High Level of Pre-existing NRTI Resistance Prior to Switching to B/F/TAF

Study GS-US-380-4030

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Introduction

- Treatment guidelines recommend triple therapy with INSTIs including B/F/TAF and DTG + F/TAF as preferred initial regimens (EACS, DHHS, IAS-USA)

- Newer INSTIs (Dolutegravir, Bictegravir): potent, well tolerated, OD dosing, no food requirement, few drug-drug interactions

- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is approved for the treatment of HIV-1 infection (treatment-naïve and virologically suppressed without resistance)¹,²

- B/F/TAF safety, efficacy, and lack of emergent resistance have been demonstrated in controlled clinical trials³⁻¹⁰
Introduction

- Treatment guidelines recommend triple therapy with INSTIs including B/F/TAF and DTG + F/TAF as preferred initial regimens (EACS, DHHS, IAS-USA)

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- B/F/TAF safety, efficacy, and lack of emergent resistance have been demonstrated in controlled clinical trials  

Does switching from DTG + F/TAF or F/TDF to the single tablet regimen B/F/TAF provide comparable virologic control in patients with or without pre-existing resistance?

DTG, dolutegravir; F/TAF, emtricitabine/tenofovir alafenamide; F/TDF, emtricitabine/tenofovir disoproxil fumarate; INSTI, Integrase Strand Transfer Inhibitor; OD, once daily

Study 380-4030: Design

- Phase 3, randomised, double-blind, multi-centre, active-controlled study

HIV-suppressed adults on regimen containing DTG + F/TAF or F/TDF
- HIV-1 RNA <50 copies/mL for ≥ 3 or 6 months*
- No documented INSTI resistance or virological failure on INSTI containing regimen

*6 months if known NRTI resistance

Primary Endpoint
HIV-1 RNA ≥ 50c/mL
(4% non-inferiority margin)

ClinicalTrials.gov: NCT03110380

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**Primary Endpoint**

HIV-1 RNA ≥ 50c/mL (4% non-inferiority margin)

<table>
<thead>
<tr>
<th>Week 0</th>
<th>W12 IDMC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=284</td>
<td>B/F/TAF 50/200/25 mg OD</td>
</tr>
<tr>
<td>n=281</td>
<td>DTG + F/TAF Placebo OD</td>
</tr>
</tbody>
</table>

**Randomisation stratified by:**

- F/TAF vs F/TDF at baseline
- Documented or suspected history of NRTI resistance

**ClinicalTrial.gov:** NCT03110380

*Pre-specified Analysis by the IDMC, Independent Data Monitoring Committee*
Methods: Baseline NRTI resistance categories

- At randomisation, the Investigator assigned the resistance category based upon HIV-1 historical genotype if available, and antiretroviral treatment history for “suspected” resistance.
- NRTI resistance was stratified into 3 categories. For participants that qualified for more than one resistance category, stratification was prioritised by category 1, then 2, then 3:
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NRTI resistance was stratified into 3 categories. For participants that qualified for more than one resistance category, stratification was prioritised by category 1, then 2, then 3:

**Category 1**
- K65R/E/N
- ≥ 3 TAMs (including M41L or L210W)
- T69 insertions

**Category 2**
- M184I/V
- Other TAM patterns
- K70E/G/M/Q/S/T, L74V/I, V75A/S/M/T, Y115F, T69D, or Q151M

**Category 3**
- No mutations

High NRTI Resistance
Low/Other NRTI Resistance
No NRTI Resistance

TAMs are M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/R/N

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Methods

• Final resistance categories were assigned post-randomisation, based on:
  • historical data
  • Investigator suspicion of resistance
  • baseline genotyping using proviral HIV-1 DNA genotype*

• Randomisation assignments remained blinded

• Here we present baseline resistance analyses and blinded virological outcome data at the Week 12 IDMC data cut

*GenoSure Archive assay, Monogram Biosciences
IDMC, Independent Data Monitoring Committee

