

CLINICAL IMPACT OF ANTIRETROVIRAL AGENTS USED IN OPTIMIZED BACKGROUND THERAPY WITH FOSTEMSAVIR IN HEAVILY TREATMENT-EXPERIENCED ADULTS WITH HIV-1: EXPLORATORY ANALYSES OF THE PHASE 3 BRIGHTHE STUDY

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Introduction

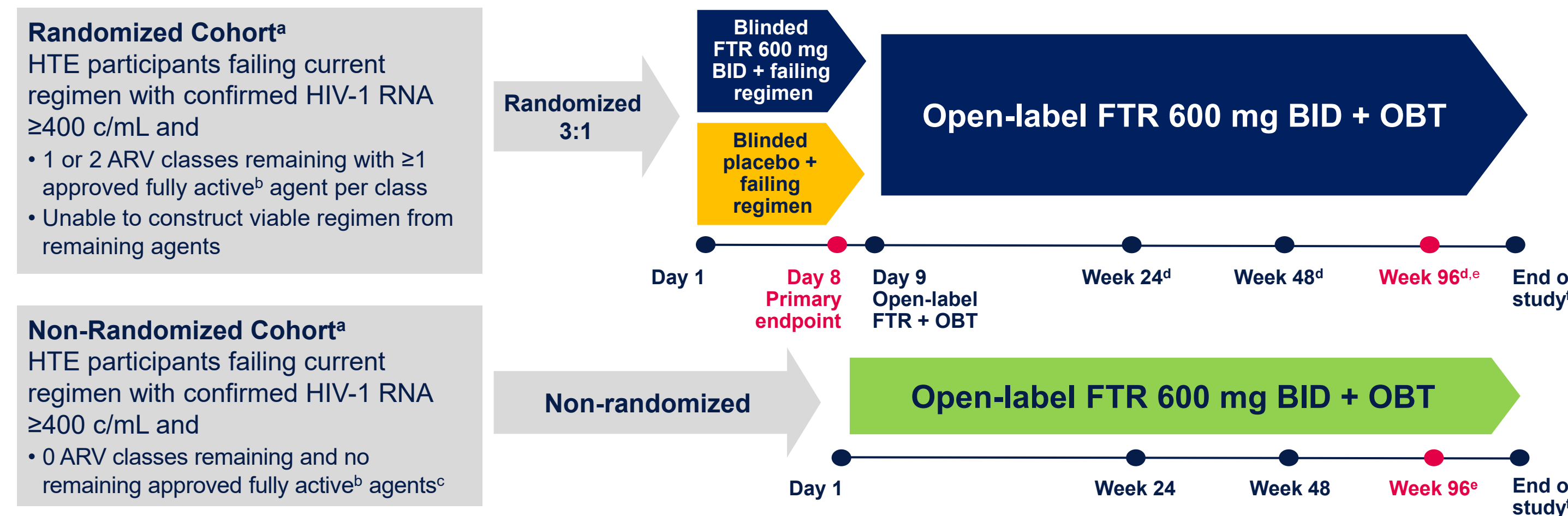
- Fostemsavir, an oral prodrug of the first-in-class attachment inhibitor temsavir, is approved for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced (HTE) adults who are otherwise unable to form a suppressive antiretroviral (ARV) regimen due to resistance, prior intolerance, or other safety concerns¹⁻⁴
- In the phase 3 BRIGHTHE study, in HTE adults with advanced HIV-1 disease and limited treatment options, fostemsavir plus optimized background therapy (OBT) was generally well tolerated and showed a trend of increasing virologic and immunologic response rates through 96 weeks¹⁻⁵
- This post hoc analysis evaluated the most common ARVs included in the initial OBT and their association with Week 96 virologic response

Methods

Study Design

- BRIGHTHE is an ongoing phase 3 study evaluating twice-daily (BID) fostemsavir 600 mg plus OBT in HTE adults failing ARV therapy with limited treatment options (Figure 1)

