CLINICAL SIGNIFICANCE OF GP120 POLYMORPHISMS, TMR IC_{50} FC, AND HIV-1 SUBTYPE IN BRIGHTE

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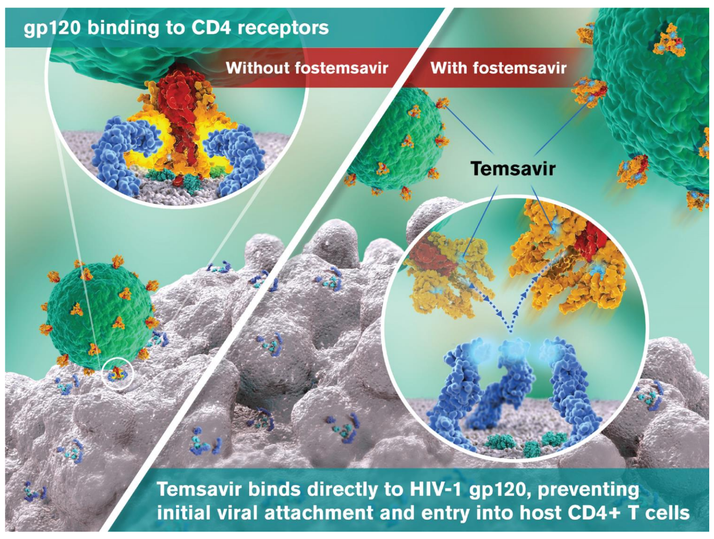
P019

Introduction

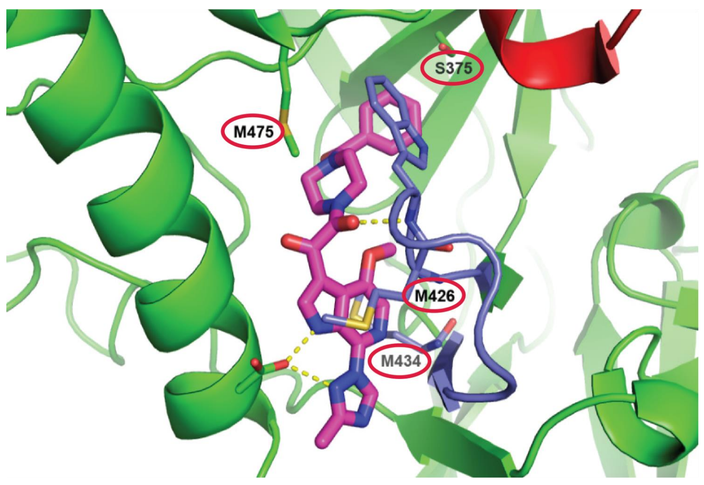
- Fostemsavir (FTR) is a prodrug of temsavir (TMR), a first-in-class attachment inhibitor approved in the United States for heavily treatment-experienced (HTE) adults living with multidrug-resistant HIV-1 who are unable to form a viable combination antiretroviral (ARV) regimen out of remaining fully active agents[1,2]
- TMR binds to HIV-1 gp120, preventing viral attachment to, and entry into, host CD4+ T cells and other immune cells (Figure 1)[1,2]

Figure 1. Mechanism of Action of TMR[1,2]



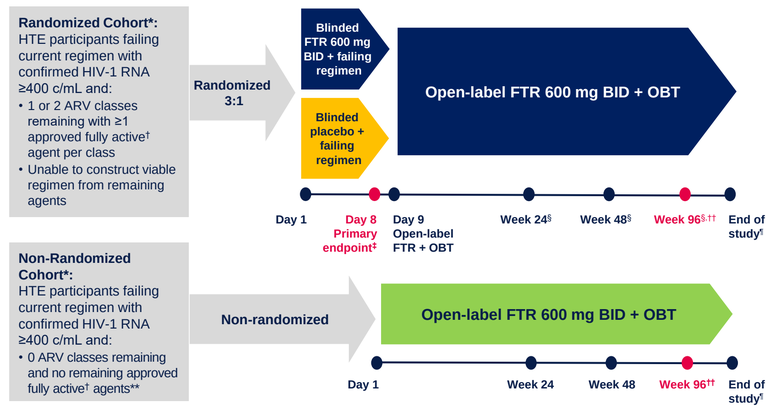
- Among clinical isolates of HIV-1, a broad (>6-log) range of in vitro susceptibility to TMR has been observed, likely due to the substantial diversity in HIV-1 gp120[3,4]
- Previous studies have identified amino acid substitutions at 4 gp120 positions that may influence HIV-1 susceptibility to TMR: S375H/I/M/N/T, M426L/P, M434I/K, and M475I (Figure 2)[4-6]
- A reliable clinical cutoff for in vitro FTR susceptibility tests has not yet been determined

