EMERGENT RESISTANCE TO ANTIRETROVIRAL AGENTS USED IN OPTIMIZED BACKGROUND THERAPY WITH FOSTEMSAVIR: WEEK 96 RESULTS OF THE PHASE 3 BRIGHTE STUDY IN HEAVILY TREATMENT-EXPERIENCED ADULTS LIVING WITH MULTIDRUG-RESISTANT HIV-1

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Presenter Disclosure Information

- Margaret Gartland
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Background

- Fostemsavir (Rukobia™), an oral prodrug of the gp120-directed attachment inhibitor temsavir, is indicated in combination with other antiretrovirals (ARVs) for the treatment of adults with multidrug-resistant HIV-1 infection for whom it is otherwise not possible to construct a suppressive ARV regimen
- In the phase 3 BRIGHTE study, fostemsavir was generally safe and well tolerated and was associated with durable virologic responses through Week 96[1-3]
- Protocol-defined virologic failure (PDVF) through Week 96 in the BRIGHTE study was not consistently associated with emergent genotypic or phenotypic changes to fostemsavir[1-3]
- The current analysis evaluates emergent changes in viral susceptibility to ARVs in the initial optimized background therapy (OBT) for BRIGHTE study participants in the Randomized Cohort (RC) who met criteria for PDVF[a] through Week 96

[a]PDVF before Week 24: confirmed or last available before discontinuation HIV-1 RNA ≥400 c/mL after confirmed suppression to <400 c/mL or confirmed or last available before discontinuation >1 $\log_{10}$ c/mL increase in HIV-1 RNA above nadir where nadir is ≥40 c/mL; PDVF on or after Week 24: confirmed or last available before discontinuation HIV-1 RNA ≥400 c/mL.

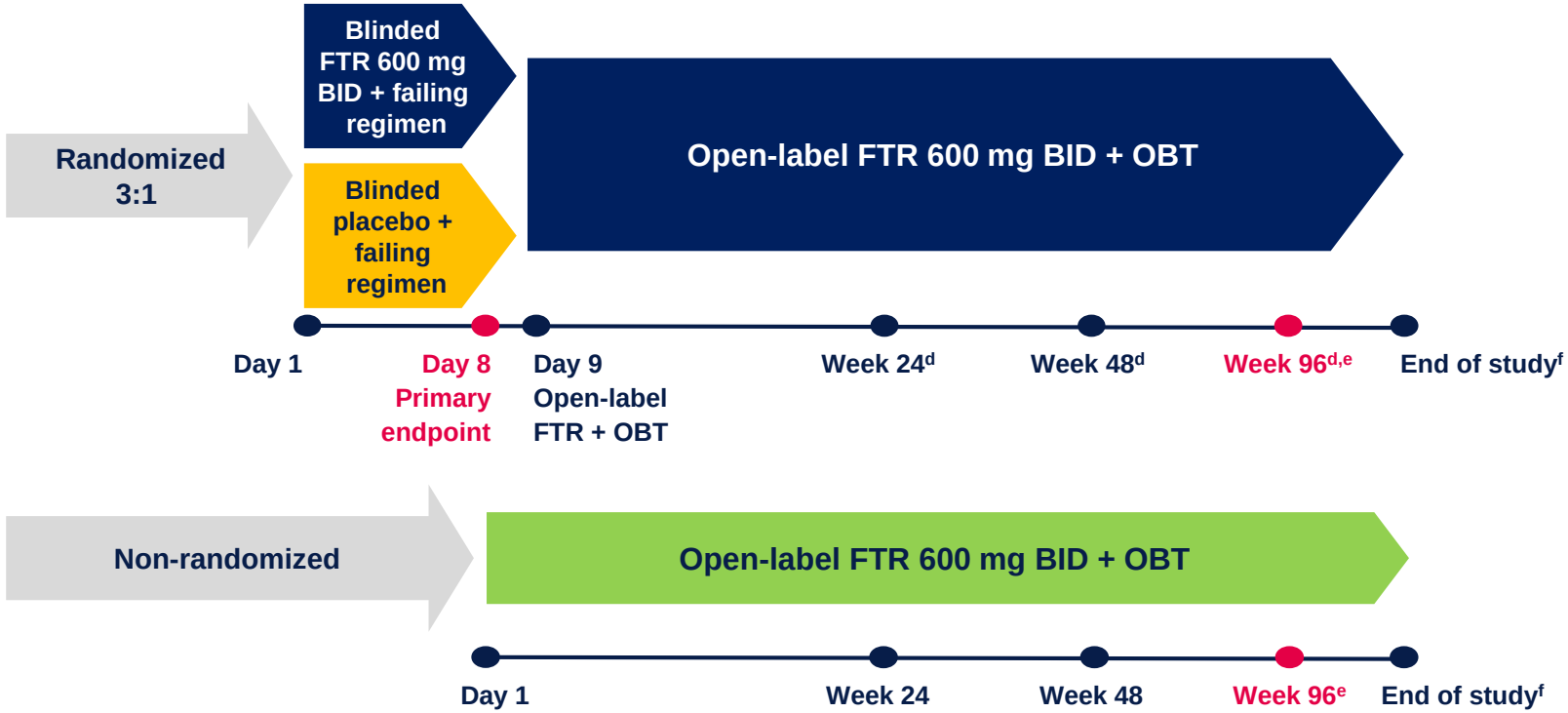
1. Kozal et al. *N Engl J Med*. 2020;382:1232-1243. **2.** Lataillade et al. *Lancet HIV*. 2020;7:e740-e751. **3.** Ackerman et al. *AIDS*. 2021;35:1061-1072.

