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Biktarvy® (BIC/FTC/TAF) Viral Blips

This document is in response to your request for a summary of key data regarding the frequency and impact of viral blips in virologically suppressed (VS) people with HIV-1 (PWH) treated with Biktarvy® (bictegravir/emtricitabine/tenofovir alafenamide [BIC/FTC/TAF]). This response was developed according to principles of evidence-based medicine and contains data from phase 3 clinical studies.

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Summary

Clinical Data on Viral Blips in Participants Treated With BIC/FTC/TAF

Analyses from several phase 3 clinical studies in participants with HIV who were ARV-naive and VS showed that rates of viral blips were low, were similar between BIC/FTC/TAF and comparator arms, and did not clinically affect virologic outcomes.[1-6]

Viral Load Assays

PWH with undetectable viral loads can have incidents of detectable viral loads due to intrinsic viral load assay variability.[7]

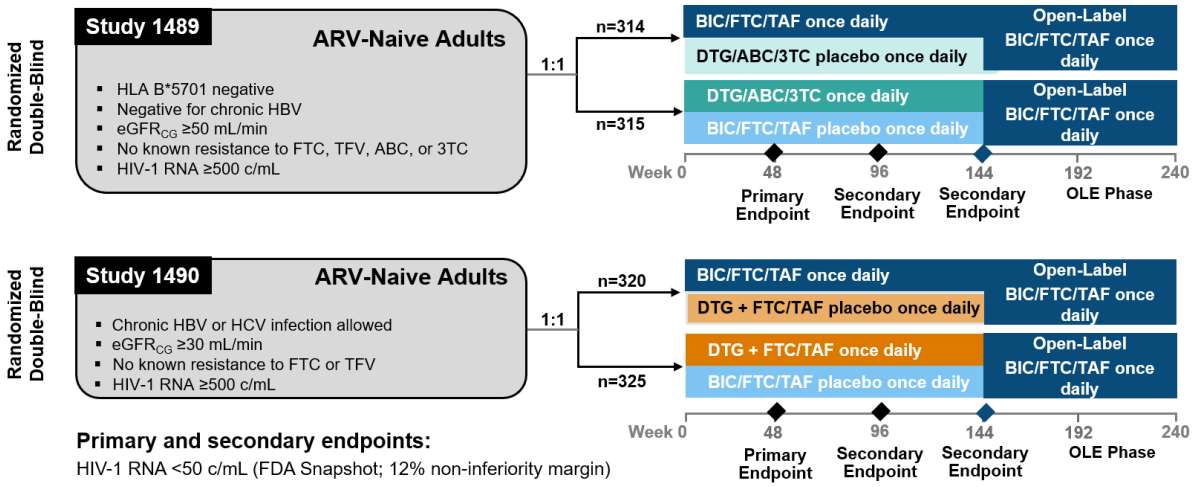
Clinical Data on Viral Blips in Participants Treated With BIC/FTC/TAF

Studies GS-US-380-1489 and GS-US-380-1490

Study designs and demographics

Study 1489 and 1490 were phase 3, randomized, double-blind, active-controlled, non-inferiority clinical studies that compared BIC/FTC/TAF (Study 1489, n=314; Study 1490, n=320) with DTG/ABC/3TC (Study 1489, n=315) or DTG + FTC/TAF (Study 1490, n=325) in adult PWH who were ARV naive (Figure 1).[8,9]

Figure 1. Studies 1489 and 1490: Study Designs[8-11]



Abbreviations: HLA=human leukocyte antigen; TFV=tenofovir.

Table 1. Studies 1489 and 1490: Baseline Demographics and Disease Characteristics[8,12-14]

Key Demographics and Characteristics	Study 1489		Study 1490	
	BIC/FTC/TAF (n=314)	DTG/ABC/3TC (n=315)	BIC/FTC/TAF (n=320)	DTG + FTC/TAF (n=325)
Age, median (range), years	31 (18–71)	32 (18–68)	33 (18–71)	34 (18–77)
Male, n (%)	285 (91)	282 (90)	280 (88)	288 (89)
Black or African descent, n (%)	114 (36)	112 (36)	97 (30)	100 (31)
Hispanic/Latinx ethnicity, n (%)	72 (23)	65 (21)	83 (26)	81 (25)
HIV-1 RNA, median (IQR), log_{10} c/mL	4.42 (4.03–4.87)	4.51 (4.04–4.87)	4.43 (3.95–4.9)	4.45 (4.03–4.84)
>100,000 c/mL, n (%)	53 (17)	50 (16)	66 (21)	54 (17)
CD4 count, median (IQR), cells/mcL	443 (299–590)	450 (324–608)	440 (289–591)	441 (297–597)
<200 cells/mcL, n (%)	36 (11)	32 (10)	44 (14)	34 (10)
$eGFR_{CG}$, median (IQR), mL/min	126 (108–146)	123 (107–144)	120 (101–142)	121 (103–145)

Viral blip analysis[1]

All participants with ≥1 on-treatment post-baseline HIV-1 RNA value were included in a viral blip analysis through Week 144 (N=1240). Viral blips were defined as a single HIV-1 RNA ≥50 c/mL, preceded and followed by HIV-1 RNA <50 c/mL, after achievement of confirmed virologic suppression (defined as two consecutive HIV-1 RNA values of <50 c/mL). The proportion of participants who experienced viral blips in this analysis was similar across treatment arms. Furthermore, the proportion of participants who experienced low-level (HIV-1 RNA <200 c/mL) or high-level (HIV-1 RNA ≥200 c/mL) viral blips was similar between treatment arms (Table 2).

