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MAJOR ARTICLE

Inflammatory Biomarker Reduction With Fostemsavir Over 96 Weeks in Heavily Treatment-Experienced Adults With Multidrug-Resistant HIV-1 in the BRIGHTE Study

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Background. Fostemsavir, a first-in-class attachment inhibitor that binds to the viral envelope protein gp120, is approved for heavily treatment-experienced persons with HIV-1 with limited treatment options. We explored changes in immunologic and coagulopathy parameters in the BRIGHTE study: a phase 3 trial that evaluated fostemsavir plus optimized background therapy in heavily treatment-experienced adults with multidrug-resistant HIV-1.

Methods. CD4+ T-cell count, CD4+/CD8+ ratio, soluble CD14, soluble CD163, and D-dimer levels were measured through 96 weeks in participants with 1 or 2 fully active antiretroviral agents available at screening. No formal statistical analyses were performed.

Results. Among 272 participants, increases were observed from baseline to week 96 in CD4+ T-cell count (mean increase, +205 cells/mm^3) and CD4+/CD8+ ratio (mean increase, +0.24). The proportion of observed participants with a CD4+/CD8+ ratio ≥0.45 increased from 9% (25/272) at baseline to 40% (85/213) at week 96. From baseline to week 96, we also observed trends toward decreases in the following (mean [SD] change): soluble CD14, −738.2 (981.8) µg/L; soluble CD163, −138.0 (193.4) µg/L; and D-dimer, −0.099 (0.521) mg/L fibrinogen-equivalent units. Decreases in biomarkers were generally observed among subgroups by baseline disease characteristics, virologic response, and CD4+ T-cell count.

Conclusions. These data suggest that heavily treatment-experienced persons with multidrug-resistant HIV-1 treated with fostemsavir + optimized background therapy may have improvements in immune parameters, including markers of monocyte activation and coagulopathy.

Clinical Trials Registration. NCT02362503 (ClinicalTrials.gov; https://clinicaltrials.gov/study/NCT02362503).

Keywords. biomarkers; CD4+ T-cell count; CD4+/CD8+ ratio; fostemsavir; heavily treatment experienced.

Despite viral suppression with antiretroviral therapy (ART), persons with HIV have a higher risk of non–AIDS-defining events, such as cardiovascular disease, neurocognitive impairment, and cancer, as well as increased mortality, as compared with the general population [1–4]. While multiple factors contribute to this increased risk, residual inflammation and immune activation, even in the absence of detectable viremia, are considered among the major driving factors [5]. This low-grade inflammatory state is characterized by persistently elevated levels of monocyte/macrophage activation, represented by elevated concentrations of soluble CD14 (sCD14) and soluble CD163 (sCD163) [6–8], and residual coagulopathy, represented by elevated D-dimer levels [9, 10], among other biomarkers. Moreover, levels of these biomarkers correlate with morbidity and mortality in persons with HIV, even in the context of suppressive ART [7–11]. Heavily treated multidrug-resistant (MDR) disease or incomplete virologic control is particularly associated with higher residual inflammation [12–14].

Fostemsavir, the prodrug of temsavir, is a first-in-class attachment inhibitor approved for use in combination with other antiretrovirals (ARVs) in adults with MDR HIV-1 who are otherwise unable to construct a suppressive regimen [15–17]. At week 96 of the phase 3 BRIGHTE study—which evaluated fostemsavir in combination with optimized background therapy (OBT) in heavily treatment-experienced (HTE) adults with MDR HIV-1—60% of participants with 1 or 2 fully active ARVs achieved virologic suppression (HIV-1 RNA <40 copies/mL; Snapshot analysis) [18]. Robust immune reconstitution was also observed, with a mean increase in CD4+ T-cell count of +205 cells/mm^3.

Temsavir binds near the CD4 binding site of HIV-1 gp120 and allosterically prevents the conformational changes in

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gp120 necessary for it to stably bind to CD4, thereby inhibiting HIV-1 attachment to target cells [19, 20]. Available evidence suggests that the continual inflammatory state associated with HIV may be partially mediated by gp120 that persists despite virologic suppression [21, 22]. With its ability to obstruct membrane-associated and soluble gp120 binding to CD4, temsavir may modulate systemic inflammation in addition to its antiviral effect. In a phase 2b study, adults with HIV-1 treated with fostemsavir-based regimens had more substantive and consistent decreases in sCD14 concentrations as compared with those treated with a boosted protease inhibitor–based regimen, even though virologic suppression rates and CD4+ T-cell count increases were similar between groups [23]. Here, we explored the immunologic response to fostemsavir + OBT and changes in sCD14, sCD163, and D-dimer levels in BRIGHTE participants after 96 weeks.