BRIGHTE Study Design

- BRIGHTE is an ongoing phase 3 study evaluating fostemsavir 600 mg BID plus OBT in HTE adults failing ARV therapy with limited treatment options

Randomized Cohort[a]
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and
- 1 or 2 ARV classes remaining with ≥1 approved fully-active[b] agent per class
- Unable to construct viable regimen from remaining approved agents

Non-randomized Cohort[a]
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and
- 0 ARV classes remaining and no remaining approved fully-active[b] agents[c]

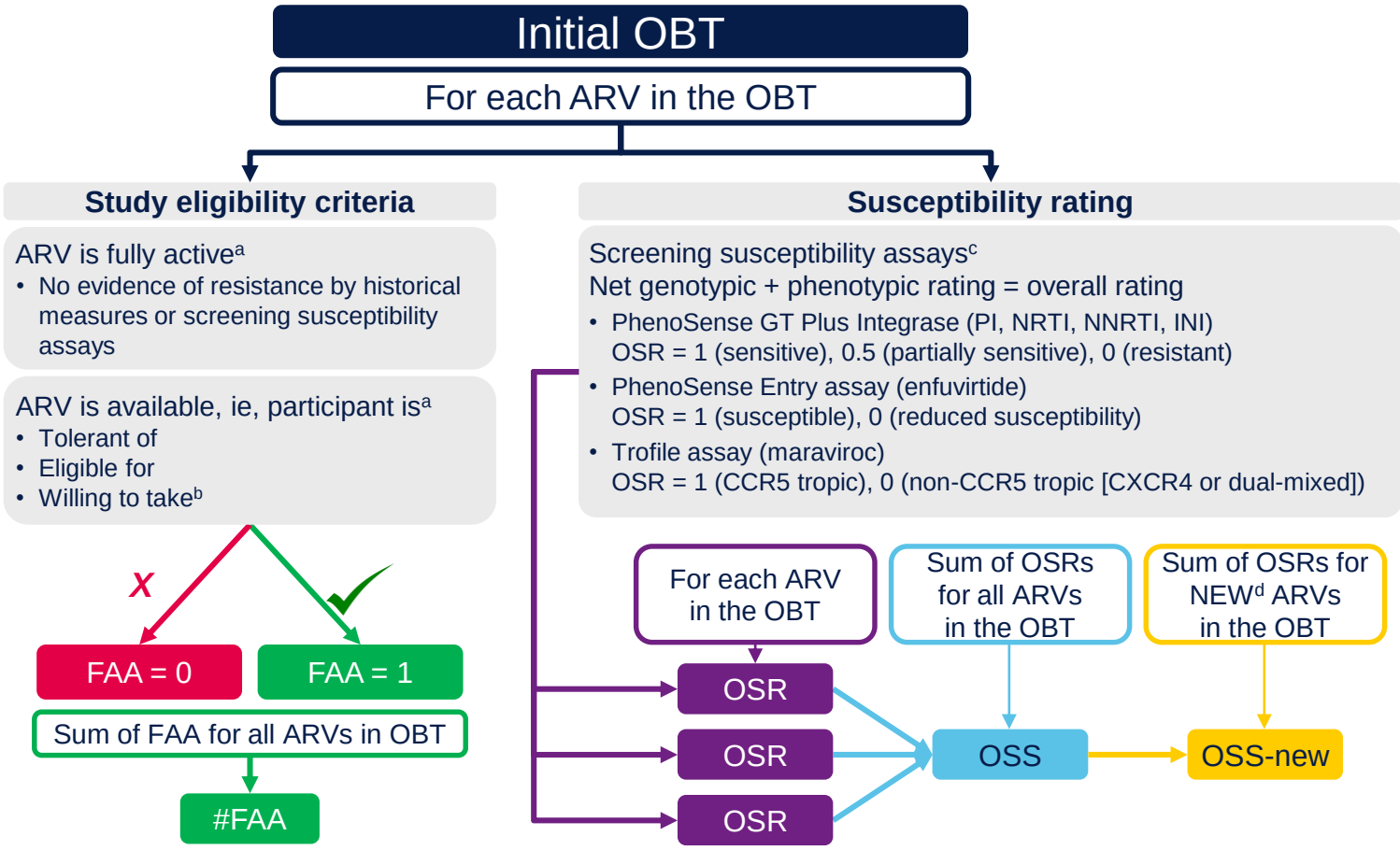


ARV, antiretroviral; BID, twice daily; FTR, fostemsavir; HTE, heavily treatment experienced; OBT, optimized background therapy.

[a]There were no screening temsavir susceptibility criteria. [b]Fully active is based on susceptibility (current or historical resistance measures) and availability (the participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the ARV). [c]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [d]Measured from the start of open-label FTR 600 mg BID + OBT. [e]The Week 96 database lock was August 14, 2018 (first participant, first visit: February 23, 2015; last participant, first dose of study treatment: August 11, 2016; last participant, last visit for Week 96: June 22, 2018). [f]The study is expected to be conducted until participants can access FTR through other means (eg, marketing approval).

Methods

- At screening, RC participants in BRIGHTE had 1 or 2 fully-active ARVs remaining
