ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA <500,000 copies/ml

Reported by Jules Levin

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IAS: Dolutegravir-Lamivudine as initial therapy in HIV-1 infected, ARV-naïve patients: 96 week results of the PADDLE trial - (07/25/17)

Conclusions

- In this pilot study, DTG+3TC demonstrated potent virologic efficacy with study entry VL up to 500,000 copies/mL

- Virologic failure was uncommon and associated with suboptimal adherence
  - 3 patients met PDVF, one of whom had emergent R263RK mixture and M184V

- Future work in A5353:
  - Investigate baseline and on-treatment RT and INI minority variants in the participants with virologic failure and a matched control group
  - Perform phenotyping on the participant with emergent R263K/R mixture
  - Analysis of pharmacogenetics associations

- Two large randomized studies (GEMINI-1 and GEMINI-2) are underway and will provide more data on the resistance barrier of DTG+3TC
ACTG A5353: A pilot study of dolutegravir (DTG) + lamivudine (3TC) for initial treatment of HIV-1-infected participants with HIV-1 RNA <500,000 copies/ml

Background

Dolutegravir (DTG) + Lamivudine (3TC) is an investigational 2 drug regimen.

**Strengths of DTG + 3TC**
- Two potent, well tolerated drugs
- Robust resistance profile of DTG – no emergent resistance in almost 1400 participants in phase 2/3 trials (48-144 weeks) of DTG + 2NRTIs
- Potential for co-formulation
- Possibly reduced risk of cumulative adverse effects
- Could save $550 million to >$3 billion in ART costs in the US over 5 years

**Unknowns and potential weaknesses**
- Efficacy at baseline VL > 100,000 copies/mL (cpm)
- Low resistance barrier of 3TC
- Contraindicated with hepatitis B co-infection
- Efficacy in compartments (genital, CNS) and pregnancy

PADDLE

A pilot study of DTG 50 mg + 3TC 300 mg daily

- Showed plasma VL < 50 cpm at week 48 in 18/20 participants (1 suicide; 1 protocol defined virologic failure, PDVF)

Limitations
- Small sample size (N=20), single arm
- Excluded screening VL >100,000 cpm
- Excluded screening CD4 count < 200 cells/mm$^3$
- Data insufficient to justify enrollment of participants with high baseline VL in phase 3 studies
- Genotyping performed on the participant with PDVF showed no reverse transcriptase (RT) mutations; integrase did not amplify

ACTG A5353
Study Design and Objectives
Phase II, single-arm, 52-week, pilot study of DTG 50mg + 3TC 300 mg daily in treatment-naïve participants with VL ≥1000 and <500,000 cpm

Primary Objective
- To estimate the virologic success rate at week 24

Key Secondary Objectives
- Compare efficacy with baseline VL ≤100,000 vs >100,000 cpm
- Describe emergent integrase and RT resistance during virologic failure
- Evaluate safety and tolerability
- Explore impact of minority drug-resistant variants and drug exposure/adherence on observed outcomes

Key Eligibility Criteria

- Antiretroviral drug naïve
- VL ≥1000 and <500,000 cpm
  - Pre-specified enrollment of ≥ 25% with VL >100,000 cpm
- No evidence of RT, integrase, or major protease resistance mutation
  - Integrase genotyping was performed by the study at screening
- Negative hepatitis B surface antigen
- No active/anticipated HCV treatment within study period.
  - HCV infection alone was not exclusionary

Outcome Measures

Primary Efficacy Outcome
Virologic success at week 24, defined as on-treatment VL < 50 cpm, using the FDA Snapshot definition.