Table 2. Studies 1489 and 1490: Occurrence of Viral Blips Through Week 144[1]

	All (N=1240)	Study 1489		Study 1490	
		BIC/FTC/TAF (n=308)	DTG/ABC/3TC (n=309)	BIC/FTC/TAF (n=306)	DTG + FTC/TAF (n=317)
Experienced viral blips, n (%)	143 (11.5)	39 (12.4)	49 (15.6)[a]	32 (10.2)	23 (7.1)[b]
Experienced multiple viral blips, n (%)	33 (2.7)	9 (2.9)	11 (3.6)	7 (2.3)	6 (1.9)
Viral blip events, n	186	49	66[c]	40	31[d]

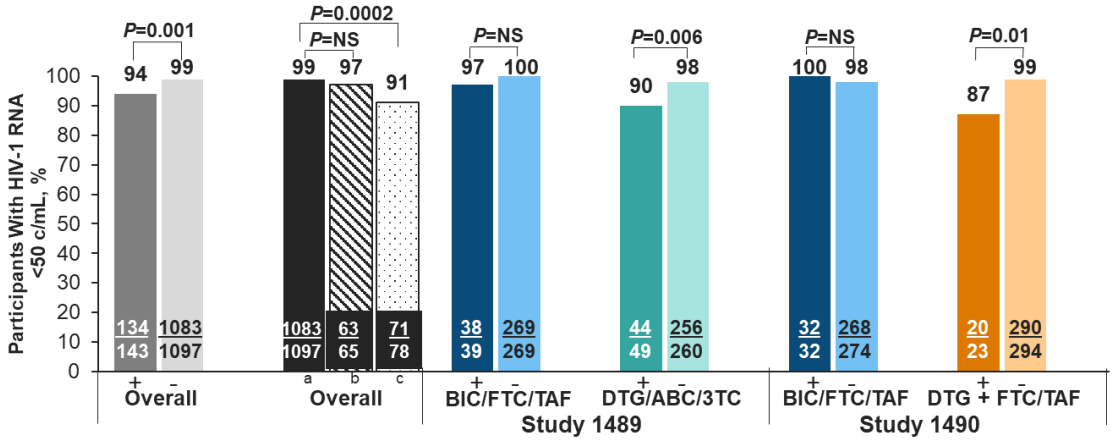
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		All (N=1240)	Study 1489		Study 1490	
			BIC/FTC/TAF (n=308)	DTG/ABC/3TC (n=309)	BIC/FTC/TAF (n=306)	DTG + FTC/TAF (n=317)
Participants with viral blips, n (%)	<200 c/mL	65 (5.2)	18 (5.8)	17 (5.5)	19 (6.2)	11 (3.5)
	≥200 c/mL	78 (6.3)	21 (6.8)	32 (10.4)	13 (4.2)	12 (3.8)
Participants with viral blips per study visit, %		1.3	1.4	1.8	1.1	0.8

[a]*P*=0.3. [b]*P*=0.2. [c]*P*=0.53. [d]*P*=0.55.

In the BIC/FTC/TAF treatment arms, there was no significant difference in efficacy between participants who did and did not experience viral blips. Among participants who received DTG-containing regimens, efficacy was significantly lower in those who experienced viral blips than in those who did not. Overall, at Week 144, the percentage of participants who were VS was lower among those who experienced viral blips, including high-level viral blips (HIV-1 RNA ≥200 c/mL), than among those who did not (Figure 2).

Figure 2. Studies 1489 and 1490: Virologic Outcomes of Participants With Viral Blips vs No Viral Blips at Week 144 Using LOCF[1]



Abbreviation: NS=not significant.
[a]No viral blips. [b]Viral blips <200 c/mL. [c]Viral blips ≥200 c/mL.
Note: The "+" symbol denotes the presence of viral blips; the "-" symbol denotes the absence of viral blips.

Across all treatment arms, high-level viral blips were observed more often in participants with a cumulative adherence rate ≤95% than in participants with a cumulative adherence rate >95%. In the overall population, low-level viral blips (HIV-1 RNA <200 c/mL) were observed more frequently in participants with a cumulative adherence rate >95% than in participants with ≤95% adherence; study authors suggested this may be due in part to assay variation. Very low-level blips (HIV-1 RNA 20–50 c/mL) were observed in comparable proportions across all treatment arms and did not impact virologic outcomes.

Safety[14]

In Study 1489, participants treated with BIC/FTC/TAF reported fewer TRAEs than did those taking DTG/ABC/3TC (30% vs 42%, respectively; *P*=0.0021). SAEs occurred in 13% of participants in the BIC/FTC/TAF arm and in 17% of participants in the DTG/ABC/3TC arm. Drug-related nausea occurred in significantly fewer participants in the BIC/FTC/TAF arm than in the DTG/ABC/3TC arm (6% vs 18%, respectively; *P*<0.0001). AEs led to DTG/ABC/3TC discontinuation in 2% of participants; no AEs led to discontinuation in the

BIC/FTC/TAF arm. Three deaths were documented, none of which were considered treatment-related.

In Study 1490, participants treated with BIC/FTC/TAF reported similar rates of TRAEs compared to those taking DTG + FTC/TAF (22% vs 29%, respectively). SAEs occurred in 20% of participants in the BIC/FTC/TAF arm and in 12% of participants in the DTG + FTC/TAF arm. Nausea was the most common TRAE: BIC/FTC/TAF, 3%; DTG + FTC/TAF, 5%. AEs that led to study drug discontinuation occurred in 6% of participants in each arm. Three and 4 deaths were documented in the BIC/FTC/TAF and DTG + FTC/TAF arms, respectively; none of which were considered treatment related.

