Virtual CROI 2021: Key Treatment Studies

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No conflicts of interest or relationships to disclose.
Outline

1. Update from IMPAACT 2010
2. Update from ATLAS-2M
3. Lenacapavir: Capella Study
Update from IMPAACT 2010
• ART options in pregnancy remain limited

• IMPAAACT 2010 is a global, multicenter, randomized trial of ART-naïve pregnant women with HIV started on:
  - TAF/FTC + DTG vs
  - TDF/FTC + DTG vs
  - TDF/FTC/EFV

• Interim results through delivery outcome (CROI 2020)
  - DTG-containing arms had superior virologic efficacy
  - TAF/FTC + DTG had lowest rate of adverse pregnancy outcomes
Study Design: IMPAAACT 2010

Arm 1: Maternal DTG+FTC/TAF During Pregnancy and Postpartum

Arm 2: Maternal DTG+FTC/TDF During Pregnancy and Postpartum

Arm 3: Maternal EFV/FTC/TDF During Pregnancy and Postpartum

Enrollment at 14-28 weeks gestation

Completion of follow-up at 50 weeks postpartum

Weeks on Study Antepartum

Weeks on Study Postpartum
### Study Design: Maternal Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DTG+FTC/TAF (n=217)</th>
<th>DTG+FTC/TDF (n=215)</th>
<th>EFV/FTC/TDF (n=211)</th>
<th>Total (n=643)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median years)</strong></td>
<td>26.8</td>
<td>26.0</td>
<td>26.6</td>
<td>26.6</td>
</tr>
<tr>
<td><strong>Enrolled in Africa</strong></td>
<td>187 (86%)</td>
<td>189 (88%)</td>
<td>188 (89%)</td>
<td>564 (88%)</td>
</tr>
<tr>
<td><strong>Gestational age (median weeks)</strong></td>
<td>22.1</td>
<td>21.3</td>
<td>22.1</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>CD4 count (median cells/mm(^3))</strong></td>
<td>407</td>
<td>481</td>
<td>439</td>
<td>466</td>
</tr>
<tr>
<td><strong>HIV-1 RNA (median copies/mL)</strong></td>
<td>781</td>
<td>715</td>
<td>1357</td>
<td>903</td>
</tr>
<tr>
<td><strong>HIV-1 RNA &lt;50</strong></td>
<td>36 (16%)</td>
<td>37 (17%)</td>
<td>27 (13%)</td>
<td>100 (16%)</td>
</tr>
<tr>
<td><strong>ART in pregnancy prior to entry</strong></td>
<td>176 (81%)</td>
<td>180 (84%)</td>
<td>176 (83%)</td>
<td>532 (83%)</td>
</tr>
<tr>
<td><strong>Median days on ART</strong></td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><em><em>BMI</em> (kg/m2), median (Q1,Q3)</em>*</td>
<td>25.1 (22.5, 29.4)</td>
<td>24.5 (22.0, 28.1)</td>
<td>24.2 (21.5, 28.0)</td>
<td>24.7 (22.0, 28.4)</td>
</tr>
</tbody>
</table>

Median duration of antepartum follow-up: 17.4 weeks, *Pre-pregnancy BMI was not available
Study Design: Outcomes Evaluated

- Virologic efficacy to 50 weeks post-partum
- Safety outcomes to 50 weeks post-partum
  - Maternal grade 3 or higher adverse events
  - Infant grade 3 or higher adverse events
  - Infant mortality
  - Infant HIV infection
Results: IMPAACT 2010 Virologic Efficacy

Maternal HIV-1 RNA Suppression at week 50 postpartum

- Combined DTG Arms: 96.3%
- EFV/FTC/TDF: 96.4%

p = 0.97

Per ITT analysis

Maternal Virologic Failure
2 successive HIV RNA ≥ 200 copies/mL at or after 24 weeks on study

- DTG+FTC/TAF: 4.1%
- DTG+FTC/TDF: 5.1%
- EFV/FTC/TDF: 10.4%

p = 0.63, p = 0.012, p = 0.040

Post hoc statistical comparisons

Chinula L et al, Virtual CROI 2021, Abstract #177
Results: IMPAACT 2010 Adverse Events

