Clinical Significance of gp120 Polymorphisms, TMR IC_{50} FC, and HIV-1 Subtype in BRIGHTE

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Introduction

- Fostemsavir (FTR) is a prodrug of temsavir (TMR), a first-in-class, investigational attachment inhibitor being developed for heavily treatment-experienced (HTE) adults living with multi-drug–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]
- 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 cut-off for *in vitro* FTR susceptibility tests has not yet been determined.

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

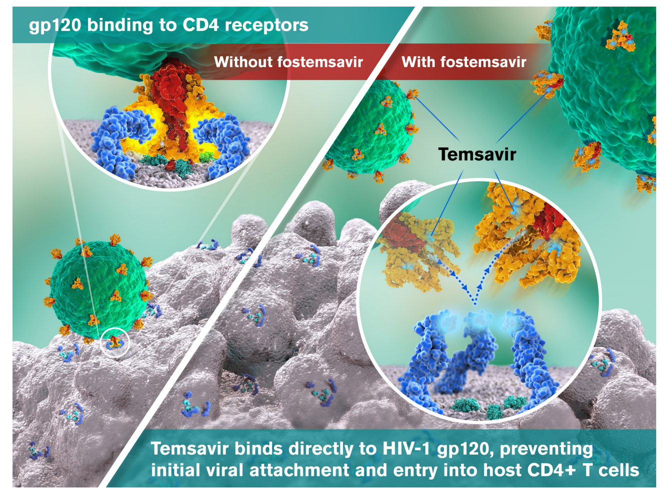
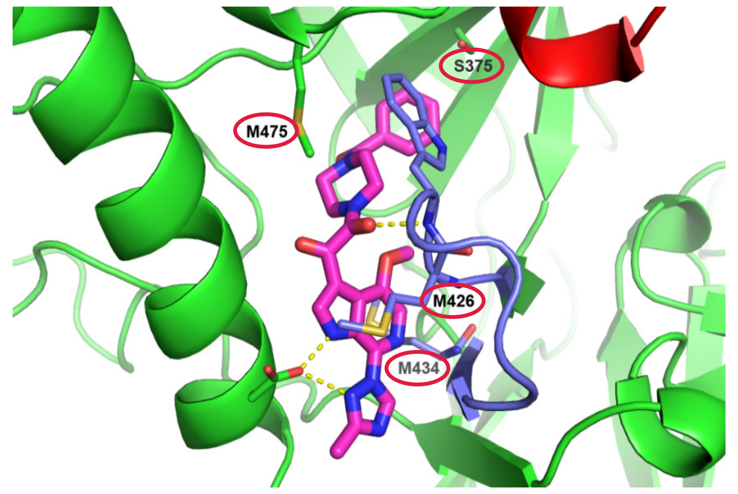
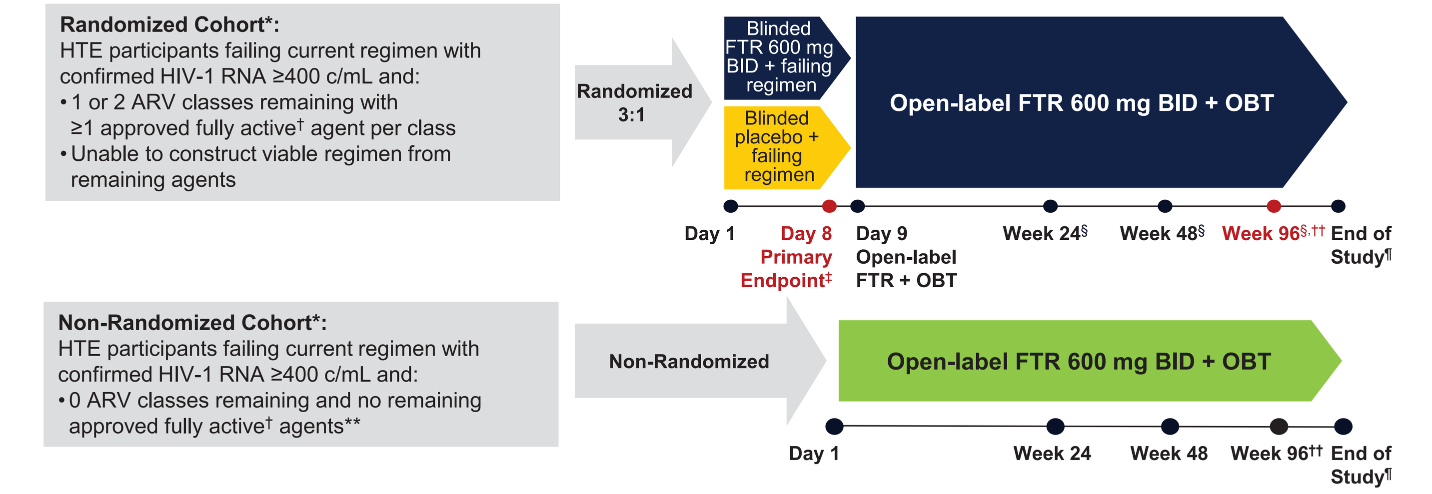

