CD4 T-cell, CD4/CD8 Ratio Improvement and a General Reduction in Inflammatory Biomarkers With Low-Level Viremia (LLV) up to Week 192 With Fostemsavir (FTR)-Based Regimens in Individuals With Multidrug-Resistant (MDR) HIV-1

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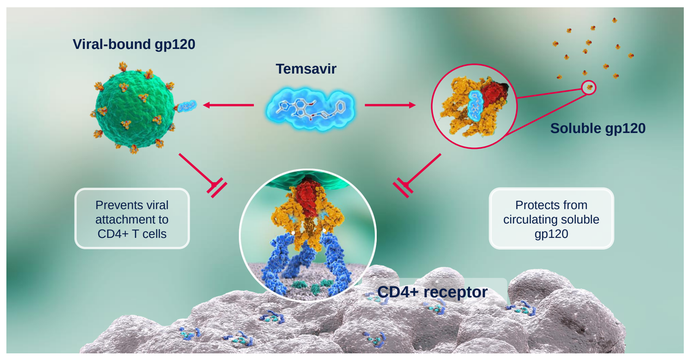
Key Takeaways

- The phase 3 BRIGHTE study evaluated fostemsavir (FTR) + optimized background therapy (OBT) in people living with multidrug-resistant HIV-1 and limited antiretroviral (ARV) options
- Immunologic improvements were observed through 4 years in participants receiving FTR in BRIGHTE, with robust improvements among those with viral suppression or low-level viremia (LLV)
- A general decrease in biomarkers of immune activation was observed in participants with viral suppression and those with LLV 40 to <400 c/mL
- Results underscore the value of FTR-based regimens for sustained improvement in immunologic parameters and selected inflammatory biomarkers in some individuals with incomplete virologic suppression

Introduction

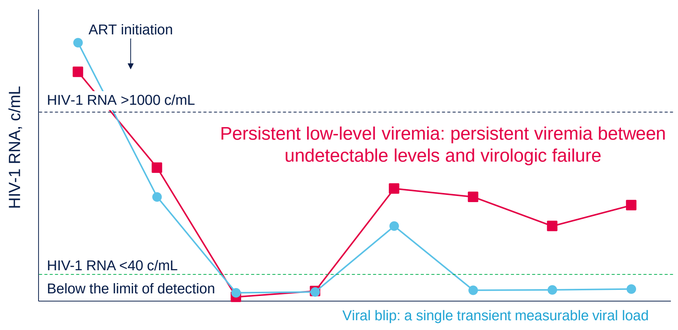
- FTR, the prodrug of the first-in-class attachment inhibitor temsavir, is indicated in combination with other ARVs for individuals with multidrug-resistant HIV-1 who are heavily treatment-experienced and unable to construct suppressive regimens[1]
- Temsavir binds to both membrane-associated and soluble HIV-1 gp120 to prevent gp120 attachment to CD4 on host cells (Figure 1)[2,3]
- Soluble gp120 has been associated with immune dysfunction, sustained inflammation, and increased cardiovascular disease risk in people living with HIV-1[4]

Figure 1. Mechanism of Action by Which Temsavir Binds to Membrane-Associated gp120 and Soluble gp120[2,3]



- Persistent low-level viremia, defined as LLV between 40 and 1000 c/mL, remains an ongoing challenge in the management of HIV-1 (Figure 2)[5]
  - LLV can be divided into lower (40 to <400 c/mL) and higher (400 to 1000 c/mL) categories and is differentiated from a viral blip, which is a single transient measurable viral load

Figure 2. Diagram of Low-Level Viremia as Differentiated From a Viral Blip



LLV has been associated with higher risk of
- Mortality[5]
- AIDS-related events/mortality[6]
- Serious non–AIDS-related events including malignancies and cardiovascular disease[5,7,8]
- Antiretroviral resistance[8]
- Virologic failure[7,9]
- Increased biomarkers of immune activation and inflammation[8]