Figure 2. 3D Ribbon Structure of gp120 Bound to TMR[7]



- BRIGHTE (NCT02362503; Figure 3) is an ongoing phase 3 study investigating the efficacy and safety of FTR plus optimized background therapy (OBT) in HTE individuals who were failing their current regimen (confirmed HIV-1 RNA ≥400 c/mL)[1,2]
- Here we present the impact of key baseline (BL) factors including gp120 polymorphisms, TMR IC_{50} fold-change (FC), and HIV-1 subtype on short-term virologic outcomes and durability of response to FTR in the Randomized Cohort (RC)

Figure 3. Study Design



***There were no screening temsavir IC_{50} 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] the ARV). ‡FTR demonstrated superior efficacy compared with placebo after 8 days of functional monotherapy. §Measured from the start of open-label FTR 600 mg BID + OBT. The last participant initiated OBT in August 2016. ¶The study is expected to be conducted until an additional option, rollover study, or marketing approval is in place. **Use of investigational agents as part of OBT was permitted. ††Week 96 database lock August 14, 2018. ClinicalTrials.gov identifier: NCT02362503; EudraCT number: 2014-002111-41.

Methods

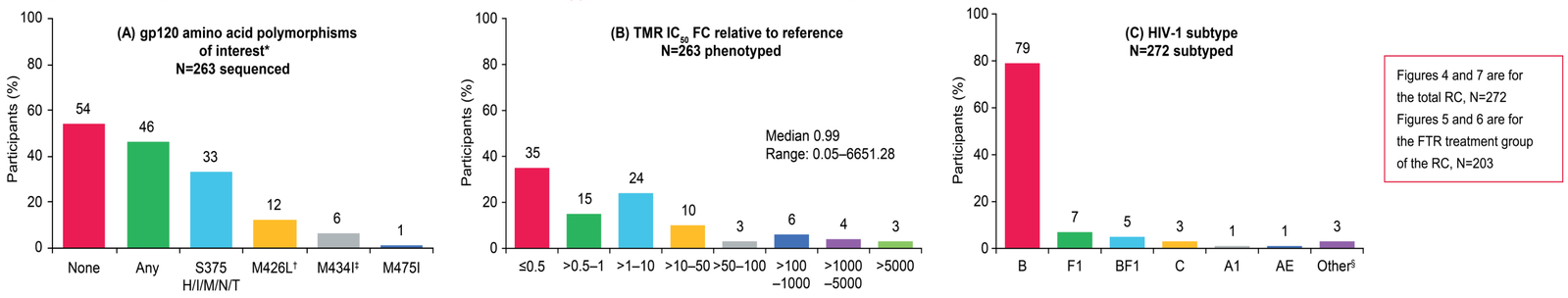
- RC participants, with fully active ARVs available in 1-2 classes, were randomized (3:1) to blinded FTR 600 mg (n=203) or placebo (n=69) twice daily (BID) plus failing regimen for 8 days of functional monotherapy, followed by open-label FTR 600 mg BID plus OBT (N=272)
- Impact of BL factors (gp120 polymorphisms, TMR IC_{50} FC relative to reference virus [IC_{50} ~1 nM], OSS of the failing regimen, and HIV-1 subtype) on changes in HIV-1 RNA from Day 1 to 8, proportion of participants with a clinically relevant (>0.5 log_{10}) decrease in HIV-1 RNA at Day 8, and virologic response (HIV-1 RNA <40 c/mL) by FDA Snapshot analysis[8] at Week 96 were evaluated