Figure 1. BRIGHTHE Study Design

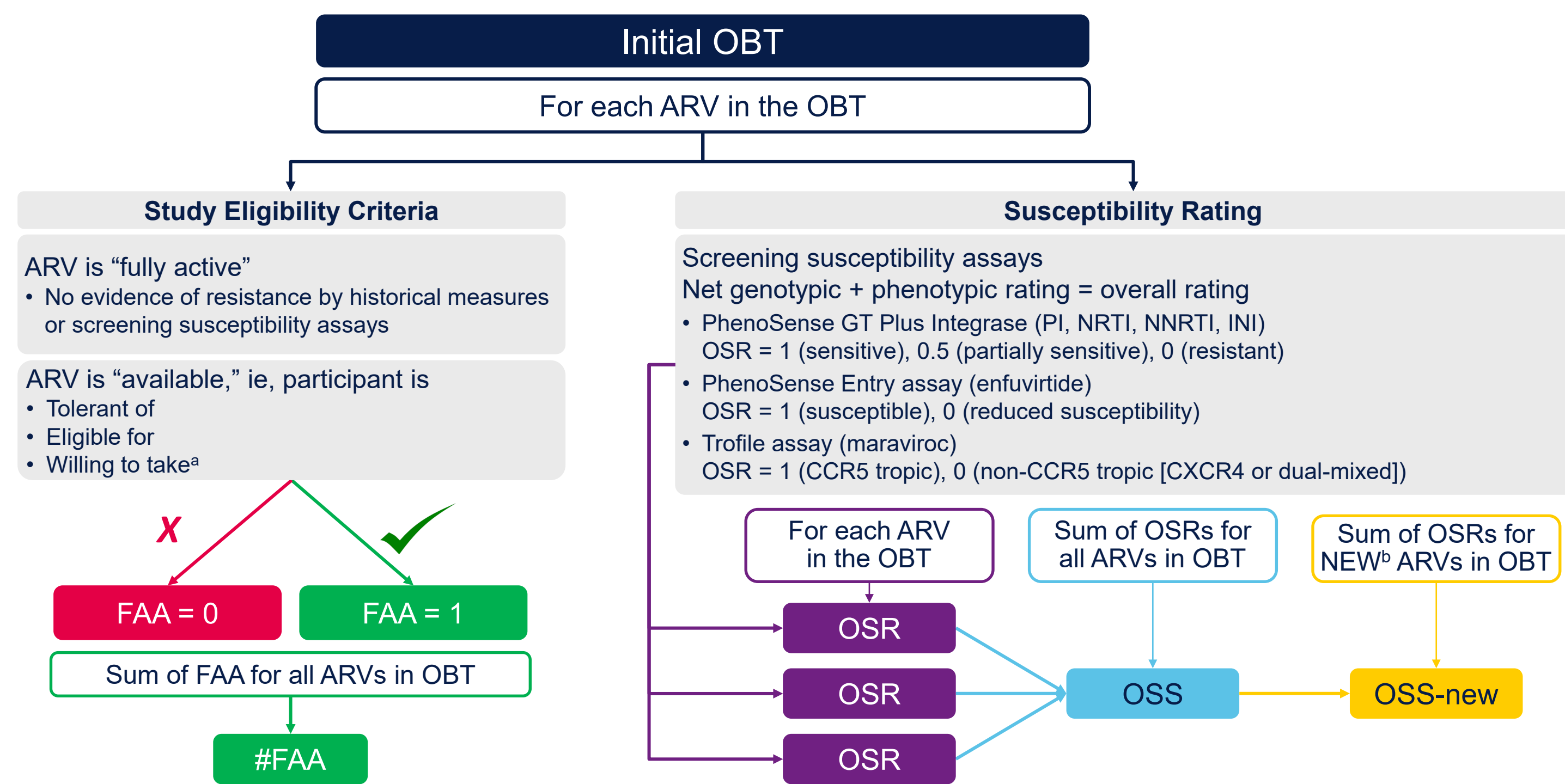


*There were no screening temsavir susceptibility criteria. [†]Fully active is based on susceptibility (current or historical resistance measures) and availability (the participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the antiretroviral). [‡]Use of investigational agents as part of OBT was permitted in the Non-randomized Cohort only. [§]Measured from the start of open-label FTR 600 mg BID + OBT. [¶]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). ^{||}The study is expected to be conducted until participants can access FTR through other means (eg, rollover study or marketing approval).

Analysis

- The composition of the OBT was summarized for both study cohorts
- For the Randomized Cohort (RC), virologic response (HIV-1 RNA <40 c/mL, by Snapshot analysis) through Week 96 was analyzed by subgroups based on
 - ARVs in the initial OBT
 - Overall susceptibility scores (OSS, OSS-new) for the initial OBT (Figure 2)
 - Number of fully active and available ARVs (FAA) in the initial OBT

Figure 2. Susceptibility Ratings and Scores



FAA, fully active and available; OSR, overall susceptibility rating; OSS, overall susceptibility score. [†]For enfuvirtide only (twice-daily injectable). [‡]New ARVs are those that have never been previously taken by the participant.

