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Long-term efficacy and safety of fostemsavir among subgroups of heavily treatment-experienced adults with HIV-1

Peter Ackerman[a], Melanie Thompson[b], Jean-Michel Molina[c], Judith Aberg[d], Isabel Cassetti[e], Michael Kozal[f], Antonella Castagna[g], Marcelo Martins[h], Moti Ramgopal[i], Eduardo Sprinz[j], Sandra Treviño-Pérez[k], Adrian Streinu-Cercel[l], Gulam H. Latiff[m], Gilles Pialoux[n], Princy N. Kumar[o], Marcia Wang[p], Shiven Chabria[a], Amy Pierce[q], Cyril Llamoso[a] and Max Lataillade[a]

Objectives: The aim of this study was to understand how demographic and treatment-related factors impact responses to fostemsavir-based regimens.

Design: BRIGHTE is an ongoing phase 3 study evaluating twice-daily fostemsavir 600 mg and optimized background therapy (OBT) in heavily treatment-experienced individuals failing antiretroviral therapy with limited treatment options (Randomized Cohort 1-2 and Nonrandomized Cohort 0 fully active antiretroviral classes).

Methods: Virologic response rates (HIV-1 RNA <40 copies/ml, Snapshot analysis) and $CD4^+$ T-cell count increases in the Randomized Cohort were analysed by prespecified baseline characteristics (age, race, sex, region, HIV-1 RNA, $CD4^+$ T-cell count) and viral susceptibility to OBT. Safety results were analysed by baseline characteristics for combined cohorts (post hoc).

Results: In the Randomized Cohort, virologic response rates increased between Weeks 24 and 96 across most subgroups. Virologic response rates over time were most clearly associated with overall susceptibility scores for new OBT agents (OSS-new). $CD4^+$ T-cell count increases were comparable across subgroups. Participants with baseline $CD4^+$ T-cell counts less than 20 cells/μl had a mean increase of 240 cells/μl. In the safety population, more participants with baseline $CD4^+$ T-cell counts less than 20 vs. at least 200 cells/μl had grade 3/4 adverse events [53/107 (50%) vs. 24/96 (25%)], serious adverse events [58/107 (54%) vs. 25/96 (26%)] and deaths [16/107 (15%) vs. 2/96 (2%)]. There were no safety differences by other subgroups.

Conclusion: Week 96 results for BRIGHTE demonstrate comparable rates of virologic and immunologic response (Randomized Cohort) and safety (combined cohorts) across

[a]ViiV Healthcare, Branford, Connecticut, [b]AIDS Research Consortium of Atlanta, Atlanta, Georgia, USA, [c]Hospital Saint-Louis/Lariboisière, Assistance Publique hopitaux de Paris, Université de Paris, INSERM U944, Paris, France, [d]Icahn School of Medicine at Mount Sinai, New York, New York, USA, [e]Helios Salud, AIDS Care Center Infectious Diseases, Buenos Aires, Argentina, [f]Yale University School of Medicine and VA Connecticut Healthcare System, New Haven, Connecticut, USA, [g]IRCCS San Raffaele Hospital and Vita-Salute San Raffaele University, Milan, Italy, [h]Instituto Oulton, Cordoba, Argentina, [i]Midway Specialty Care Center, Fort Pierce, Florida, USA, [j]Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil, [k]Mexico Centre for Clinical Research, Mexico City, Mexico, [l]National Institute of Infectious Diseases 'Prof. Dr. Matei Balş,' Bucharest, Romania, [m]Maxwell Centre, Durban, South Africa, [n]Hôpital Tenon, Assistance Publique Hôpitaux de Paris, Paris, France, [o]Georgetown University School of Medicine, Washington, District of Columbia, [p]GlaxoSmithKline, Upper Providence, Pennsylvania, and [q]ViiV Healthcare, Research Triangle Park, North Carolina, USA.

Correspondence to Peter Ackerman, MD, Project Physician Lead, ViiV Healthcare, 36 East Industrial Road, Branford, CT 06405, USA.

Tel: +1 203 643 6420; e-mail: peter.x.ackerman@viivhealthcare.com

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subgroups. OSS-new is an important consideration when constructing optimized antiretroviral regimens for heavily treatment-experienced individuals with limited remaining treatment options.

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Keywords: antiretroviral agents, attachment inhibitor, fostemsavir, heavily treatment-experienced, multiple antiretroviral drug resistance, optimized background therapy, susceptibility score

Introduction

There is a continued need for development of new classes of antiretroviral drugs with novel mechanisms of action that are well tolerated and lack cross-resistance to currently available therapies. This need is particularly urgent for heavily treatment-experienced individuals with multidrug-resistant HIV-1 who are unable to form a suppressive antiretroviral regimen from remaining currently available agents [1–4]. For individuals with multidrug-resistant HIV-1 experiencing virologic failure, current international guidelines recommend a new treatment regimen with at least 2, preferably 3, fully active antiretroviral agents based on resistance mutations (current and historical) and treatment history [1,3]. Use of experimental agents or those with novel mechanisms of action is advised where other options are limited [1,3]. Management of multidrug-resistant HIV-1 in heavily treatment-experienced adults may be complicated by a range of factors, including advanced HIV disease with low $CD4^+$ T-cell count ($\leq$200 cells/μl), multiple comorbid medical conditions requiring concomitant medications, difficult social circumstances and a lack of adherence (periodic or persistent) to complex regimens [1,3,5,6].

Fostemsavir (Rukobia, ViiV Healthcare, Research Triangle Park, North Carolina, USA), a prodrug of the first-in-class attachment inhibitor temsavir, was recently approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of multidrug-resistant HIV-1 infection in heavily treatment-experienced adults with limited antiretroviral treatment options [7–11]. Temsavir has a novel mechanism of action, binding to HIV-1 gp120 and preventing viral attachment to and entry into host $CD4^+$ T cells and other immune cells [12]. Fostemsavir has no cross-resistance to currently available antiretrovirals, including other entry inhibitors, and can be used regardless of tropism [13–15]. Fostemsavir has few drug–drug interactions and can be administered with most drugs prescribed for the management of HIV-1 and associated comorbidities without the need for dose adjustment [16].