Table 1. Plasma HIV-1 RNA Log_{10} (c/mL) Change From Day 1 to Day 8 by Susceptibility of ARVs in the Failing Regimen at Baseline (Randomized Cohort)

	FTR 600 mg BID			Placebo		
Baseline OSS[a]	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Overall[b]	195	−0.816 (0.722)	−0.908 (−1.336, −0.314)	65	−0.168 (0.637)	−0.015 (−0.248, 0.159)
0	55	−0.833 (0.749)	−1.030 (−1.357, −0.317)	16	0.119 (0.600)	0.080 (−0.077, 0.256)
>0 to 1	76	−0.773 (0.747)	−0.932 (−1.362, −0.096)	28	−0.046 (0.524)	0.052 (−0.161, 0.280)
>1 to 2	27	−0.847 (0.708)	−0.851 (−1.324, −0.211)	6	−0.423 (0.340)	−0.359 (−0.570, −0.241)
>2	30	−0.828 (0.666)	−0.761 (−1.235, −0.562)	13	−0.555 (0.734)	−0.214 (−0.911, −0.052)
Missing[c]	7	−0.969 (0.692)	−1.092 (−1.254, −0.410)	2	−0.896 (0.994)	−0.896 (−1.599, −0.193)

ARV, antiretroviral; OSS, overall susceptibility score; SR, susceptibility rating. [a]OSS is the sum of SR for ARVs in the failing regimen at baseline. PhenoSense GT® Plus Integrase (net assessment) SR = 1 (sensitive), 0.5 (partially sensitive), 0 (resistant); PhenoSense Entry assay (enfuvirtide) SR = 1 (susceptible), 0 (reduced susceptibility); Trofile assay (maraviroc) SR = 1 (CCR5 antagonist activity "YES"), 0 (activity "NO"). [b]Includes participants for whom data describing HIV-1 RNA change from Day 1 to Day 8 are available. [c]Susceptibility score is missing if any component of a participant's failing regimen is not sequenced or if the participant is missing a baseline test.

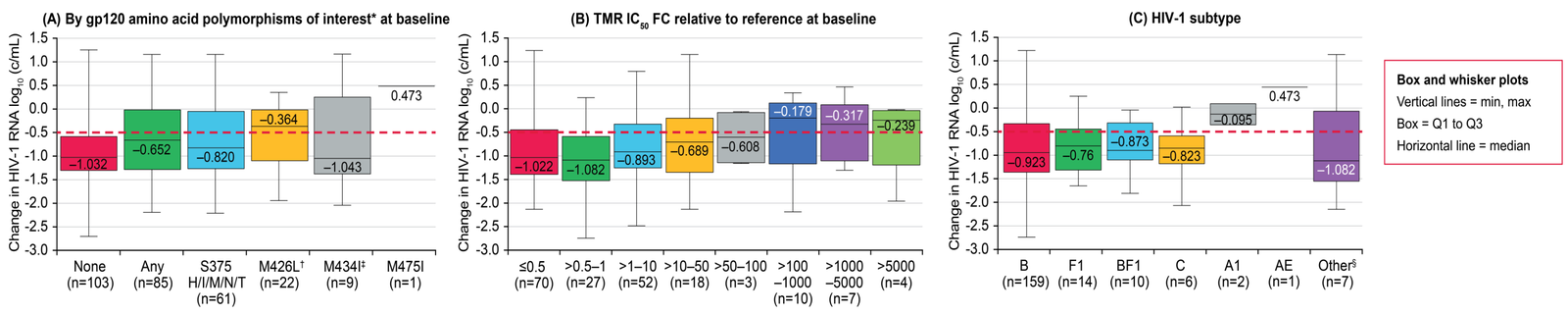
Figure 4. BL Characteristics of Evaluable Participants: (A) gp120 Polymorphisms of Interest, (B) TMR IC_{50} FC, and (C) HIV-1 Subtype



Figures 4 and 7 are for the total RC, N=272
Figures 5 and 6 are for the FTR treatment group of the RC, N=203