- Changes from baseline to PDVF in number of fully-active and available agents (FAA), overall susceptibility score (OSS), and overall susceptibility rating (OSR) for ARVs in the initial OBT were evaluated based on net assessment from resistance testing results



ARV, antiretroviral; OBT, optimized background therapy; PDVF, protocol-defined virologic failure; RC, Randomized Cohort.

[a]At PDVF, full activity was based on susceptibility according to Monogram susceptibility assays at PDVF and availability according to the baseline assessment. [b]For enfuvirtide only (twice-daily injectable). [c]Genotypic and phenotypic susceptibility testing was carried out by Monogram Biosciences for all participants at screening and at the time of failure for those meeting PDVF criteria. [d]New ARVs are those that have never been previously taken by the participant.

Changes in Distribution of Susceptibility Scores for the Initial OBT

- 63 RC participants met criteria for PDVF through Week 96

#FAA

At baseline

At PDVF, n (%)[a]	0 (n=4)	1 (n=30)	2 (n=29)
0	3 (75)	9 (30)	4 (14)
1	0	5 (17)	9 (31)
2	0	9 (30)	4 (14)
>2	0	5 (17)	7 (24)
Missing	1 (25)	2 (7)	5 (17)

21/55 (38%)

12/55 (22%)

22/55 (40%)

OSS

At baseline

At PDVF, n (%)[a]	>0-1 (n=9)	>1-2 (n=30)	>2 (n=23)	Missing (n=1)
0	5 (56)	6 (20)	1 (4)	0
>0-1	2 (22)	12 (40)	0	1 (100)
>1-2	1 (11)	6 (20)	5 (22)	0
>2	0	2 (7)	14 (61)	0
Missing	1 (11)	4 (13)	3 (13)	0

3/54 (6%)

22/54 (41%)

29/54 (54%)

OSS-new

At baseline

At PDVF, n (%)[a]	0 (n=21)	>0-1 (n=27)	>1-2 (n=14)[b]	Missing (n=1)
0	21 (100)	9 (33)	2 (14)	1 (100)
>0-1	0	15 (56)	3 (21)	0
>1-2	0	0	7 (50)	0
>2	0	0	0	0
Missing	0	3 (11)	2 (14)	0