Results

Baseline Characteristics

- Most BRIGHTHE study participants were male and White (Table 1)
- Compared with the Non-randomized Cohort (NRC), the initial OBT for participants in the RC included fewer ARVs, but more were classified as FAA (Table 1)

Table 1. Baseline Characteristics

Parameter, n (%) ^a	RC (N=272)	NRC (N=99)
Sex, female	72 (26)	10 (10)
Age, ≥50 years	110 (40)	55 (56)
Race		
African American/African heritage	60 (22)	23 (23)
White	185 (68)	74 (75)
History of AIDS	231 (85)	89 (90)
HIV-1 RNA, ≥100,000 c/mL	80 (29)	15 (15)
CD4+ T-cell count		
<200 cells/mm ³	199 (73)	79 (80)
<20 cells/mm ³	72 (26)	40 (40)
Prior ARV therapy		
>15 years	182 (67)	80 (81)
≥5 regimens	226 (83)	90 (91)
Number of ARVs in initial OBT		
Mean (SD)	3.6 (1.4)	4.7 (1.3)
Median (range)	4 (0 ^b -8)	5 (1-8)
Susceptibility scores for initial OBT, mean (SD)		
#FAA	1.4 (0.6)	0.2 (0.4)
OSS	2.2 (0.8)	1.6 (1.1)
OSS-new	1.3 (0.8)	0.5 (0.7)

^aUnless otherwise specified. ^b1 participant discontinued during the blinded phase and never received an OBT.

Composition of the Initial OBT

- Integrase inhibitors (INI), particularly dolutegravir BID, were frequently used in both cohorts (Figure 3)
- Protease inhibitors (PI), particularly darunavir BID, and nucleoside reverse transcriptase inhibitors (NRTI) were more commonly used in the NRC than RC (Figure 3)

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Figure 3. Most Common ARVs in the Initial OBT by (A) Class and (B) Agent