SOLAR Study[2]

A phase 3b, randomized (ratio of 2:1), open-label, multicenter, noninferiority study assessed the efficacy and safety of switching to CAB + RPV IM Q8W compared with continuing BIC/FTC/TAF in VS PWH. An exploratory analysis assessed HIV-1 RNA samples to evaluate the effect of viral blips (single HIV-1 RNA of 50–200 c/mL preceded and followed by HIV-1 RNA <50 c/mL) on CVF (two consecutive HIV-1 RNA values ≥200 c/mL) from baseline through Month 12. Of the 670 participants included in the mITT-E analysis, 447 participants (67%) switched to CAB + RPV IM Q8W, and 223 participants (33%) continued to receive BIC/FTC/TAF. Baseline characteristics were similar between arms.

From baseline through Month 12, viral blips were reported in 4% of participants in both the CAB + RPV IM Q8W arm (n/N=19/447) and the BIC/FTC/TAF arm (n/N=9/223); of the participants with viral blips, 5% (1/19) and 11% (1/9), respectively, had HIV-1 RNA ≥50 c/mL at Month 12. Neither of the 2 participants in the CAB + RPV IM Q8W arm who had CVF had viral blips through Month 12.

Study GS-US-380-1878

Study design and demographics

A phase 3, prospective, randomized, open-label clinical study was conducted to compare switching to BIC/FTC/TAF 50/200/25 mg STR (n=290) with staying on a baseline regimen of boosted DRV or ATV + 2 NRTIs (FTC/TDF or ABC/3TC; n=288) in VS adult PWH (Figure 3).[3,15] Viral loads were obtained at Weeks 4, 8, and 12 and then every 12 weeks through Week 48.[16]

Figure 3. Study 1878: Study Design[3,15]

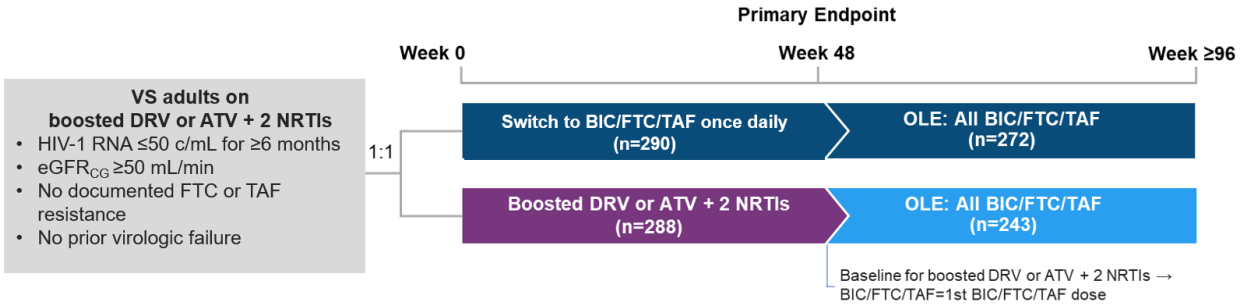


Table 3. Study 1878: Baseline Demographics and Disease Characteristics[3,15]

Key Demographics and Characteristics	BIC/FTC/TAF (n=290)	Boosted DRV or ATV + 2 NRTIs (n=288)
Age, median (range), years	48 (20–74)	47 (21–79)
Male, %	84	82
Race/ethnicity, White/Black or African descent/ Hispanic or Latinx, %	65/27/21	66/25/16
CD4 count, median, cells/mcL	617	626
$eGFR_{CG}$, median, mL/min	107	105

Safety[15]

Both regimens were well tolerated. Any-grade AEs that occurred in ≥5% of participants in either the BIC/FTC/TAF or boosted DRV or ATV + 2 NRTIs treatment arms were headache (12% vs 4%, respectively), diarrhea (8% vs 6%), nasopharyngitis (7% vs 12%), URTI (7% vs 8%), back pain (4% vs 6%), and arthralgia (4% vs 5%). The most common (≥2%) TRAEs for BIC/FTC/TAF were headache (5%) and flatulence, nausea, and diarrhea (2% each).

OLE analysis

An analysis of participants who switched to BIC/FTC/TAF in the OLE phase was conducted to measure the frequency of viral blips, preexisting resistance, and virologic outcomes. To be included, participants were required to have no documented or suspected resistance to FTC or TAF and no prior virologic failure. Historical genotypes were collected if available but was not required for study entry. Efficacy was analyzed in participants who switched to BIC/FTC/TAF in the OLE phase and had ≥1 HIV-1 RNA measurement during the OLE while on treatment. Virologic outcomes based on the last available on-treatment HIV-1 RNA were classified as either success (HIV-1 RNA <50 c/mL) or failure (HIV-1 RNA ≥50 c/mL). Resistance testing was attempted for all participants in the resistance analysis population (CVF with HIV-1 RNA ≥200 c/mL at the confirmation visit or HIV-1 RNA ≥200 c/mL at Week 48 or last visit on study drug). A viral blip was defined as a single HIV-1 RNA ≥50 c/mL after the baseline visit, preceded and followed by HIV-1 RNA <50 c/mL.[3,17]

Efficacy and safety

Efficacy was high in the OLE phase, and no treatment-emergent resistance developed. HIV-1 RNA was <50 c/mL in 99% of participants who were receiving BIC/FTC/TAF at their last study visit (BIC/FTC/TAF median treatment duration: 101 weeks; maximum duration: 181 weeks; Table 4).[3,11] No safety data were available for the OLE phase.

