Highlights from CROI 2017 and IAS 2017
Focus on Antiretroviral Therapy

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San Antonio, Texas: August 21-23, 2017

Financial Relationships With Commercial Entities

- Dr Eron received research grants awarded to his institution from Gilead Sciences, Inc, Janssen, and ViiV Healthcare, and has served as a consultant to Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen, Merck, and ViiV Healthcare. (Updated 08/17/17)

Learning Objectives

After attending this presentation, learners will be able to:

- List the approximate changes in estimated HIV incidence overall and in individual risk groups from 2008 to 2014
- Describe at least two combination antiretroviral therapies that are in development that use only two active antiretroviral agents.
- List the three factors that had the greatest impact (attributable risk) on myocardial infarction in HIV-infected patients in the NA-ACCORD study.
Outline of the Talk

• HIV Epidemiology
• Where we are with Antiretroviral Therapy
• New Antiretroviral therapy – coming soon
• New Antiretroviral therapy – what the future may hold
• New uses of existing ART
  – Dolutegravir/rilpivirine, dolutegravir mono-therapy
• Complications of HIV and its treatment
• HIV Prevention

ARS Question #1

• The CDC estimates that HIV incidence in the US from 2008 to 2014 has
  1. Increased by about 4% per year
  2. Was essentially stable as it has been for 15 years
  3. Decreased by about 3.5% per year
  4. Decreased by about 6.0% per year
  5. Unsure

- Cross-sectional, two-stage cluster sample
  - 286 randomly sampled enumeration areas
  - 6,417 households (HH)

Substantial Progress in Confronting the HIV Epidemic in Swaziland

- Population: 1,451,428
- Rural population: 79%
- Median age: 21.4 years
- Population growth rate: 1.1%
- HIV prevalence: 32%, SHMBS1, 2011

Notes:
- The CDC estimates that HIV incidence in the US from 2008 to 2014 has increased by about 4% per year.
- Was essentially stable as it has been for 15 years.
- Decreased by about 3.5% per year.
- Decreased by about 6.0% per year.

- Estimated annual percentage change is different from zero at the 5% significant level.

- Adjusted for missing risk factor information. Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.

- Data include persons with diagnosis of HIV infection regardless of stage of disease at diagnosis.

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- South African Reserve
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ANTIRETROVIRAL THERAPY

INCREASED PERSISTENCE OF INITIAL ART WITH INSTI-CONTAINING REGIMENS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>0.49 (0.35, 0.69)</td>
<td>0.70 (0.46, 1.06)</td>
</tr>
<tr>
<td>bPI</td>
<td>1.24 (1.05, 1.47)</td>
<td>1.24 (1.01, 1.53)</td>
</tr>
<tr>
<td>Other</td>
<td>1.47 (1.24, 1.75)</td>
<td>1.21 (0.99, 1.46)</td>
</tr>
<tr>
<td>NRTI</td>
<td>2.98 (2.38, 3.74)</td>
<td>1.72 (1.35, 2.19)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Ref.</td>
<td>Ref.</td>
</tr>
</tbody>
</table>
ANTIRETROVIRAL THERAPY – NEW AGENTS

Randomized Double-blind Phase III study of Bictegravir/TAF/FTC vs. Dolutegravir/ABC/3TC

GS-US-360-1489 Study Design

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Bictegravir/TAF/FTC</th>
<th>Dolutegravir/ABC/3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) median (IQR)</td>
<td>50 (42, 57)</td>
<td>50 (45, 58)</td>
</tr>
<tr>
<td>Male, %</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Resistance, %</td>
<td>26</td>
<td>36</td>
</tr>
<tr>
<td>Baseline viral load, copies/mL</td>
<td>6.3 ± 0.1</td>
<td>6.3 ± 0.1</td>
</tr>
<tr>
<td>CD4 count, copies/mL</td>
<td>279 ± 217</td>
<td>271 ± 260</td>
</tr>
<tr>
<td>NRTI-experienced, %</td>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

Virologic Outcome at Week 48

No resistance in either arm

More nausea with DTG/ABC/3TC: 22.9% vs 10.2%

Gallant et al IAS 2017

Randomized Double-blind Phase III study of Bictegravir/TAF/FTC vs. Dolutegravir plus TAF/FTC

Methods

Study Design

Baseline Characteristics

No resistance in either arm

More nausea with DTG/ABC/3TC: 22.9% vs 10.2%

Sax et al IAS 2017
No emergence of resistance in either arm
No substantial differences in adverse events or laboratory abnormalities between arms.