METHODS

Study Design

BRIGHTE (ClinicalTrials.gov identifier, NCT02362503) is an ongoing, 2-cohort, phase 3 clinical trial at 108 investigational sites across Africa, Asia-Pacific, Europe, North America, and South America. Participants were HTE adults (aged ≥18 years) whose current ART regimen (HIV-1 RNA ≥400 copies/mL) was failing with ≤2 fully active and approved ARVs available at screening. Participants with 1 or 2 fully active ARVs remaining were assigned to the randomized cohort (RC), whereas those with no fully active ARVs remaining were assigned to the non-randomized cohort (NRC). The RC was termed as such because participants were randomly assigned 3:1 in a double-blind manner to receive either fostemsavir (600 mg twice daily) or placebo in combination with their current failing regimen for 8 days before transitioning to open-label fostemsavir + OBT. This short-term placebo-controlled efficacy assessment is consistent with guidance for the clinical development of ARVs for people with MDR HIV-1 who are HTE [24, 25]. Standard noninferiority trials may not be feasible in people with MDR HIV-1 who are HTE due to a lack of an appropriate active control. Furthermore, this population often requires use of individualized background therapy, and longer-term placebo-controlled comparisons are not appropriate as continued use of an unmodified failing regimen increases the risk of emergent ARV resistance [24].

The primary end point was mean change in $\log_{10}$ HIV-1 RNA at day 8 in the RC. The NRC received open-label fostemsavir + OBT starting on day 1. Before week 24, protocol-defined virologic failure was defined as either of the following:

- Confirmed (or last available before discontinuation) HIV-1 RNA ≥400 copies/mL after confirmed suppression to <400 copies/mL
- Confirmed (or last available before discontinuation) increase >1 $\log_{10}$ copies/mL in HIV-1 RNA above nadir, where nadir is ≥40 copies/mL

At or after week 24, protocol-defined virologic failure was defined as confirmed (or last available before discontinuation) HIV-1 RNA ≥400 copies/mL. Detailed descriptions of the BRIGHTE study design have been published [18, 26].

Key secondary objectives included change from baseline in CD4+ T-cell count and CD4+/CD8+ ratio at weeks 24, 48, and 96 in the cohort with 1 or 2 fully active ARVs at baseline (RC). CD4+/CD8+ ratio is a marker of risk of non–AIDS-related morbidity and mortality, independent of CD4+ T-cell count [27]. CD4+/CD8+ ratio <0.3 is associated with a significantly higher risk of severe non–AIDS-defining events or death as compared with CD4+/CD8+ ratio >0.45; thus, a ratio ≥0.45 was used as a cutoff in the current study. An exploratory end point assessed the impact of fostemsavir + OBT on the serum and plasma concentrations of sCD14, sCD163, and D-dimer in the RC. Biomarker data were collected at baseline and weeks 12, 24, 48, and 96, and the protocol was amended to allow for biomarker collection beyond week 96. Samples for biomarker analysis were not collected from the NRC.

Patient Consent Statement

The BRIGHTE study was conducted in accordance with the laws and guidelines established in the 2008 Declaration of Helsinki. Approval and oversight were provided by national or regional institutional review boards or ethics committees. All participants provided written informed consent before initiation of any study procedures.

Analyses

Participant serum or plasma samples were sent to centralized locations for testing: ICON Laboratory Services for sCD14 and D-dimer and Myriad RBM for sCD163. Soluble CD14 concentrations were determined by a quantitative sandwich enzyme immunoassay (Quantikine Human sCD14 Immunoassay; R&D Systems Inc) with a reference range of 800 to 3200 µg/L. Soluble CD163 concentrations were evaluated with xMAP Technology (Luminex Corporation), a fluorescence-based assay with microspheres coated with sCD163-specific capture reagents and a secondary antibody labeled with a fluorescent reporter molecule. Reference values for sCD163 were not available. D-dimer levels were measured with a photometric-based assay (STA-Liatest D-Di; Diagnostica Stago SAS), with a reference value <0.500 mg/L fibrinogen-equivalent units. CD4+ and CD8+ T-cell counts and percentages were assessed by flow cytometry. Biomarkers were evaluated post hoc across subgroups by week 96 clinical outcomes (virologic response, change from baseline in CD4+ T-cell count, and protocol-defined virologic failure), baseline disease characteristics (HIV-1 RNA, CD4+ T-cell count,

and number of fully active agents in initial OBT), and baseline demographics (age, sex, race, and geographic region). No formal statistical analyses were performed.

