical genotypes (if available), phenotypes (if available), and ART history
- Final category: assigned post-randomization based on cumulative historical data, investigator assessment of suspected resistance, and baseline genotyping using proviral DNA genotype (GenoSure Archive®, Monogram Biosciences, South San Francisco, California, USA)
  - No genotypic data and no suspicion of resistance was assigned to category 3

Blip Analysis

- Participants with ≥1 on-treatment post-baseline HIV-1 RNA value were included in this analysis
  - All on-treatment HIV-1 RNA data through Week 48 were included
- Viral blip was defined as a post-baseline HIV-1 RNA value ≥50 copies/mL preceded and followed by HIV-1 RNA <50 copies/mL
- Virologic outcomes at Week 48 were measured by the last on-treatment observation carried forward (LOCF) method

Results

Table 2: Preexisting NRTI Resistance

Category	NRTI-R Mutation, n (%)	At Stratification N=565*	Final N=565*	B/F/TAF n=284*	DTG + F/TAF n=281*
1	K65R/E/N or ≥3 TAMs†	15 (3)	30 (5)	16 (6)	14 (5)
2	Other NRTI-R	63 (11)	108 (19)	55 (19)	53 (19)
3	No NRTI mutation	487 (86)	427 (76)	213 (75)	214 (76)

*Stratification category was assigned at randomization by investigator based on review of historical genotype or phenotype (if available), and ART history; final category was assigned post-randomization and additionally included proviral DNA genotyping data; 20 participants were stratified to categories 1 or 2 based on investigator-suspected NRTI-R (19 participants in category 2 and 1 participant in category 1), which was not confirmed by historical genotype or proviral DNA genotype; †Includes K65R/E/N or ≥3 TAMs that include M41L or L210W, or T69 insertions.

Table 3: Viral Blips Through Week 48

	B/F/TAF n=283*	DTG + F/TAF n=279*	All n=562*
Experienced any blips, n (%)	8 (2.8)	7 (2.5)	15 (2.7)
	p=1.0†		
Experienced >1 blip, n (%)	1 (0.4)‡	0	1 (0.2)‡
Participants with ≥1 blip/study visit, %	0.5	0.4	0.4

*2 participants in B/F/TAF group and 1 in DTG + F/TAF group did not have on-treatment post-baseline data and were not included in blip analysis; †Fisher exact test comparing % of participants with blips in B/F/TAF group vs DTG + F/TAF group; ‡1 B/F/TAF participant had 2 blips and no preexisting NRTI-R.

- Viral blips were infrequent in this study and similar proportions of participants experienced blips in both treatment groups

Figure 2: Frequency of Viral Blips by Study Visit Through Week 48

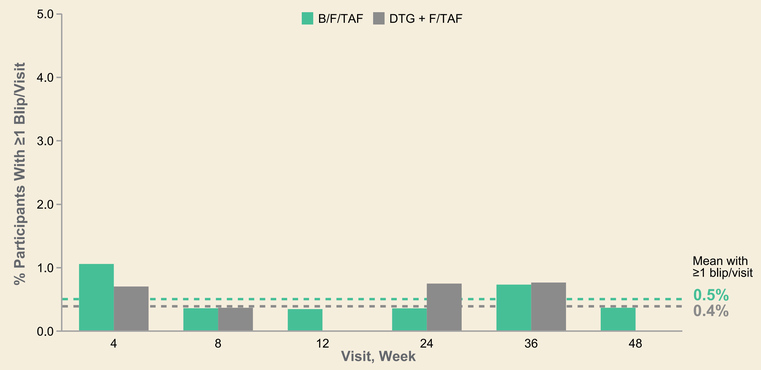
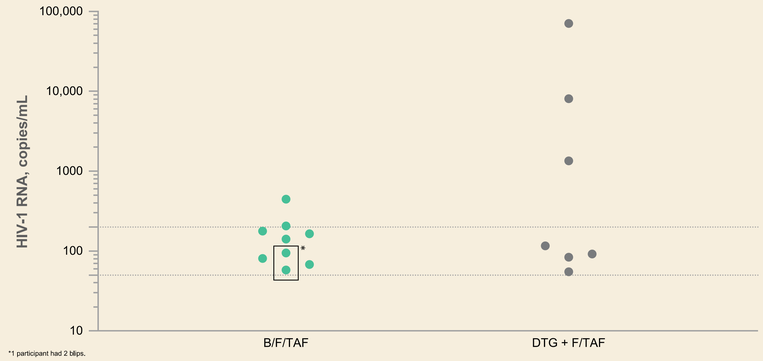


