PE1/19

Long-term Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide After Switch From Boosted Protease Inhibitor-Based Regimens Including in Those With Preexisting Resistance and Viral Blips

Kristen Andreatta, Silvia Chang, Madalyn Delaney, Madeleine Willkom, Ross Martin, Hiba Graham, 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

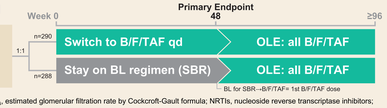
- The single-tablet regimen of bictegravir (BIC), emtricitabine (FTC), and tenofovir alafenamide (TAF; B/F/TAF) is a DHHS, EACS, and IAS-USA guidelines-recommended regimen for adults, adolescents, and children aged >6 years,[1-4] with demonstrated safety and efficacy, and a high barrier to resistance
- Previously reported results from the Phase 3 Study 1878 (ClinicalTrials.gov NCT02603107) demonstrated that switching to B/F/TAF was noninferior to continuing a boosted protease inhibitor (PI)–based regimen in virologically suppressed adults at Week 48 and continued to have high efficacy through long-term follow-up[5,6]
  - No treatment-emergent viral resistance to B/F/TAF was observed
- Proviral DNA genotype can help guide regimen switching and decrease risk of virologic failure[7,8]
- Viral blips (single HIV-1 RNA value ≥50 copies [c]/mL preceded and followed by HIV-1 RNA <50 c/mL) can occur for several reasons:
  - In successfully treated people with HIV, blips may reflect residual viral replication, random biological fluctuation, immune activation and inflammation, or assay variation[2,9,10]
  - Viral blips may be a marker for future virologic failure to some antiretroviral regimens, but data on the impact on clinical outcomes are conflicting[11-13]

Objectives

- To quantify preexisting resistance and frequency of viral blips, and assess virologic outcomes through the end of study for participants in Study 1878

Methods

Study 1878 Design



ATV, atazanavir; BL, baseline; DRV, darunavir; eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault formula; NRTIs, nucleoside reverse transcriptase inhibitors; OLE; open-label extension.

- Phase 3, randomized, open-label, multicenter, active-controlled study
- During OLE, participants transitioned to commercial B/F/TAF as it became available
  - BL for SBR→B/F/TAF group was measured from start of B/F/TAF in OLE

Baseline Genotypic Analyses

- Historical HIV-1 genotyping reports were collected if available
- HIV-1 proviral DNA genotype testing (GenoSure Archive®, Monogram Biosciences, Inc., South San Francisco, California, USA) was performed on BL samples retrospectively (hereafter referred to as BL DNA genotype)
  - Bioinformatic filters removed APOBEC-mediated hypermutated deep-sequence reads from GenoSure Archive results to prevent overreporting of E138K, M184I, and M230I in reverse transcriptase (RT) and G163R in integrase (IN)
- Participants with preexisting resistance detected after enrollment continued study drug and remained on study

Resistance Analysis Population

- Resistance testing was performed for participants with confirmed virologic failure (HIV-1 RNA ≥50 c/mL at 2 consecutive visits) and HIV-1 RNA ≥200 c/mL at the confirmation visit, or with HIV-1 RNA ≥200 c/mL at Week 48 or last visit on study drugs
- Plasma HIV-1 RNA genotyping and phenotyping (PhenoSense® GT, GeneSeq® Integrase, and PhenoSense Integrase®, Monogram)

HIV-1 Drug Resistance Substitutions (based on IAS-USA)[14]

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)
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
PI-R	**RPV-R:** L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L
INSTI-R	D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/I/S/T, N83D, I84V, N88S, L90M
	Primary: T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K
	Secondary: 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

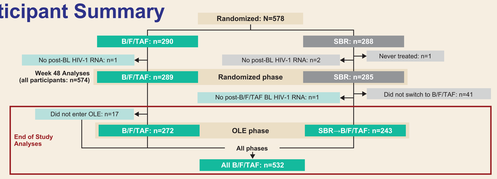
INSTI, IN strand transfer inhibitor; NNRTI, non-NRTI; R, resistance; RPV, rilpivirine; TAMs, thymidine analog mutations.