RESULTS

Study Population

Overall, 272 participants were included in the intention-to-treat–exposed population in the cohort with 1 or 2 fully active ARVs at baseline. Participants were primarily White (68%) and male (74%) with a median age of 48 years (Table 1). At baseline, median (range) CD4+ T-cell count was 100 (0–1160) cells/mm^3, and mean (SD) CD4+ T-cell count was 152 (182) cells/mm^3. Of 272 participants, 199 (73%) had a CD4+ T-cell count <200 cells/mm^3, and 97 (36%) had a CD4+ T-cell count <50 cells/mm^3; 212 (78%) had a CD4+/CD8+ ratio <0.30. Median (range) viral load was 4.66 (1.59–6.91) $\log_{10}$ copies/mL. When the open-label fostemsavir + OBT period began, 142 (52%) and 114 (42%) participants had 1 and 2 fully active ARVs available in their initial OBT, respectively. The remaining 16 (6%) participants had 0 fully active ARVs available in their initial OBT, with 6 having ≥1 fully active ARV at screening but no fully active ARVs in their initial OBT, 5 having no fully active ARVs at screening and assignment to the RC in error, and 5 having discontinued the study during the double-blind period before starting OBT. The most common agents in the initial OBT were dolutegravir (84%), emtricitabine or lamivudine (50%), darunavir (49%), and tenofovir disoproxil fumarate (42%; Supplementary Table 1).

Table 1. Demographics and Baseline Disease Characteristics in the Randomized Cohort: ITT-E Population

Parameter	Randomized Cohort (n = 272)
Sex: female	72 (26)
Age, y, median (range)	48 (18–73)
<35	61 (22)
35–49	101 (37)
≥50	110 (40)
Race	
White	185 (68)
Black or African American	60 (22)
American Indian or Alaska Native	7 (3)
Asian	2 (<1)
Native Hawaiian or other Pacific Islander	1 (<1)
Other races[a]	17 (6)
CD4+ T-cell count, cells/mm^3, median (range)	100 (0–1160)
<20	72 (26)
20 to <50	25 (9)
50 to <100	39 (14)
100 to <200	63 (23)
≥200	73 (27)
CD4+/CD8+ ratio, mean (SD)	0.20 (0.24)
HIV-1 RNA, $\log_{10}$ copies/mL, median (range)	4.66 (1.59–6.91)
<1000	31 (11)
1000 to <10 000	44 (16)
10 000 to 100 000	117 (43)
≥100 000	80 (29)
History of AIDS[b]	231 (85)
No. of fully active available ARVs in initial OBT	
0[c]	16 (6)
1	142 (52)
2	114 (42)
Biomarkers, mean (SD)	
Soluble CD14, µg/L[d]	2502.5 (1034.6)
Soluble CD163, µg/L[e]	545.2 (212.5)
D-dimer, mg/L FEU[f]	0.487 (0.379)

Data are presented as No. (%) unless noted otherwise.

Abbreviations: ARV, antiretroviral; FEU, fibrinogen-equivalent units; ITT-E, intention to treat exposed; OBT, optimized background therapy.

[a]Includes mixed race (n = 14), Hispanic (n = 2), and North African (n = 1).

[b]Determined by nadir CD4+ T-cell count <200 cells/mm^3 or report of AIDS on disease history case report form.

[c]Includes participants who discontinued the study during the double-blind period before starting OBT, those who had ≥1 fully active ARV at screening but no fully active ARVs in their initial OBT, and those who had no fully active ARVs at screening and were assigned to the randomized cohort in error.

[d]n = 258.

[e]n = 256.

[f]n = 259.

Immunologic Response

Through week 96, participants with 1 or 2 fully active ARVs at baseline had an increase in CD4+ T-cell count (baseline mean, 152 cells/mm^3; mean change from baseline, +205 cells/mm^3) and CD4+/CD8+ ratio (baseline mean, 0.20; mean change from baseline, +0.24; Figure 1*A* and 1*B*), as previously reported [18]. Numeric increases were observed across all baseline CD4+ T-cell count subgroups, including participants with baseline CD4+ T-cell count <20 cells/mm^3 (baseline mean, 6 cells/mm^3; mean change from baseline, +240 cells/mm^3; Figure 1*C*). Moreover, the proportion of observed participants with a CD4+/CD8+ ratio >0.45 increased from 9% (25/272) at baseline to 40% (85/213) at week 96. Numeric increases in mean CD4+ T-cell count were also observed through 96 weeks among participants with HIV-1 RNA <400 copies/mL by Snapshot analysis (baseline mean, 186 cells/mm^3; mean change from baseline to week 96, +221 cells/mm^3) and among those with HIV-1 RNA ≥400 copies/mL by Snapshot analysis (baseline mean, 77 cells/mm^3; mean change from baseline to week 96, +130 cells/mm^3; Figure 1*D*).