BRIGHTE (ClinicalTrials.gov, NCT02362503) is an ongoing phase 3 study investigating the efficacy and safety of fostemsavir and optimized background therapy (OBT) in heavily treatment-experienced individuals who were failing their current antiretroviral regimen (confirmed HIV-1 RNA $\geq$400 copies/ml) with limited remaining antiretroviral treatment options [7,17]. The study has two cohorts, a Randomized Cohort including participants with at least one but no more than two fully active antiretroviral agents that could be paired with fostemsavir upon entry into the trial and a Nonrandomized Cohort of heavily treatment-experienced participants with zero remaining fully active and approved antiretroviral options at study start who were allowed the use of other investigational antiretrovirals in their OBT through co-enrolment in other clinical trials. The Nonrandomized Cohort was essentially a compassionate-use group intended to make investigational therapy available to the most vulnerable individuals in the HTE population.

In the Randomized Cohort, treatment with fostemsavir plus OBT resulted in a virologic response (HIV-1 RNA $<$40 copies/ml by Snapshot analysis) in 144 out of 272 (53%) participants at Week 24 and 163 out of 272 (60%) at Week 96, and a continuous increase in $CD4^+$ T-cell count through Week 96 (mean +205 cells/μl at Week 96) [7,17]. Across both cohorts, fostemsavir and OBT was well tolerated with few adverse events leading to discontinuation and no new safety signals observed relative to earlier fostemsavir clinical trials [7,17].

Heavily treatment-experienced individuals with HIV-1 represent a diverse population and it is important to understand how different demographic and treatment-related factors may affect responses to fostemsavir treatment. We previously reported subgroup analyses of efficacy data from the Randomized Cohort of the BRIGHTE study showing no effect of age, sex, race or geographic region on short-term virologic response to fostemsavir functional monotherapy (8 days of blinded fostemsavir and failing antiretroviral regimen) or durability of response (through Week 48) to fostemsavir and OBT [7]. Here, we present prespecified and post hoc subgroup analyses of virologic and immunologic responses through Week 96 for the Randomized Cohort and post hoc subgroup analyses of cumulative safety endpoints for the combined cohorts.

Materials and methods

Methods

Study design and participants

BRIGHTE enrolled participants at 108 international investigational sites between February 2015 and May 2016 [7]. The study design has been previously described [7,17]. Briefly, eligible participants were adults (aged ≥18 years) who had a plasma HIV-1 RNA at least 400 copies/ml on their current failing antiretroviral regimen and were unable to form a complete antiretroviral regimen out of remaining fully active agents. Full activity was based on susceptibility (according to current and historical resistance measures) and availability (tolerance, eligibility, and in the case of enfuvirtide only, willingness to take the antiretroviral agent).

Participants with at least one remaining fully active antiretroviral drug in at least one but no more than two antiretroviral classes at baseline entered the Randomized Cohort. These participants were randomly assigned to receive blinded fostemsavir (600 mg twice daily) or placebo along with their current failing regimen from Day 1 to Day 8. After Day 8, all Randomized Cohort participants received open-label fostemsavir with an individualized OBT regimen. To reflect real-world clinical practice, the OBT was chosen at the complete discretion of the treating investigator (with no protocol-defined requirement for inclusion of fully active antiretrovirals).

Participants with no remaining approved fully active antiretroviral drugs entered the Nonrandomized Cohort and received open-label fostemsavir (600 mg twice daily) with an individualized OBT from Day 1. Participants in the Nonrandomized Cohort were allowed to co-enrol in other investigational antiretroviral trials, such as the phase 3 ibalizumab study, TMB-301.

The BRIGHTE study was conducted in accordance with international laws and guidelines consistent with the Declaration of Helsinki principles, with oversight from national, regional or institutional review boards or ethics committees. All study participants provided informed consent. BRIGHTE is expected to continue until participants can access fostemsavir through other means.

Procedures

HIV-1 RNA measurements (Abbott RealTime HIV-1 Assay; Abbott Molecular, Des Plaines, Illinois, USA) and other serologies were carried out at central laboratory facilities. Safety assessments included monitoring of adverse events, clinical laboratory tests, vital signs, electrocardiograms and physical examinations. Genotypic and phenotypic assays were performed on screening plasma samples by Monogram Biosciences (South San Francisco, California, USA) using their proprietary assays (PhenoSense GT Plus Integrase, Trofile and PhenoSense Entry).

The predicted antiviral activity of the initial OBT was quantified using the number of fully active antiretrovirals (#FAA) according to study entry criteria (based on susceptibility and availability), and susceptibility scoring [see Figure, Supplemental Digital Content (SDC) 1, http://links.lww.com/QAD/C33, which summarizes susceptibility parameters used to define subgroups based on OBT]. For genotypic, phenotypic and overall susceptibility scores (GSS, PSS and OSS, respectively), each antiretroviral agent in the OBT was assigned a susceptibility rating based, respectively, on the genotypic susceptibility rating (GSR), phenotypic susceptibility rating (PSR) or net susceptibility rating (OSR) results from the Monogram assays (1.0 = full activity, 0.5 = partial activity, 0 = resistance, as described in SDC 2, http://links.lww.com/QAD/C34, which explains the scoring systems for the different Monogram assays), and the susceptibility ratings were summed. 'OSS-new' was a variation of OSS in which antiretroviral agents previously used by the participant contributed an OSR of 0. Stanford GSS (S-GSS) was determined using the Stanford University HIV Drug Resistance Database algorithm [18] applied to sequence data from the Monogram genotypic assays (as detailed in SDC 3, http://links.lww.com/QAD/C35, which explains the scoring system for S-GSS).

Statistical analysis

The intention-to-treat-exposed (ITT-E) population and the safety population included all participants who received at least one dose of study treatment. Virologic response rates (proportion of participants with HIV-1 RNA <40 copies/ml) were determined by Snapshot analysis [19] of the ITT-E population, with missing HIV-1 RNA or change in OBT due to lack of efficacy classified as treatment failure. Planned subgroup analyses, conducted for efficacy endpoints in the Randomized Cohort, were based on age, race, sex, geographic region, baseline HIV-1 RNA categories (based on the latest predose assessment available), baseline $CD4^+$ T-cell categories (based on the latest predose assessment available) and #FAA, GSS, PSS and OSS of the initial OBT. Post hoc subgroup analyses were conducted for efficacy endpoints by subgroup based on OSS-new and S-GSS. No statistical testing was performed between subgroups. For changes in efficacy parameters from baseline, point estimates and associated 95% CIs are provided by subgroup.

