High Level of Preexisting NRTI Resistance Prior to Switching to B/F/TAF: Study 4030

Video Link

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650) 574-3000
Fax: (650) 578-9264

Acosta RK[1], Willkom M[1], Andreatta K[1], Liu H[1], Martin R[1], Chang S[1], Martin H[1], Collins S[1], Slade P[2], White KL[1]

[1]Gilead Sciences, Inc, Foster City, USA, [2]Gilead Sciences, Melbourne, Australia

Background

- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is approved by the US FDA, Europe EMA and Australia TGA for treatment of HIV-1 infection (treatment-naïve and virologically suppressed without resistance)[1,2]
- B/F/TAF safety, efficacy, and lack of emergent resistance have been demonstrated in controlled clinical trials
  - Treatment-naïve adults: 2 Phase 3 studies of 634 participants through 96 weeks[3-6]
  - Suppressed switch adults: 4 Phase 3 studies of 1090 participants through 48 weeks[7-10]
  - Suppressed switch in adolescents and children: 1 Phase 2/3 study of 100 participants through 48 weeks[11]
- Study GS-US-380-4030 is a phase 3, randomized, double-blinded study of HIV-1 RNA suppressed participants switching 1:1 to dolutegravir (DTG) + F/TAF or B/F/TAF for 48 weeks
  - Types of resistance at study entry:

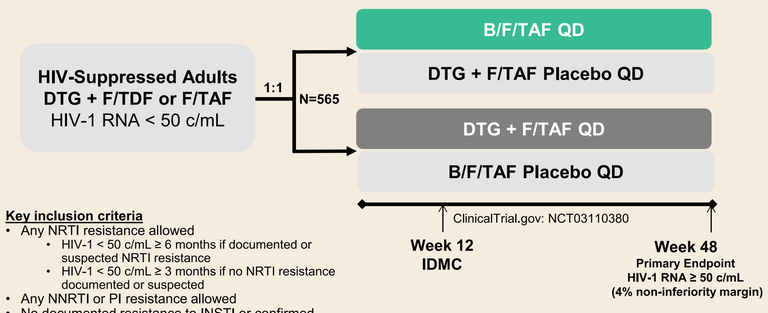
NRTI-R	allowed	PI-R	allowed
NNRTI-R	allowed	INSTI-R	excluded

- Proviral DNA genotyping (archive assays) can detect previously undocumented drug resistance in suppressed patients but can be insensitive[12-14]
- Here, we present baseline resistance analyses and early blinded outcome data from the Week 12 Independent Data Monitoring Committee (IDMC)

Methods

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

Phase 3, randomized, double-blind, multicenter, active-controlled study



Key inclusion criteria
- Any NRTI resistance allowed
  - HIV-1 < 50 c/mL ≥ 6 months if documented or suspected NRTI resistance
  - HIV-1 < 50 c/mL ≥ 3 months if no NRTI resistance documented or suspected
- Any NNRTI or PI resistance allowed
- No documented resistance to INSTI or confirmed virologic failure while on an INSTI-containing regimen
- HBV and/or HCV coinfections allowed

- GS-US-380-4030 randomization was stratified by prior NRTI use (F/TAF vs. F/tenofovir disoproxil fumarate [TDF]) and documented or suspected history of NRTI resistance
- NRTI resistance was stratified into 3 categories. For participants that qualified for more than one resistance category, stratification was prioritized by Category 1, then 2, then 3 as shown below

Category 1: High NRTI Resistance	Category 2: Low/Other NRTI Resistance	Category 3: No NRTI Resistance
• K65R/E/N • ≥ 3 TAMs (including M41L or L210W) • T69 insertions	• M184I/V • Other TAM patterns • K70E/G/M/Q/S/T, L74V/I, V75A/S/M/T, Y115F, T69D, or Q151M	No Mutations

TAMs are M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N

  - At randomization, the Investigator assigned the resistance category based upon HIV-1 historical genotype, if available, and antiretroviral treatment history for "suspected" resistance

- Final resistance categories were assigned post-randomization and were based on historical data, Investigator suspicion of resistance, and baseline genotyping using proviral HIV-1 DNA genotype (GenoSure Archive assay, Monogram Biosciences)
  - No genotypic data and no suspicion of resistance was assigned to category 3
  - Proviral assay limitations
    - Cellular APOBEC-mediated hypermutation may introduce STOP codons and some substitutions associated with drug resistance (E138K, M184I, and M230I in RT; G163R in IN). Utilization of bioinformatics filters to remove hypermutated deep sequence reads mitigates over-reporting of these substitutions.
    - Lack of sensitivity to detect resistance previously reported by plasma HIV-1 RNA genotyping. For example only 43% of previously documented M184V/I was detected by the Archive assay in one recent study[12]
- Virologic outcomes were assessed at the Week 12 IDMC (Independent Data Monitoring Committee) data cut, when all participants had reached Week 12 or discontinued. Randomization assignments remained blinded and pooled results are presented
  - Last available on-treatment HIV-1 RNA: < 50 copies/mL or ≥ 50 copies/mL
  - 3 participants (none had resistance; category 3) had no on-treatment post-baseline data and were not included in the efficacy analysis
  - Median treatment exposure duration at the time of this analysis was 28 weeks