**LATTE-2: Study of Long Acting Cabotegravir and Rilpivirine – 96 week data**

### Inclusion Criteria
- ≥18 years old
- Naive to antiretroviral therapy
- CD4+ ≥200 cells/mm³

### Exclusion Criteria
- Positive for hepatitis B
- ALT ≥5×ULN
- Creatinine clearance <50 mL/min

**Qualification for maintenance**
- HIV-1 RNA <50 c/mL between Week 4 and Day 1

### Comparable Response Across Arms
**Week 96 HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)**
New Antiretrovirals – Coming Soon

• Doravirine
  – Randomized double blind comparison to DRV/r
    • 383 per arm median CD4 approximately 425 cells/mm³
    • 84% vs. 80% at 48 weeks – no resistance in DRV/r arm, one in DOR arm
  – Randomized double-blind comparison to EFV (both FDC TDF/FTC)
    • 364 per arm, mean CD4 approximately 420 cells/mm³
    • 84% vs. 81% at 48 weeks, less NNRTI resistance (1.6% vs. 3.3%)
    • Fewer drug-related AE, less rash, significantly less neuropsychiatric events

• Single tablet Protease inhibitor – DRV/cobi/TAF/FTC
  – Randomized open-label maintenance vs. continued boosted PI in suppressed patients 24 week data (N = 1149)
    • 96.3% vs 95.5% with rare virologic failure (0.3 vs. 0.5%), no resistance


ANTIRETROVIRAL THERAPY – NEW STUDIES OF APPROVED AGENTS

Tsepamo 2-year analysis: EFV/TDF/FTC, the first-line WHO recommended regimen, is safer than older ART regimens in pregnancy

Zash et al. CROI 2017

Birth Outcomes with ART in Botswana: Tsepamo
### Tsepalmo: Birth Outcomes in Botswana When Initiating First-line DTG vs EFV in Pregnancy

- Prospective cohort study in HIV-infected women initiating ART with EFV/FTC/TDF vs DTG/FTC/TDF while pregnant (N = 5438)

#### Adverse Birth Outcomes (ABO), n (%)

<table>
<thead>
<tr>
<th></th>
<th>DTG (n = 845)</th>
<th>EFV (n = 4593)</th>
<th>aRR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>34 (4.0)</td>
<td>103 (2.2)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>30 (3.6)</td>
<td>100 (2.2)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Neurocortical death</td>
<td>11 (1.3)</td>
<td>60 (1.3)</td>
<td>1.0 (0.7-1.6)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>149 (17.8)</td>
<td>35 (4.2)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>SGA (&lt; 10th percentile weight)</td>
<td>156 (18.7)</td>
<td>51 (6.1)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>Very SGA (&lt; 3rd percentile weight)</td>
<td>51 (6.1)</td>
<td>302 (6.7)</td>
<td>0.9 (0.7-1.2)</td>
</tr>
</tbody>
</table>

*For DTG vs EFV; adjusted for maternal age, education, gravida.

- Few first-trimester ART exposures (DTG, n = 116; EFV, n = 396)
- Only 1 major congenital abnormality observed (skeletal dysplasia in EFV-exposed group)
- Investigators concluded ABO risks comparable when initiating first-line DTG vs EFV in pregnancy.
**Snapshot Outcomes at Week 48 (Pooled)**

**Virologic outcomes**
- DTG + RPV (n=513)
- CAR (n=511)

**Adjusted treatment difference (95% CI)**
- Adjusted for age and second 3rd agent.

**Percentage-point difference**
- DTG + RPV is non-inferior to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48.

**DAWNING Study – Dolutegravir in Second Line**

- Open-label randomized noninferiority phase IIIb study
- **Randomization**
- Week 24 interim analysis
- Week 48 primary analysis
- Week 52