Table 4. Study 1878 OLE: Virologic Outcomes[11a]

HIV-1 RNA at Last Study Visit, n/N (%)	BIC/FTC/TAF		Boosted DRV or ATV + 2 NRTIs	
	Randomized Phase, Week 48	Randomized Phase and OLE, End of Study	Randomized Phase, Week 48	→ BIC/FTC/TAF OLE Phase, End of Study
<50 c/mL	284/289 (98)	285/289 (99)	279/285 (98)	240/243 (99)
≥50 c/mL	5/289 (2)	4/289 (1)	6/285 (2)	3/243 (1)

[a]HIV-1 RNA values corrected per author communication.

Viral blip analysis[3]

The occurrence of viral blips was infrequent, and the rate was similar between treatment arms in the OLE (BIC/FTC/TAF, 4% and boosted DRV or ATV + 2 NRTIs →

BIC/FTC/TAF, 6%). The majority of participants with viral blips had virologic suppression at the last study visit (Table 5).

Table 5. Study 1878 OLE: Viral Blip Occurrence Overview[3]

Viral Blip Occurrence		BIC/FTC/TAF		Boosted DRV or ATV + 2 NRTIs	
		Randomized Phase	OLE Phase	Randomized Phase	→BIC/FTC/TAF OLE Phase
Experienced viral blips, n/N (%)		17/289 (6)	12/272 (4)	24/285 (8)	14/243 (6)
Study visits, n		1727	1721	1678	1537
Viral blip events, n		17	13	32	18
Viral blips per study visit, %		1	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)[a]	0	0	1/14 (17)[b]

[a]Participants had viral blips at Week 48 but were later resuppressed to HIV-1 RNA <50 c/mL at end of study.
[b]This participant had HIV-1 RNA ≥50 c/mL at the last study visit but was later resuppressed to <50 c/mL on commercial BIC/FTC/TAF.

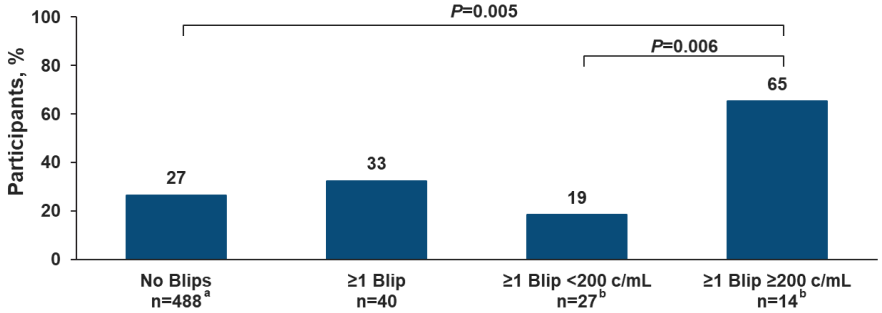
No significant differences were observed in baseline characteristics, preexisting resistance, or adherence between participants with ≥1 viral blip and those with no viral blips (Table 6). Lower adherence (<95% by pill count) was significantly associated with high-level viral blips (HIV-1 RNA ≥200 c/mL; Figure 4).

Table 6. Study 1878 OLE: Viral Blip Status According to Select Baseline Characteristics and Adherence for All Participants Who Received BIC/FTC/TAF[3]

	BIC/FTC/TAF (n=532)		*P*-Value
	≥1 Viral Blip (n=40)	No Viral Blip (n=492)	
Adherence by pill count, mean (range), %	96 (86–100)	96 (24–100)[a]	0.78
Baseline CD4 count, mean (range), cells/mcL	588 (172–2015)	667 (122–2582)	0.14
Baseline resistance, n/N (%)	18/40 (45)	199/458 (43)[b]	0.85
Baseline M184V/I mutation, n/N (%)	3/40 (8)[c]	59/458 (13)[b]	0.32

[a]Excluded 4 participants due to lack adherence data.
[b]Excluded 34 participants due to lack of baseline genotype data.
[c]At last study visit, all participants had HIV-1 RNA <50 c/mL.

Figure 4. Study 1878 OLE: Adherence <95% by Viral Blip HIV-1 RNA Category for All Participants Who Received BIC/FTC/TAF (n=532)[3]



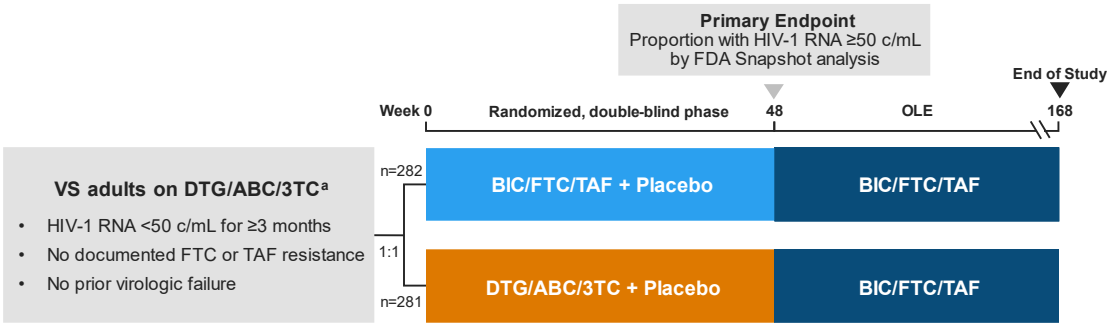
[a]Excluded 4 participants due to lack of adherence data.
[b]One participant experienced viral blips with HIV-1 RNA of <200 c/mL and HIV-1 RNA of ≥200 c/mL, which was counted in both treatment arms.