Protocol Defined Virologic Failure (PDVF) Definition
Confirmed VL >400 cpm at week 16 or 20
or
Confirmed VL >200 cpm at/after week 24
Participant Disposition Up to Week 24

- 165 screened
- 122 enrolled
- 120 initiated DTG + 3TC
  - 37 > 100,000 copies/mL
  - 83 ≤ 100,000 copies/mL
- 43 did not enroll
  - 9 genotype failed
  - 14 RNA/ltc out of range
  - 9 not willing to enroll
  - 7 screening window expired
  - 4 illness
- 2 ineligible and excluded
  - K1ESN at screening
- 4 discontinued study & DTG+3TC before week 24
  - 2 moved out of area
  - 1 incarcerated
  - 1 unable to contact
  - 3 discontinued DTG+3TC before week 24
  - 1 pregnancy
  - 1 non-compliance
  - 1 unable to attend clinic

Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA Category</th>
<th>&gt; 100,000 cpm (N=37)</th>
<th>≤100,000 cpm (N=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (Q1, Q3)</td>
<td>30 (25, 40)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td>27%</td>
<td>29%</td>
</tr>
<tr>
<td>Black Non-Hispanic</td>
<td>32%</td>
<td>43%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>CD4 Count</strong></td>
<td>Median (Q1, Q3)</td>
<td>350 (173, 458)</td>
</tr>
<tr>
<td>(cells/µl)</td>
<td>&lt;200</td>
<td>30%</td>
</tr>
<tr>
<td>HIV-1 RNA (log_{10} cpm)</td>
<td>Median (Q1, Q3)</td>
<td>5.23 (5.09, 5.46)</td>
</tr>
<tr>
<td>(cpm)</td>
<td>&lt;10,000</td>
<td>--</td>
</tr>
<tr>
<td>10,000 - 99,999</td>
<td>--</td>
<td>58%</td>
</tr>
<tr>
<td>100,000 - 200,000</td>
<td>62%</td>
<td>--</td>
</tr>
<tr>
<td>&gt; 200,000</td>
<td>38%</td>
<td>--</td>
</tr>
</tbody>
</table>
## Primary Outcome: FDA Snapshot at Week 24

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA</th>
<th>(&gt; 100,000 \text{ cpm})</th>
<th>(\leq 100,000 \text{ cpm})</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA (&lt; 50 \text{ cpm})</td>
<td>33 (89%) [75%, 97%]</td>
<td>75 (90%) [82%, 96%]</td>
<td>108 (90%) [83%, 95%]</td>
</tr>
<tr>
<td><strong>Virologic success</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Virologic non-success</strong></td>
<td>3 (8%)</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>HIV-1 RNA (\geq 50 \text{ cpm})</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Discontinued study treatment for other reasons while HIV RNA (\geq 50^*)</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>No virologic data in window</strong></td>
<td>1 (3%)</td>
<td>6 (7%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Discontinued study treatment for other reasons #</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>On study but missing data in window</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* Poor adherence, # Lost to follow-up, pregnancy

[95% Confidence intervals] for proportion of participants with virologic success at Week 24

### FDA Snapshot Virologic Non-Success: HIV-1 RNA to Week 24

![Graph 1](image1.png)

![Graph 2](image2.png)
Protocol-Defined Virologic Failures (PDVF): HIV-1 RNA and DTG Levels to Week 24

CD4 Count Changes
Adverse Events

- Two participants experienced Grade 3 possibly/probably treatment-related adverse events
  - Creatinine clearance
  - Palpitations
- No Grade 4 adverse events
- No discontinuations due to adverse events

Acknowledgements

**A5353 Team**
- Co-Chairs: Babafemi Taiwo, Trip Gulick
- Clinical Trials Specialist: Elizabeth Hawkins
- Statistician: Summer Zheng, Andrei Stefanescu
- Data Managers: Melissa Mineo, Bernadette Jerocki
- Pharmacist: Oladapo Ali
- Virologist: Carole Wallis
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- Leb Tech: Gerald Tegha
- Leb Data Managers: Adam Marcella, Allison Reding, Laura Hovind
- CSS: Angel Hernandez
- DAIDS: Katy Godfrey
- ViIV: Kim Smith, Belinda Ha

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- Houston (8)
- UNC (7)
- Vanderbilt (7)
- Trinity (7)
- Ohio State (5)
- Wash U (4)
- Miriam (4)
- Chelsea (4)
- USC (3)
- Puerto Rico (3)
- Brigham (2)
- Harbor (2)
- UCSD (2)
- Cincinnati (2)
- Emory (2)
- Cornell (2)
- Penn (2)
- Columbia (2)
- Rochester (2)
- MGH (1)
- UCLA (1)

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