gp120 binding to CD4 receptors
Without fostemsavir
With fostemsavir
Temsavir
Temsavir binds directly to HIV-1 gp120, preventing initial viral attachment and entry into host CD4+ T cells

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


S375
M475
M426
M434

- 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

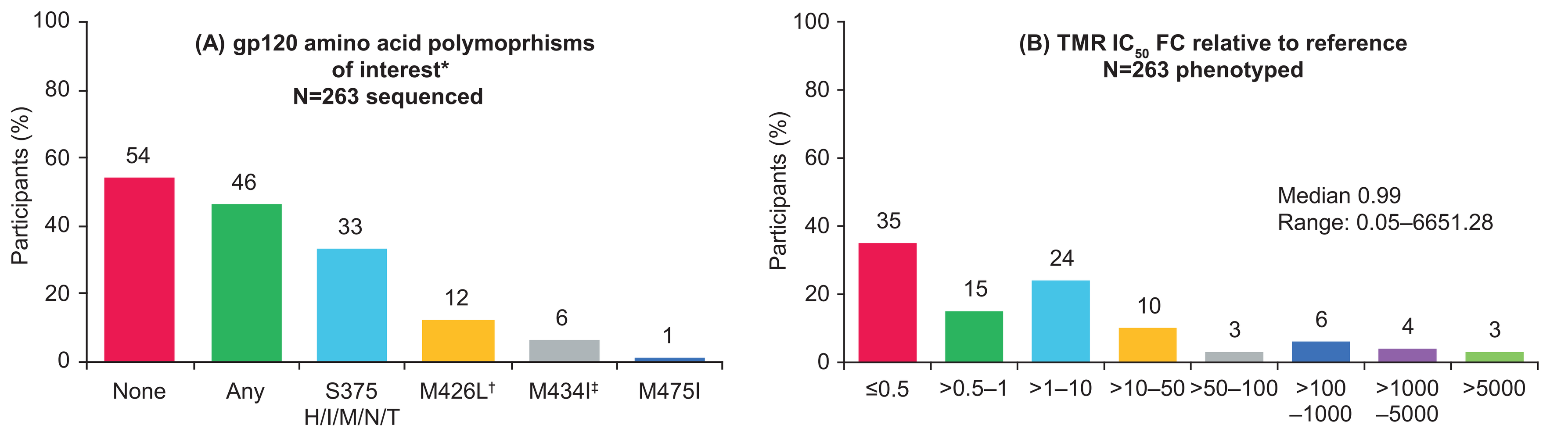

Randomized Cohort*:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
• 1 or 2 ARV classes remaining with ≥1 approved fully active† agent per class
• Unable to construct viable regimen from remaining agents
Randomized 3:1
Blinded FTR 600 mg BID + failing regimen
Blinded placebo + failing regimen
Open-label FTR 600 mg BID + OBT
Day 1
Day 8 Primary Endpoint‡
Day 9 Open-label FTR + OBT
Week 24§
Week 48§
Week 96§,††
End of Study¶
Non-Randomized Cohort*:
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
• 0 ARV classes remaining and no remaining approved fully active† agents**
Non-Randomized
Open-label FTR 600 mg BID + OBT
Day 1
Week 24
Week 48
Week 96††
End of Study¶

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).
- The impacts of BL factors (gp120 polymorphisms, TMR IC_{50} FC relative to reference virus, 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.