Post hoc subgroup analyses were also conducted for cumulative safety data in subgroups of the total study population (including Randomized and Nonrandomized Cohorts) based on age, race, sex, geographic region, baseline $CD4^+$ T-cell count and baseline history of AIDS.

Role of funding source

The study was initially funded and sponsored by Bristol-Myers Squibb, who participated in the study design and initial data collection. In February 2016, funding and sponsorship of the study transitioned to ViiV Healthcare

with study management support from GlaxoSmithKline. Both ViiV Healthcare and GlaxoSmithKline participated in data collection, data analysis and data interpretation. All authors had full access to the data and vouch for the completeness and accuracy of the data analyses presented, and the fidelity of the study to the protocol. The first draft of the manuscript was prepared by a professional medical writer (paid for by the funder), under the guidance of the corresponding author, and was edited and revised by all authors. The corresponding author had final responsibility for the decision to submit for publication.

Results

A total of 371 participants were enrolled and treated, 272 in the Randomized Cohort and 99 in the Nonrandomized Cohort, and included in the ITT-E population (see Figure, SDC 4, http://links.lww.com/QAD/C36, which shows full participant disposition). At the Week 96 data cutoff (14 August 2018), 213 (78%) participants in the Randomized Cohort and 61 (62%) in the Nonrandomized Cohort remained in the study. The most common reasons for study withdrawal were lack of efficacy ($n = 12$), nonadherence ($n = 11$) and death ($n = 9$) in the Randomized Cohort and death ($n = 15$), lack of efficacy ($n = 6$) and nonadherence ($n = 6$) in the Nonrandomized Cohort. Adverse events led to withdrawal in seven and four participants, respectively. One participant in the placebo group withdrew before starting open-label fostemsavir treatment and was not included in the safety population. Among all participants, 22% were women, 22% were Black/African–American and 44% were aged at least 50 years (Table 1). Most participants

Table 1. Baseline characteristics (ITT-E population).

Parameter, *n* (%)[a]	Randomized Cohort ($n = 272$)	Nonrandomized Cohort ($n = 99$)	Total ($N = 371$)
Age, median (range), years	48 (18–73)	50 (17–72)	49 (17–73)
Age ≥50 years	110 (40)	55 (56)	165 (44)
Sex, female	72 (26)	10 (10)	82 (22)
Region			
North America[b]	108 (40)	56 (56)	164 (44)
South America[c]	105 (39)	14 (14)	119 (32)
Europe	51 (19)	27 (27)	78 (21)
Rest of world	8 (3)	2 (2)	10 (3)
Race			
White	185 (68)	74 (75)	259 (70)
Black/African–American	60 (22)	23 (23)	83 (22)
Other[d]	27 (10)	2 (2)	29 (8)
History of AIDS[e]	231 (85)	89 (90)	320 (86)
Duration of prior ART (years)			
≤10	41 (15)	5 (5)	46 (12)
>10–15	44 (16)	11 (11)	55 (15)
>15–20	90 (33)	22 (22)	112 (30)
>20	92 (34)	58 (59)	150 (40)
Unknown	5 (2)	3 (3)	8 (2)
Number of prior ART regimens			
2–4	43 (16)	8 (8)	51 (14)
5 or more	226 (83)	90 (91)	316 (85)
Unknown	3 (1)	1 (1)	4 (1)
HIV-1 RNA, median (range), $\log_{10}$ copies/mL	4.7 (1.6–6.9)	4.3 (1.6–6.6)	4.6 (1.6–6.9)
HIV-1 RNA (copies/ml)			
<400	21 (8)	5 (5)	26 (7)
400 to <1000	10 (4)	4 (4)	14 (4)
1000 to <100 000	161 (59)	75 (76)	236 (64)
100 000 to <500 000	59 (22)	13 (13)	72 (19)
≥500 000	21 (8)	2 (2)	23 (6)
$CD4^+$ T-cell count, median (range), cells/μl	99.5 (0–1160)	41.0 (0–641)	80.0 (0–1160)
$CD4^+$ T-cell count (cells/μl)			
<20	72 (26)	40 (40)	112 (30)
20 to <50	25 (9)	14 (14)	39 (11)
50 to <200	102 (38)	25 (25)	127 (34)
200 to <500	58 (21)	18 (18)	76 (20)
≥500	15 (6)	2 (2)	17 (5)

ART, antiretroviral treatment; ITT-E, intention-to-treat-exposed.
[a]Data are *n* (%) unless stated otherwise.
[b]Includes Canada, USA and Puerto Rico.
[c]Includes Argentina, Brazil, Chile, Colombia, Mexico and Peru.
[d]Other includes American Indian/Alaskan Native ($n = 8$), Native Hawaiian/Other Pacific Islander ($n = 1$), Asian ($n = 2$) and other ($n = 18$). Ethnicity was also recorded for 262 participants (including all US participants and some non-US participants), 107 (29%) of whom identified as Hispanic or Latino.
[e]History of AIDS = yes if a participant has nadir $CD4^+$ T-cell count <200 cells/μl or if response to 'does participant have AIDS?' on disease history case report form is yes.