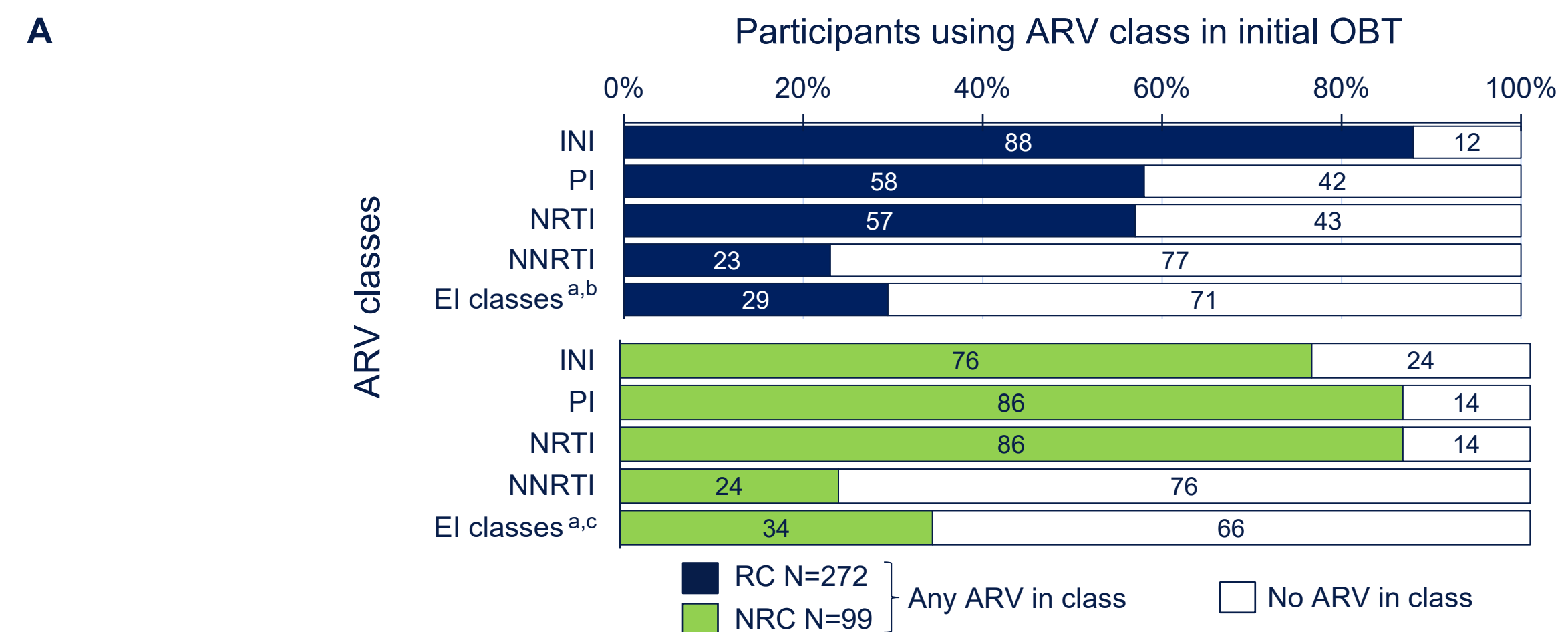


Table 2. Week 96 Virologic Response and CD4+ T-cell Count Change From Baseline at Week 96 by ARVs in the Initial OBT (RC)

ARV class	ARV agent, n (%)	RC (N=272)	NRC (N=99)
INI	Dolutegravir QD/BID ^d	58 (21)/171 (63)	6 (6)/68 (69)
PI	Darunavir QD/BID ^e	35 (13)/99 (36)	8 (8)/63 (64)
NRTI	FTC or 3TC	136 (50)	76 (77)
	TDF or TAF ^f	116 (43)	74 (75)
NNRTI	Etravirine	54 (20)	21 (21)
EI classes ^g	Maraviroc	52 (19)	8 (8)
	Ibalizumab ^h	0	15 (15)
	Enfuvirtide	28 (10)	11 (11)
INI + PI	Dolutegravir + darunavir	117 (43)	55 (56)

EI, entry inhibitor. ^aEI classes include the CCR5 inhibitor (maraviroc), post-attachment inhibitor (ibalizumab), and fusion inhibitor (enfuvirtide) classes. ^bNo participants in the RC used ibalizumab, which was investigational at the time of study enrollment and was only permitted in the NRC. ^c15 participants in the NRC used ibalizumab. ^dTotal dolutegravir use: 229/272 (84%) in the RC and 74/99 (75%) in the NRC. ^eTotal darunavir use: 134/272 (49%) in the RC and 71/99 (72%) in the NRC. ^fMostly TDF (5 participants [2 RC, 3 NRC] used TAF).

Impact of OBT on Virologic and Immunologic Responses in the RC

- In the RC, Week 96 virologic response rates and change from baseline in CD4+ T-cell count were similar regardless of the presence or absence of core ARV agents, except for dolutegravir (Tables 2 and 3)
- Virologic response rate and mean change from baseline in CD4+ T-cell count were higher among participants who included dolutegravir in the initial OBT than among those without dolutegravir in the initial OBT

Table 3. Week 96 Virologic Response Rates by Susceptibility Rating of Core ARVs in the OBT (RC)

ARV class	ARV agent	HIV-1 RNA <40 c/mL (Snapshot analysis), n/N (%)		Change in CD4+ T-cells/mm ³ (observed analysis), mean (SD) [n]	
		ARV present	ARV absent	ARV present	ARV absent
INI	Any	152/239 (64)	11/33 (33)	214.8 (187.1) [198]	72.0 (203.5) [15]
	Dolutegravir, any	146/229 (64)	17/43 (40)	216.2 (188.5) [191]	105.0 (190.8) [22]
	Dolutegravir, QD	40/58 (69)		162.8 (136.0) [46]	
	Dolutegravir, BID	106/171 (62)		233.2 (199.7) [145]	
PI	Any	94/158 (59)	69/114 (61)	195.0 (191.8) [130]	220.0 (190.7) [83]
	Darunavir, any	83/134 (62)	80/138 (58)	180.6 (179.8) [110]	230.6 (200.5) [103]
	Darunavir, QD	17/35 (49)		173.8 (129.6) [25]	
	Darunavir, BID	66/99 (67)		182.6 (192.6) [85]	
NNRTI	Any	41/62 (66)	122/210 (58)	196.5 (245.3) [52]	207.4 (171.1) [161]
	Etravirine	35/54 (65)	128/218 (59)	211.7 (227.0) [46]	202.8 (181.0) [167]
EI classes ^a	Maraviroc	25/52 (48)	138/220 (63)	142.8 (215.7) [36]	217.4 (184.1) [177]
	Enfuvirtide	13/28 (46)	150/244 (61)	194.4 (158.7) [20]	Not reported
NRTI	Any	92/154 (60)	71/118 (60)	225.6 (195.5) [118]	178.8 (183.6) [95]
	FTC or 3TC	82/136 (60)	81/136 (60)	205.6 (161.0) [106]	203.9 (218.0) [107]
	TDF or TAF	72/116 (62)	91/156 (58)	237.0 (200.8) [88]	182.0 (181.7) [125]
NRTI + INI	Any	87/134 (65)	76/138 (55) ^b	233.9 (196.5) [111]	173.0 (181.1) [102] ^b
	Any	117/190 (62) ^b	200.0 (208.0) [66]	206.9 (184.0) [147] ^b	
PI + INI	Any	86/141 (61)	77/131 (59) ^b	201.0 (195.6) [119]	209.5 (186.6) [94] ^b
	Dolutegravir + darunavir	75/117 (64)	88/155 (57) ^b	188.1 (183.0) [99]	219.2 (198.0) [114] ^b