Efficacy Analyses

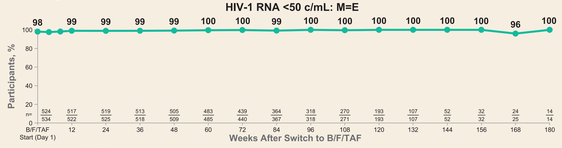
- Analyses included all participants who had ≥1 on-treatment HIV-1 RNA measurement
- Viral blip: after the BL visit, a single HIV-1 RNA value ≥50 c/mL preceded and followed by HIV-1 RNA <50 c/mL
- Virologic outcome:
  - Proportion of participants with HIV-1 RNA <50 c/mL by missing=excluded (M=E) approach
  - Proportions of participants with HIV-1 RNA < and ≥50 c/mL by last-observation-carried-forward imputation; participants with early discontinuation had virologic outcomes determined based on last available on-treatment HIV-1 RNA measurement

Results

Participant Summary



Virologic Outcome: All B/F/TAF-Treated Participants*



*Includes participants in all-B/F/TAF group (n=532) plus those who received B/F/TAF, but had no post-B/F/TAF BL on-treatment HIV-1 RNA data (n=2).

- High levels of virologic suppression were maintained after switching to B/F/TAF from a boosted PI-based regimen
  - Median duration of B/F/TAF exposure: 101 weeks (interquartile range 72–120; maximum 181)

Baseline Resistance Data Sources

Participants, n (%)*	B/F/TAF n=289 PR/RT	B/F/TAF n=289 IN	SBR n=285 PR/RT	SBR n=285 IN	All N=574 PR/RT	All N=574 IN
BL data available	276 (96)	259 (90)	247 (87)	227 (80)	523 (91)	486 (85)
Historical genotype*	141 (49)	5 (2)	122 (43)	11 (4)	263 (46)	16 (3)
BL DNA genotype	259 (90)	259 (90)	223 (78)	223 (78)	482 (84)	482 (84)

*99% of historical genotypes were plasma HIV-1 RNA genotypes and 1% were HIV-1 DNA genotypes. PR, protease.

Resistance Substitutions at Baseline

	B/F/TAF: n=289	SBR: n=285
PR/RT data available, n	**276**	**247**
NRTI-R, n cumulative (%) [n historical; n BL DNA]	**63 (23%) [7; 62]**	**41 (17%) [9; 36]**
K65R	4 (1%) [0; 4]	5 (2%) [1; 4]
M184V/I	44 (16%) [1; 44]	20 (8%) [0; 19]
Any TAM	30 (11%) [7; 29]	28 (11%) [8; 24]
1–2 TAMs	20 (7%) [7; 19]	15 (6%) [3; 13]
≥3 TAMs	10 (4%) [0; 10]	3 (1%) [5; 11]
Other (L74I/V, Y115F, Q151M)	4 (1%) [0; 4]	2 (1%) [1; 1]
NNRTI-R, n cumulative (%) [n historical; n BL DNA]	**79 (29%) [29; 72]**	**59 (24%) [24; 51]**
K103N/S	43 (16%) [19; 39]	32 (13%) [13; 29]
RPV-R	35 (13%) [10; 32]	28 (11%) [10; 22]
PI-R, n cumulative (%) [n historical; n BL DNA]	**29 (11%) [6; 27]**	**25 (10%) [4; 22]**
ATV or DRV associated*	3 (1%) [0; 3]	5 (2%) [0; 5]
IN data available, n	**259**	**227**
Primary INSTI-R, n cumulative (%) [n historical; n BL DNA]	**6 (2%) [0; 6]**	**8 (4%) [0; 8]**
T97A	4 (2%) [0; 4]	3 (1%) [0; 3]
Other†	2 (1%) [0; 2]	5 (2%) [0; 5]
Secondary INSTI-R, n cumulative (%) [n historical; n BL DNA]	**134 (52%) [2; 132]**	**96 (42%) [7; 95]**
M50I	53 (20%) [1; 53]	36 (16%) [2; 36]
S119P/R/T	87 (34%) [1; 87]	56 (25%) [3; 55]
E157K/Q	14 (5%) [0; 14]	6 (3%) [0; 6]

