Financial Relationships With Commercial Entities

- Dr Eron received research grants awarded to his institution from Gilead Sciences, Inc, Janssen Therapeutics, Inc, and ViV Healthcare. He has served as a consultant to AbbVie, Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Therapeutics, Inc, Merck, and ViV Healthcare (Updated 02/22/17)
Outline of the Talk

• HIV Epidemiology
• Where we are with Antiretroviral Therapy
• New Antiretroviral therapy – what the future may hold
• New uses of existing ART
  – Dolutegravir/ritonavir, dolutegravir mono-therapy, DTG/3TC for maintenance
• Antiretroviral Resistance
• Complications of HIV and its treatment
  – Lung cancer, cardiovascular risk
• Prevention of STI
  – Post exposure STI 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
State by State Estimated Incidence, Prevalence and Undiagnosed in US
Satcher et al CDC CRIO 2017

- Eight states had a significantly decreasing estimated incidence
  - Wash DC (10% per year), Georgia (6.1%), Illinois (4.3%), Maryland (7.5%), New York (5.1%), North Carolina (4.9%), Pennsylvania (7.3%), Texas (2.4%)

- Multiple states had increasing prevalence with NY having >145,000 PWLHIV in 2014

- 19.2% of infections were undiagnosed in Texas (highest percentage)

- Five states (California, Georgia, Texas, New York and Florida) accounted for 52% of incident infections and 51% of undiagnosed infections in 2014
Viral load tests among 630,965 persons living with diagnosed HIV, 2014, 23 US Jurisdictions

<table>
<thead>
<tr>
<th>Median: 2 tests Mean: 1.8 tests</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more VLs</td>
<td>339,515</td>
<td>54%</td>
</tr>
<tr>
<td>One VL</td>
<td>92,309</td>
<td>14%</td>
</tr>
<tr>
<td>No VL</td>
<td>199,141</td>
<td>32%</td>
</tr>
</tbody>
</table>

Viral suppression among 630,965 persons living with diagnosed HIV, 2014, 23 US Jurisdictions

<table>
<thead>
<tr>
<th>Last VL suppressed in 2014</th>
<th>Durable VS in 2014</th>
<th>Namer virally suppressed in 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 369,451)</td>
<td>(n = 309,472)</td>
<td>(n = 31,149)</td>
</tr>
<tr>
<td>57%</td>
<td>48%</td>
<td>8%</td>
</tr>
</tbody>
</table>

- Includes persons with only 1 VL in 2014 and last VL in 2013 <200 copies/mL

**Increased Persistence of Initial ART With INSTI-containing Regimens**

<table>
<thead>
<tr>
<th>Discontinuation</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>0.49 (0.35, 0.69)</td>
</tr>
<tr>
<td>bPI</td>
<td>1.24 (1.05, 1.47)</td>
</tr>
<tr>
<td>Other</td>
<td>1.47 (1.24, 1.75)</td>
</tr>
<tr>
<td>NRTI</td>
<td>2.98 (2.38, 3.74)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

**InCRO 2017**

**ANTIRETROVIRAL THERAPY**

Whites, MSM and older individuals were more likely to have durable suppression.
Monoclonal Antibodies for HIV treatment
Not bNAb

• Ibalizumab
  – Binds second domain of CD4 molecule
  – IV administration every 2 week – Phase 3 study: IV infusion every 2 weeks
  – 7 days functional mono-therapy in highly experienced patients (35% resistant to multiple agents in 4 or more classes). Then optimization of treatment
    – 40 patients enrolled with mean CD4 cell count of 150 cells/mm³
    – 83% had > 0.5 log₁₀ decline and 60% had a ≥ 1.0 log₁₀ decline over 7 days
    – 43% had HIV RNA < 50 c/mL at week 24
    – Anticipated NDA filing this year
  
  Lewis et al CROI 2017

• Pro-140 (Lalezari et al CROI 2017)
  – Binds to CCR5 molecule – R5 only virus
  – Pilot study – single drug maintenance of suppression – every 2 week sub injection
  – 31 participants began a 12 week study – 16 remained suppressed on mono-therapy and entered extension phase. At 2 yrs 10/16 remained < 50 c/mL
  – UB-421 (Wang et al CROI 2017)
    – Binds first domain of CD4 molecule
    – Pilot study – single drug maintenance of suppression – weekly or every other week IV infusion for 8 doses
      – 14/14 and 15/15 remained suppressed for 2 or 4 months respectively. 3 and 4 participants in each arm had single HIV RNA blip.
      – All re-suppressed on cART immediately following infusion period (or after viral rebound off all therapy in 5 participants)
New NRTI with broad activity against resistant variants (GS-9131)

GS-9131 (Prodrug of GS-9148)

EC_{50} = 0.29 - 48 nM in PBMCs

EC_{50} = 10.6 µM in MT2 cells

HIV-1 RT = 2.3 µM

DNA Pol γ = >300 µM

GS-9148 - diphosphate (Active Metabolite)

HIV-1 RT Chain-terminator

Inside Cell

Intracellular Metabolism of GS-9131

Plasma

- GS-9131 exhibited potent activity against HIV-1 with most patterns of NRTI resistance