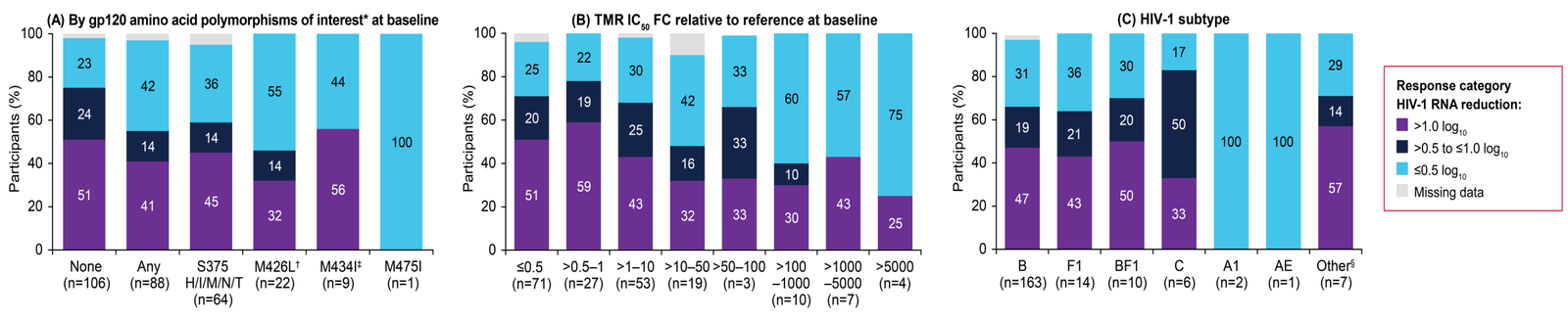
Footnotes for Figures 4-7: *S375H/I/M/N/T, M426L/P, M434I/K, and M475I. Numbers include mixtures. †No M426P was detected. ‡No M434K was detected. §Other includes non-analyzable/not reported, G, AG, or recombinant virus/mixtures.

Figure 5. Change in HIV-1 RNA from Day 1 at Day 8 in FTR Group by (A) BL gp120 Polymorphisms of Interest, (B) BL TMR IC_{50} FC, and (C) HIV-1 Subtype



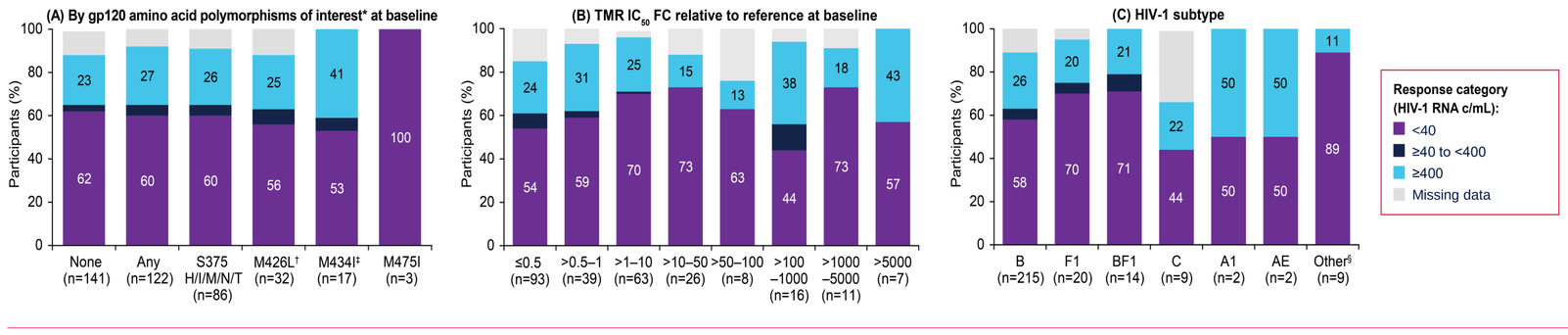
Box and whisker plots
Vertical lines = min, max
Box = Q1 to Q3
Horizontal line = median

Figure 6. Virologic Response Category at Day 8 in FTR Group by (A) BL gp120 Polymorphisms of Interest, (B) BL TMR IC_{50} FC, and (C) HIV-1 Subtype



Response category HIV-1 RNA reduction:
- >1.0 log_{10}
- >0.5 to ≤1.0 log_{10}
- ≤0.5 log_{10}
- Missing data