**Key eligibility criteria:**
- On first-line 2 NRTIs + NNRTI regimen for ≥6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs
- Stratification: by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)

**Primary endpoint:**
- Proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

**Similar result regardless of BL VL, CD4 or # of active NRTIs**

**Snapshot Outcomes at Week 24:**

**ITT-E and PP Populations**

**Virologic outcomes**
- DTG + 2 NRTIs
- LPV/RTV + 2 NRTIs

**Treatment differences (95% CI)**
- Similar result regardless of BL VL, CD4 or # of active NRTIs.
### Snapshot Outcomes at Week 24: ITT-E

<table>
<thead>
<tr>
<th></th>
<th>DTG + 2 NRTIs (n=312)</th>
<th>LPV/r + 2 NRTIs (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tolerability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic response (%)</td>
<td>82 (25)</td>
<td>69 (22)</td>
</tr>
<tr>
<td>Virologic nonresponse (%)</td>
<td>12 (4)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Data in window not below &lt;50 c/mL (%)</td>
<td>10 (3)</td>
<td>21 (7)</td>
</tr>
<tr>
<td>Changes in ART (%)</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Discontinued study due to AE or death (%)</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Discontinued study for other reasons (%)</td>
<td>4 (1.3)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Virologic data during window but on study (%)</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

8 vs. 24 with confirmed VF – no PT on DTG arm developed new resistance, 3 on LPV/r developed NRTI resistance.

### ARS Question #2

- Switching to dolutegravir monotherapy in patients on combination ART with suppressed HIV RNA
  1. Results in rapid virologic failure
  2. Results in low level viremia in a minority of patients but no resistance emergence
  3. Results in low level viremia in a minority of patients with integrase inhibitor resistance emerging in some patients
  4. Shows sustained virologic suppression similar to continued therapy
  5. Unsure
104 patients on cART – initially randomized to immediate switch to DTG mono-therapy or delayed switch after 24 weeks.

In the concurrent control group on cART, VF was observed significantly less (3/152 vs 8/96, p=0.03). Endpoint > 200 c/mL

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**Comprehensive Assessment of Resistance Mutations Selected by Dolutegravir (DTG) in Subjects Failing DTG-Monotherapy after Switching from other Therapies (Redomo Study)**

Blanco et al CROI 2017

- 122 patients from 3 sites switched to DTG mono-therapy – 11 had virologic failure
- In 5 of 11 DTG was their first INSTI. And 8 of 11 were suppressed > 3 years
- Adherence was less than 95% in 4 of 11
- Weeks (median, IQR) from VF until GRT: 5 (3-14)