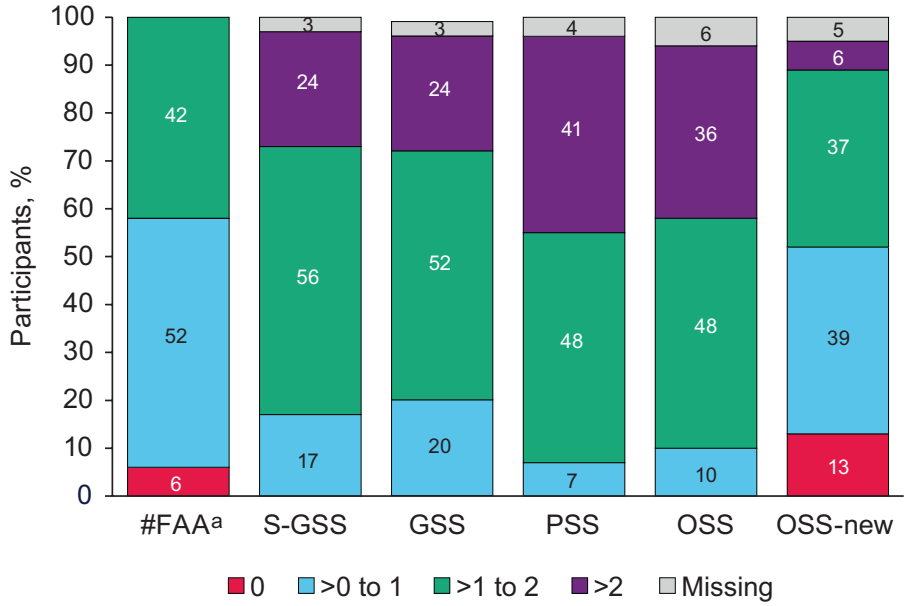

Fig. 1. Distribution of susceptibility scores for initial OBT (Randomized Cohort). #FAA, number of fully active antiretrovirals according to study entry criteria; GSS, genotypic susceptibility score; OBT, optimized background therapy; OSS, overall susceptibility score; PSS, phenotypic susceptibility score; S-GSS, Stanford GSS. [a]For this column, the categories are all whole numbers (0, 1 and 2). The 16 (6%) participants with 0 FAA included those who discontinued during the double-blind period and never initiated OBT, had exhausted all FAA at screening and were incorrectly assigned to the Randomized Cohort, or had at least one FAA at screening but did not receive these drugs as part of their initial OBT.

(86%) had a previous history of AIDS; median baseline HIV-1 RNA was 4.6 $\log_{10}$ copies/ml, and median baseline $CD4^+$ T-cell count was 80 cells/μl.

In the Randomized Cohort, 73 and 26% of participants had baseline $CD4^+$ T-cell count less than 200 and less than 20 cells/μl, respectively, and 29% had baseline HIV-1 RNA at least 100 000 copies/ml.

Using #FAA, 52 and 42% of participants had one or two fully active antiretrovirals in their initial OBT, respectively (Fig. 1). Similarly, by OSS-new, 52% of participants had an OBT susceptibility score of 1 or less, 37% had a score more than 1–2 and 6% had a score more than 2. Conversely, by OSS, 10% had a score of 1 or less, 48% had a score more than 1–2 and 36% had a score more than 2. Susceptibility scores for the initial OBT could be more than 2 because of the contribution of partially active antiretroviral agents; an OBT with one fully active antiretroviral (susceptibility rating 1) and three partially active antiretrovirals (susceptibility rating 0.5 each) would yield an OBT susceptibility score of 2.5. As previously reported [7], in the Randomized Cohort, dolutegravir [DTG; 229/272 (84%)] was the most common antiretroviral agent in the initial OBT followed by darunavir [DRV; $n = 134$ (49%)] and tenofovir disoproxil fumarate [TDF; 116 (43%)]. By #FAA, 65, 17 and 7% of all randomized participants had fully active DTG, DRV or TDF as part of their initial OBT, respectively (see Figure, SDC 5, http://links.lww.com/QAD/C37, which shows the most common agents in the OBT by susceptibility rating).

The number of participants with HIV-1 RNA less than 40 copies/ml in the Randomized Cohort increased from 144 (53%) at Week 24 to 163 (60%) at Week 96, by Snapshot analysis. This increase was influenced by a total of 63 participants who first achieved undetectable HIV-1 RNA levels after Week 24 ($n = 39$) or Week 48 ($n = 24$). At Week 96, virologic response rates were similar across subgroups for age, sex, race and geographic region (Table 2 and Figure, SDC 6, http://links.lww.com/QAD/C38, which shows Week 96 virologic response rates by subgroup). Virologic response rates were sustained over time in all these subgroups, and in most cases, increased between Weeks 24 and 96 (Figs. 2 and 3). Through Week 96, virologic response rates were lowest at all time points for participants with baseline viral load at least 100 000 copies/ml and those with baseline $CD4^+$ T-cell count less than 20 cells/μl; however, individuals in these subgroups did show improvements in virologic response rates over time (increasing from 35% at Week 24 to 49% at Week 96 and from 32% at Week 24 to 46% at Week 96, respectively).

The clearest association between Week 96 virologic response rates and OBT susceptibility score was seen using OSS-new (Table 2 and SDC 6, http://links.lww.com/QAD/C38), and this association persisted through Week 96 (Fig. 3). The lowest rates of virologic response (HIV-1 RNA <40 copies/ml) at all time points were

Table 2. HIV-1 RNA less than 40 copies/ml (Snapshot analysis, $N = 272$) and CD4$^+$ T-cell count change from baseline (observed analysis) at Week 96 by subgroup (Randomized Cohort).

