Long-Term B/F/TAF Switch Efficacy in Patients with Archived Pre-Existing Resistance

Poster 0552

Kristen Andreatta, Madeleine Willkom, Ross Martin, Silvia Chang, Hui Liu, Ya-Pei Liu, Hiba Graham, Hal Martin, and Kirsten L. White

Gilead Sciences, Inc., Foster City, CA, USA

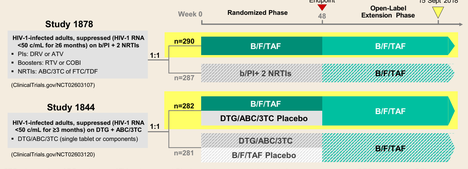
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: 800-445-3235
Kristen.Andreatta@gilead.com

Background

- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is approved by the US FDA and EMA 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 has 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 adolescents and children: 1 Phase 2/3 study of 100 participants through 48 weeks[11]
- In studies 1878 and 1844, virologically suppressed participants switched to B/F/TAF from boosted protease inhibitor (b/PI)- or dolutegravir (DTG)-based triple therapy, completed the 48 week randomization phase, and then continued B/F/TAF in an open label extension phase
  - No HIV-1 genotyping was performed at screening; participants with documented resistance to study drugs or prior virologic failures were excluded
  - Historical genotypic data were available for 49% of participants; the remaining 51% had no HIV-1 genotyping or resistance data available at study start
- Proviral DNA genotyping (archive) assays can detect previously undocumented drug resistance in suppressed patients but are insensitive[12-14]
- Here, we present resistance analyses and virologic outcomes after >2 years of B/F/TAF treatment in studies 1878 and 1844

Methods

Figure 1. Overview of B/F/TAF Switch Studies



3TC = lamivudine; ABC = abacavir; ATV = atazanavir; bPI = boosted protease inhibitor; c/mL = copies per milliliter; COBI = cobicistat; DRV = darunavir; DTG = dolutegravir; FTC = emtricitabine; NRTI = nucleos(t)ide reverse transcriptase inhibitor; RTV = ritonavir; TDF = tenofovir disoproxil fumarate

Resistance Assessments at Enrollment

- Historical plasma HIV-1 RNA genotypes were collected but not required for study entry. Documented or suspected resistance to study drugs was excluded if identified prior to randomization
  - Previous virologic failure or regimen changes for reasons other than simplification/ modernization/toxicity also was excluded
- Whole blood was collected at baseline for potential proviral DNA archive genotyping

Baseline Genotypic Analyses

- HIV-1 proviral DNA genotyping (GenoSure Archive, Monogram Biosciences) was conducted after enrollment from baseline samples
  - All B/F/TAF-treated participants from study 1878 and B/F/TAF-treated participants with longest antiretroviral therapy (ART) histories (pre-2003 or unknown ARV initiation date) from study 1844
- Proviral assay features
  - Deep sequencing-based genotyping of integrated HIV-1 proviral DNA for detection of archived drug resistance in patients with inadequate viral loads for routine plasma RNA genotyping
- Proviral assay limitations
  - Cellular APOBEC-mediated hypermutation may introduce STOP codons and some substitutions associated with drug resistance (E138K, M184I, and M230I in reverse transcriptase; G163R in integrase). 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]

Methods (cont'd)

- Baseline HIV-1 genotypes comprised cumulative data from all historical and proviral genotypes

Post-baseline Resistance Analyses

- Resistance analysis population (RAP)
  - Confirmed virologic failure on study drug (two consecutive visits with HIV-1 RNA ≥ 50 c/mL) and HIV-1 RNA ≥ 200 c/mL at the confirmation
  - HIV-1 RNA ≥ 200 c/mL at Week 48 or last visit on study drug
- Plasma HIV-1 RNA genotype and phenotype (PhenoSenseGT, GeneSeq IN, and PhenoSense IN, Monogram Biosciences)