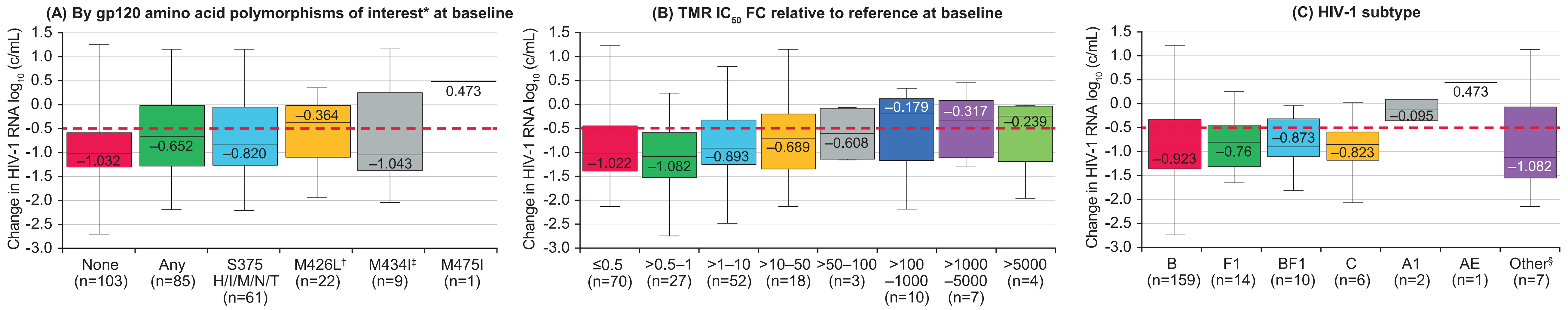
Figure 4. BL Characteristics of Evaluable Participants (A) gp120 Polymorphisms of Interest (B) TMR IC_{50} FC (C) HIV-1 Subtype


(A) gp120 amino acid polymoprhisms of interest* N=263 sequenced
Participants (%)
54 None
46 Any
33 S375 H/I/M/N/T
12 M426L†
6 M434I‡
1 M475I
(B) TMR IC50 FC relative to reference N=263 phenotyped
Median 0.99
Range: 0.05–6651.28
35 ≤0.5
15 >0.5–1
24 >1–10
10 >10–50
3 >50–100
6 >100–1000
4 >1000–5000
3 >5000
(C) HIV-1 subtype N=272 subtyped
79 B
7 F1
5 BF1
3 C
1 A1
1 AE
3 Other§

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

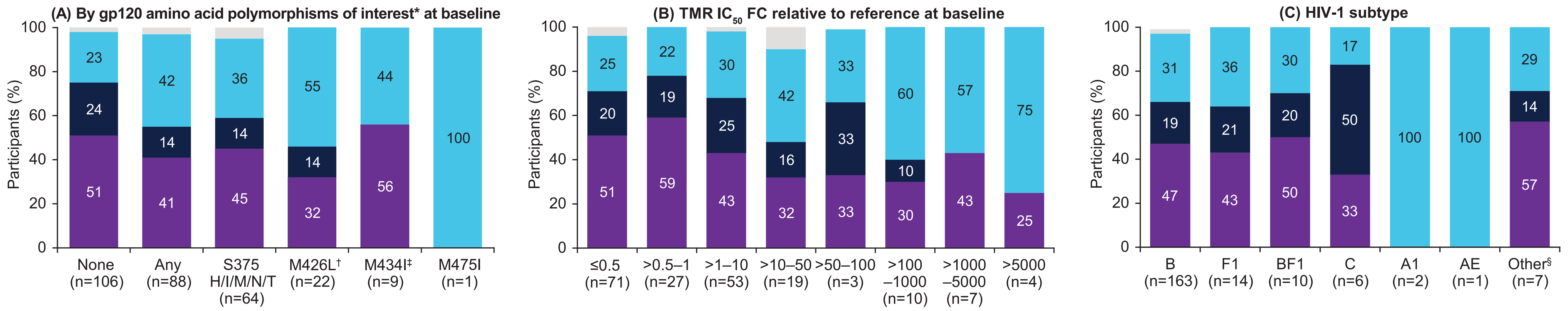
Footnotes for Figures 4 to 7: *S375H/I/M/N/T, M426L/P, M434I/K, and M475I. Numbers include mixtures. †No M426P was detected. ‡No M434K was detected. §Other includes: non-analyzable/not reported, G, AG or recombinant virus/mixtures.

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


(A) By gp120 amino acid polymorphisms of interest* at baseline
Change in HIV-1 RNA log10 (c/mL)
None (n=103) –1.032
Any (n=85) –0.652
S375 H/I/M/N/T (n=61) –0.820
M426L† (n=22) –0.364
M434I‡ (n=9) –1.043
M475I (n=1) 0.473
(B) TMR IC50 FC relative to reference at baseline
≤0.5 (n=70) –1.022
>0.5–1 (n=27) –1.082
>1–10 (n=52) –0.893
>10–50 (n=18) –0.689
>50–100 (n=3) –0.608
>100 –1000 (n=10) –0.179
>1000 –5000 (n=7) –0.317
>5000 (n=4) –0.239
(C) HIV-1 subtype
B (n=159) –0.923
F1 (n=14) –0.76
BF1 (n=10) –0.873
C (n=6) –0.823
A1 (n=2) –0.095
AE (n=1) 0.473
Other§ (n=7) –1.082

