Introduction

Tamsavir (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 who are unable to form a viable combination antiretroviral (ARV) regimen out of remaining fully active agents.2,3

TMR binds to HIV-1 gp120, preventing viral attachment to, and entry into, host CD4+ T cells and other immune cells (Figures 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 gp120.4

Previous studies have identified amino acid substitutions at 4-gp120 positions that may influence HIV-1 susceptibility to TMR: S373T/HMM4, M426L/PLP, M434I/K, and M475I (Figure 2).4

A robust clinical cutoff for in vitro susceptibility tests has not yet been determined.

CLINICAL SIGNIFICANCE OF GP120 POLYMORPHISMS, TMR IC50 FC, AND HIV-1 SUBTYPE IN BRIGHTE

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Table 1. Plasma HIV-1 RNA Log10 (c/mL) Change From Day 1 to Day 8 by Susceptibility of ARVs in the Failing Regimen at Baseline (Randomized Cohort)

<table>
<thead>
<tr>
<th>Baseline OSS</th>
<th>n</th>
<th>FTR 600 mg BID</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Overall</td>
<td>195</td>
<td>-0.816 (0.722)</td>
<td>-0.908 (-1.336, -0.314)</td>
</tr>
<tr>
<td>0</td>
<td>55</td>
<td>-0.833 (0.749)</td>
<td>-1.030 (-1.357, -0.317)</td>
</tr>
<tr>
<td>&gt;0 to 1</td>
<td>76</td>
<td>-0.773 (0.747)</td>
<td>-0.932 (-1.362, -0.096)</td>
</tr>
<tr>
<td>&gt;1 to 2</td>
<td>27</td>
<td>-0.847 (0.708)</td>
<td>-0.851 (-1.324, -0.211)</td>
</tr>
<tr>
<td>≥3</td>
<td>30</td>
<td>-0.828 (0.666)</td>
<td>-0.761 (-1.235, -0.562)</td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
<td>-0.969 (0.692)</td>
<td>-1.092 (-1.254, -0.410)</td>
</tr>
</tbody>
</table>

Table 2. Median IC50 (μM) and Corresponding 95% Confidence Interval of TMR Plus OBT (FTR) vs Placebo Plus OBT at Week 96 by HIV-1 Subtype

<table>
<thead>
<tr>
<th>HIV-1 Subtype</th>
<th>Median IC50 (μM) (95% CI)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>CCR5 antagonist</td>
<td>2.5 (1.0, 5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-CCR5 antagonist</td>
<td>2.5 (1.0, 5.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 3. Study Design

Figure 4. BL Characteristics of Evaluate Participants:
(A) gp120 Polymorphisms of Interest, (B) TMR IC50 FC, and (C) HIV-1 Subtype

Figure 5. Change in HIV-1 RNA from Day 1 at Day 8 in FTR Group by (A) BL gp120 Polymorphisms of Interest, (B) TMR IC50 FC, and (C) HIV-1 Subtype

Figure 6. Virologic Response Category at Day 8 in FTR Group by (A) BL gp120 Polymorphisms of Interest, (B) TMR IC50 FC, and (C) HIV-1 Subtype

Figure 7. Virologic Response Category at Week 96 (Snapshot Analysis) by (A) BL gp120 Polymorphisms of Interest, (B) TMR IC50 FC, and (C) HIV-1 Subtype

Conclusions

The randomized cohort of HTE participants in the BRIGHTE trial:

- There was a broad range of TMR IC50 FC at baseline but most (87%) were <100 μM.
- Increased baseline TMR IC50 FC, or the presence of preexisting gp120 polymorphisms at positions of interest, did not preclude participants from achieving a reduction in HIV-1 RNA of >1 log10 at Day 8 and did not impact durability of response (HIV-1 RNA <40 c/mL).
- Virologic response at Day 8 of TMR functional monotherapy and at subsequent time points on FTR + OBT (Week 96) was not significantly impacted by baseline IC50 or SA.

Results confirm that in participants receiving TMR functional monotherapy, improving the phenotype of an HIV-1 IC50 <400 μM attributable to the contribution of FTR, rather than the retained activity of the background therapy.

References

2. Plummer WD, Jr. HIV Drug Therapy Glasgow 2020; October 5-8, 2020; Glasgow, Scotland.

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.