### Table 1: Adherence and Viral Load Data

<table>
<thead>
<tr>
<th>Pt code</th>
<th>Prior IsSTI without VF</th>
<th>Weeks UVL before DTG-M</th>
<th>Baseline VL</th>
<th>VLs on DTG-M</th>
<th>ADH</th>
<th>Weeks to VF</th>
<th>VL at VF</th>
<th>Weeks to GRT</th>
<th>VL at GRT</th>
<th>First IN</th>
<th>GRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>B001</td>
<td>None</td>
<td>768</td>
<td>&lt;37</td>
<td>330</td>
<td>98% (PC)</td>
<td>8</td>
<td>330</td>
<td>8</td>
<td>330</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B002</td>
<td>RAL (LLV)</td>
<td>86</td>
<td>86 (prior 71,51)</td>
<td>80 (16), 171 (18), 122 (32), 3228 (48)</td>
<td>98% (PC)</td>
<td>16</td>
<td>80</td>
<td>32</td>
<td>122</td>
<td>118R</td>
<td></td>
</tr>
<tr>
<td>B003</td>
<td>None</td>
<td>312</td>
<td>&lt;37</td>
<td>26180</td>
<td>50% (PC)</td>
<td>20</td>
<td>26180</td>
<td>28</td>
<td>6014</td>
<td>148K,138K</td>
<td></td>
</tr>
<tr>
<td>B004</td>
<td>RAL (LLV/GRT:WT)</td>
<td>12</td>
<td>249 (prior &lt;37)</td>
<td>123 (12), 1350 (24)</td>
<td>82% (PC)</td>
<td>0</td>
<td>123</td>
<td>32</td>
<td>22170</td>
<td></td>
<td>92Q,155H</td>
</tr>
<tr>
<td>B007</td>
<td>EGV</td>
<td>240</td>
<td>&lt;37</td>
<td>57 (52), 51 (64), &lt;37 (88)</td>
<td>100% (PC)</td>
<td>52</td>
<td>57</td>
<td>64</td>
<td>57</td>
<td></td>
<td>97A,155H</td>
</tr>
<tr>
<td>B008</td>
<td>None</td>
<td>480</td>
<td>&lt;50</td>
<td>190 (32), 1350 (36), 40000 (40)</td>
<td>88% (PC)</td>
<td>32</td>
<td>190</td>
<td>36</td>
<td>1350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M001</td>
<td>RAL</td>
<td>232</td>
<td>21</td>
<td>55 (2), 168 (13), 239 (15)</td>
<td>60% (SQ)</td>
<td>0</td>
<td>55</td>
<td>16</td>
<td>239</td>
<td></td>
<td>148R,140S</td>
</tr>
<tr>
<td>M002</td>
<td>None</td>
<td>228</td>
<td>&lt;20</td>
<td>538 (24), 11000 (28)</td>
<td>100% (SQ)</td>
<td>24</td>
<td>538</td>
<td>29</td>
<td>11000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C001</td>
<td>EVG</td>
<td>20</td>
<td>&lt;50</td>
<td>306 (24), 583 (28)</td>
<td>100% (SQ)</td>
<td>24</td>
<td>306</td>
<td>24</td>
<td>306</td>
<td></td>
<td>118R</td>
</tr>
<tr>
<td>B005</td>
<td>RAL, EGV</td>
<td>432</td>
<td>&lt;37</td>
<td>179 (13), 71 (14), 56 (16)</td>
<td>98% (PC)</td>
<td>13</td>
<td>179</td>
<td>14</td>
<td>71</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>B006</td>
<td>None</td>
<td>172</td>
<td>&lt;37</td>
<td>355 (72), 1355 (76), 1397 (80), &lt;37 (92)</td>
<td>100% (PC)</td>
<td>72</td>
<td>355</td>
<td>76</td>
<td>1355</td>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

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**HIV AND COMPLICATIONS**
ARS Question #3

- Myocardial infarctions in the HIV positive population are predominantly due to:
  1. Low nadir CD4 cell count with persistent inflammation
  2. Use of abacavir
  3. Typical cardiovascular risk factors (e.g. smoking, hypertension and lipid abnormalities)
  4. Unsure
NA-ACCORD: Contributions to MI Risk in HIV+ Subjects

Population attributable fractions and 95% confidence intervals for traditional and HIV-related factors, and hepatitis C virus infection, NA-ACCORD (1 Jan 2000 – 31 Dec 2013).

Population attributable fractions have been adjusted for all the risk factors in the figure, as well as age, sex, race, HIV transmission risk, diabetes, and stage 4 chronic kidney disease.

Population attributable traction (PAF)

HIV PREVENTION

• IPERGAY – subanalysis
  – Suggests that intermittent PrEP is effective in MSM with less frequent intercourse
  – 6 infections with PCB vs. none on TDF/FTC
  – Median 5 episodes of sex per month, 9.5 TDF/FTC pills per month

• HPTN 077 – Cabotegravir LA in low risk Men and Women
  – Every 8 week cabotegravir LA met PK targets and was safe
  – Comparative trials vs. TDF/FTC in high risk MSM and women is sub-Saharan Africa are underway and about to start (respectively).

• MK-8591 (NRTTI)
  – Effective protection in a macaque challenge model

Anton et al IAS 2017 and Landovitz et al and Markowitz et al IAS 2017
Acknowledgements

• Beatriz Grinsztejn
• Bach-Yen Nguyen
• Ken Atuff
• Mark Warshberg
• David Piontkowski

• Sonia Napravnik
• Thibaut Deyde
• Chuck Fields
• Anton Pozniak
• Kathleen Squires

Question and Answer Period

• Use the microphones or Q-cards for questions
• If you are participating via the live webcast, please email your questions to RWCCwebcast@iasusa.org