Study GS-US-380-1844

Study design

A phase 3, randomized, double-blind study evaluated the safety and efficacy of switching to BIC/FTC/TAF (n=282) compared with staying on a baseline regimen of DTG + ABC/3TC or DTG/ABC/3TC STR (n=281) in VS adult PWH.[16] An analysis measured the frequency of viral blips, preexisting resistance, and virologic outcomes through Week 168, including the OLE phase after Week 48 (Figure 5). Historical genotyping was collected if available but was not required for study entry. Efficacy was analyzed in all participants with ≥1 on-treatment HIV-1 RNA measurement. Virologic outcomes were determined for all participants who switched to BIC/FTC/TAF, based on the last available on-treatment HIV-1 RNA, and were classified as either success (HIV-1 RNA <50 c/mL) or failure (≥50 c/mL). Resistance testing was attempted for all participants in the resistance analysis population (HIV-1 RNA ≥200 c/mL at the confirmation visit, Week 48, or last visit on study drugs). Resistance data were available through historical genotype or retrospective baseline proviral genotype. A viral blip was defined as a single HIV-1 RNA ≥50 c/mL after the baseline visit, preceded and followed by HIV-1 RNA <50 c/mL.[4]

Figure 5. Study 1844: Study Design[4]



[a]Could include components of an STR.

Efficacy[4]

Efficacy was high in both the randomized and OLE phases, and no treatment-emergent resistance developed. HIV-1 RNA was <50 c/mL in 98% of participants who were receiving BIC/FTC/TAF at their last study visit (BIC/FTC/TAF median treatment duration: 96 weeks; maximum duration: 168 weeks; Table 7).

Table 7. Study 1844: Virologic Outcomes[4]

HIV-1 RNA at Last Visit, n/N (%)	BIC/FTC/TAF		DTG/ABC/3TC	
	Randomized Phase, Week 48	Randomized Phase and OLE, End of Study	Randomized Phase, Week 48	→BIC/FTC/TAF OLE Phase, End of Study
<50 c/mL	277/281 (99)	276/281 (98)	280/281 (>99)	259/264 (98)
≥50 c/mL	4/281 (1)	5/281 (2)	1/281 (<1)	5/264 (2)

Viral blip analysis[4]

Viral blips were experienced by 0.3% to 0.6% of participants who received BIC/FTC/TAF per study visit (Table 8). Eighty-three percent of participants (19/23) who experienced viral blips with BIC/FTC/TAF in the randomized and OLE phases had HIV-1 RNA <200 c/mL.

Table 8. Study 1844: Viral Blip Occurrence Overview[4]

Viral Blip Occurrence		BIC/FTC/TAF		DTG/ABC/3TC	
		Randomized Phase	OLE Phase	Randomized Phase	→BIC/FTC/TAF OLE Phase
Experienced viral blips, n/N (%)		11/281 (4)	6/259 (2)	16/281 (6)	2/264 (1)
Study visits, n		1885	1486	2281	1268
Viral blips, n		12	7	19	4
Viral blips per study visit, %		0.6	0.5	0.8	0.3
HIV-1 RNA at last visit, n/N (%)	<50 c/mL	10/11 (91)	6/6 (100)	16/16 (100)	1/2 (50)
	≥50 c/mL	1/11 (9)[a]	0	0	1/2 (50)[b]

[a]Discontinued study with HIV-1 RNA 499 c/mL and resistance test assay failure.
[b]Experienced 4 viral blips during the study between 50 and 200 c/mL.

No significant differences were observed in baseline characteristics, preexisting resistance, or adherence between participants with ≥1 viral blip and those with no viral blips (Table 9). Adherence was not significantly lower in participants with viral blips with HIV-1 RNA >200 c/mL than in participants without viral blips.

Table 9. Study 1844: Blip Status According to Select Baseline Characteristics and Adherence for All Participants Who Received BIC/FTC/TAF[4]

	BIC/FTC/TAF (n=545)		*P*-Value
	≥1 Viral Blip (n=19)	No Viral Blip (n=526)	
Adherence by pill count, mean (range), %	95 (83–100)	96 (58–100)[a]	0.6
Baseline CD4 count, mean (range), cells/mcL	731 (124–2444)	850 (309–1782)	0.2
Baseline resistance,[b] n/N (%)	3/18 (17)	158/504 (31)	0.3
Baseline M184V/I mutation,[b] n/N (%)	1/18 (6)[c]	16/504 (3)	0.5

[a]Four participants without adherence data were excluded.
[b]Participants were excluded if they did not have baseline genotype data: ≥1 blip, n=22; and no viral blips, n=1.
[c]This participant also had K103N mutation.