- BRIGHTE evaluated FTR in people with multidrug-resistant HIV-1 who were heavily treatment-experienced; participants could continue FTR if they had LLV
- We assessed CD4+ T-cell recovery and biomarkers of immune activation and residual coagulopathy in participants with LLV

Methods

- BRIGHTE participants were adults with multidrug-resistant HIV-1 on a failing regimen (HIV-1 RNA ≥400 c/mL) with ≤2 fully active approved ARV classes remaining
- Participants with 1 to 2 fully active ARVs remaining were enrolled in the Randomized Cohort and randomly assigned 3:1 to receive FTR 600 mg twice daily or placebo + current failing regimen for 8 days followed by open-label FTR + OBT
- Serum or plasma concentrations of soluble (s)CD14, sCD163, and D-dimer were monitored as exploratory outcomes
- Immunologic and biomarker outcomes according to viral load category at each respective visit through Week 192 were analyzed post hoc in the Randomized Cohort
  - LLV was defined as HIV-1 RNA 40 to <400 c/mL (lower LLV) and 400 to 1000 c/mL (higher LLV)
  - Week 192 was used as the data cutoff for these analyses because subsequent results were impacted by study completion and the COVID-19 pandemic
- Immunologic outcomes and changes in biomarker concentrations were summarized using descriptive statistics

Results

Study Population

Table. Demographics and Baseline Characteristics: Randomized Cohort

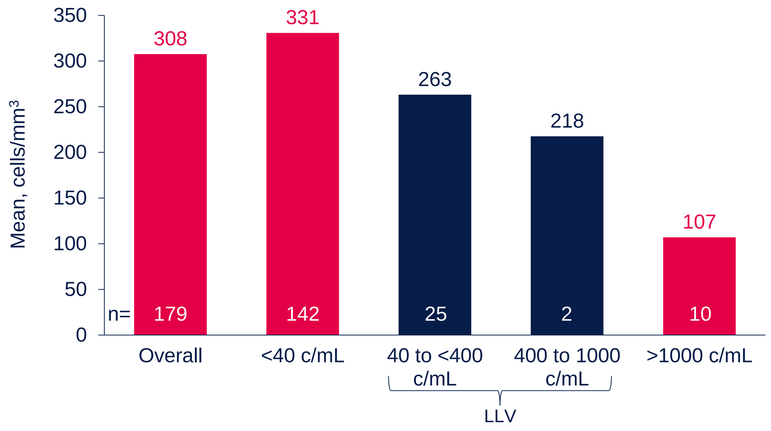
Characteristic	Randomized Cohort (N=272)	Characteristic	Randomized Cohort (N=272)
Age, n (%), y		CD4+ T-cell count, n (%), cells/mm^3	
<35	61 (22)	<350	243 (89)
35 to <50	100 (37)	350 to <500	14 (5)
≥50	111 (41)	≥500	15 (6)
Sex, n (%)		Biomarkers, mean (SD) [n]	
Male	201 (74)	sCD14, µg/L	2502.5 (1034.6) [258]
Female	71 (26)	sCD163, µg/L	545.2 (212.5) [256]
Race, n (%)		D-dimer, mg/L FEU	0.488 (0.379) [259]
Black or African American	60 (22)	No. of fully active ARVs in initial OBT, n (%)	
White	185 (68)	0	15 (6)[b]
Other races[a]	27 (10)	1	142 (52)
HIV-1 RNA, n (%), c/mL		2	115 (42)
<400	21 (8)		
400 to <1000	10 (4)		
≥1000	241 (89)		

FEU, fibrinogen-equivalent units. [a]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, individuals of multiple races, and individuals of other races. [b]Includes participants who discontinued the study during the blinded period and never started OBT, not treated with a fully active ARV in initial OBT despite having a fully active ARV available at screening, and inadvertently assigned to the Randomized Cohort despite having no fully active ARV available at screening.