Changes in sCD14, sCD163, and D-dimer

In the observed analysis, numeric decreases from baseline were observed in all 3 biomarkers evaluated through week 96 (Figure 2). Mean (SD) change from baseline in sCD14 was −738.2 (981.8) µg/L; in sCD163, −138.0 (193.4) µg/L; and in D-dimer, −0.099 (0.521) mg/L fibrinogen-equivalent units. Changes in each biomarker were generally similar across subgroups by demographics and baseline characteristics (Supplementary Figures 1 and 2), although there were small numbers of participants in some subgroups. D-dimer levels numerically increased at weeks 24 and 48 in female participants,

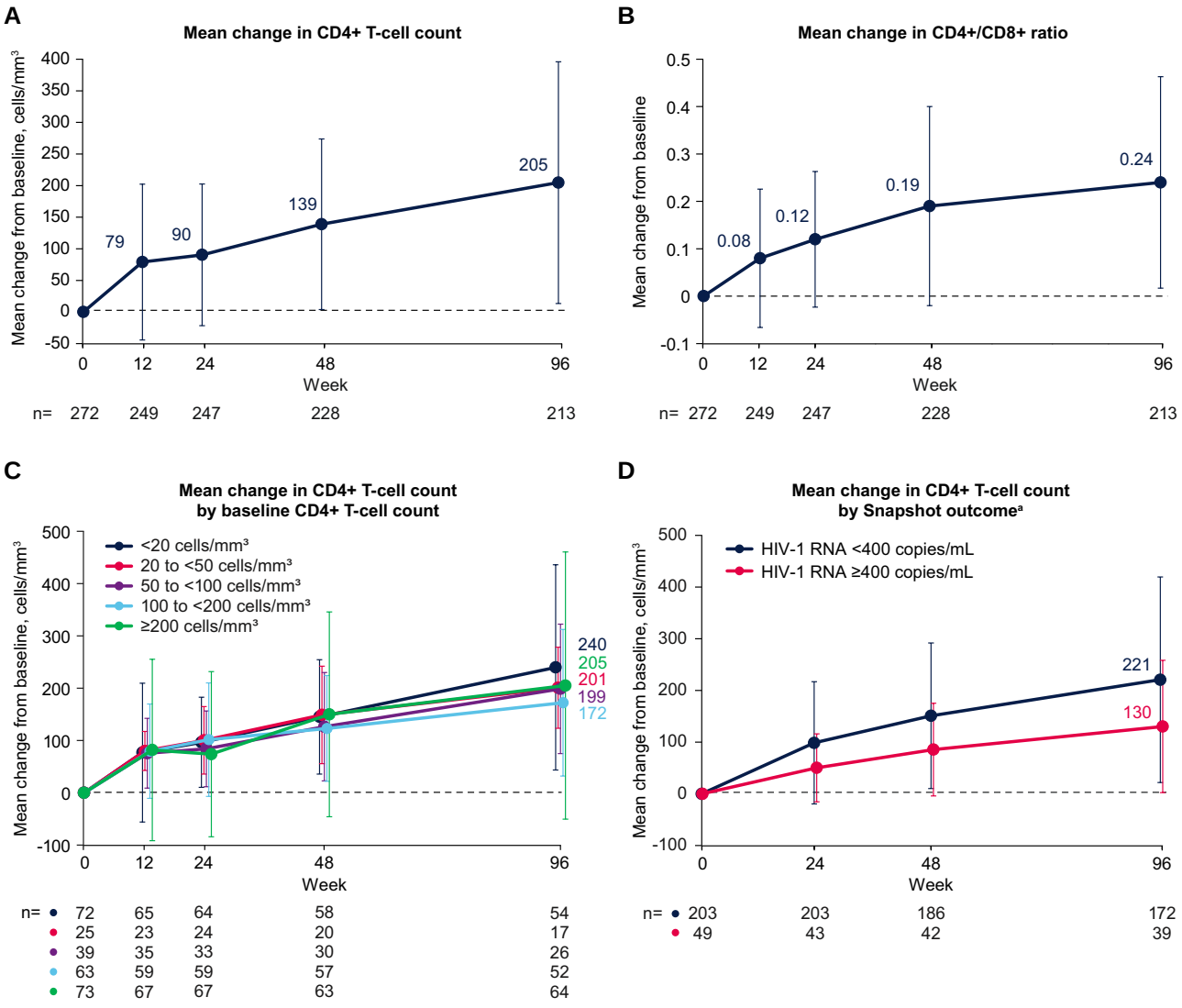

Figure 1. Mean change from baseline: *A*, CD4+ T-cell count; *B*, CD4+/CD8+ ratio. Mean change from baseline in CD4+ T-cell count: *C*, by baseline CD4+ T-cell count; *D*, by Snapshot virologic outcome at the same time point. [a] At week 24, 1 participant did not have virologic data in window (mean change in CD4+ T-cell count, +142.0 cells/mm^3). At week 96, 2 participants did not have virologic data in window (mean change in CD4+ T-cell count, +290.5 cells/mm^3). Snapshot data not available for week 12. Error bars represent SD.

although variability was high at these time points and then declined below baseline levels at week 96.