Maternal & Infant Grade 3 or Higher Adverse Events by Arm Through 50 Weeks Postpartum

- Maternal Grade ≥3 AE
  - DTG+FTC/TAF: 25.1%
  - DTG+FTC/TDF: 27.9%
  - EFV/FTC/TDF: 25.3%
- Infant Grade ≥3 AE
  - DTG+FTC/TAF: 30.8%
  - DTG+FTC/TDF: 28.6%
  - EFV/FTC/TDF: 30.9%
- Infant Deaths
  - DTG+FTC/TAF: 1.0%
  - DTG+FTC/TDF: 2.0%
  - EFV/FTC/TDF: 6.9%
- Stillbirth or Infant Deaths*
  - DTG+FTC/TAF: 4.6%
  - DTG+FTC/TDF: 7.0%
  - EFV/FTC/TDF: 8.5%

*Post hoc analysis

Chinula L et al, Virtual CROI 2021, Abstract #177
Results: IMPAACT 2010 Infant HIV Infection

4 infants had HIV infection all were breastfed and received ARV prophylaxis

- DTG+FTC/TAF: 0.98% (2/208), p=0.28
- DTG+FTC/TDF: 0.50% (1/202), p=0.31
- EFV/FTC/TDF: 0.55% (1/202), p=0.47

Chinula L et al, Virtual CROI 2021, Abstract #177
Summary: IMPAAACT 2010

• TAF and DTG were safe through 50-week post-partum data

• All regimens were safe and efficacious
  - Infant mortality higher in EFV arm
  - More women had virologic failure in the EFV arm

Take-Away Point: This provides additional reassuring data about DTG and TAF use in pregnancy and post-partum
Update from ATLAS-2M
Background: ATLAS-2M

• ATLAS (CROI 2019): CAB/RPV IM q4w in treatment-experienced PWH was non-inferior to standard PO ART
  - 3 virologic failures occurred

• ATLAS-2M (CROI 2020): CAB/RPV IM q8w in treatment-experienced PWH was non-inferior to q4w at 48 weeks
  - Participants preferred q8w dosing
  - 10 virologic failures (VFs) occurred
    • 8 in q8w arm, 2 in q4w arm
  - Majority with VF failed with both NNRTI and INSTI RAMs
**Study Design: ATLAS-2M**

**Primary Endpoint:** Proportion of participants with HIV RNA ≥ 50 copies/mL

**Other Endpoints:** Incidence of confirmed virologic failure (VF), incidence of viral resistance in participants with confirmed VF (CVF), safety and tolerability

Jaeger H et al, Virtual CROI 2021, Abstract #401
Results: ATLAS-2M 96 Week Data

Jaeger H et al, Virtual CROI 2021, Abstract #401
## Results: ATLAS-2M Adverse Effects

Table adapted from Jaeger H et al:

<table>
<thead>
<tr>
<th>Category</th>
<th>Q8W n = 522</th>
<th>(n)</th>
<th>(%)</th>
<th>Q4W n = 523</th>
<th>(n)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event (AE)</td>
<td>488</td>
<td>522</td>
<td>93</td>
<td>499</td>
<td>523</td>
<td>95</td>
</tr>
<tr>
<td>AE leading to withdrawal</td>
<td>18</td>
<td></td>
<td>3</td>
<td>19</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td># of injections</td>
<td>12,832</td>
<td></td>
<td></td>
<td>23,855</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site reaction (ISR) events</td>
<td>3400</td>
<td></td>
<td></td>
<td>4157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISR pain</td>
<td>2662</td>
<td></td>
<td>21</td>
<td>3295</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>ISR nodule</td>
<td>188</td>
<td></td>
<td>1</td>
<td>297</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>ISR discomfort</td>
<td>134</td>
<td></td>
<td>1</td>
<td>148</td>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Median duration, days (IQR)</td>
<td>3 (2,5)</td>
<td></td>
<td></td>
<td>3 (2,5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Participants withdrawing for injection-related reasons</td>
<td>7 (1)</td>
<td></td>
<td></td>
<td>11 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Results: ATLAS-2M Resistance