Safety[16,18]

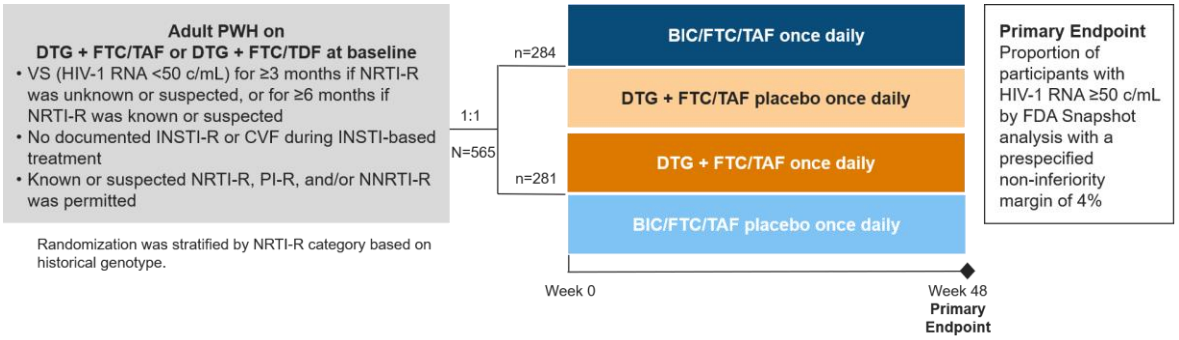
At Week 168, the most common any-grade AEs reported in ≥5% of participants in the BIC/FTC/TAF arm were URTI, nasopharyngitis, diarrhea, arthralgia, back pain, headache, sinusitis, bronchitis, and syphilis. TRAEs were reported in 39 participants (7%), and most were Grade 1. Headache was the most frequently reported TRAE (2%). In participants treated with BIC/FTC/TAF, a total of 7 AEs (1%) led to study discontinuation: headache (n=3), vomiting (n=1), cerebrovascular accident (n=1), abnormal dreams (n=1), and suicidal ideation (n=1, not considered related to study treatment by investigator).[16,18]

Study GS-US-380-4030

Study design

A phase 3, randomized, double-blind, multicenter, active-controlled study evaluated the efficacy of BIC/FTC/TAF (n=284) vs DTG + FTC/TAF (n=281) in VS PWH, including those with known baseline resistance mutations (Figure 6). The final analysis included additional baseline resistance data obtained through proviral DNA testing, which provided genotypic resistance data for 83% of participants. Population genotyping and phenotyping for RT, PR, and IN were conducted at CVF, Week 48, or at the last visit.[5,19]

Figure 6. Study 4030: Study Design[5,19]



Viral blip analysis

A viral blip analysis was conducted and included all participants who had ≥1 on-treatment post-baseline HIV-1 RNA value through Week 48. Any post-baseline HIV-1 RNA ≥50 c/mL preceded and followed by an HIV-1 RNA <50 c/mL was considered a viral blip.[5]

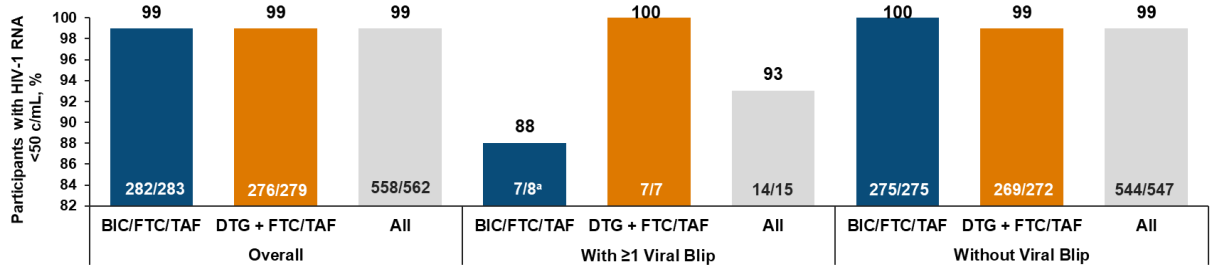
Fifteen participants (2.7%) experienced viral blips in this study, and the incidence was similar between treatment arms (Table 10; *P*=1). One participant experienced >1 viral blip. Most of the viral blips that occurred in participants treated with BIC/FTC/TAF were <200 c/mL, and all participants with viral blips ≥200 c/mL were VS at Week 48. Baseline NRTI-R was not associated with an increased occurrence of viral blips (Table 10). Virologic suppression at Week 48 was not affected by the occurrence of viral blips (Figure 7).[5]

Table 10. Study 4030: Viral Blips According to Baseline Resistance Category[5,19]

Category, n (%) or n/N (%)		BIC/FTC/TAF[a] (n=284)	DTG + FTC/TAF[a] (n=281)
Participants with viral blip		8 (2.8)[b]	7 (2.5)
Experienced viral blip	Resistance Category 1: High[c]	1/16 (6)	0/14
	Resistance Category 2: Low[d]	0/55	1/53 (2)
	M184V/I (from Categories 1 + 2)	1/47 (2)	1/34 (3)
	Resistance Category 3: None[e]	7/212 (3)	6/212 (3)

[a]Twenty participants were stratified to Categories 1 or 2 based on investigator-suspected NRTI-R that was not confirmed by genotyping: 1 participant in the BIC/FTC/TAF treatment arm and 2 participants in the DTG + FTC/TAF treatment arm were not included in the viral blip analysis; thus, the viral blip analysis population was as follows: BIC/FTC/TAF, n=283 and DTG + FTC/TAF, n=279.
[b]One participant without known preexisting NRTI-R experienced 2 viral blips.
[c]K65R/E/N, ≥3 TAMs, including M41L or L210W, or T69 insertions.
[d]M184V/I, K70E/G/M/Q/S/T, L74V/I, V75A/S/M/T, Y115F, T69D, Q151M, M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/R/N mutations.
[e]No NRTI-R–associated mutations.