Numeric improvements in biomarkers occurred among participants with and without a virologic response (HIV-1 RNA <40 copies/mL) at week 96 (Figure 3*A*–*C*), in participants with or without protocol-defined virologic failure at week 96 (Figure 3*D*–*F*), and across CD4+ T-cell count subgroups at week 96 (Figure 4), although some subgroups included small numbers of participants.

DISCUSSION

Treatment with fostemsavir + OBT resulted in increases in CD4+ T-cell count and CD4+/CD8+ ratio through week 96. Numeric increases in CD4+ T-cell count were observed regardless of baseline CD4+ T-cell count and week 96 virologic response. We also observed trends toward improvements in biomarkers of monocyte/macrophage activation (sCD14 and sCD163) and coagulopathy (D-dimer), which are independently associated with increased risk of AIDS- and non–AIDS-related morbidity and mortality [7–11].

In the observed analysis, the proportion of participants with a CD4+/CD8+ ratio >0.45 increased from 9% to 40%, and the overall mean increase in CD4+ T-cell count was +205 cells/mm^3. Achieving a CD4+/CD8+ ratio ≥0.45 has been shown to be clinically significant [27, 28], and exceeding an absolute CD4+ T-cell count of 200 cells/mm^3 reduces the risk of opportunistic infections and need for opportunistic infection

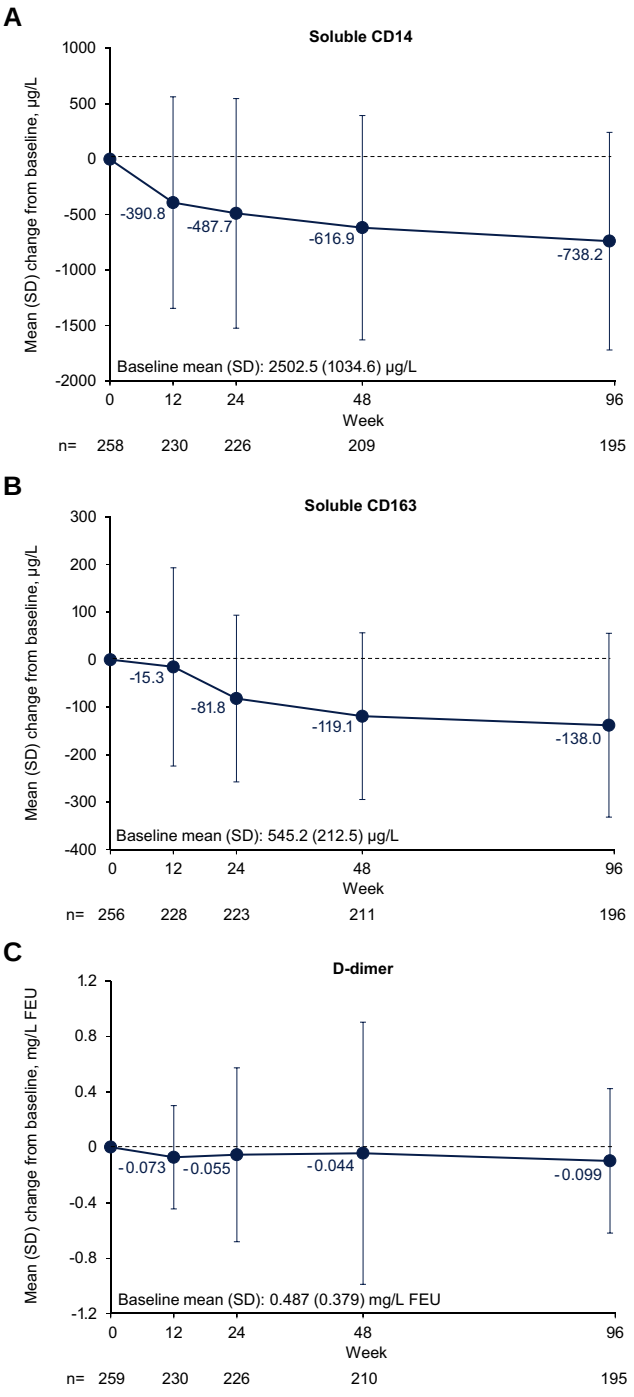

Figure 2. Mean change from baseline: *A*, soluble CD14; *B*, soluble CD163; *C*, D-dimer. Error bars represent SD. Reference range was 800 to 3200 µg/L for soluble CD14, <0.500 mg/L FEU for D-dimer, and unavailable for soluble CD163. FEU, fibrinogen-equivalent units.

prophylaxis [29]. In alignment with this, a separate BRIGHTE analysis found that participants who achieved CD4+ T-cell counts ≥200 cells/mm^3 at any time did not experience any new AIDS-defining events after week 48 and had lower rates of all-cause adverse events as compared with those who sustained CD4+ T-cell counts <200 cells/mm^3 [30].

