00136: A RANDOMIZED TRIAL OF SWITCHING TREATMENT-EXPERIENCED ADULTS FROM PI/r TO DTG

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Switching Treatment-Experienced, Integrase Inhibitor-Naïve, Virally Suppressed HIV-1 Infected Adults from Ritonavir-boosted Protease Inhibitors to Dolutegravir: An Open-Label Randomized Controlled Trial

Second line switch to DTG (2SD)

Final (Week 48) Results
Background

- Almost all second-line patients in Kenya are currently on ATV/r or LPV/r
- PI/r have several challenges: pill burden, tolerability, toxicity, drug interactions, cost
- DTG is superior to ATV/r\(^1\) or DRV/r\(^2,3\) as first-line
- DTG is superior to LPV/r\(^4\) and non-inferior to DRV/r\(^5\) as second-line after NNRTI-based failure
- Switching virally-suppressed patients from first-line PI/r to DTG results in non-inferior viral suppression, improved patient satisfaction, improved lipid profiles\(^6,7\)
- Switching virally-suppressed patients from PI/r-based second-line to DTG has not been evaluated

Primary Objective

• To evaluate the non-inferiority of switching to a DTG containing regimen relative to maintaining a PI/r containing second-line regimen in virologically suppressed, INSTI-naive HIV-1 positive adults (≥ 18 years old) as determined by having HIV-1 RNA ≥ 50 copies/ml at week 48
**Study Design**

- Multi-center: 4 sites in Kenya located in Nairobi, Kiambu and Kisumu Counties
- Enrolled between Feb and Sep 2020 and followed up for 48 weeks
- No assessment of prior ARV drug resistance

- Adults (≥ 18 years)
- On PI/r-based 2nd line with 2 NRTIs for ≥ 24 weeks
- VL < 50 copies/ml for ≥ 12 weeks
- No prior INSTI exposure
- If WOCBP: on effective contraception

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*NRTIs could be changed for clinical indications
**FDA snapshot analysis with non-inferiority margin of 4%
Analysis

• Efficacy analysis
  • Analysis for ITT-E population using FDA snapshot method
  • Non-inferiority was established if upper bound of the 95% CI for the difference in % of participants with HIV-1 RNA of >50 copies/ml was <4%

• Safety analysis
  • Incidence and severity of all AEs, SAEs and lab abnormalities in counts and percentages
  • Group comparisons using Fisher’s exact test
Non inferiority trials

- It is not statistically possible to prove that two treatments are identical, it is possible to determine that a new treatment is not worse than the control treatment by an acceptably small amount, with a given degree of confidence.

- This is the premise of a randomized, non-inferiority trial.

- The null hypothesis in a non-inferiority study states that the primary end point for the experimental treatment is worse than that for the positive control treatment by a prespecified margin, and rejection of the null hypothesis at a pre-specified level of statistical significance is used to support a claim that permits a conclusion of non-inferiority.

Non-Inferiority trials - possible outcomes

- Noninferiority and superiority
- Noninferiority
- Noninferiority and inferiority
- Inconclusive
- Inferiority

Potential Outcomes

Ratio of Event Rates (95% CI):
Test Treatment vs. Active Control

Noninferiority null hypothesis: $P_T/P_C \geq \text{margin}$
Noninferiority alternative hypothesis: $P_T/P_C < \text{margin}$
Results: Enrollment

1,114 assessed for eligibility

319 excluded
- 195 did not meet eligibility criteria
  - 151 VL ≥ 50 copies/ml at screening or within 12 weeks prior to enrollment
  - 15 grade 3 or 4 lipid abnormality at screening
  - 11 no prior treatment failure
  - 8 WOCBP declined to use effective contraception
  - 5 Prior INSTI exposure
  - 4 CrCl < 50 ml/min in conjunction with HBV infection, or advanced renal insufficiency requiring dialysis
  - 1 acute opportunistic infection within 4 weeks prior to enrollment
- 89 declined to participate
- 33 did not return for randomization within 28 days from screening
- 2 study recruitment closed before returned for randomization

795 randomized

398 allocated to switch to DTG
397 allocated to remain on pre-enrollment PI/r
Results: Enrollment

398 allocated to switch to DTG
• 1 did not receive treatment
  • 1 withdrew consent
  • 0 failed to comply with the protocol