Figure 7. Study 4030: Efficacy Outcomes at Week 48 for Participants With and Without Viral Blips Using LOCF[5]



[a]One participant in the BIC/FTC/TAF treatment arm with no preexisting NRTI-R had HIV-1 RNA of 2340 c/mL at Week 48 but was resuppressed at the next visit.

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Safety[20]

The most commonly (≥10%) reported AEs in either arm were nasopharyngitis, diarrhea, and URTI. TRAEs that occurred in ≥2% in either arm were diarrhea and headache.
Six participants (2%) in each arm discontinued the study because of AEs. There was 1 death documented in each arm; the death in the BIC/FTC/TAF arm was considered unrelated to study drug by the investigator.

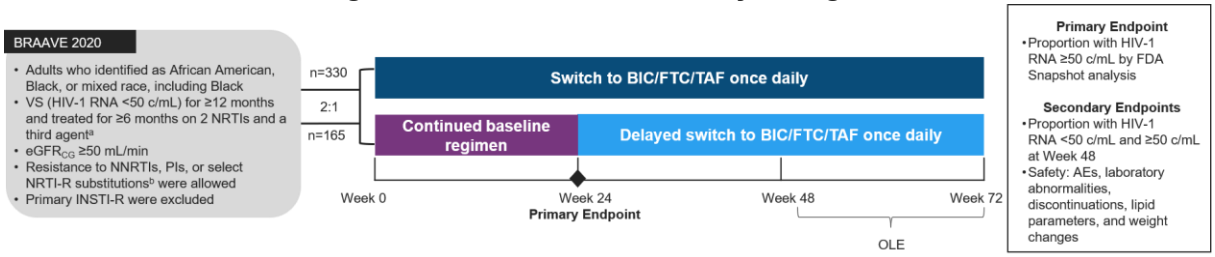
BRAAVE 2020

Study design

The BRAAVE 2020 study was a phase 3, randomized, open-label, multicenter study that evaluated the efficacy and safety of switching to BIC/FTC/TAF vs continuing with a baseline regimen of 2 NRTIs plus a third agent in VS PWH who self-identified as African American, Black, or mixed race, including Black (Figure 8).[6]

Baseline resistance was analyzed with historical genotypes, if available, and HIV-1 proviral DNA genotype testing was retrospectively performed on baseline samples. Participants with preexisting resistance detected after enrollment were permitted to continue in the study. The resistance analysis population included any participant with CVF (HIV-1 RNA ≥50 c/mL at two consecutive visits) and HIV-1 RNA ≥200 c/mL at the confirmation visit or with HIV-1 RNA ≥200 c/mL at Weeks 24, 48, or 72, or last visit, with no resuppression of HIV-1 RNA to <50 c/mL while on study treatment.[21,22] Secondary INSTI-R was the most frequently observed preexisting resistance substitution (Table 11).[6]

Figure 8. BRAAVE 2020: Study Design[6,21]



Abbreviations: NNRTI=non-nucleos(t)ide reverse transcriptase inhibitor; PI=protease inhibitor.
[a]The allowed third agents included any INSTI except BIC, any PI, maraviroc, or any NNRTI except etravirine.
[b]Except K65R/E/N, T69 insertions, or ≥3 TAMs.

Table 11. BRAAVE 2020: Resistance Substitutions at Baseline[6]

Baseline Genotype, n or n (%)	Cumulative Baseline Genotype
PR/RT	468
NNRTI-R	101 (22)
NRTI-R	68 (15)
PI-R	61 (13)
IN	453
Primary INSTI-R	11 (2)
Secondary INSTI-R	227 (50)

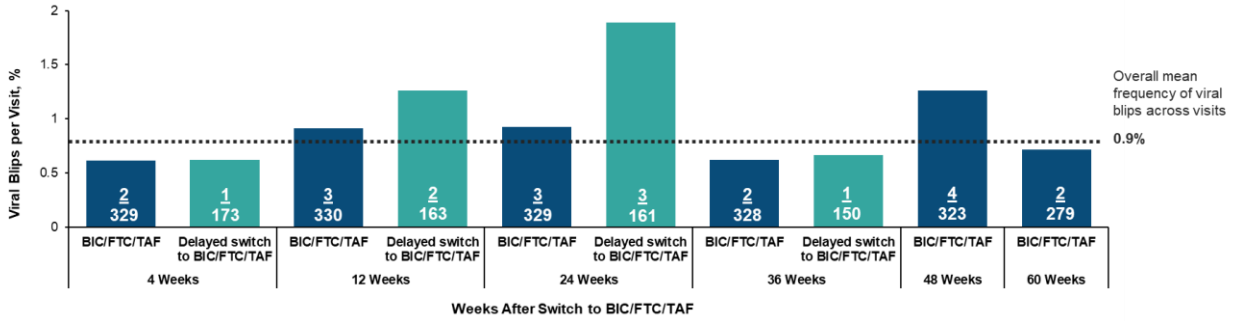
Results through Week 72[6]

By the last visit, virologic suppression was achieved by 99% of participants (486/489) overall and by 100% of participants (22/22) who had ≥1 viral blip. Viral blips occurred at a mean

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frequency of 0.9% of study visits (Figure 9); 21 participants experienced 1 blip, and 1 participant experienced 2 blips at 4 and 12 weeks after switching to BIC/FTC/TAF. Fifty-seven percent of viral blips (13/23) were HIV-1 RNA <200 c/mL.
No treatment-emergent resistance was observed during the study through Week 72.