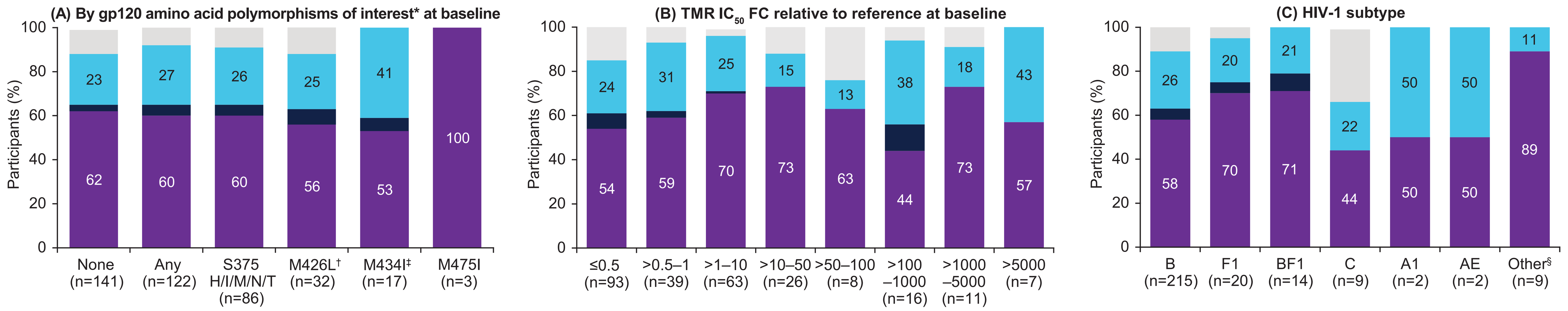
Box and whisker plots
Vertical lines = min, max
Box = Q1 to Q3
Horizontal line = median

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


(A) By gp120 amino acid polymorphisms of interest* at baseline
Participants (%)
None (n=106) 51 24 23
Any (n=88) 41 14 42
S375 H/I/M/N/T (n=64) 45 14 36
M426L† (n=22) 32 14 55
M434I‡ (n=9) 56 44
M475I (n=1) 100
(B) TMR IC50 FC relative to reference at baseline
≤0.5 (n=71) 51 20 25
>0.5–1 (n=27) 59 19 22
>1–10 (n=53) 43 25 30
>10–50 (n=19) 32 16 42
>50–100 (n=3) 33 33 33
>100 –1000 (n=10) 30 10 60
>1000 –5000 (n=7) 43 57
>5000 (n=4) 25 75
(C) HIV-1 subtype
B (n=163) 47 19 31
F1 (n=14) 43 21 36
BF1 (n=10) 50 20 30
C (n=6) 33 50 17
A1 (n=2) 100
AE (n=1) 100
Other§ (n=7) 57 14 29

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 (C) HIV-1 Subtype


(A) By gp120 amino acid polymorphisms of interest* at baseline
Participants (%)
None (n=141) 62 23
Any (n=122) 60 27
S375 H/I/M/N/T (n=86) 60 26
M426L† (n=32) 56 25
M434I‡ (n=17) 53 41
M475I (n=3) 100
(B) TMR IC50 FC relative to reference at baseline
≤0.5 (n=93) 54 24
>0.5–1 (n=39) 59 31
>1–10 (n=63) 70 25
>10–50 (n=26) 73 15
>50–100 (n=8) 63 13
>100 –1000 (n=16) 44 38
>1000 –5000 (n=11) 73 18
>5000 (n=7) 57 43
(C) HIV-1 subtype
B (n=215) 58 26
F1 (n=20) 70 20
BF1 (n=14) 71 21
C (n=9) 44 22
A1 (n=2) 50 50
AE (n=2) 50 50
Other§ (n=9) 89 11

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**):
 - Median change in HIV-1 RNA was smaller among participants with vs. without BL gp120 polymorphisms of interest (–0.65 $\log_{10}$ vs. –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) HIV-1 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 heavily-treatment-experienced participants in the BRIGHTE trial:
 - There was a broad range of TMR IC_{50} FC at baseline but most (87%) were <100-fold.
 - 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 timepoints on FTR + OBT (Week 96) was not reliably predicted by baseline factors (genotypic, phenotypic, or HIV-1 subtype), but remained highly context dependent.

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