0/57 (0%)

43/57 (75%)

14/57 (25%)

Increase

No change

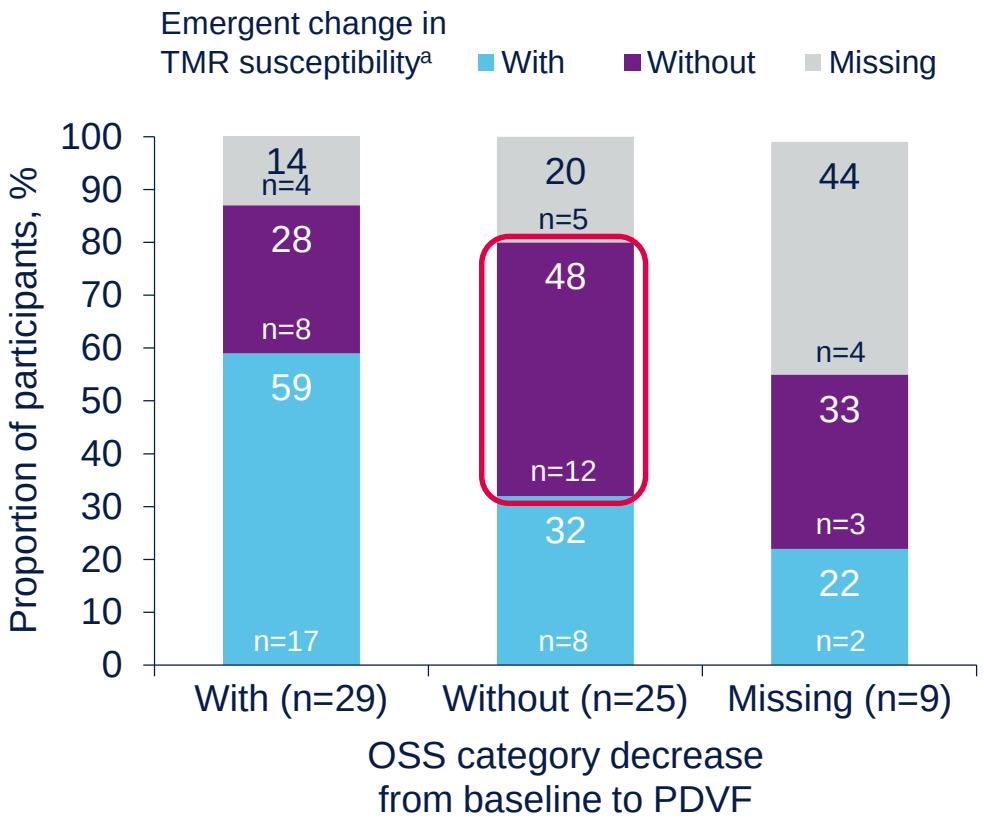
Decrease

- Susceptibility scores remained unchanged or increased at PDVF by #FAA, OSS, and OSS-new in 60% (33/55), 46% (25/54), and 75% (43/57) of RC participants, respectively, indicating a lack of emergent resistance to ≥1 component of initial OBT
- Decreases in #FAA were similar in participants with 1 or 2 FAAs at baseline (9/30 [30%] vs 13/29 [45%], respectively)
- Of 17 participants with increases in #FAA and data available at baseline and PDVF, 10 had no emergent changes in susceptibility to temsavir
- 17/63 (27%) RC participants with PDVF through Week 96 subsequently achieved HIV-1 RNA <40 c/mL before the Week 96 data lock (August 2018) while still receiving fostemsavir (11 with no changes in OBT)

#FAA, number of fully-active antiretrovirals; OBT, optimized background therapy; OSS, overall susceptibility score; PDVF, protocol-defined virologic failure; RC, Randomized Cohort.
[a]PDVF susceptibility data are selected from first of confirmed PDVF date, suspected PDVF (sentinel) date, or first date within 6 months after sentinel date. Percentages reported are based on the sample size of each baseline value.
[b]Of 17 participants in the RC with OSS-new >2 at baseline, none met PDVF through Week 96.