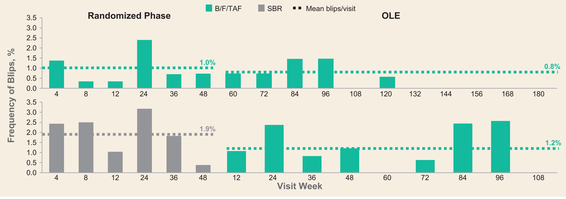
*I47V, I50L/V, I54M/L, L76V, I84V, and N88S in PR; †B/F/TAF: S147G or E92G (cumulative n=1 each); SBR: E92G (cumulative n=2), or S146G, Q148R, or N155H (cumulative n=1 each).

Overview of Viral Blips

Study Phase		B/F/TAF Randomized	B/F/TAF OLE	SBR Randomized	SBR→B/F/TAF OLE
Participants, n		289	272	285	243
Experienced blips, n (%)		17 (6)	12 (4)	24 (8)	14 (6)
Visits, n		1727	1721	1678	1537
Blip events, n (%)		17	13	32	18
Blips/visit, %		1.0	0.8	1.9	1.2
HIV-1 RNA at last visit, n/N (%)	<50 c/mL	15/17 (88)	12/12 (100)	24/24 (100)	13/14 (93)
	≥50 c/mL	2/17 (12)*	0	0	1/14 (7)†

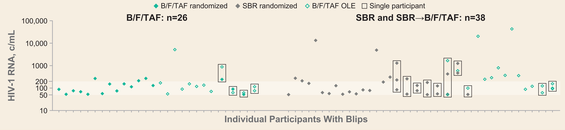
*2 participants had blips at Week 48 visit and HIV-1 RNA <50 c/mL at end of study; †Last visit on B/F/TAF was ≥50 c/mL, but resuppressed to <50 c/mL on commercial B/F/TAF.

Blip Frequency by Study Visit



- Viral blips occurred at a frequency of ~1% for B/F/TAF-treated participants vs 2% for SBR participants

HIV-1 RNA at Viral Blip



- Most blips were <200 c/mL:
  - 33/48 blips (69%) for participants on B/F/TAF in the randomized and OLE phases (median treatment duration: 109 weeks)
  - 21/32 blips (66%) for SBR participants in the randomized phase (median treatment duration: 48 weeks)

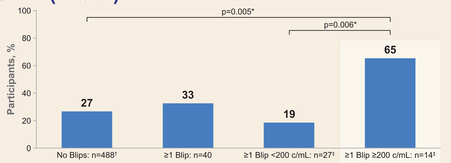
Baseline Characteristics and Adherence by Blip Status: All B/F/TAF

	All B/F/TAF: n=532 ≥1 Blip: n=40	All B/F/TAF: n=532 No Blips: n=492	p-Value
Mean adherence by pill count, % (range)	96 (86–100)	96 (24–100)*	0.78†
Mean BL CD4 cells/μL (range)	588 (172–2015)	667 (122–2582)	0.14†
BL resistance, n/n (%)	18/40 (45)	199/458 (43)‡	0.85§
BL M184V/I, n/n (%)	3/40 (8)‖	59/458 (13)‡	0.32§

*4 participants without adherence data were excluded; †2-tailed t-test; ‡34 participants without BL genotypic data were excluded; §Fisher exact test; ‖All 3 participants had HIV-1 RNA <50 c/mL at last visit.

- BL characteristics, preexisting resistance, and overall adherence were not significantly different for participants with ≥1 vs no blips
  - Other BL characteristics not significantly associated with blips: race and gender

Adherence <95% by Blip HIV-1 RNA Category: All B/F/TAF (n=532)



*Fisher exact test; †4 participants without adherence data were excluded; ‡1 participant had blips with HIV-1 RNA < and ≥200 c/mL, and was counted in both groups.