EI, entry inhibitor. ^aEI classes used in the RC include the CCR5 inhibitor (maraviroc) and fusion inhibitor (enfuvirtide) classes. ^bAbsence of at least one of the agents in the specified combination.

Table 4. Week 96 Virologic Response Rates by Susceptibility Rating of Core ARVs and Susceptibility Score of the Initial OBT (RC)

ARV agent	HIV-1 RNA <40 c/mL (Snapshot analysis), n/N (%)			
	OSS		OSS-new	
	= 1.0	<1.0	= 1.0	<1.0
Dolutegravir, any	127/190 (67)	13/32 (41)	118/167 (71)	22/55 (40)
Dolutegravir, QD	37/52 (71)		36/48 (75)	
Dolutegravir, BID	90/138 (65)		82/119 (69)	
Darunavir, any	50/79 (63)	32/53 (60)	25/31 (81)	58/103 (56)
Darunavir, QD	15/30 (50)		8/11 (73)	
Darunavir, BID	35/49 (71)		17/20 (85)	
Etravirine	34/48 (71)	1/6 (17)	29/39 (74)	6/15 (40)
Maraviroc	24/49 (49)	0/1 (0)	19/36 (53)	5/14 (36)
Enfuvirtide	13/26 (50)	0/1 (0)	6/13 (46)	7/15 (47)

OSS, overall susceptibility rating.

- Among participants who included dolutegravir in the initial OBT, it represented the only fully active ARV by OSS and OSS-new in 16.2% (37/229) and 34.5% (79/229) of cases, respectively (Table 4)
- When dolutegravir was the only fully active agent in the initial OBT, it was dosed twice daily (BID) in ~75% of cases
- Among participants who had dolutegravir as the only fully active agent in their initial OBT, ~65% achieved virologic suppression at Week 96

Table 5. Week 96 Virologic Response by Susceptibility Rating of Core ARVs and Susceptibility Score of the Initial OBT (RC)

Fully active core ARV agent ^a	HIV-1 RNA <40 c/mL (Snapshot analysis), n/N (%)					
	OSS			OSS-new		
	N ^b	<2	≥2	N ^b	<2	≥2
Dolutegravir, any	188	24/37 (65)	102/151 (68)	165	52/79 (66)	65/86 (76)
Dolutegravir, BID	136	19/29 (66)	70/107 (65)	117	40/59 (68)	41/58 (71)
Darunavir, any	76	2/3 (67)	45/73 (62)	30	1/2 (50)	23/28 (82)
Darunavir, BID	47	1/2 (50)	32/45 (71)	20	0/1 (0)	17/19 (89)
Etravirine	47	0/1 (0)	33/46 (72)	38	2/4 (50)	26/34 (76)
Maraviroc	49	1/3 (33)	23/46 (50)	36	1/5 (20)	18/31 (58)
Enfuvirtide	26	0/5 (0)	13/21 (62)	13	0/5 (0)	6/8 (75)

OSS, overall susceptibility rating; OSS, overall susceptibility score. ^aFully active based on OSS or OSS-new of 1.0. ^bN=the number of participants with OSS or OSS-new of 1.0 for the indicated core ARV and a valid OSS or OSS-new for the initial OBT.

Conclusions

- In the BRIGHTHE study, HTE participants achieved durable rates of virologic response across a wide range of OBT combined with fostemsavir
- Overall, dolutegravir (BID) was the most common ARV included in the OBT
- The inclusion of dolutegravir in the OBT (particularly fully active dolutegravir) appeared to have the greatest impact on efficacy outcomes at Week 96