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

Video Link

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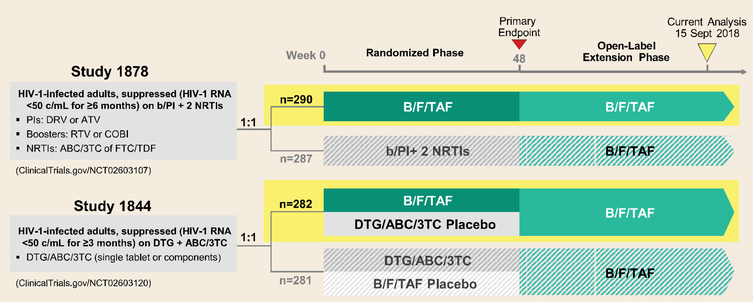
Background

- 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 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]
- 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/L/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 Analysis

- 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

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. Pre-existing NRTI, NNRTI and PI Resistance 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. Pre-existing INSTI Resistance 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)
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. Virologic Outcomes Stratified by Pre-existing Resistance

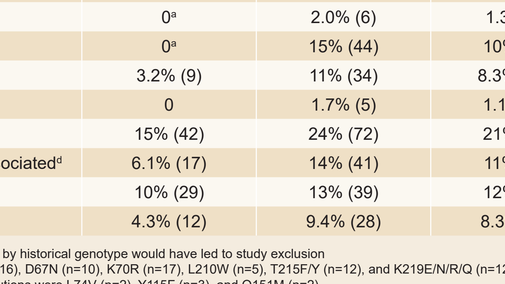


Table 7. Virologic Outcomes by Baseline Resistance

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 Any Primary resistance	99% (282/286) 97% (155/189)	0.5
NRTI-R No NRTI-R	96% (67/70) 99% (370/375)	0.1
M184V/I No M184V/I	95% (42/44) 99% (395/401)	0.2
Any TAM No TAM	95% (35/37) 99% (402/408)	0.1
NNRTI-R No NNRTI-R	99% (91/92) 98% (346/353)	1.0
Rilpivirine-associated No Rilpivirine-associated	98% (49/50) 98% (388/395)	1.0
PI-R No PI-R	100% (37/37) 98% (400/408)	1.0
Primary INSTI-R No Primary INSTI-R	100% (6/6) 98% (301/308)	1.0
Secondary INSTI-R No Secondary INSTI-R	98% (157/181) 98% (150/153)	1.0

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		P value[b]
	M184V/I n=44	Wild-type M184[a] n=401	
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

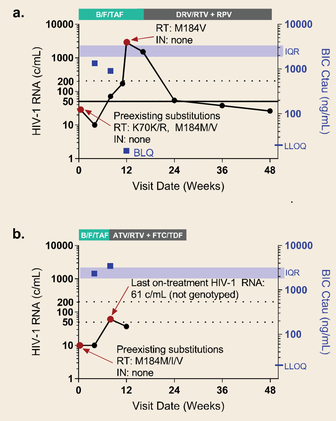
Table 9. Association of M184V/I with Other Primary Resistance Substitutions

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

	Proportion of Participants, % (n)	
	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. Two Participants with Archived M184V/I and HIV-1 RNA ≥50 c/mL



- 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
- Withdrew study consent Week 12
- 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 studies1,16); 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 & Acknowledgements

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