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Results: Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>B/F/TAF or DTG + F/TAF (N=565)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>51 (20-79)</td>
</tr>
<tr>
<td>Male, %</td>
<td>86</td>
</tr>
<tr>
<td>Black or African Race, %</td>
<td>23</td>
</tr>
<tr>
<td>Hispanic/Latino Ethnicity, %</td>
<td>20</td>
</tr>
<tr>
<td>Median CD4 cell count, cells/µL (IQR)</td>
<td>646 (474,830)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 copies/mL at baseline</td>
<td>98%</td>
</tr>
<tr>
<td>Median eGFR$_{CG}$, mL/min (IQR)</td>
<td>99 (81,119)</td>
</tr>
<tr>
<td>NRTIs at baseline</td>
<td></td>
</tr>
<tr>
<td>F/TAF, %</td>
<td>69</td>
</tr>
<tr>
<td>F/TDF, %</td>
<td>31</td>
</tr>
</tbody>
</table>

eGFR$_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault; IQR, interquartile range.
Results: Baseline Genotypic Data Sources

<table>
<thead>
<tr>
<th>Historical Genotype</th>
<th>Proviral DNA</th>
<th>Any Genotype</th>
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<tbody>
<tr>
<td>HIV-1 RNA ≥400 c/mL</td>
<td>HIV-1 RNA &lt;50 c/mL</td>
<td>83% (470/565)</td>
</tr>
<tr>
<td>50% (285/565)</td>
<td>69% (391/565)</td>
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# High Level of Pre-existing NRTI Resistance Prior to Switching to B/F/TAF

<table>
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<th>Category</th>
<th>NRTI Mutation</th>
<th>Initial Categorisation by Investigators n (%)</th>
<th>Final Categorisation n (%)</th>
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<tr>
<td>1</td>
<td>K65R/E/N or ≥ 3 TAMs</td>
<td>15 (3%)</td>
<td>30 (5%)</td>
</tr>
<tr>
<td>2</td>
<td>Any Other Pattern</td>
<td>63 (11%)</td>
<td>108 (19%)</td>
</tr>
<tr>
<td>3</td>
<td>No NRTI Mutation</td>
<td>487 (86%)</td>
<td>427 (76%)</td>
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### High Level of Pre-existing NRTI Resistance Prior to Switching to B/F/TAF

#### Table: Initial and Final Categorisation by Investigators

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#### Additional Resistance Analysis Sets

- **Any PI, NRTI, NNRTI, INSTI Resistance Mutation**: 222 (39%)
- **Any NRTI-R**: 138 (24%)
  - **M184V/I (from Category 1 or 2)**: 81 (14%)
- **Any NNRTI-R**: 118 (21%)
- **Any PI-R**: 38 (7%)
- **Any INSTI-R**: 20 (4%)

M184V or M184I cause resistance to FTC and 3TC; the INSTI-R isolates are sensitive to BIC.

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Results: Detection of M184V/I in Baseline Genotypic Data

Baseline M184V/I detected in 14% all participants (81/565)

- 51% (41/81) by Historical Genotype
  - 14% (41/285) of all with Historical Genotypes

- 49% (40/81) Previously Undocumented M184V/I by Proviral Genotype
  - 11% (40/357) of all with Proviral Genotypes & no prior known M184V

34/41 participants had both historical and Proviral genotypes
- 50% (17/34) of historical M184V/I was missed by Proviral
- 50% (17/34) of historical M184V/I was confirmed by Proviral

- 25% (10/40) had historical WT M184M but M184V/I found by Proviral
- 75% (30/40) found by Proviral in absence of historical data
### Final NRTI resistance category

<table>
<thead>
<tr>
<th>Category</th>
<th>NRTI Mutation</th>
<th>Baseline Drug Resistance (N=565)</th>
<th>Virologic Suppression (N=562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. K65R/E/N or ≥ 3 TAMs</td>
<td>30 (5%)</td>
<td>97% (29/30)</td>
<td></td>
</tr>
<tr>
<td>2. Any Other Pattern</td>
<td>108 (19%)</td>
<td>99% (107/108)</td>
<td></td>
</tr>
<tr>
<td>3. No NRTI Mutation</td>
<td>427 (76%)</td>
<td>99% (421/424)</td>
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### Additional Resistance Analysis Sets