397 included in ITT-E analysis

15 discontinued treatment due to lack of efficacy*
15 discontinued treatment for reasons other than lack of efficacy
• 5 failed to comply with protocol requirements
• 4 became pregnant
• 3 died
• 1 adverse event requiring study drug substitution
• 1 adverse event leading to withdrawal
• 1 dispensing error affecting study drug
• 0 lost to follow-up
18 had low adherence**
2 did not meet inclusion criteria

362 included in the per protocol analysis

397 allocated to remain on pre-enrollment PI/r
• 3 did not receive treatment
  • 1 withdrew consent
  • 2 failed to comply with the protocol

394 included in ITT-E analysis

14 discontinued treatment due to lack of efficacy*
10 discontinued treatment for reasons other than lack of efficacy
• 1 failed to comply with protocol requirement
• 3 became pregnant
• 3 died
• 2 adverse event requiring study drug substitution
• 0 adverse event leading to withdrawal
• 0 dispensing error affecting study drug
• 1 lost to follow-up
20 had low adherence**
1 did not meet inclusion criteria

363 included in the per protocol analysis
## Results: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DTG group (n=397)</th>
<th>PI/r group (n=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Female (cisgender), %</td>
<td>67.5%</td>
<td>65.0%</td>
</tr>
<tr>
<td>Median CD4 count, cells/µl</td>
<td>438</td>
<td>397</td>
</tr>
<tr>
<td>HBV co-infection, %</td>
<td>3.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Median time on PI/r, years</td>
<td>5.5</td>
<td>5.4</td>
</tr>
<tr>
<td>PI/r at randomization, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATV/r</td>
<td>77.3%</td>
<td>81.5%</td>
</tr>
<tr>
<td>LPV/r</td>
<td>22.7%</td>
<td>18.5%</td>
</tr>
<tr>
<td>NRTI at randomization, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/3TC</td>
<td>51.9%</td>
<td>53.8%</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>44.1%</td>
<td>41.4%</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>4.0%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
Results: Virologic outcome at week 48, ITT-e snapshot

- All participants but one with Protocol Defined Virologic Failure (PDVF) in the DTG arm had VL levels between 50 to 200 copies/mL and no samples amplified for genotypic resistance testing
- 5 participants with PDVF in the PI/r arm had VL ≥ 400 copies/mL and both amplified with no PI/r resistance mutations detected; all other participants with PDVF in the PI/r had VL levels between 50 to 400 copies/mL and did not amplify for genotypic resistance testing
Analysis of Primary and Secondary End Points

**Analysis of primary end point:** DTG non-inferior to PI/r (VL ≥ 50 copies/mL) at week 48

**Analysis of secondary efficacy end point:** DTG non-inferior to PI/r (VL <50 copies/mL) at week 48

- **DTG**
- **PI/r**

-3.1
-0.04
3.0

4% non-inferiority margin

-10% non-inferiority margin

Difference, %
## Results: Safety

<table>
<thead>
<tr>
<th></th>
<th>DTG group (n=397)</th>
<th>PI/r group (n=394)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (AE)</td>
<td>257 (64.7%)</td>
<td>248 (62.9%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>92 (23.2%)</td>
<td>78 (19.8%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Grade 3-4 AE</td>
<td>35 (8.8%)</td>
<td>43 (10.9%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>23 (5.8%)</td>
<td>27 (6.9%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Serious AE</td>
<td>10 (2.5%)</td>
<td>8 (2.0%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Deaths</td>
<td>3 (0.8%)</td>
<td>(0.8%)</td>
<td>0.99</td>
</tr>
<tr>
<td>AE leading study drug discontinuation</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
<td>0.31</td>
</tr>
</tbody>
</table>
Results: Safety

Percentage change from baseline to week 48 in fasting lipid concentrations, fasting glucose and body-mass index. Abbreviations: DTG, dolutegravir; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PI/r, ritonavir-boosted protease inhibitor.
Conclusion

• Switching from PI/r to DTG may be an effective and safe strategy for treatment experienced virally suppressed adults with no prior INSTI-exposure, even without knowledge of prior resistance
Acknowledgements

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UNIVERSITY OF NAIROBI

Thika and Kiambu level 5 Hospitals