	HIV-1 RNA <40 copies/ml		Change from baseline in CD4$^+$ T-cell count (cells/μl)	
Subgroups	*N*	*n* (%) [95% CI]	*N*	Mean [95% CI]
Total Randomized Cohort	272	163 (60) [54–66]	213	205 [179–231]
Age (years)				
<35	61	35 (57) [45–69]	48	292 [225–359]
35 to <50	101	61 (60) [51–69]	81	166 [133–199]
≥50	110	67 (61) [52–70]	84	193 [151–234]
Sex				
Male	200	118 (59) [52–66]	157	187 [161–213]
Female	72	45 (63) [51–73]	56	255 [190–320]
Race				
White	185	103 (56) [49–63]	137	210 [176–243]
Black or African–American	60	41 (68) [56–79]	51	204 [153–254]
Geographic region				
North America	108	61 (56) [47–66]	82	147 [112–182]
South America	105	67 (64) [54–72]	89	211 [175–247]
Europe	51	28 (55) [41–68]	37	306 [219–392]
Baseline HIV-1 RNA (copies/ml)				
<1000	31	23 (74) [57–86]	25	137 [53–220]
1000 to <10 000	44	32 (73) [58–84]	38	147 [85–210]
10 000 to <100 000	117	69 (59) [50–68]	91	218 [180–256]
≥100 000	80	39 (49) [38–60]	59	250 [200–300]
Baseline CD4$^+$ T-cell count (cells/μl)				
<20	72	33 (46) [35–57]	54	240 [186–293]
20 to <50	25	14 (56) [37–73]	17	201 [161–241]
50 to <100	39	21 (54) [39–68]	26	199 [149–249]
100 to <200	63	41 (65) [53–76]	52	172 [133–211]
≥200	73	54 (74) [63–83]	64	205 [141–269]
Initial OBT #FAA				
1	142	92 (65) [57–72]	120	206 [174–238]
2	114	68 (60) [51–68]	87	195 [153–238]
Initial OBT S-GSS				
>0 to 1	46	24 (52) [38–66]	34	236 [178–293]
>1 to 2	151	96 (64) [56–71]	121	210 [173–248]
>2	66	41 (62) [50–73]	55	169 [125, 213]
Initial OBT GSS				
>0 to 1	55	31 (56) [43–69]	45	224 [180–268]
>1 to 2	142	92 (65) [57–72]	112	215 [174–255]
>2	65	39 (60) [48–71]	53	165 [120–210]
Initial OBT PSS				
>0 to 1	20	12 (60) [39–78]	7	206 [157–254]
>1 to 2	130	77 (59) [51–67]	99	209 [170–248]
>2	112	72 (64) [55–73]	93	201 [159–242]
Initial OBT OSS				
>0 to 1	27	14 (52) [34–69]	22	201 [155–247]
>1 to 2	131	77 (59) [50–67]	100	206 [167–245]
>2	99	65 (66) [56–74]	82	202 [157–248]
Initial OBT OSS-new				
0	35	11 (31) [19–48]	21	142 [75–210]
>0 to 1	105	61 (58) [49–67]	85	219 [179–258]
>1 to 2	101	69 (68) [59–77]	83	192 [148–237]
>2[a]	17	15 (88) [66–97]	15	270 [145–395]

#FAA, number of fully active antiretrovirals according to study entry criteria; GSS, genotypic susceptibility score; OBT, optimized background therapy; OSS, overall susceptibility score; PSS, phenotypic susceptibility score; S-GSS, Stanford GSS. Only subgroups that include ≥20 participants are shown. Other results can be seen in Supplemental Digital Content 6 and 7, which show virologic response rates and change from baseline in CD4$^+$ T-cell count, respectively, at Week 96.

[a]Included for comparison with other OBT susceptibility scores.

among participants with an OSS-new score of 0 for their initial OBT (34% at Week 24 and 31% at Week 96 compared with 65% at Week 24 and 88% at Week 96 for those with an OSS-new score of >2; Fig. 3). In contrast, there was no clear trend towards increased virologic response rate with increases in S-GSS, GSS, PSS, OSS or #FAA (Fig. 3).

In the Randomized Cohort, mean (SD) increase in CD4$^+$ T-cell count from baseline was 205 (191) cells/μl at Week 96. Increases in CD4$^+$ T-cell count were generally consistent across subgroups with the exception of greater mean increases among participants aged less than 35 years [292 cells/μl; 95% confidence interval (95% CI), 225–359] compared with those aged 35 to less than 50 years

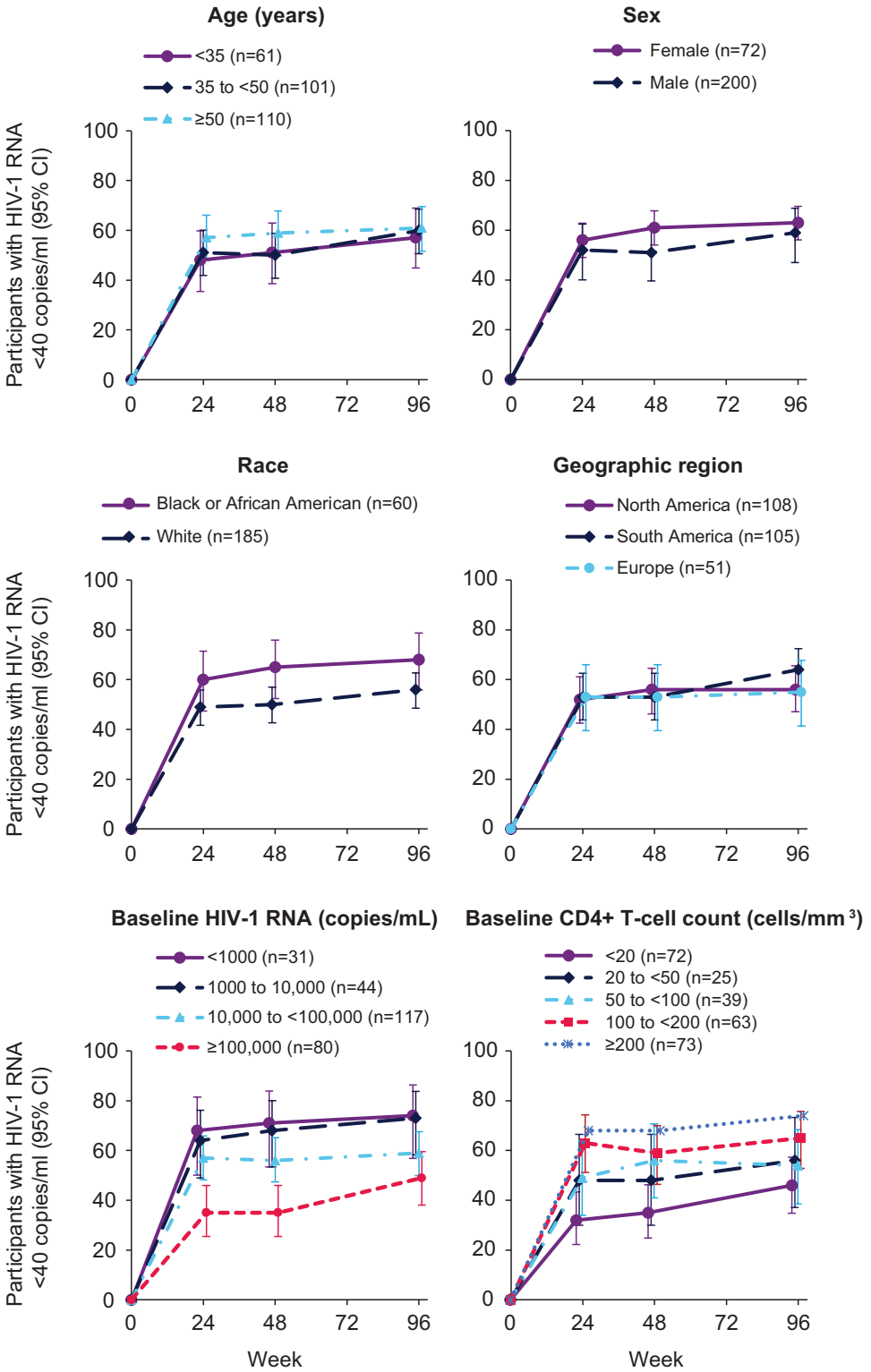

Fig. 2. HIV-1 RNA less than 40 copies/ml through Week 96 (Snapshot analysis, *N* = 272) by subgroup. Only subgroups that include ≥20 participants are shown. 95% CIs were not calculated for the baseline CD4$^+$ T-cell ≥200 cell/μl subgroup.