Table 1. HIV-1 Drug Resistance Substitutions

Coding region	Resistance Category	Amino Acid Substitutions (based on IAS-USA[15])
RT	Primary 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
	Primary 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
PR	Primary 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
IN	Primary INSTI-R	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
	Secondary INSTI-R	M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, 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

IN = integrase; INSTI = IN strand transfer inhibitor; NRTI = nucleos(t)ide RT inhibitor; NNRTI = nonnucleoside RT inhibitor; -R = resistance; RT = reverse transcriptase; PI = PR inhibitor; PR = protease; TAMs = thymidine analog-associated mutations

Efficacy Analyses

- Participants included in analysis switched to B/F/TAF on study Day 1 and had ≥1 on-treatment post-baseline HIV-1 RNA measurement
- Outcomes were determined by last available on-treatment HIV-1 RNA through September 15, 2018
  - All participants with post-baseline data, including those with early discontinuation, had virologic outcomes determined
  - Virologic success (HIV-1 RNA <50 c/mL) or virologic failure (HIV-1 RNA ≥50 c/mL)
- Statistical comparisons were performed using Fishers' Exact test or Student's t-test as appropriate

Results

Table 2. Virologic Outcomes for the Pooled B/F/TAF Group

As of September 15, 2018 the duration of B/F/TAF treatment was median 116 weeks (IQR 108-120 weeks) and 89% of participants completed Week 96

Time of Analysis	Virologic Outcome	Last Available On-treatment HIV-1 RNA	Proportion of Participants, % (n/N)[a]
Week 48	Success	<50 c/mL	98.4% (561/570)
	Failure	≥50 c/mL	1.6% (9/570)[b,c]
September 15, 2018	Success	<50 c/mL	98.4% (561/570)
	Failure	≥50 c/mL	1.6% (9/570)[b,d]

a. 2 randomized and treated participants had no post-baseline visits and were excluded from analysis
b. 7 participants discontinued at or before Week 48 with HIV-1 RNA ≥50 c/mL and are failures in both analysis sets
   – 3 had HIV-1 RNA ≥200 c/mL and were in the resistance analysis population with no resistance development
   – 4 had HIV-1 RNA <200 c/mL and did not qualify for post-baseline testing
c. 2 participants had HIV-1 RNA ≥50 c/mL at Week 48 and resuppressed to <50 c/mL
d. 2 participants had HIV-1 RNA ≥50 c/mL at last visit before September 15, 2018 and resuppressed to <50 c/mL

Table 3. Resistance Development through Current Analysis

	Proportion of Participants, % (n)
	Pooled B/F/TAF n=570
Resistance Analysis Population (RAP)[a]	0.9% (5)
Developed Resistance	0

a. Includes all participants analyzed for emergent resistance from baseline through September 15, 2018

- **High levels of suppression were maintained through Week 48 and current analysis; no treatment-emergent resistance to B/F/TAF has been detected to date**

Results (cont'd)

Table 4. Baseline Genotypic Data Sources

	Proportion of Participants, % (n)	
	Pooled B/F/TAF n=570	
	HIV-1 PR/RT Data	HIV-1 IN Data
Baseline Data Available	78% (445)	55% (314)
Historical Genotype	49% (280)	4.0% (23)
Baseline Proviral Genotype	52% (298)	52% (298)
Both Historical and Proviral Genotype	23% (133)	1.2% (7)

Table 5. Frequencies of Pre-existing NRTI, NNRTI, and PI Resistance Associated Substitutions at Baseline