#### Overall Summary of CVFs through Week 96

<table>
<thead>
<tr>
<th>Arm</th>
<th>n</th>
<th>CVFs n (%)</th>
<th>CVFs with RPV RAMs*</th>
<th>RPV RAMs observed at failure</th>
<th>CVFs with INSTI RAMs*</th>
<th>INSTI RAMs observed at failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q4W</td>
<td>523</td>
<td>2 (0.4)</td>
<td>1/2</td>
<td>K101E, M230L</td>
<td>2/2</td>
<td>E138E/K, Q148R, N155N/H</td>
</tr>
</tbody>
</table>

*For those with observed RAMs at failure: 7/7 Q8W and 1/1 Q4W CVFs had RPV resistance (fold-change >2), and 3/5 Q8W and 1/2 Q4W CVFs had CAB resistance (fold-change >25).

- Total VF from ATLAS-2M = 11 (9 in q8w arm, 2 in q4w arm)
- One additional VF occurred between weeks 48 and 96 in the q8w arm
  - K103N and Y181C detected at VF & retrospectively at baseline in PBMC
  - No INSTI RAMs present at VF or baseline, though substitution L74I was present at baseline
- 10/11 with confirmed VF resuppressed on an alternative regimen
- All with confirmed VF retained DTG susceptibility
Summary: ATLAS-2M 96-Week Data

• Virologic efficacy, adverse events, and injection site reactions were similar in IM CAB/RPV q8w and q4w arms

• Confirmed VF occurred in 11 PWH
  - 9 in the q8w arm, 2 in the q4w arm

• Most PWH with VF acquired both NNRTI and INSTI RAMs

Take-Away Point: Q8W dosing of CAB/RPV is effective and there are few VFs, but with failure, RAMs occurred
Lenacapavir: Capella Study
Background: Lenacapavir

- Novel HIV-1 capsid inhibitor, formerly known as GS-6207, that can be given as a long-acting subcutaneous injection
- Currently in development as a component of long-acting therapy for HIV-1
- Has activity in NRTI, NNRTI, INSTI, and PI-resistant HIV-1
Study Design: Lenacapavir in MDR HIV-1

Key eligibility criteria:
- HIV-1 RNA ≥400 copies/mL
- Resistance to ≥2 agents from 3 of 4 main ARV classes
- ≤2 fully active agents

Randomized cohort (Double blind)
- n=24
  - Oral LEN*
    - Failing regimen
- n=12
  - Placebo
    - Failing regimen

Functional monotherapy (14-d)
- SC LEN* Q6M for 52 weeks
  - OBR
- Oral LEN* SC LEN* Q6M for 52 weeks
  - OBR

Maintenance

Nonrandomized cohort (Open label)
- n=36
  - Oral LEN*
    - SC LEN* Q6M for 52 weeks
      - OBR

*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.
OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).

Segal-Maurer S et al, Virtual CROI 2021, Abstract #127
Results: Lenacapavir in MDR HIV-1

Primary Endpoint
% Achieving HIV-1 RNA Decline
≥0.5 log_{10} copies/mL

p<0.0001

88

Participant Characteristics:
- Median age: 52
- Median CD4 cell count: 150 cells/mm³
- Median number of prior ARV regimens: 11
- Median years since HIV diagnosis: 24

Segal-Maurer S et al, Virtual CROI 2021, Abstract #127
Summary: Lenacapavir in MDR HIV-1

• In the Capella study, early data shows that use of lenacapavir demonstrated antiviral activity against MDR HIV after 14 days and led to virologic suppression when paired with an OBR

Take-Away Point: Although much more data is needed, lenacapavir has the potential to become an important tool against MDR HIV in heavily treatment experienced PWH
1. IMPAACT 2010: Data at 50 weeks post-partum show that TDF/FTC + DTG, TAF/FTC + DTG, and TDF/FTC/EFV are safe ART options during pregnancy and in the post-partum period.

2. ATLAS-2M: Data at 96 weeks demonstrated virologic efficacy and safety of CAB/RPV IM q8w dosing, as compared to q4w dosing, with 11 total VFs (and RAMs).

3. Capella Study: Early data of lenacapavir, a novel capsid inhibitor that can be administered in a long-acting fashion, demonstrated antiviral activity against MDR HIV.
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