Table 1. Study GS-US-380-4030 HIV-1 Primary Drug Resistance Substitutions

Coding region	Resistance Category	Amino Acid Substitutions
RT	NRTI-R	K65R/E/N, T69 insertions, T69D, K70E/G/M/Q/R/S/T, L74V/I, V75A/M/S/T, 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
PR	PI-R	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M
IN	INSTI-R	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K

Results

Table 2. Participant Demographics

	B/F/TAF or DTG + F/TAF (N=565)
Median age, years (range)	51 (20-79)
Male, %	86
Race, %	
White	71
Black or African descent	23
Hispanic/Latino Ethnicity, %	20
Median CD4 cell count, cells/μL (IQR)	646 (474, 830)
HIV-1 RNA < 50 copies/mL at baseline	98%
Median $eGFR_{CG}$, mL/min (IQR)	99 (81, 119)
NRTIs at baseline	
F/TAF, %	69
F/TDF, %	31

Table 3. Baseline Genotypic Data Sources

	Percent of Participants (n) B/F/TAF or DTG + F/TAF N=565	
	HIV-1 PR/RT Data	HIV-1 IN Data
With Any Baseline Data	83% (470)	73% (413)
Historical Genotype	50% (285)	10% (54)
Baseline Proviral Genotype[a]	69% (391)	69% (391)
Both Historical and Proviral Genotype	36% (206)	6% (32)

a. The GenoSure Archive assay reports data for PR, RT, and IN

- Pre-switch genotypic data for PR/RT and/or IN were available for 470/565 participants (83%)

Table 4. Baseline Drug Resistance Categorization (N=565)

Category	NRTI Mutation	Initial Categorization by Investigators n (%)[a]	Final Categorization n (%)[a]
1	K65R/E/N or ≥ 3 TAMs	15 (3%)	30 (5%)[b]
2	Any Other Pattern	63 (11%)	108 (19%)[b]
3	No NRTI Mutation	487 (86%)	427 (76%)
Additional Resistance Analysis Sets			
Any PI, NRTI, NNRTI, INSTI Resistance Mutation			222 (39%)
Any NRTI-R			138 (24%)
M184V/I (from Category 1 or 2)			81 (14%)
Any NNRTI-R			118 (21%)
Any PI-R			38 (7%)
Any INSTI-R			20 (4%)[c]

a. Initial categorization was assigned at randomization by Investigators based on historical genotype, if available, and Investigator opinion of suspected resistance. Final categorization was assigned post-randomization and was based on historical genotype, Investigator opinion of suspected resistance, and retrospective proviral genotyping results
b. 20 participants were stratified to categories 1 or 2 based on Investigator opinion of suspected NRTI resistance (19 participants to category 2, and 1 participant to category 1) that was not confirmed by historical genotype or proviral DNA genotype
c. INSTI-R mutations present in proviral DNA genotypes were T97A (n=12), Y143H (n=2), S147G (n=1), Q148H + G140S (n=1), N155H/S (n=2), and R263K (n=2). Bictegravir retains full activity against all single INSTI resistance mutants *in vitro*

Table 5. HIV-1 RNA < 50 copies/mL at Week 12 IDMC (Blinded) by Resistance Category

	B/F/TAF or DTG + F/TAF (N=562)[a]
	HIV-1 RNA < 50 c/mL; % (n/N)
All Participants	**99% (557/562)[b]**
Final NRTI Resistance Category	
1: K65R or ≥ 3 TAMs	97% (29/30)
2: Any Other Pattern	99% (107/108)
3: No Mutations	99% (421/424)
Additional Resistance Analysis Sets	
Any PI, NRTI, NNRTI, INSTI Resistance Mutation	99% (220/222)
Any NRTI-R	99% (136/138)
M184V/I (from Category 1 or 2)	98% (79/81)[c]
Any NNRTI-R	99% (117/118)
Any PI-R	97% (37/38)
Any INSTI-R	100% (20/20)

a. 3 participants from resistance category 3 had no post-baseline on-treatment data and were not included in this analysis
b. 5 participants had HIV-1 RNA ≥ 50 copies/ml at their last measurement in this analysis: 1 category 1 participant—59 copies/mL and later resuppressed; 1 category 2 participant—120 copies/mL and later resuppressed; 3 category 3 participants—205 copies/mL and later resuppressed; 357 copies/mL; and 25100 copies/mL. Those with ≥ 200 copies/mL were included in the resistance analysis population if they did not resuppress
c. Of the 81 participants with M184V or M184I, 71 had M184V, 6 had M184I, and 4 had M184V/I

Table 6. GS-US-380-4030 Week 12 IDMC (Blinded) Resistance Analysis of Virologic Failures