(166 cells/μl; 95% CI, 133–199) and participants from Europe (306 cells/μl; 95% CI, 219–392) compared with those from North America (147 cells/μl; 95% CI, 112–182; Table 2 and Figure, SDC 7, http://links.lww.com/QAD/C39, which shows change from baseline in CD4$^+$ T-cell count at Week 96 by subgroup). Differences in mean increase in CD4$^+$ T-cell count between subgroups based on OSS-new were less consistent than differences seen for

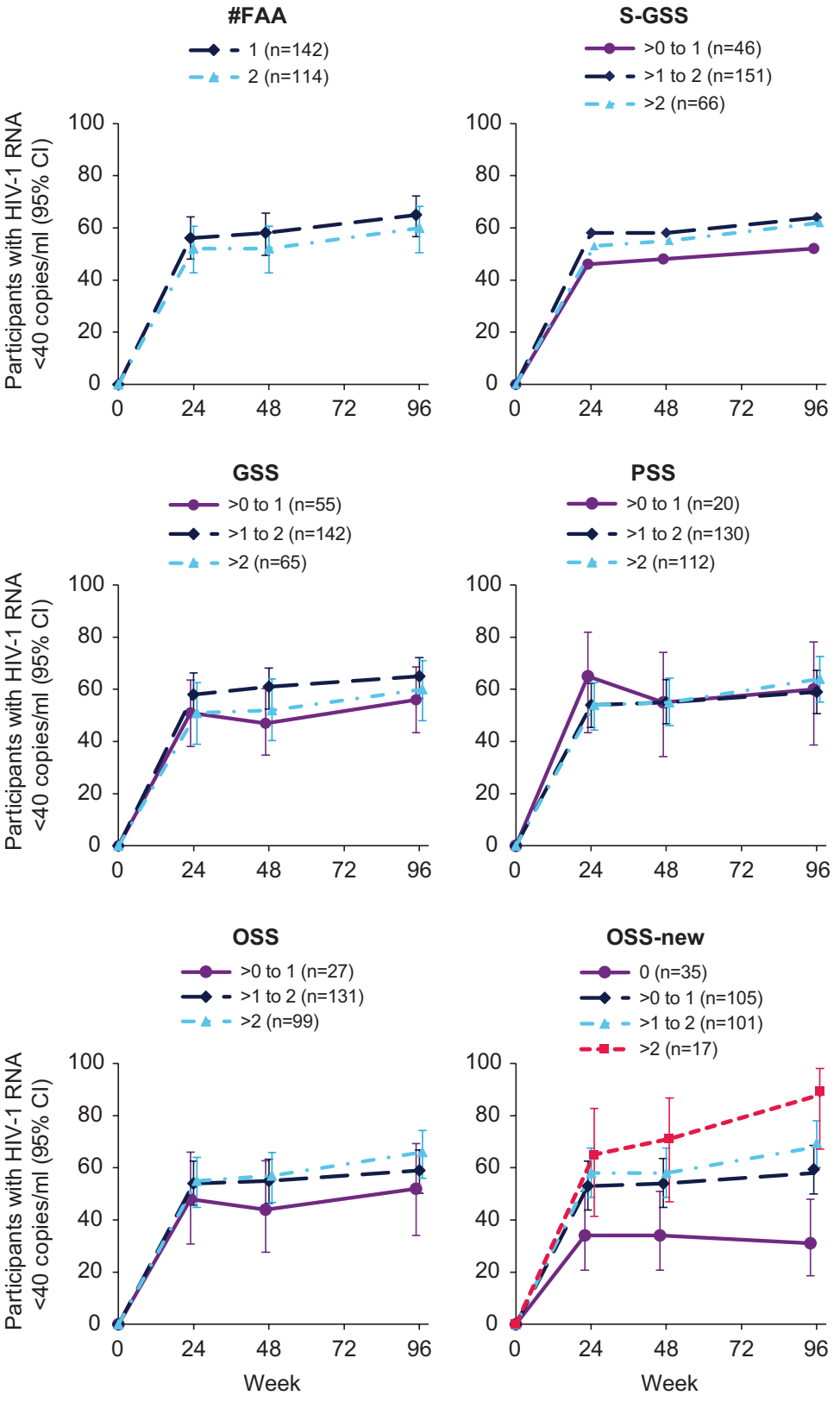

Fig. 3. HIV-1 RNA less than 40 copies/ml through Week 96 (Snapshot analysis, $N = 272$) by initial optimized background susceptibility scores. Only subgroups that include ≥20 participants are shown. 95% CIs were not calculated for the subgroups based on S-GSS. #FAA, number of fully active antiretrovirals according to study entry criteria; GSS, genotypic susceptibility score; OBT, optimized background therapy; OSS, overall susceptibility score; PSS, phenotypic susceptibility score; S-GSS, Stanford GSS.

Table 3. Week 96[a] safety summary by baseline CD4$^+$ T-cell count (total safety population, $N = 370$[b]).

