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Immune Recovery Continues to Improve Over 5 Years With Fostemsavir Despite Emergent gp120 Substitutions

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Key Takeaways

- **In the pivotal BRIGHTE study, fostemsavir (FTR) demonstrated durable long-term efficacy in people with multidrug-resistant HIV-1. This Week 240 analysis examines whether gp120 substitutions associated with reduced FTR susceptibility affect immune reconstitution**
- **Irrespective of gp120 substitutions, participants generally experienced increases in CD4+ T-cell count, CD4+ percentage, and CD4+/CD8+ ratio through Week 240**
- **Inflammatory biomarkers were generally stabilized through 5 years and the safety profile was consistent with the broader BRIGHTE population**
- **Immune recovery with FTR is maintained despite gp120 substitutions associated with reduced susceptibility, supporting sustained immunological benefit through 5 years**

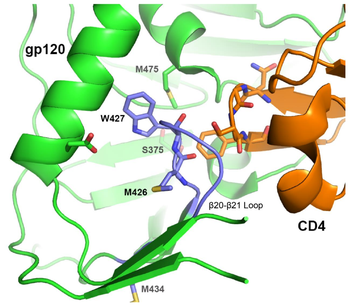
Plain Language Summary

- Fostemsavir continued to support immune recovery over 240 weeks, even in people whose HIV developed gp120 changes linked to reduced sensitivity to fostemsavir
- Key measures of immune health generally improved, including CD4+ T-cell count, CD4+ percentage, and the CD4+/CD8+ ratio, regardless of these gp120 changes
- Despite gp120 substitutions associated with reduced susceptibility, fostemsavir use demonstrated a sustained immunological benefit through Week 240

Introduction

- Fostemsavir (FTR) showed virologic and immunologic improvement in individuals with multidrug-resistant HIV in the BRIGHTE study through Week 336[1]
- Temsavir (TMR), the active metabolite of FTR, protects CD4+ T cells by 2 mechanisms[2]:
  1. Blocking HIV-1 attachment to the CD4 receptor; and
  2. Preventing soluble gp120 (sgp120)-mediated bystander CD4+ T-cell killing
- TMR also acts to prevent sgp120-mediated cytokine bursts by monocytes[2]
- Naturally occurring polymorphisms at specific gp120 positions (S375H/I/M/N/T/Y, M426L, M434I/K, M475I) have been associated with reduced viral susceptibility to TMR (Figure 1)[3-8]
  - Substitutions at these gp120 positions may also emerge with FTR treatment[4-8]
- While gp120 substitutions are associated with reduced viral susceptibility, their presence does not always lead to treatment failure[3]
- The direct impact of gp120 substitutions on long-term CD4+ T-cell recovery remains to be fully understood
- This analysis evaluated changes in immunologic and inflammatory outcomes in participants treated with FTR with treatment-emergent gp120 substitutions through Week 240

Figure 1. CD4+ Receptor Binding Site on HIV-1 gp120 and Key TMR Resistance-Associated Positions

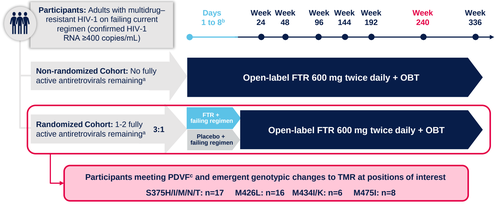


Homology model of CD4 (protein data bank code 2NXY) in brown, bound to wild-type HIV-1 JR-FL gp120, in green, with an annotation to show key amino acid positions. The β20-21 loop of gp120 separates the CD4 and TMR binding sites. Adapted from Schapiro et al.,[3] used under CC BY-NC 4.0 (https://creativecommons.org/licenses/by-nc/4.0/).