Figure 7. Virologic Response Category at Week 96 (Snapshot Analysis) by (A) BL gp120 Polymorphisms of Interest, (B) BL TMR IC_{50} FC, and (C) HIV-1 Subtype



Response category (HIV-1 RNA c/mL):
- <40
- ≥40 to <400
- ≥400
- Missing data

Results

- Among evaluable participants in the RC at BL (Figure 4)
  - 46% (122/263) had a relevant gp120 polymorphism present
  - There was a broad range of TMR IC_{50} FC (0.05 to >5000; median 0.99-fold)
  - 74% (195/263) and 87% (229/263) had TMR IC_{50} FC <10 and <100, respectively
  - The majority (79%, 216/272) had HIV-1 subtype B virus
- At Day 8 of functional monotherapy (Figures 5 and 6)
  - Participants on blinded FTR who had failing regimen overall susceptibility score (OSS) = 0 had mean decline in HIV-1 RNA at Day 8 consistent with the overall study population and equal to those with a failing regimen OSS >2 (Table 1)
    - Among blinded placebo participants, only those with failing regimen OSS >2 had a clinically meaningful mean decline (>0.5 log_{10}) in HIV-1 RNA
  - Median change in HIV-1 RNA was smaller among participants with BL gp120 polymorphisms of interest (−0.65 log_{10}) vs without (−1.03 log_{10}); however, 55% (48/88) of participants with BL gp120 polymorphisms achieved a viral load reduction >0.5 log_{10}
  - Participants with BL TMR IC_{50} FC >100 had a median change in HIV-1 RNA of <0.5 log_{10} at Day 8; however, 38% (8/21) of participants with BL TMR IC_{50} FC >100 achieved >0.5 log_{10} decline
  - Similar proportions of participants with subtype B (66%, 108/163) vs non-B (65%, 26/40) achieved >0.5 log_{10} decline in HIV-1 RNA, although the number of participants with non-B subtypes, including AE, was small (n=40 and n=1, respectively)
    - Consistent with previous observations,[3] the gp120 of the subtype AE virus carried both S375H and M475I and this participant had no reduction in HIV-1 RNA at Day 8
- At Week 96 of open-label FTR + OBT (Figure 7)
  - The proportions of participants with HIV-1 RNA <40 c/mL were comparable across all BL factors evaluated

Conclusions

- In the Randomized Cohort of HTE participants in the BRIGHTE trial
  - There was a broad range of TMR IC_{50} FC at baseline but most (87%) were <100
  - Increased baseline TMR IC_{50} FC, or the presence of predefined gp120 polymorphisms at positions of interest, did not preclude participants from achieving a reduction in HIV-1 RNA of >1 log_{10} c/mL at Day 8 and did not impact durability of response (HIV-1 RNA <40 c/mL) to FTR + OBT through Week 96 of therapy
  - Virologic response at Day 8 of FTR functional monotherapy and at subsequent time points on FTR + OBT (Week 96) was not reliably predicted by baseline factors (genotypic, phenotypic, or HIV-1 subtype), but remained highly context dependent
- Results confirm that in participants receiving FTR functional monotherapy, improved reduction in HIV-1 RNA at Day 8 is attributable to the contribution of FTR, rather than the retained activity of the background therapy

Please join us on Thursday, 8th October, for one of the two live Meet the Experts Q&A sessions with our senior medical experts around our most recent data presented at HIV Glasgow 2020.

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References: 1. Kozal et al. *N Engl J Med.* 2020;382:1232-1243. **2.** Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102. **3.** Nowicka-Sans et al. *Antimicrob Agents Chemother.* 2012;56:3498-3507. **4.** Zhou et al. *J Antimicrob Chemother.* 2014;69:573-581. **5.** Ray et al. *J Acquir Immune Defic Syndr.* 2013;64:7-15. **6.** Lataillade et al. *J Acquir Immune Defic Syndr.* 2018;77:299-307. **7.** Pancera et al. *Nat Chem Biol.* 2017;13:1115-1122. **8.** FDA. www.fda.gov/regulatory-information/search-fda-guidance-documents/human-immunodeficiency-virus-1-infection-developing-antiretroviral-drugs-treatment. Accessed January 27, 2020.

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