Emergent Changes in Susceptibility to Temsavir From BL to PDVF

With or without decrease in OSS category



Of RC participants at PDVF with available data (n=54)

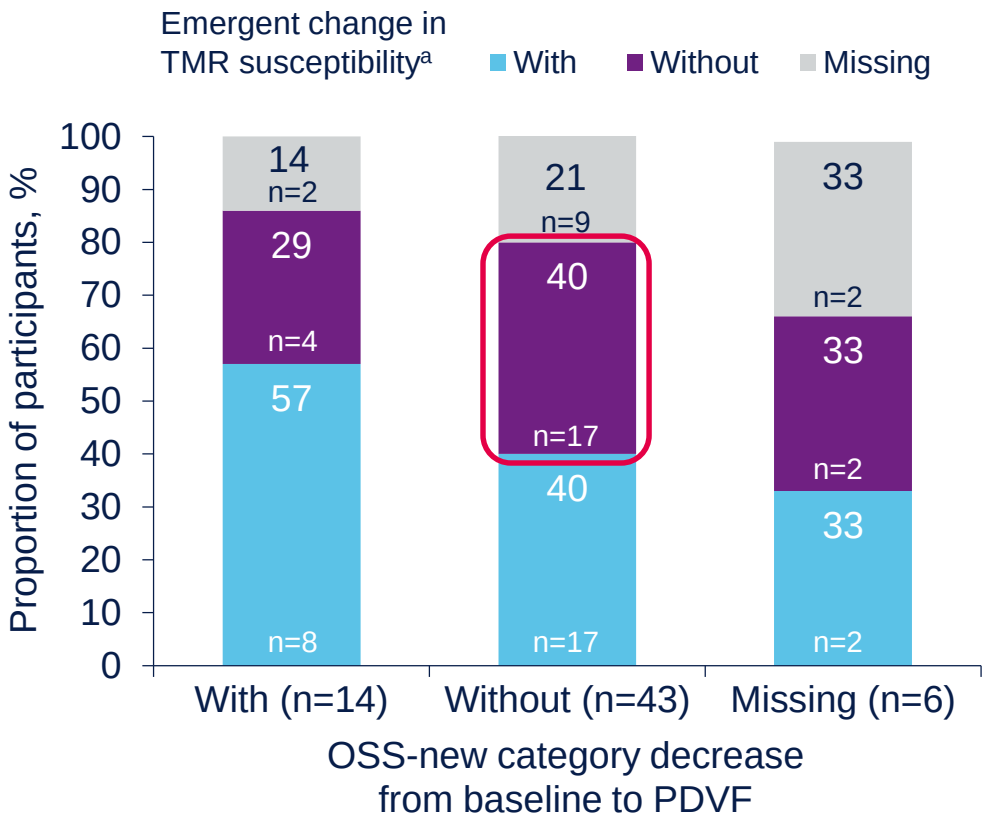
- 29 (54%) had a decrease in OSS
  - 17 (31%) had a decrease in OSS **and** emergent changes in temsavir susceptibility
  - 8 (15%) had a decrease in OSS alone
- 25 (46%) had no decrease in OSS
  - 8 (15%) had no decrease in OSS but did have changes in temsavir susceptibility
  - 12 (22%) had no decrease in OSS **and** no emergent changes in temsavir susceptibility, potentially indicative of a lack of adherence that may have contributed to PDVF

BL, baseline; OSS, overall susceptibility score; PDVF, protocol-defined virologic failure; RC, Randomized Cohort; TMR, temsavir.

[a]Change in susceptibility to temsavir as demonstrated by emergent gp160 substitutions of interest or a >3-fold change in temsavir IC_{50} FC (fold difference in 50% inhibitory concentration relative to a reference control virus).

Emergent Changes in Susceptibility to Temsavir From BL to PDVF

With or without decrease in OSS-new category



Of RC participants at PDVF with available data (n=57)

- 14 (25%) had a decrease in OSS-new
  - 8 (14%) had a decrease in OSS-new **and** emergent changes in temsavir susceptibility
  - 4 (7%) had a decrease in OSS-new alone
- 43 (75%) had no decrease in OSS-new
  - 17 (30%) had no decrease in OSS-new but did have changes in temsavir susceptibility
  - 17 (30%) had no decrease in OSS-new **and** no emergent changes in temsavir susceptibility, potentially indicative of a lack of adherence that may have contributed to PDVF

BL, baseline; OSS, overall susceptibility score; PDVF, protocol-defined virologic failure; RC, Randomized Cohort; TMR, temsavir.