Methods

- BRIGHTE (NCT02362503) is a phase 3 study in a highly treated-experienced population with limited treatment options conducted across 22 countries
- In the Randomized Cohort (RC, n=272), participants with fully active agents in 1 or 2 remaining antiretroviral classes received FTR or placebo for 8 days, followed by open-label FTR plus optimized background therapy (OBT)
- This analysis included participants who met protocol-defined virologic failure (PDVF) and had emergent genotypic changes to TMR at positions of interest (Figure 2)
  - Data were analyzed through Week 240 as time points beyond this had only singular cases at time of analysis
  - All analyses were descriptive, and no formal comparisons were made between subgroups

Figure 2. BRIGHTE Study Design



NRC, non-randomized cohort. [a]Fully active based on susceptibility (current or historical resistance) and availability (participant is tolerant of, eligible for, and willing to take [in the case of enfuvirtide only] the antiretroviral). Use of investigational agents in OBT was permitted in the NRC. [b]Participants in the RC were randomly assigned 3:1 to receive FTR 600 mg twice daily or placebo + current failing regimen for 8 days, after which all participants received open-label FTR. [c]Before Week 24, defined as confirmed or last available HIV-1 RNA ≥400 c/mL after prior confirmed suppression to <400 c/mL or >1 $\log_{10}$ increase above nadir when nadir is ≥40 c/mL. On or after Week 24, defined as confirmed or last available HIV-1 RNA ≥400 c/mL.

Results

Study Population

- Baseline demographics and characteristics in the overall RC (n=272) and by gp120 polymorphism (n=6 to 17) are shown in Table 1
- Overall, 41% were aged ≥50 years, 26% were female, and 22% identified as Black or African American (Table 1)
- In the overall RC, participants had baseline clinical characteristics consistent with advanced HIV-1, including 73% (199/272) with a CD4+ T-cell count <200 cells/mm^3

Table 1. Demographics and Clinical Characteristics

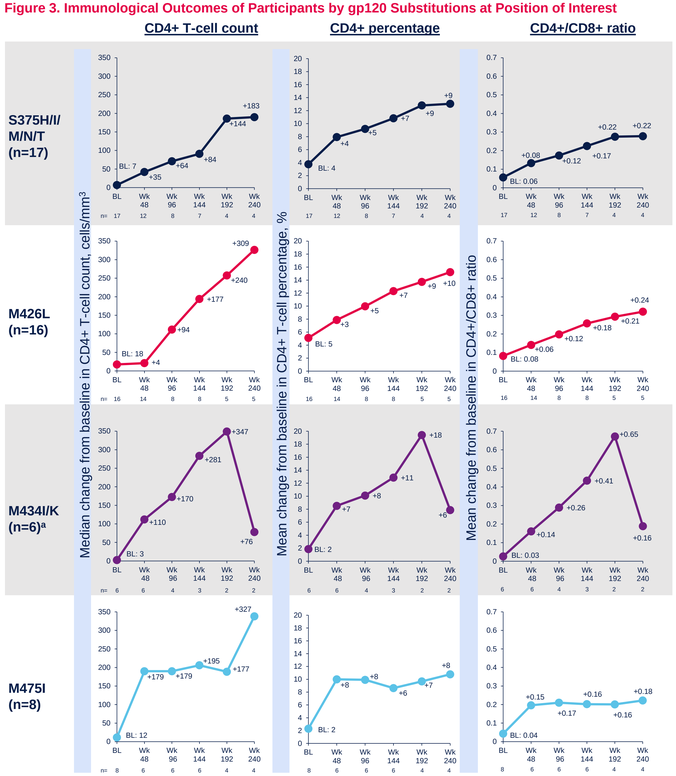
Parameter[a]	Overall RC[b] (N=272)	S375H/I/M/N/T (n=17)	M426L (n=16)	M434I/K (n=6)	M475I (n=8)
Age, years, n (%)					
<35	61 (22)	3 (18)	2 (13)	1 (17)	3 (38)
35-49	100 (37)	6 (35)	5 (31)	2 (33)	2 (25)
≥50	111 (41)	8 (47)	9 (56)	3 (50)	3 (38)
Female, n (%)	71 (26)	2 (12)	2 (13)	0	0
Race, n (%)					
Black or African American	60 (22)	3 (18)	4 (25)	0	2 (25)
White	185 (68)	10 (59)	10 (63)	5 (83)	4 (50)
Other races[c]	27 (10)	4 (24)	2 (13)	1 (17)	2 (25)
Hispanic or Latin American, n (%)[d]	79 (29)	7 (41)	3 (19)	3 (50)	6 (75)
Baseline HIV-1 RNA, median (IQR), $\log_{10}$ c/mL	4.66 (3.87-5.09)	5.02 (4.82-5.58)	5.20 (4.97-5.74)	4.97 (4.58-5.05)	5.06 (4.86-5.53)
Baseline CD4+ T-cell count, median (IQR), cells/mm^3	100 (15-207)	7 (4-30)	18 (5-90)	3 (2-4)	12 (1-33)