Improvements in CD4+ T-cell Count

- Overall, participants in the Randomized Cohort had a steady increase in CD4+ T-cell count, with a mean (SD) increase from baseline to Week 192 of 308 (225) cells/mm^3
- Robust improvements in mean CD4+ T-cell count were observed among participants with viral suppression or LLV at Week 192 (Figure 3)

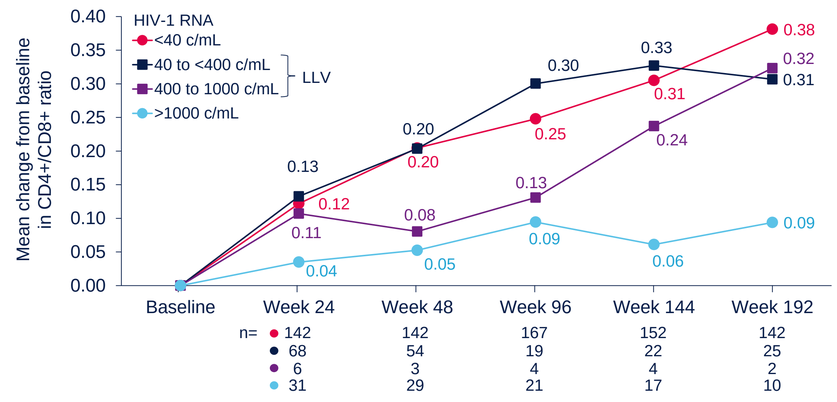
Figure 3. Mean Change From Baseline in CD4+ T-cell Count by Viral Load at Week 192: Randomized Cohort



Improvements in CD4+/CD8+ Ratio

- In the Randomized Cohort, overall mean (SD) CD4+/CD8+ ratio increased from 0.20 (0.24) at baseline to 0.56 (0.39) at Week 192
- Mean CD4+/CD8+ ratio generally improved in all viral load categories at each visit, with the most robust improvements observed in those with viral suppression or LLV (Figure 4)

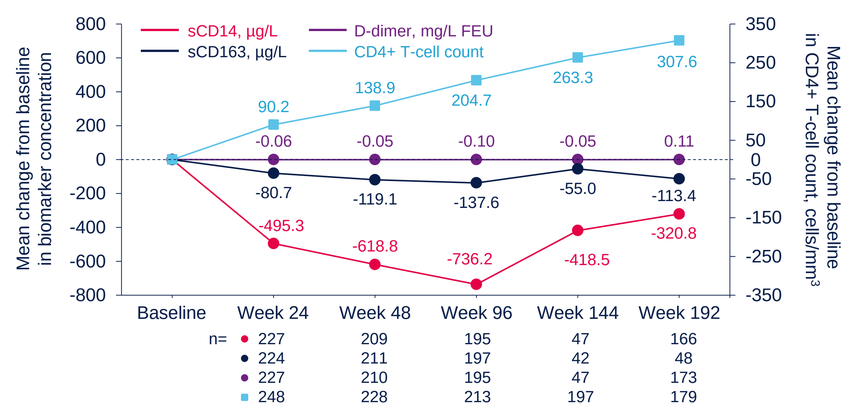
Figure 4. Mean Change From Baseline in CD4+/CD8+ Ratio by Viral Load Category at Each Respective Visit: Randomized Cohort



Inflammatory Biomarkers in the Overall Analysis

- In the overall analysis of the Randomized Cohort, mean decreases from baseline in sCD14 and sCD163 were observed through Week 192; D-dimer decreased at Weeks 24 through 144, but an increase was observed at Week 192 (Figure 5)