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<tr>
<td>Any PI, NRTI, NNRTI, INSTI Resistance Mutation</td>
<td>222 (39%)</td>
<td>99% (220/222)</td>
</tr>
<tr>
<td>Any NRTI-R</td>
<td>138 (24%)</td>
<td>99% (136/138)</td>
</tr>
<tr>
<td>M184V/I (from Category 1 or 2)</td>
<td>81 (14%)</td>
<td>98% (79/81)</td>
</tr>
<tr>
<td>Any NNRTI-R</td>
<td>118 (21%)</td>
<td>99% (117/118)</td>
</tr>
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</tr>
<tr>
<td>Any INSTI-R</td>
<td>20 (4%)</td>
<td>100% (20/20)</td>
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- High rates of virologic suppression maintained with switches to BFTAF or DTG + F/TAF through Week 12

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Resistance analysis population was any participant with a confirmed viral rebound of HIV-1 RNA ≥ 50 copies per mL, with the confirmatory HIV-1 RNA ≥ 200 copies/mL through the Week 12 IDMC data cut, or without confirmation if at the last visit, who did not resuppress while on study drug.

a. Both participants were from resistance category 3, with no NRTI-R, NNRTI-R, PI-R, or INSTI-R detected at baseline or virologic failure
### Association of M184V/I with Other Primary Resistance Mutations

<table>
<thead>
<tr>
<th>M184V/I</th>
<th>Without genotyping criteria</th>
<th>With genotyping criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>M184V/I + PI-R</td>
<td>20% (16/81)</td>
<td>94% (15/16)</td>
</tr>
<tr>
<td>M184V/I + NNRTI-R</td>
<td>51% (41/81)</td>
<td>98% (40/41)</td>
</tr>
<tr>
<td>M184V/I + other NRTI-R</td>
<td>51% (41/81)</td>
<td>98% (40/41)</td>
</tr>
<tr>
<td>M184V/I + TAMs</td>
<td>42% (34/81)</td>
<td>97% (33/34)</td>
</tr>
<tr>
<td>M184V/I + primary INSTI-R</td>
<td>6% (5/81)</td>
<td>100% (5/5)</td>
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Two patients had virologic failure at Week 24, but neither met the protocol defined criteria for genotyping (HIV-1 RNA ≥ 200 c/mL).

- a. One participant with M184V alone had a viral load of 120 c/mL and later resuppressed.
Summary

- **Resistance observed:**
  - Primary drug resistance to any class was present in 39% of participants
  - 14% had NRTI resistance known or suspected at screening, which increased to 24% using historical data and additional baseline proviral HIV-1 DNA genotyping
    - M184V/I was present in 14% of participants
  - Other studies using proviral DNA genotyping have also reported previously undocumented M184V/I and missed documented M184V/I in ~50% of cases

- **Virological efficacy maintained (blinded), with no emergent drug resistance:**
  - 99% of the 562 participants in the study maintained suppression
  - 99% of the 222 participants with any drug resistance maintained suppression
  - 98% of the 81 participants with M184V/I maintained suppression

Conclusions

- High levels of NRTI resistance may be seen in virologically suppressed patients
- Proviral DNA assays may provide valuable additional genotypic data
- HIV-1 RNA suppression was maintained with B/F/TAF or DTG + F/TAF through this blinded, preliminary Week 12 IDMC data cut in suppressed patients with pre-existing NRTI resistance including M184V/I
- 48 Week outcomes will be presented later this year
  - efficacy, safety, tolerability, PROs
Acknowledgements

- The individuals who participated in Study GS-US-380-4030
- The study site investigators and research teams
- Gilead study team (particularly Rima Acosta, Kirsten White, Sean Collins, and Neal Marshall)