Event, n (%)	Baseline CD4$^+$ T-cell count category (cells/μl)			
	<20 ($n = 107$)	20 to <200 ($n = 167$)	≥200 ($n = 96$)	Total ($N = 370$)
Any AE	103 (96)	156 (93)	88 (92)	347 (94)
AEs leading to discontinuation	11 (10)	11 (7)	4 (4)	26 (7)
Any grade 3/4 AE	53 (50)	50 (30)	24 (25)	127 (34)
SAEs	58 (54)	57 (34)	25 (26)	140 (38)
Deaths[c]	16 (15)[d]	10 (6)	2 (2)	28 (8)
Any drug-related AE	44 (41)	61 (37)	33 (34)	138 (37)
Drug-related SAEs[e]	5 (5)	2 (1)	5 (5)	12 (3)

AE, adverse event; SAE, serious adverse event.
[a]All safety data reflect cumulative results collected through the Week 96 data cutoff (14 August 2018).
[b]For participants randomized to placebo in the Randomized Cohort, only data from initiation of open-label fostemsavir dosing are presented. One participant in the placebo group withdrew before starting open-label fostemsavir treatment and is not included in the safety analysis.
[c]Including deaths that occurred after study drug discontinuation. Of the 28 deaths, seven were AIDS related, 10 were acute infections, six were non–AIDS-related malignancies and the remaining five were due to other conditions.
[d]One death in this subgroup was considered drug related (recurrent atypical mycobacterial infection due to immune reconstitution inflammatory syndrome).
[e]Drug-related SAEs included nephrolithiasis ($n = 2$), immune reconstitution inflammatory syndrome ($n = 2$) and one event each of acute kidney injury, central nervous system immune reconstitution inflammatory response, disorientation, foetal growth restriction, hepatocellular injury, hyperglycaemia, hyperkalaemia, loss of consciousness, myocarditis, generalized rash, renal impairment and rhabdomyolysis.

virologic response. Participants with CD4$^+$ T-cell count less than 20 cells/μl at baseline had a mean (SD) increase from baseline of 240 (196) cells/mm^3 (SDC 7, http://links.lww.com/QAD/C39 and Figure, SDC 8, http://links.lww.com/QAD/C40, which shows mean change from baseline in CD4$^+$ T-cell count through Week 96 by baseline CD4$^+$ T-cell count).

Across both cohorts, almost all (347/370, 94%) participants reported at least one adverse event (the most common being diarrhoea, nausea, upper respiratory tract infection and headache). Adverse events classified under infections and infestations were reported in 72% (268/370) of participants. There were few adverse events leading to discontinuation (26/370, 7%) and 38% (10/26) of these were related to infections. Through the Week 96 data cutoff, 12 (3%) participants experienced a drug-related serious adverse event (SAE), and 28 (8%) died. There were no clear differences in the safety profile across subgroups based on sex, age, race or geographic region (see Table, SDC 9, http://links.lww.com/QAD/C41, which shows safety results by subgroup). In general, adverse events were more common among participants who were the most immune suppressed at baseline (CD4$^+$ T-cell count <20 cells/μl; Table 3). Severe adverse events (grade 3–4 adverse events, SAEs and deaths) occurred more frequently among participants with baseline CD4$^+$ T-cell count less than 20 cells/μl than among those with baseline CD4$^+$ T-cell count at least 200 cells/μl: grade 3 to 4 adverse events (50 vs. 25%), SAEs (54 vs. 26%) and deaths (15 vs. 2%; Table 3).

Discussion

In the Randomized Cohort of the ongoing BRIGHTE study, treatment with fostemsavir and OBT in heavily treatment-experienced participants resulted in a virologic response rate by Snapshot analysis (ITT-E population) that was sustained through 96 weeks of treatment despite continued attrition of the study population over time. The rate of withdrawal from the study was not unexpected given the advanced disease state of the BRIGHTE population and was not notably different from other studies in people with multidrug-resistant HIV-1 [20–24]. Virologic response rates increased over time across most subgroups assessed, including participants with high baseline viral load and low baseline CD4$^+$ T-cell count, which are well established risk factors for decreased virologic response (in both treatment-naive and treatment-experienced individuals). It is notable that virologic response rates in subgroups of participants aged at least 50 years and in those identified as Black or African–American were comparable with those in other age and race subgroups, because these subgroups are disproportionately represented within the heavily treatment-experienced population in the United States and Europe [2,5].

Intriguingly, we observed for the first time in a controlled clinical trial of antiretrovirals, a continuous increase in virologic response rates in participants through Week 96, reflecting the fact that many individuals first achieved virologic response after Week 24. A combination of factors could explain this observation, including the advanced immune suppression of the study population, the necessity to use combinations of partially active antiretrovirals in the OBT and, possibly, the unique mechanism of action of temsavir. An intact immune system is important in the plasma clearance of HIV infection, thus the advanced immune suppression of many participants may have played a role in the delay of virologic responses. Indeed, rates of virologic response increased most profoundly in the subgroup of participants with lower baseline CD4$^+$ T-cell count (32–46%) and those with higher baseline viral load

(≥100 000 copies/ml; 35–49%) [12,25,26]. In addition, in the presence of multidrug-resistant virus, reliance on a background regimen of multiple partially active antiretroviral agents may result in a slower but continuous reduction in viral load.

Fostemsavir is the first approved antiretroviral to target the virus and inhibit the initial interaction with host immune cells. Temsavir, the active moiety of fostemsavir, binds directly to gp120 trimers on the surface of HIV-1 virions, near the CD4-binding pocket, locking the molecules into a fixed, closed conformation that prevents binding of gp120 to CD4 cell-surface receptors, thereby blocking viral entry into and infection of T cells and other immune cells. Virus is thus trapped in the extracellular space and subsequently cleared by the host immune system. Beyond prevention of viral entry, it has been hypothesized that temsavir binding may promote host immune recognition of autologous virus via neutralizing antibodies, which, over time, may contribute to enhanced clearance of the virus (possibly via antibody-dependent cellular cytotoxicity) [12,25,26]. Further research in this area is ongoing.

Although the primary goal of antiretroviral therapy is always to reduce HIV-1 RNA to below the limit of detection, when this is not feasible, secondary aims include reducing plasma HIV-1 RNA as much as possible and preserving or improving immunologic function to prevent disease progression [1,3]. Continuous, clinically meaningful improvement in $CD4^+$ T-cell count was seen across all subgroups, including those most immunosuppressed at baseline. The most profoundly immunosuppressed participants, those with baseline $CD4^+$ T-cell count less than 20 cells/μl, achieved a mean increase in $CD4^+$ T-cell count of 240 cells/μl by Week 96 (compared with +205 cells/μl in participants with baseline $CD4^+$ T-cell count ≥200 cells/μl). These increases in $CD4^+$ T-cell count are all the more impressive when considering that low nadir $CD4^+$ T-cell count and older age are known risk factors for muted $CD4^+$ recovery, even in cases of complete virologic suppression [27]. Significant increases in $CD4^+$ T-cell count hold the potential to be life changing for many individuals through improvement in immunologic status, reducing the need for prophylaxis against opportunistic infections, decreasing issues associated with polypharmacy (such as adherence, tolerability and toxicity) and ultimately reducing the risk of morbidity and mortality [1,3,28]. This is particularly important because advanced immune suppression is common among heavily treatment-experienced individuals [2].