Figure 9. BRAAVE 2020: Frequency of Viral Blips Through Week 60 After Switch to BIC/FTC/TAF[6]



High adherence (≥95%) to BIC/FTC/TAF was reported in 74% of participants (363/489) and in 19/22 participants with viral blips. There were no significant differences in adherence between treatment arms (*P*=0.91) or between participants who experienced viral blips and those who did not (*P*=0.24).

Safety

The rates of AEs reported through Week 24 were comparable between participants who switched to BIC/FTC/TAF and those who continued their baseline regimen. AEs that led to discontinuation of study drug were reported in 7 participants who switched to BIC/FTC/TAF and in none of the participants who continued with the baseline regimen through Week 24. The following TRAEs led to study drug discontinuation: abdominal distension and flatulence (n=1); diarrhea, dry mouth, psychomotor hyperactivity, agitation, anxiety, and insomnia (n=1); diarrhea (n=1); headache (n=1); migraine (n=1); and nightmare (n=1). Acute kidney injury led to study drug discontinuation in 1 participant but was not considered treatment related by study investigators.[23] In each arm, Grade 3 or 4 AEs and SAEs occurred in 5% and 4% of participants, respectively. TRAEs occurred in 11% of participants in the BIC/FTC/TAF arm and in none who continued their baseline regimen.[23,24]

Six additional AEs that led to study drug discontinuation between Weeks 24 and 72 and included COVID-19 (n=2); hemorrhage of intracranial aneurysm with multiple sequelae (n=1); headache and hyperhidrosis (n=1, headache was treatment-related); abdominal distension and flatulence (n=1; both were treatment-related); and change in bowel consistency and flatulence (n=1, both were treatment related).[24] No treatment-related deaths were reported through Week 48.[25]

Viral Load Assays

Systematic Review

Current HIV-1 viral load assays can have lower limits of detection (HIV-1 RNA 20 c/mL). A systematic review of viral load assays showed that sources of variability between assays include differences in technology platform, plasma input volume, and ability to detect HIV-1 subtypes. Ideally, repeated monitoring of PWH should be performed on the same

platform consistently to enable appropriate interpretation of viral load changes. PWH with undetectable viral loads can have incidents of detectable viral loads due to intrinsic viral load assay variability.[7] Previous work has shown that when switching from the older Amplicor viral load assay to the TaqMan viral load assay, there was an increase in the frequency of detectable plasma HIV-1 RNA at the 50 c/mL threshold.[26]

Data have further described the effect of intrinsic viral load assay variability when monitoring HIV-1 viral load at the lower end of the detectable range. This latter work has implications for monitoring of patients who are virologically suppressed and experience transient viral blips.[27]

In an analysis of viral load assay variability, 50 aliquots of diluted WHO HIV-1RNA standards at viral loads <200 c/mL, and multiple aliquots of plasma samples from 4 patients who experienced viral blips that ranged from 50 to 200 c/mL after having had HIV-1 RNA <50 c/mL, were quantified using the Cobas AmpliPrep/Cobas TaqMan v2.0 HIV-1 assay (Roche). The investigators found that, in WHO standard samples with HIV-1 RNA of 36 c/mL and 18 c/mL, HIV-1 viral load was quantified as being ≥50 c/mL in 66% and 18% of assay replicates, respectively. Retesting stored plasma samples from previously virologically suppressed patients who experienced low-level viremia resulted in HIV-1 RNA <50 c/mL in 14/15 (93%) of these samples. The authors recommended that, in cases of unexpected low-level viremia, retesting the same HIV RNA sample (a stored aliquot) and reconfirming undetectable viral load may prevent additional clinical visits, blood draws, laboratory tests, and patient anxiety. Conversely, confirmation of the detectable viral load on the original plasma sample would then trigger an additional laboratory visit and repeat plasma sample draw to confirm potential virologic failure.[27]

Clinical Guidelines Regarding Virologic Failure

Recommendations from the US Department of Health and Human Services (DHHS) regarding virologic failure, including viral blips, in treatment-experienced patients can be accessed using the following link: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/virologic-failure.

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Abbreviations

3TC=lamivudine
ABC=abacavir
AE=adverse event
ARV=antiretroviral
ATV=atazanavir
BIC=bictegravir
c/mL=copies per mL
CAB=cabotegravir
CD4=cluster of differentiation 4
CG=Cockcroft-Gault
CVF=confirmed virologic failure
DRV=darunavir
DTG=dolutegravir
FTC=emtricitabine
IM=intramuscular
IN=integrase
INSTI=integrase strand transfer inhibitor
INSTI-R=integrase strand transfer inhibitor resistance
LOCF=last observation carried forward
mITT-E=modified ITT exposed
NNRTI-R=non-nucleos(t)ide reverse transcriptase inhibitor resistance
NRTI=nucleos(t)ide reverse transcriptase inhibitor
NRTI-R=nucleos(t)ide reverse transcriptase inhibitor resistance
OLE=open-label extension
PI-R=protease inhibitor resistance
PR=protease
PWH=people with HIV
Q8W=once every 8 weeks
RPV=rilpivirine
RT=reverse transcriptase
SAE=serious adverse event
STR=single-tablet regimen
TAF=tenofovir alafenamide
TAM=thymidine analog mutation
TDF=tenofovir disoproxil fumarate
TRAE=treatment-related adverse event
URTI=upper respiratory tract infection
VS=virologically suppressed

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