[a]Percentages may sum to >100% due to rounding. [b]All participants who received ≥1 dose of study treatment. [c]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, individuals of multiple races, and individuals of other races. [d]Ethnicity was only required to be collected for US participants but was recorded for some but not all non-US participants.

Immunologic Changes Over Time

- Generally, numerical increases were shown in reported immunologic outcomes (CD4+ T-cell counts, CD4+/CD8+ ratio, and CD4+ T-cell percentage; Figure 3)
- These were usually observed from baseline through Week 240 across all emergent gp120 polymorphisms, although data were variable at later time points in some subgroups due to the small and declining participant numbers

Figure 3. Immunological Outcomes of Participants by gp120 Substitutions at Position of Interest



[a]Immune outcomes at Week 240 were influenced by the few participants with data (n=2). Changes from baseline to Week 240 for the 2 participants: CD4+ T-cell count, −1 and +152 cells/mm^3; CD4+ T-cell percentage, 0% and +12%; CD4+/CD8+ ratio, 0.00 and +0.33.

Safety

- Across gp120 polymorphisms, safety was generally consistent with the broader BRIGHTE population (Table 2)[9,10]

Table 2. Summary of AEs

	S375H/I/M/N/T (n=17)	M426L (n=16)	M434I/K (n=6)	M475I (n=8)
Any AEs, n (%)	16 (94)	16 (100)	6 (100)	8 (100)
Grade 3-4 AEs, n (%)	10 (59)	4 (25)	1 (17)	4 (50)
Any SAEs, n (%)	13 (76)	9 (56)	2 (33)	5 (63)
SAEs, n	42	19	7	18
Drug-related SAEs, n	1[a]	0	0	0
Fatal SAEs, n	3[b]	1[b]	0	1[b]

AE, adverse event; SAE, serious adverse event. [a]An event of supraventricular tachycardia (n=1). [b]Fatal SAEs included viral meningoencephalitis (n=1 each for S375H/I/M/N/T and M475I), pulmonary sepsis (n=1 each for S375H/I/M/N/T and M426L), and staphylococcal sepsis (n=1 in S375H/I/M/N/T).

Inflammatory Biomarkers

- Inflammatory biomarkers associated with immune activation (sCD14 and sCD163) and residual coagulopathy (D-dimer) were generally stable through Week 240, although data were variable across subgroups, likely due to the small number of participants (Figure 4)
  - These biomarkers have been linked with increased morbidity and mortality in people with HIV-1[11-13]

Figure 4. Mean Change From Baseline in Inflammatory Biomarkers[a]



[a]Inflammatory biomarker data at Week 144 were not available for individuals with M434I/K and M475I polymorphisms.

Conclusions

- Participants receiving FTR with emergent gp120 substitutions generally experienced improvement in key immune markers (CD4+ T-cell count, CD4+/CD8+ ratio, and CD4+ T-cell percentage) through Week 240 (~5 years)
- In general, systemic inflammatory biomarkers (sCD14, sCD163, and D-dimer) were stabilized from baseline through Week 240, with variability across subgroups
- The overall long-term safety profile remained consistent with previously reported BRIGHTE data[9,10]
- Results should be interpreted with consideration of the descriptive analyses, small sample sizes, and absence of formal statistical comparisons
- These findings suggest that FTR, with its unique mechanism of action in which temsavir binds and stabilizes the gp120 envelope glycoprotein, may confer sustained immune benefits despite the presence of gp120 substitutions associated with reduced drug susceptibility

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