Table 4: Blips by Baseline Resistance Category

Participants With Blips, n/N (%)	B/F/TAF n=283*	DTG + F/TAF n=279*
1: K65R/E/N or ≥3 TAMs	1/16 (6)†	0/14 (0)
2: Other NRTI-R	0/55 (0)	1/53 (2)‡
M184V/I (from categories 1 and 2)	1/47 (2)†	1/34 (3)‡
3: No NRTI mutation	7/212 (3)	6/212 (3)

*2 participants in B/F/TAF group and 1 in DTG + F/TAF group did not have on-treatment post-baseline data and were not included in blip analysis; †B/F/TAF participant who experienced blip of 141 copies/mL had 3 TAMs and M184I, and had HIV-1 RNA <50 copies/mL at Week 48; ‡DTG + F/TAF participant who experienced blip of 1350 copies/mL had M184V and HIV-1 RNA <50 copies/mL at Week 48.

Figure 3: Viral Blip Events Through Week 48



*1 participant had 2 blips.

- Most blips in B/F/TAF group were <200 copies/mL
- All participants with blips ≥200 copies/mL had HIV-1 RNA <50 copies/mL at Week 48

Table 5: Week 48 Efficacy Outcomes by LOCF of Participants With vs Without Blips

Participants With HIV-1 RNA <50 copies/mL, n/N (%)	B/F/TAF n=283*	DTG + F/TAF n=279*	All n=562*
Overall	282/283 (99)	276/279 (99)	558/562 (99)
With ≥1 blip	7/8 (88)†	7/7 (100)	14/15 (93)†
Without blip	275/275 (100)	269/272 (99)	544/547 (99)

*2 participants in B/F/TAF group and 1 in DTG + F/TAF group did not have on-treatment post-baseline data and were not included in blip analysis; †1 B/F/TAF participant with no preexisting NRTI-R had HIV-1 RNA ≥50 (2340) copies/mL at Week 48, but resuppressed at next visit.

- Blips did not affect treatment outcome through Week 48

Table 6: Resistance Analysis Population: Full Analysis Set

Participants, n	B/F/TAF n=284	DTG + F/TAF n=281
Resistance analysis population*	0	3
With blips	0	0
Emergent resistance to study drugs	0	0

*Included any participant with confirmed viral rebound of HIV-1 RNA ≥50 copies/mL, with confirmatory HIV-1 RNA ≥200 copies/mL through Week 48 or without confirmation if at last visit, who did not resuppress while on study drug.

- No participant with blips qualified for resistance analysis through Week 48

Conclusions

- Viral blips were infrequent and similar among participants switching to B/F/TAF and DTG + F/TAF (0.5% and 0.4% with ≥1 blip/visit, respectively)
- Baseline NRTI resistance did not result in higher incidence of blips
  - Of 47 B/F/TAF participants with preexisting M184V/I, 1 (2%) experienced a viral blip and all maintained suppression through 48 wk
- Blips did not lead to virologic failure or emergence of resistance using these triple-therapy regimens

References: **1.** AIDSinfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. DHHS. December 2019; **2.** Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc., rev 5/19; **3.** Biktarvy [SmPC]. Carrigtohill, Ireland: Gilead Sciences Ireland UC, 6/12/18; **4.** EACS. Guidelines Version 10.0. 11/19; **5.** Saag MS, et al. JAMA 2018;320:379-96; **6.** Sax P, et al. Clin Infect Dis 2020: in press; **7.** Garcia-Gasco P, et al. J Antimicrob Chemother 2008;61:699-704; **8.** Nettles RE, et al. JAMA 2005;293:817-29; **9.** Cohen JW, et al. J Acquir Immune Defic Syndr 2001;28:105-13; **10.** Easterbrook PJ, et al. AIDS 2002;16:1521-7; **11.** White KL, et al. AIDS 2018;32:1053-7.

Disclosures: **R.K. Acosta, H. Liu, S.E. Collins, H. Martin,** and **K.L.L. White:** Gilead.
Acknowledgments: We extend our thanks to the participants, their families, and all participating investigators and staff. This study was funded by Gilead Sciences, Inc.