Trends toward decreases in sCD14, sCD163, and D-dimer were also observed through 96 weeks, including participants with protocol-defined virologic failure at week 96 (n = 30 or 31). These decreases were consistent with prior observations [31–33]. For example, in studies of participants who were ART naive and initiated first-generation integrase strand transfer inhibitor–based ART and those who were virologically suppressed and switched to dolutegravir-based ART from 3- or 4-drug regimens, sCD14 decreased 5% to 16% from baseline at 48 or 96 weeks after treatment initiation or switch [31, 32, 34]. Likewise, in a phase 2b study of fostemsavir, greater and dose-proportionate reductions in sCD14 were observed among participants who were integrase strand transfer inhibitor naive and received various doses of fostemsavir + raltegravir + tenofovir disoproxil fumarate as compared with those who received boosted atazanavir + raltegravir + tenofovir disoproxil fumarate [23]. Furthermore, the 25% reduction in sCD163 in BRIGHTE was similar to observations in studies of participants who were ART naive and achieved virologic suppression and individuals who switched to second-line ART, in which mean sCD163 levels declined by ∼25% to 50% [31, 33]. Last, the 20% decline in D-dimer concentration at week 96 is consistent with values observed in participants who were ART naive, who experienced mean decreases ranging from ∼20% to 50% 96 weeks after treatment initiation [31]. In the BRIGHTE study, some subgroups (eg, female participants) showed changes in D-dimer levels that had considerable variability from baseline to week 96. This is likely attributable to the low numbers of participants with available data at certain time points and the various factors known to influence D-dimer levels, including fluctuating estrogen levels and immune activation [35].

The potential clinical significance of our findings merits additional investigation. Results from previous studies have shown that individuals in the highest quartile of plasma sCD14 concentration have a significantly increased risk of mortality (adjusted hazard ratio [aHR], 2.67; 95% CI, 1.55–4.61) [36]. Similarly, each quartile increase in sCD163 is associated with higher hazards of mortality (aHR, 1.35; 95% CI, 1.13–1.63) [7], and each 1-unit increase in D-dimer is associated with higher hazards of non-AIDS diseases (aHR, 1.43; 95% CI, 1.04–2.00) and composite events (non-AIDS diseases, AIDS, and death; aHR, 1.35; 95% CI, 1.03–1.77) [9]. This is particularly relevant in the BRIGHTE study population, which included a large proportion of persons with HIV-1 with very advanced disease; the severity of residual immune dysregulation may be more pronounced in those with more advanced disease despite achieving virologic suppression [37]. Thus, the biomarker changes observed in this study suggest a potential durable benefit of fostemsavir over a long period, including potential improvements in those with advanced disease at treatment initiation. To date, no data on biomarker changes are available for ARVs recently approved for this population (eg, ibalizumab [38] and lenacapavir [39]).