[a]Change in susceptibility to temsavir as demonstrated by emergent gp160 substitutions of interest or a >3-fold change in temsavir IC_{50} FC (fold difference in 50% inhibitory concentration relative to a reference control virus).

Changes in Distribution of Susceptibility Scores for OBT ARVs

- Most RC participants with fully-active (FAA = 1) DTG or DRV in initial OBT retained full activity at PDVF (DTG, 75%; DRV, 82%)
- Most participants sensitive (OSR = 1) to DTG or DRV at baseline retained full sensitivity at PDVF (DTG, 72%; DRV, 89%)
- Of 25 participants sensitive to DTG as a newly used ARV (OSR-new = 1) at baseline, 20 (80%) retained sensitivity at PDVF
  - 2/25 (8%) participants had a decrease in OSR-new = 1 at PDVF; both were integrase inhibitor–experienced and had previously received RAL

DTG (n=50)

FAA	At baseline	
At PDVF, n (%)[a]	0 (n=18)	1 (n=32)
0	15 (83)	5 (16)
1	2 (11)	24 (75)

OSR	At baseline		
At PDVF, n (%)[a]	0 (n=6)	0.5 (n=7)	1 (n=36)
0	6 (100)	6 (86)[b]	4 (11)[c]
0.5	0	0	3 (8)[c]
1	0	0	26 (72)

OSR-new	At baseline		
At PDVF, n (%)[a]	0 (n=19)	0.5 (n=5)	1 (n=25)
0	19 (100)	4 (80)[d]	1 (4)[d]
0.5	0	0	1 (4)[d]
1	0	0	20 (80)

DRV (n=30)

	At baseline	
At PDVF, n (%)[a]	0 (n=19)	1 (n=11)
0	9 (47)	1 (9)
1	8 (42)	9 (82)

	At baseline		
At PDVF, n (%)[a]	0 (n=6)	0.5 (n=5)[e]	1 (n=18)[e]
0	4 (67)	1 (20)	1 (6)
0.5	1 (17)	2 (40)	0
1	1 (17)	0	16 (89)

	At baseline		
At PDVF, n (%)[a]	0 (n=30)	0.5 (n=0)	1 (n=0)
0	30 (100)	0	0
0.5	0	0	0
1[f]	0	0	0

Increase | No change | Decrease

ARV, antiretroviral; FAA, fully-active antiretroviral; DRV, darunavir; DTG, dolutegravir; OSR, overall susceptibility rating; PDVF, protocol-defined virologic failure; RAL, raltegravir; RC, Randomized Cohort.

Participants with missing data at baseline or PDVF are not shown.

[a]PDVF susceptibility data are selected from first of confirmed PDVF date, suspected PDVF (sentinel) date, or first date within 6 months after sentinel date. Percentages reported are based on the sample size of each baseline value. [b]All 6 had previous integrase inhibitor treatment experience, 4/6 with RAL, 2/6 with DTG + RAL. [c]All 7 had previous integrase inhibitor treatment experience, 1/7 with DTG, 2/7 with RAL, 4/7 with DTG + RAL. [d]All 6 had previous integrase inhibitor treatment experience, 6/6 with RAL. [e]All 23 had previous DRV treatment experience. [f]Of 31 participants in the RC who had sensitivity to DRV as a new agent (OSR-new = 1), none met PDVF through Week 96.

Participants With Emergent Decrease in OSR to DTG Had Emergence of Diverse Genotypes Reflecting Prior Integrase Inhibitor Use

Participant	OSR		OSR-new		Prior ART	Integrase inhibitor resistance–associated mutations	
	Baseline	PDVF	Baseline	PDVF		Baseline	PDVF
1	0.5	0	0	0	RAL, DTG	L74M, T97A, Y143C	L74M, T97A, E138A, Y143C, N155H
2						G140S, Q148H	T97A, E138E/K, G140S, Q148H
3	0.5	0	0.5	0	RAL	L74M, E92Q	L74M, E92Q, S147G
4						G140S, Q148H	G140S, Q148H, N155N/H
5						E138A, G140S, Q148H	L74L/M, T97T/A, E138A/T, G140S, Q148H
6						L74M, Q148R	L74I/M, T97A, E138K, Q148R
7	1	0	0	0	RAL, DTG	None	T97A, E138A, G140S, Q148H
8						None	L74M, T97A, S147G, N155H
9						None	None[a]
10	1	0.5	0	0	RAL, DTG	None	G140G/S, Q148Q/H
11	1	0.5	0	0	DTG	None	R263K[b]
12	1	0.5	1	0.5	RAL	None	T97T/A, S147S/G, N155H
13	1	0	1	0	RAL	None	T97T/A, E138E/K, G140S, Q148H, N155N/H