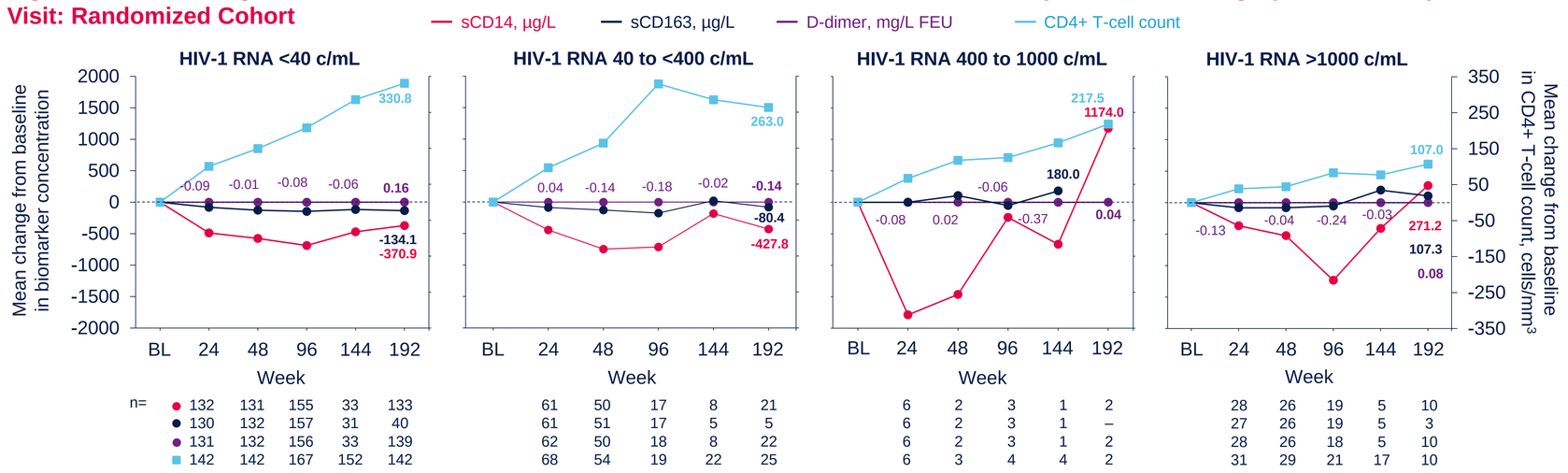
Figure 5. Mean Change From Baseline in Biomarker Concentrations and CD4+ T-cell Count in the Overall Analysis: Randomized Cohort



Inflammatory Biomarkers Across Viral Load Categories

- In the Randomized Cohort, mean change from baseline in biomarkers fluctuated with time in some viral load subgroups and varied by viral load category; in general, the greatest improvements were observed in participants with undetectable viral load and lower LLV (<400 c/mL; Figure 6)

Figure 6. Mean Change From Baseline in Biomarker Concentrations and CD4+ T-cell Count by Viral Load Category at Each Respective Visit: Randomized Cohort



Mean change in D-dimer is displayed for each week because the scale of change in D-dimer was smaller than the other biomarkers; bolded values represent the mean change at the last available time point.

Limitations

- Study limitations include no comparator group beyond the initial blinded period, variability in OBT composition, unknown level of adherence, low numbers of participants in some viral load subgroups, use of descriptive statistics, and participants with viral blips were not removed from viral load analyses

Conclusions

- Improvements in CD4+ T-cell count and CD4+/CD8+ ratio were observed through 4 years among participants receiving FTR in the BRIGHTE study, with the most robust improvements among those with viral suppression or LLV
- A general decrease in biomarkers of immune activation was observed in participants with viral suppression as well as those with LLV 40 to <400 c/mL, consistent with a decrease in systemic inflammation
- D-dimer levels slightly decreased in all viral load subgroups through Week 144 but slightly increased at Week 192 in all but the LLV 40 to <400 c/mL group, possibly representing fluctuations due to factors known to influence D-dimer levels in people living with HIV-1[10]
- These findings highlight the value of FTR-based regimens for sustained improvement in CD4+ T-cell count, CD4+/CD8+ ratio, and selected inflammatory biomarkers among some individuals with incomplete virologic suppression

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