	Proportion of Participants, % (n)		
	Genotype Source		Total with Any Baseline Data n=445
Resistance Class	Historical n=280	Proviral DNA n=298	
NRTI-R	3.2% (9)	22% (67)	16% (70)
K65R/N	0[a]	2.0% (6)	1.3% (6)
M184V/I	0[a]	15% (44)	10% (44)
Any TAM	3.2% (9)	11% (34)	8.3% (37)[b]
Other	0	1.7% (5)	1.1% (5)[c]
NNRTI-R	15% (42)	24% (72)	21% (92)
Rilpivirine-associated[d]	6.1% (17)	14% (41)	11% (50)
K103N/S	10% (29)	13% (39)	12% (53)
PI-R	4.3% (12)	9.4% (28)	8.3% (37)

a. K65N/R and M184V/I by historical genotype would have led to study exclusion
b. TAMs were M41L (n=16), D67N (n=10), K70R (n=17), L210W (n=5), T215F/Y (n=12), and K219E/N/R/Q (n=12)
c. Other NRTI-R substitutions were L74V (n=2), Y115F (n=3), and Q151M (n=2)
d. Rilpivirine-associated resistance defined as having ≥1 of the following substitutions: L100I, K101E/P, V106A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V Y188L, G190E, H221Y, F227C, or M230I/L

Table 6. Frequencies of Pre-existing INSTI Resistance Associated Substitutions at Baseline

	Proportion of Participants, % (n)		
	Genotype Source		Total n=314
Resistance Class	Historical n=23	Proviral DNA n=298	
Primary INSTI-R	4.3% (1)	2.0% (6)	1.9% (6)[a]
E92G	0	0.3% (1)	0.3% (1)
T97A	1.3% (1)	1.3% (4)	1.3% (4)
S147G	0	0.3% (1)	0.3% (1)
Secondary INSTI-R	57% (13)	50% (149)	51% (161)

a. All INSTI-R substitutions, including the 6 primary INSTI-R substitutions, have predicted sensitivity to bictegravir.

Figure 2. Long-term Virologic Outcomes Stratified by Pre-existing Resistance at Baseline

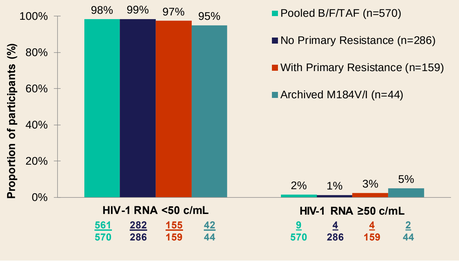


Table 7. Long-term Virologic Outcomes by Baseline Resistance Category

Resistance Category	Proportion of Participants with HIV-1 RNA <50 c/mL, % (n/N)	P Value[a]
All participants	98% (561/570)	-
No Primary Resistance	99% (282/286)	0.5
Any Primary Resistance	97% (155/159)	
NRTI-R	96% (67/70)	0.1
No NRTI-R	99% (370/375)	
M184V/I	95% (42/44)	0.2
No M184V/I	99% (395/401)	
Any TAM	95% (35/37)	0.1
No TAM	99% (402/408)	
NNRTI-R	99% (91/92)	1.0
No NNRTI-R	98% (346/353)	
Rilpivirine-associated	98% (49/50)	1.0
No Rilpivirine-associated	98% (388/395)	
PI-R	100% (37/37)	1.0
No PI-R	98% (400/408)	
Primary INSTI-R	100% (6/6)	1.0
No Primary INSTI-R	98% (301/308)	
Secondary INSTI-R	98% (157/161)	1.0
No Secondary INSTI-R	98% (150/153)	

a. P value determined by Fisher's exact test

- **Long-term B/F/TAF efficacy was not affected by pre-existing primary PR, RT, and/or IN resistance at baseline**

Table 8. Baseline Characteristics Stratified by M184V/I Detection

	Any Baseline Genotype n=445		
	M184V/I n=44	Wild-type M184V n=401	P value[b]
Mean age, years (range)	51 (29–65)	45 (20–74)	<0.001
Male, % (n)	82% (36)	87% (348)	0.4
Mean CD4 count, cells/μL (range)	645 (217–1415)	716 (124–2582)	0.1
Mean time since ART initiation, years (range)	15 (3–29)	8 (0.3–29)	<0.001
Mean time on prior regimen, years (range)	7 (0.8–20)	4 (0.3–20)	<0.001
Baseline ARV regimen, % (n)			
DTG/ABC/3TC	5% (2)	42% (167)	<0.001
Boosted PI + 2 NRTIs	95% (42)	58% (234)	

a. Wild-type M184 by historical and/or proviral baseline genotype
b. P values were calculated by Student's t-test (2-tailed) for mean data and Fisher's Exact test for percentage data