Participants with only one fully active antiretroviral agent as part of their initial OBT did as well in terms of virologic response through Week 96 as participants with two fully active agents. Similarly, differences in S-GSS, GSS, PSS and OSS of the initial OBT were not associated with any clear trends in efficacy outcomes over time. Notably, these scores are limited in that they are based only on the results of screening drug susceptibility analyses and therefore cannot account for the possible presence of archived drug-resistant virus. This may be of particular importance in the BRIGHTE study, in which there were high levels of prior exposure to all antiretroviral classes [7,17]. For example, in the Randomized Cohort, darunavir was included in the OBT and classified as fully active by OSR (OSR = 1) in 29% of participants; however, because most of these participants had previously received darunavir, it was classified as fully active by OSR-new in only 11%. In contrast, OSS-new was clearly associated with virologic response rates, thus emphasizing the importance of considering prior exposure to antiretroviral agents when constructing regimens in individuals with multidrug-resistant HIV-1. This relationship between OSS-new and virologic outcomes in individuals with multidrug-resistant HIV-1 is consistent with previous studies conducted in similar populations [29].

A favourable safety profile is important for highly treatment-experienced individuals because prior intolerance and toxicity issues with currently approved antiretroviral drugs may have already played a role in limiting treatment options. Safety and tolerability are particularly important for older individuals who are more likely to have preexisting comorbidities requiring concomitant therapies and who represent a large proportion of the heavily treatment-experienced population [6]. In BRIGHTE, the frequency and profile of adverse events, including the most severe adverse events, are consistent with what has been reported in previous clinical trials of antiretrovirals in participants with multidrug-resistant HIV-1 [20,29–31]. Consistent with the severity of immune compromise in the study population, infections were the most common cause of adverse events. Fostemsavir-containing regimens were well tolerated through Week 96 across all demographic subgroups based on sex, age and race, including among participants aged at least 50 years. As expected, severe safety events (i.e. grade 3–4 adverse events, SAEs and deaths) were more frequent in the most immunocompromised participants with the lowest baseline $CD4^+$ T-cell count. However, the frequency of drug-related adverse events did not differ across baseline $CD4^+$ T-cell count categories, suggesting immune status did not impact fostemsavir tolerability.

The limitations of this analysis, such as small sample size, single-arm study design and broad diversity of background regimen, are inherent to clinical trials conducted in heavily treatment-experienced participants who have highly individualized treatment needs and limit the conclusive observations that can be drawn from any subgroup analysis of results. Subsequent studies should aim to include a greater proportion of women and diverse

ethnic groups to allow for more robust analyses of responses to treatment across a broad population. Nevertheless, these results provide important information for clinicians treating heavily treatment-experienced people with HIV-1 in real-life clinical practice.

Conclusion

Subgroup analyses of the Week 96 BRIGHTE data for the Randomized Cohort show robust and sustained efficacy with fostemsavir across a wide spectrum of heavily treatment-experienced adults with HIV-1 and limited treatment options. There were no clear differences in virologic response rates among subgroups based on demographic characteristics. Safety across subgroups for the combined cohorts was comparable. These results support fostemsavir as a therapeutic option that may be uniquely suited to address the needs of the heavily treatment-experienced population. Response rates were clearly impacted by OSS-new, a measure of the potential activity of the OBT that includes consideration of treatment history, emphasizing the importance of considering possible archived drug resistance when selecting antiretrovirals for this population. These data suggest that OSS-new may be an important measure to consider when constructing optimized antiretroviral regimens for heavily treatment-experienced people with multidrug-resistant HIV-1 and limited remaining treatment options.

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Conflicts of interest

P.A., S.C., A.P., C.L. and M.L. are employees of ViiV Healthcare and hold stock in GlaxoSmithKline. M.T. has participated in clinical trials for ViiV Healthcare, Bristol-Myers Squibb, Cepheid, Cytodyn, Gilead, GlaxoSmithKline, Merck Sharp and Dohme, and Frontier Biotechnologies through AIDS Research Consortium of Atlanta. J.-M.M. has received honoraria for advisory board participation from ViiV Healthcare, Gilead, Merck and Sanofi and a grant from Gilead. J.A. has participated in clinical trials for Atea, Bristol-Myers Squibb, ViiV Healthcare, Gilead, Janssen, Merck, Pfizer, Regeneron, Frontier Technology and Shionogi, for which her institution received grants, and has received personal fees for scientific advisory board participation from Gilead, Merck, Janssen, Medicure, Theratechnologies and ViiV Healthcare. I.C. has served as the principal investigator for studies funded by ViiV Healthcare, Merck and Janssen, for which her institution received grants, and has received honoraria for advisory board participation from ViiV Healthcare, Merck and Janssen. M.K. has served as the principal investigator for studies funded by ViiV Healthcare and Gilead, for which his institution has received grants. M.R. has received speaking and/or consulting fees from Gilead, ViiV Healthcare, Janssen and Merck. E.S. has received grants and/or personal fees for advisory board participation from GlaxoSmithKline, Janssen, Merck, Pfizer and Gilead. G.P. has received grants and/or personal fees from Gilead, Nephrotek, ViiV Healthcare, AbbVie, Merck Sharp and Dohme, Bristol-Myers Squibb and Boehringer Ingelheim. P.N.K. has received grants and/or personal fees for advisory board participation from GlaxoSmithKline, Merck and Theratechnologies and holds stock in GlaxoSmithKline, Pfizer, Johnson and Johnson, Merck and Gilead. M.W. is an employee of and holds stock in GlaxoSmithKline. A.C., M.M., S.T-P., A.S-C. and G.H.L. have no conflicts to disclose. This study was funded by ViiV Healthcare.

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Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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