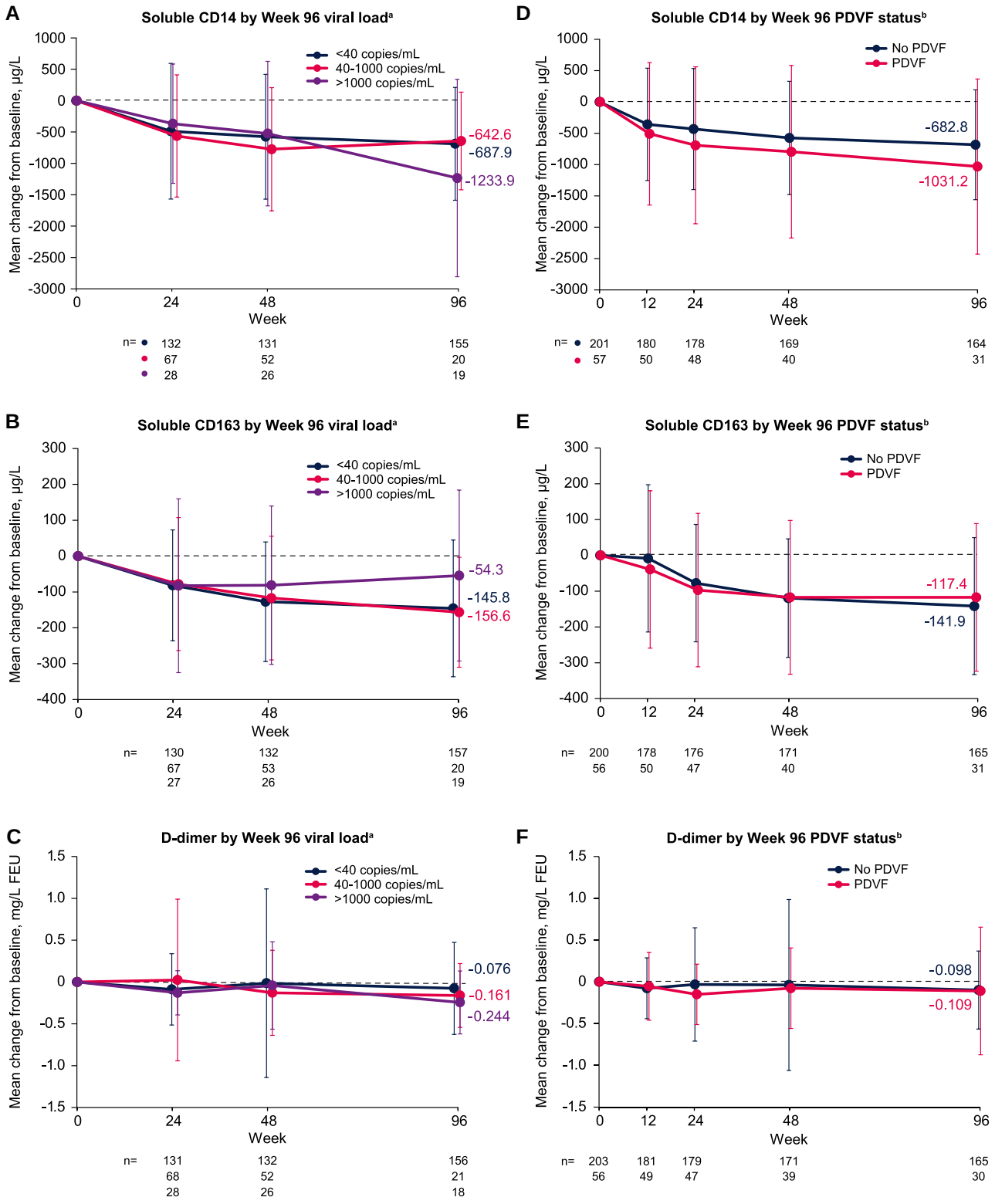

Figure 3. Mean change from baseline in soluble CD14, soluble CD163, and D-dimer by week 96: *A–C*, virologic response; *D–F*, PDVF status. [a] Low numbers of participants in some subgroups. Data not available for week 12. [b] Before week 24, PDVF was defined as HIV-1 RNA ≥400 copies/mL after confirmed suppression to <400 copies/mL or an increase >1 $\log_{10}$ copies/mL in HIV-1 RNA above a nadir level ≥40 copies/mL. At or after week 24, PDVF was defined as HIV-1 RNA ≥400 copies/mL. Error bars represent SD. FEU, fibrinogen-equivalent units; PDVF, protocol-defined virologic failure.