	B/F/TAF or DTG + F/TAF (N=565)
Resistance analysis population	2[a]
Emergent resistance	0

Resistance analysis population was any participant with a confirmed viral rebound of HIV-1 RNA ≥ 50 copies per mL, with the confirmatory HIV-1 RNA ≥ 200 copies/mL through the Week 12 IDMC data cut, or without confirmation if at the last visit, who did not resuppress while on study drug.

a. Both participants were from resistance category 3, with no NRTI-R, NNRTI-R, PI-R, or INSTI-R detected at baseline or virologic failure

Figure 2. Detection of M184V/I in Baseline Genotypic Data

Baseline M184V/I detected in 14% of all patients (81/565)

51% (41/81) M184V/I by Historical Genotype
14% (41/285) of all with Historical Genotypes
- 34/41 participants had both historical and Proviral genotypes
  - 50% (17/34) of historical M184V/I was confirmed by Proviral
- 50% (17/34) of historical M184V/I was missed by Proviral

49% (40/81) Previously Undocumented M184V/I by Proviral Genotype
11% (40/357) of all with Proviral Genotypes and no prior known M184V/I
- 25% (10/40) had historical WT M184M but M184V/I found by Proviral
- 75% (30/40) found by Proviral in absence of historical data

Table 7. Association of M184V/I with Other Primary Resistance Mutations

	Percent of Participants (n/N) Participants with Baseline M184V/I n=81	HIV-1 RNA <50 c/mL at Week 12 IDMC (Blinded)
M184V/I alone	**26% (21/81)**	**95% (20/21)[a]**
M184V/I + ≥ 1 primary resistance substitution	**74% (60/81)**	**98% (59/60)[b]**
M184V/I + PI-R	20% (16/81)	94% (15/16)
M184V/I + NNRTI-R	51% (41/81)	98% (40/41)
M184V/I + other NRTI-R	51% (41/81)	98% (40/41)
M184V/I + TAMs	42% (34/81)	97% (33/34)
M184V/I + primary INSTI-R	6% (5/81)	100% (5/5)

Two patients had virologic failure at Week 24, but neither met the protocol defined criteria for genotyping (HIV-1 RNA ≥ 200 c/mL)
a. One participant with M184V alone had a viral load of 120 c/mL and later suppressed
b. One participant with M184I and M41L, L210W, and T215Y NRTI-R mutations; K101E, V106A, Y181C, and G190A NNRTI-R mutations; and D30N and L90M PI-R mutations had a viral load of 59 c/mL and later suppressed

Conclusions

- High levels of NRTI resistance were present in the HIV-1 RNA suppressed participants enrolled in Study GS-US-380-4030
  - Primary drug resistance to any class was present in 39% of participants
  - 14% had NRTI resistance known or suspected at screening, which increased to 24% using historical data and additional baseline proviral HIV-1 DNA genotyping
    - M184V/I was present in 14% of participants
  - Other studies using proviral DNA genotyping have also reported previously undocumented M184V/I[13] and missed documented M184V/I in ~50% of cases[12]
- HIV-1 RNA suppression was maintained at high rates with switch to B/F/TAF or DTG + F/TAF through this blinded Week 12 IDMC data cut, with no emergent drug resistance
  - 99% of the 562 participants in the study maintained suppression
  - 99% of the 222 participants with any drug resistance maintained suppression
  - 98% of the 81 participants with M184V/I maintained suppression
- A triple therapy regimen of B/F/TAF or DTG + F/TAF may be an effective treatment option for virologically suppressed patients with or without evidence of preexisting NRTI resistance including M184V/I

References

1. BIKTARVY® (bictegravir, emtricitabine, and tenofovir alafenamide) Tablets for Oral Use Prescribing Information. Gilead Sciences, Initial US Approval 2018.
2. Biktarvy: EPAR – Product Information. European Medicines Association, 2018.
3. Gallant J, et al., *The Lancet* (2017) 390(10107): 2063-2072.
4. Sax PE, et al., *The Lancet* (2017) 390(10107): 2073-2082.
5. Wohl D, et al., ID Week (2018) Presentation #74246.
6. Stellbrink HJ, et al., HIV Glasgow (2018) Presentation #4185960.
7. Daar ES, et al., *The Lancet* HIV (2018) 5(7): e347-e356.
8. Molina JM, et al., *The Lancet* HIV (2018) 5(7): e357-e365.
9. Kityo C, et al., CROI (2018) Presentation #500.
10. Sax PE, et al., IAS (2019) Abstract submitted.
11. Gaur AH, et al., CROI (2019) Presentation #2571
12. Perez-Valero I, et al., IAC (2018) Presentation #TUAB0104.
13. Andreatta K, et al., HIV Glasgow (2018) Presentation #P298.
14. Thielen A, European Meeting on HIV & Hepatitis (2018) Presentation #5.

Acknowledgements

We extend our thanks to the participants and their families, study investigators and staff.
These studies were funded by Gilead Sciences, Inc.