ART, antiretroviral therapy; DTG, dolutegravir; OSR, overall susceptibility rating; PDVF, protocol-defined virologic failure; RAL, raltegravir.

Resistance-associated mutations are as listed in the 2017 IAS-USA update.[1]

[a]Participant was off treatment at the time of PDVF. [b]Partial phenotypic sensitivity to DTG.

1. Wensing et al. *Top Antivir Med*. 2016;24:132-133.

Changes in Distribution of Susceptibility Scores for OBT ARVs (cont)

ETR (n=11)

FAA

At PDVF, n (%)[a]	At baseline 0 (n=5)	At baseline 1 (n=6)
0	1 (20)	3 (50)
1	3 (60)	3 (50)

OSR

At PDVF, n (%)[a]	At baseline 0 (n=1)	At baseline 0.5 (n=1)	At baseline 1 (n=9)
0	0	1 (100)	3 (33)
0.5	0	0	0
1	0	0	6 (67)

OSR-new

At PDVF, n (%)[a]	At baseline 0 (n=6)	At baseline 0.5 (n=0)	At baseline 1 (n=5)
0	6 (100)	0	2 (40)
0.5	0	0	0
1	0	0	3 (60)

MVC (n=18)

At PDVF, n (%)[a]	At baseline 0 (n=1)	At baseline 1 (n=17)
0	1 (100)	8 (47)
1	0	7 (41)

At PDVF, n (%)[a]	At baseline 0 (n=1)	At baseline 1 (n=17)[e]
0	1 (1007)	8 (47)
1	0	7 (41)

At PDVF, n (%)[a]	At baseline 0 (n=7)	At baseline 1 (n=11)
0	7 (100)	5 (45)
1	0	5 (45)

Increase
No change
Decrease

- 3/6 (50%) participants with ETR and 7/17 (41%) with MVC as fully-active agents in initial OBT met PDVF and retained full activity at PDVF

FAA, fully-active antiretroviral; ETR, etravirine; MVC, maraviroc; OSR, overall susceptibility rating; PDVF, protocol-defined virologic failure.

Participants with missing data at baseline or PDVF are not shown.

[a]PDVF susceptibility data are selected from first of confirmed PDVF date, suspected PDVF (sentinel) date, or first date within 6 months after sentinel date. Percentages reported are based on the sample size of each baseline value.

Conclusions

- In RC participants in BRIGHTE receiving fostemsavir in combination with 1 or 2 fully-active agents and experiencing PDVF through Week 96, emergent resistance to ARVs in the OBT was not consistently observed; incomplete treatment adherence may have contributed to this finding:
  - Several RC participants met PDVF through Week 96 and subsequently achieved HIV-1 RNA <40 c/mL before the Week 96 data lock while still receiving fostemsavir with no change in OBT, indicative of suboptimal adherence
  - A proportion of participants without decrease in OSS or OSS-new category for the initial OBT also had no changes in susceptibility to temsavir, suggesting a lack of drug-selective pressure
- Incidence of PDVF and proportion with decreases in #FAA were similar between participants with 1 vs 2 FAAs in initial OBT, suggesting no increased risk of PDVF with 1 FAA
- OSS-new remained unchanged in the majority of RC participants: OSS-new may be a predictor of virologic outcome in heavily treatment-experienced individuals
- Interpretation of data from participants who experienced PDVF in BRIGHTE is confounded by highly individualized OBTs and unique ARV resistance profiles at baseline and the time of virologic failure
- Overall, results support the use of fostemsavir in the heavily treatment-experienced population with limited treatment options

ARV, antiretroviral; FAA, fully-active antiretroviral; OBT, optimized background therapy; OSS, overall susceptibility score; PDVF, protocol-defined virologic failure; RC, Randomized Cohort.

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