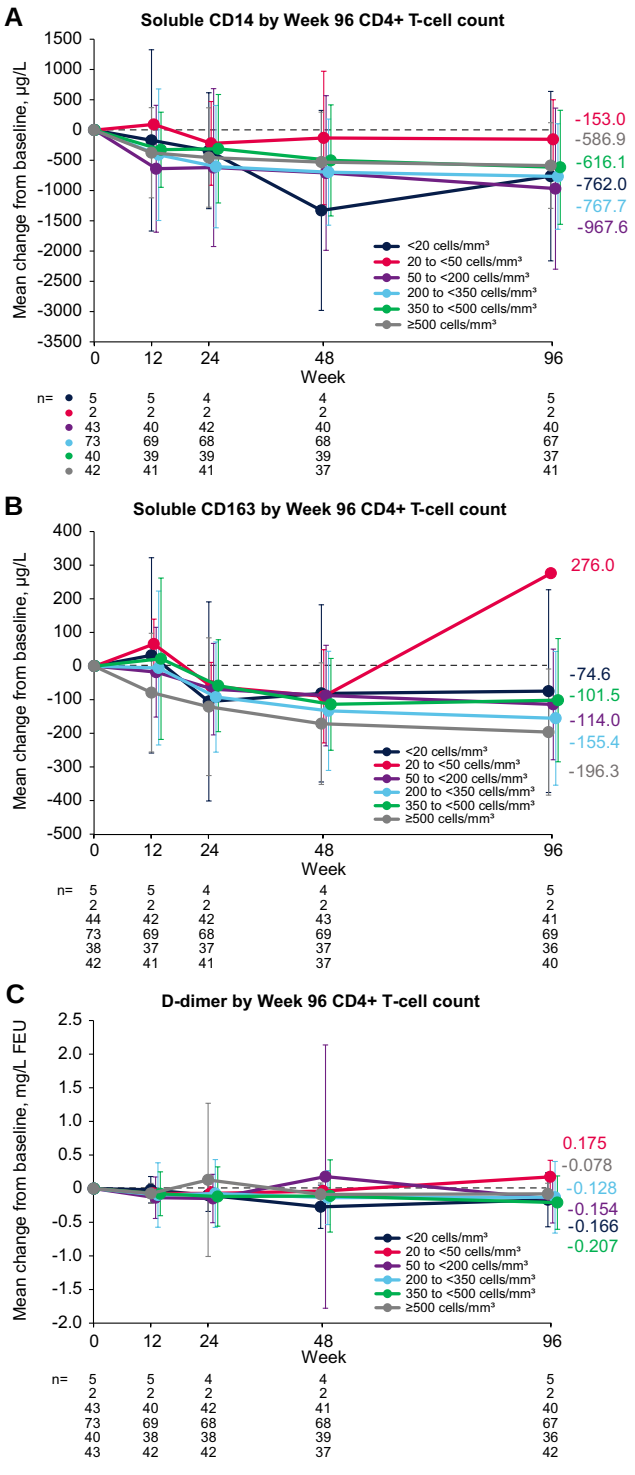

Figure 4. Mean change from baseline: *A*, soluble CD14; *B*, soluble CD163; *C*, D-dimer by week 96 CD4+ T-cell count. Conclusions drawn from these data are limited due to low numbers of participants in some subgroups. Error bars represent SD. FEU, fibrinogen-equivalent units.

Soluble gp120 is detectable in the plasma and tissues of some persons with HIV-1 on ART despite having undetectable viral loads [21, 22, 40]. This presence is associated with higher amounts of inflammatory and immunomodulatory cytokines, consistent with in vitro observations demonstrating that gp120 induces the secretion of proinflammatory cytokines and stimulates toll-like receptors due to their clustering with CCR5 and CXCR4 coreceptors [21, 40–43]. Additionally, individuals with subclinical cardiovascular disease who have detectable levels of soluble gp120 and antibodies targeting a conserved CD4-induced epitope have larger atherosclerotic plaques, suggestive of a higher risk of cardiovascular disease [40]. The higher sCD14 levels observed in persons with HIV-1 may reflect the activation of monocytes by soluble gp120 [6, 44]. Higher amounts of monocyte-derived proinflammatory cytokines such as interleukin 6 and tumor necrosis factor α are also observed [43], which are by themselves associated with higher morbidity and mortality [10, 45]. However, gp120-monocyte interactions are only 1 of several mechanisms by which HIV-1 can elicit inflammation and immune activation [46, 47]. Furthermore, sCD14 and sCD163 are secreted by other myeloid cells [48]. Temsavir could have secondary effects on inflammation-associated comorbidities in persons with HIV-1 by blocking monocyte activation via soluble gp120. In support of this possibility, in vitro investigations have shown that temsavir can block cytokine bursts from monocytes exposed to soluble gp120 and that these cytokine bursts require gp120 engagement with CD4 [44]. Yet, these observations need to be confirmed by in vivo data.

Strengths of this study include the unique population of HTE persons with HIV-1 and the broad geographic representation of study participants. The primary limitations of this study are the lack of a control group and the absence of formal statistical analyses. After an initial 8-day period, all participants received fostemsavir + OBT, prohibiting our ability to determine any direct effects of fostemsavir on inflammation and the immune response beyond its antiviral effect. Furthermore, the assessed biomarkers can be influenced by non–HIV-related factors that were not accounted for in the analysis (eg, body mass index, comorbidities, adherence, coinfections). Biomarkers were not assessed in individuals with no fully active ARVs at baseline who initiated fostemsavir, and these data would be valuable. However, we previously reported improvements in CD4+ T-cell count and CD4+/CD8+ ratio through 96 weeks in this group [18]. Additional limitations include the exploratory nature of the analysis, the small participant numbers in select subgroups, and the lack of diversity in the study population, which was primarily White and male. Yet, comparable changes in CD4 + T-cell count were observed across subgroups by age, race, and sex at birth in the BRIGHTE population [49]. HTE persons with HIV-1 may face challenges in maintaining adherence, but drug levels were not assessed and adherence was not evaluated beyond week 24.

Among participants with 1 or 2 fully active ARVs in their OBT at baseline in the BRIGHTE study, increases in CD4+

T-cell count and CD4+/CD8+ ratio were observed through 2 years of treatment with fostemsavir + OBT. This increase was coupled with a trend toward decreases in biomarkers of monocyte and macrophage activation and coagulation. Future research will aim to assess the changes in other biomarkers of systemic inflammation in HTE persons with HIV-1 treated with fostemsavir + OBT, as well as the clinical relevance of these changes, and investigate the broader pathogenic effects of gp120.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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

Patient consent statement. The BRIGHTE study was conducted in accordance with the laws and guidelines established in the 2008 Declaration of Helsinki. Approval and oversight were provided by national or regional institutional review boards or ethics committees. All participants provided written informed consent before initiation of any study procedures.

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Potential conflicts of interest. A. C., M. P., S. C., A. P., J. R. C.-M., M. W., F. D., and A. R. T. are or were employees of ViiV Healthcare or GSK at the time of the analysis and may own stock in GSK.

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