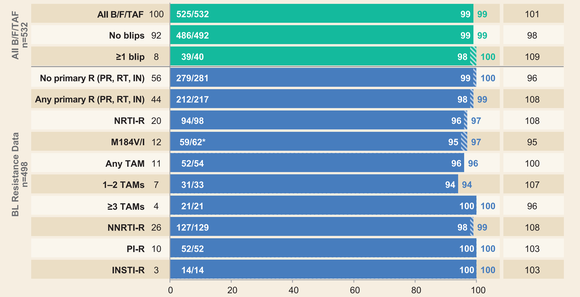
- Blips with HIV-1 RNA ≥200 c/mL (range 213–43,000 c/mL) were significantly associated with <95% adherence

Efficacy Outcomes and Resistance Analysis Population

Study Phase		B/F/TAF Randomized	B/F/TAF Randomized and OLE	SBR Randomized	SBR→B/F/TAF OLE
Study visit		Week 48	End of study	Week 48	End of study
Median study drug duration, weeks		48	120	48	72
Participants, n		289	272	285	243
HIV-1 RNA at last visit, n/n (%)	<50 c/mL	284/289 (98)	27/281 (98)	279/285 (98)	259/264 (98)
	≥50 c/mL	5/289 (2)	5/281 (2)	6/285 (2)	5/264 (2)
Analyzed for resistance (PR/RT/IN), n		2	3	6	1
Resuppressed to <50 c/mL, n		1	2	2	1
Any emergent resistance, n		0	0	1 (L74I in RT)	0

- High efficacy was observed in both the randomized and OLE phases
- There was no treatment-emergent resistance to B/F/TAF

Virologic Outcomes by Archived Resistance or Blips in All B/F/TAF Group



*Of 3 participants with M184V/I and HIV-1 RNA ≥50 c/mL at their last visit, 2 had HIV-1 RNA <100 c/mL (1 resuppressed on commercial B/F/TAF and 1 on ATV/ritonavir + F/tenofovir disoproxil fumarate), and 1 experienced confirmed virologic failure with HIV-1 RNA of 2880 c/mL, documented poor adherence, undetectable BIC plasma concentrations, and no treatment-emergent resistance, and discontinued at the following visit with HIV-1 RNA of 1510 c/mL.

- High efficacy was maintained in participants with archived resistance or viral blips

Conclusions

- High levels of virologic suppression were maintained after switching to B/F/TAF, with no treatment-emergent resistance
  - 99% of participants had HIV-1 RNA <50 c/mL at their last study visit (B/F/TAF duration: median 101 and maximum 181 weeks)
- 44% of B/F/TAF-treated participants had ≥1 primary resistance-associated substitution at BL, including 12% with M184V/I and 11% with ≥1 TAM
  - 98% with any primary resistance, 95% with M184V/I, and 96% with TAMs had HIV-1 RNA <50 c/mL at last visit
- Viral blips were infrequent among B/F/TAF-treated participants, occurring in ~1% per study visit, and did not affect virologic outcomes
  - Viral blips ≥200 c/mL were associated with lower adherence (<95% by pill count)
- Long-term suppression and the absence of treatment-emergent resistance demonstrate the durable efficacy of B/F/TAF

References: **1.** EACS European AIDS Clinical Society. Guidelines Version 10.1, Oct 2020; **2.** Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Dept of Health and Human Services; 2021; **3.** Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. Dept of Health and Human Services; 2020; **4.** Saag MS, et al. JAMA.2020;324:1651-69; **5.** Daar ES, et al. Lancet HIV 2018;5:e347-56; **6.** Rockstroh JK, et al. HIV Glasgow 2020, poster P036; **7.** Armenia D, et al. J Clin Virol 2018;104:61-4; **8.** Cutrell AG, et al. AIDS 2021;35:1333-42; **9.** Younas M, et al. Front Immunol 2021;12:663843; **10.** Zoufaly A, et al. HIV Med 2014;15:449-57; **11.** Gagliardini R, et al. Open Forum Infect Dis 2018;5:ofy113; **12.** Grennan JT, et al. J Infect Dis 2012;205:1230-8; **13.** Porter DP, et al. Antivir Ther 2017;22:495-502; **14.** Wensing AM, et al. Top Antivir Med 2017;24:132-41.

Acknowledgments: We extend our thanks to the participants, their families, and all participating study investigators and staff. This study was funded by Gilead Sciences, Inc.