- **Preexisting M184V/I was associated with greater age, longer time since ART initiation, longer time on prior regimen, and current suppression on a regimen of b/PI + 2 NRTIs**

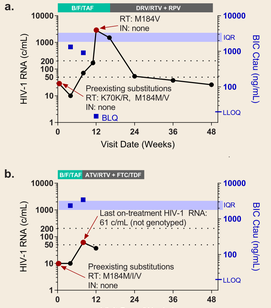
Table 9. Association of M184V/I with Other Primary Resistance Substitutions

Duration of B/F/TAF treatment for participants with M184V/I was median 111 weeks (IQR 97-119 weeks)

	Proportion of Participants, % (n/N)	
	Participants with Baseline M184V/I n=44	HIV-1 RNA <50 c/mL at Last Visit
M184V/I alone	**27% (12/44)**	**92% (11/12)**
M184V/I + ≥1 primary resistance substitution	**73% (32/44)**	**97% (31/32)**
M184V/I + NNRTI-R	50% (22/44)	100% (22/22)
M184V/I + other NRTI-R	41% (18/44)	94% (17/18)
M184V/I + TAMs	34% (15/44)	93% (14/15)
M184V/I + PI-R	11% (5/44)	100% (5/5)
M184V/I + primary INSTI-R	0	–

- **M184V/I was frequently detected with other primary resistance substitutions, but was the only resistance detected in 27% of cases**

Figure 3. Virologic Profiles of Participants with Archived M184V/I and HIV-1 RNA ≥50 c/mL (n=2)



- Confirmed virologic failure Week 12
  - HIV-1 RNA 2860 c/mL
  - BIC concentration BLQ
- No de novo resistance development
- Discontinued B/F/TAF Week 16
  - HIV-1 RNA 1510 c/mL
  - Participant's decision
- Adherence through discontinuation
  - 76% by pill count

- Discontinued B/F/TAF Week 8
  - HIV-1 RNA 61 c/mL (too low for resistance testing)
  - Participant's decision
- Withdrew study consent Week 12
- Adherence through discontinuation
  - 71% by pill count

BIC = bictegravir; BLQ = below limit of quantification (BLQ for BIC indicates missing ≥8 consecutive doses); Ctau = concentration at end of dosing interval; IQR = interquartile range (1951 – 3088 ng/mL for BIC Ctau; N = 1193 HIV-1-infected B/F/TAF-treated participants from 4 Phase 3 studies[3-10]); LLOQ = lower limit of quantification (20 ng/mL for BIC Ctau)

Conclusions

- Virologically suppressed participants switched to B/F/TAF maintained high rates of viral suppression (98% HIV-1 RNA <50 c/mL) in long term follow-up with no treatment emergent resistance observed
- Proviral DNA genotyping detected previously undocumented M184V/I in 10% of participants (n=44)
  - Participants with M184V/I were older, had longer ART durations (mean 15 years, but lowest 3 years), and more frequently switched from boosted-PI regimens
  - M184V/I was often linked with other resistance substitutions: 73% had M184V/I with another primary resistance substitution
- In participants with pre-existing drug resistance, B/F/TAF maintained high rates of virologic suppression
  - 98% (155/159) of participants with any pre-existing primary NRTI, NNRTI, PI, or INSTI resistance
  - 95% (42/44) of participants with archived M184V/I
- A triple therapy regimen of B/F/TAF may be an effective treatment option for suppressed patients with certain pre-existing resistance including, but not limited to, 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 #257.
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.
15. Wensing AM, et al., *Top Antivir Med* (2017) 24:4.
16. Custodio JM et al., CROI (2018) Presentation #34.

Acknowledgments

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

Presented at the Conference on Retroviruses and Opportunistic Infections, Seattle, WA, March 4-7, 2019