Unboosted Protease Inhibitor (GS-PI1)

- Similar in vitro activity to darunavir and atazanavir
  - Greater impact of protein adjustment
  - High barrier to resistance in in vitro selection experiments
  - Activity against many PI-resistant variants
  - Very slow clearance in human liver microsomes
  - 12-14 hour ½ life in rats and dogs
    - Compared to 0.4 to 1.3 DRV and ATV

White, CROI, 2017, Presentation # 436

NRTI Mutation Susceptibility of HIV-1 to ARVs (Fold change vs WT)

<table>
<thead>
<tr>
<th>NRTI Mutation</th>
<th>GS-9131</th>
<th>GS-9148</th>
<th>TFV</th>
<th>FTC</th>
<th>ABC</th>
<th>ddI</th>
<th>ZDV</th>
<th>d4T</th>
</tr>
</thead>
<tbody>
<tr>
<td>K65R</td>
<td>0.56</td>
<td>0.66</td>
<td>1.98</td>
<td>8.22</td>
<td>2.46</td>
<td>1.87</td>
<td>0.23</td>
<td>1.22</td>
</tr>
<tr>
<td>M184V</td>
<td>0.31</td>
<td>0.43</td>
<td>0.47</td>
<td>&gt;110</td>
<td>2.82</td>
<td>1.29</td>
<td>0.19</td>
<td>0.61</td>
</tr>
<tr>
<td>L74V</td>
<td>0.61</td>
<td>0.66</td>
<td>0.57</td>
<td>1.30</td>
<td>1.93</td>
<td>1.34</td>
<td>0.22</td>
<td>0.86</td>
</tr>
<tr>
<td>L74I</td>
<td>0.67</td>
<td>0.75</td>
<td>0.82</td>
<td>0.92</td>
<td>1.13</td>
<td>0.90</td>
<td>0.40</td>
<td>0.74</td>
</tr>
<tr>
<td>K65R+M184V</td>
<td>0.40</td>
<td>0.42</td>
<td>1.20</td>
<td>&gt;110</td>
<td>7.72</td>
<td>3.16</td>
<td>0.17</td>
<td>0.85</td>
</tr>
<tr>
<td>K70E+M184V</td>
<td>0.28</td>
<td>0.31</td>
<td>0.58</td>
<td>&gt;110</td>
<td>6.19</td>
<td>1.52</td>
<td>0.10</td>
<td>0.60</td>
</tr>
<tr>
<td>L74V+M184V</td>
<td>0.40</td>
<td>0.38</td>
<td>0.35</td>
<td>&gt;110</td>
<td>6.41</td>
<td>2.35</td>
<td>0.12</td>
<td>0.73</td>
</tr>
<tr>
<td>4'TAM (4Y)</td>
<td>0.68</td>
<td>0.69</td>
<td>1.69</td>
<td>3.60</td>
<td>2.15</td>
<td>1.05</td>
<td>9.85</td>
<td>1.51</td>
</tr>
<tr>
<td>4'TAM (4F)</td>
<td>0.73</td>
<td>0.83</td>
<td>1.36</td>
<td>3.88</td>
<td>1.57</td>
<td>0.96</td>
<td>9.60</td>
<td>1.38</td>
</tr>
<tr>
<td>4'TAM (4Y)+M184V</td>
<td>0.41</td>
<td>0.45</td>
<td>0.85</td>
<td>&gt;110</td>
<td>4.66</td>
<td>1.35</td>
<td>1.91</td>
<td>1.35</td>
</tr>
<tr>
<td>6TAMs</td>
<td>1.50</td>
<td>1.65</td>
<td>4.2</td>
<td>5.70</td>
<td>4.70</td>
<td>1.86</td>
<td>379</td>
<td>3.20</td>
</tr>
<tr>
<td>6TAMs+M184V</td>
<td>0.75</td>
<td>0.85</td>
<td>2.07</td>
<td>&gt;110</td>
<td>9.60</td>
<td>1.96</td>
<td>32</td>
<td>2.54</td>
</tr>
<tr>
<td>T69insertion</td>
<td>1.11</td>
<td>1.39</td>
<td>5.70</td>
<td>7.68</td>
<td>5.59</td>
<td>3.1</td>
<td>&gt;664</td>
<td>3.57</td>
</tr>
<tr>
<td>Q151M</td>
<td>0.97</td>
<td>0.89</td>
<td>0.78</td>
<td>1.40</td>
<td>3.59</td>
<td>3.99</td>
<td>1.97</td>
<td>3.20</td>
</tr>
<tr>
<td>Q151M Complex</td>
<td>3.79</td>
<td>3.79</td>
<td>1.53</td>
<td>4.67</td>
<td>6.96</td>
<td>8.22</td>
<td>46</td>
<td>10</td>
</tr>
<tr>
<td>Q151M Complex+M184V</td>
<td>0.88</td>
<td>0.96</td>
<td>1.24</td>
<td>&gt;110</td>
<td>&gt;35</td>
<td>88</td>
<td>7.06</td>
<td></td>
</tr>
</tbody>
</table>
Capsid Inhibitor: GS-CA1 Mode of Action Summary

Tse et al CROI 2017 Abstract 38

- EC_{50} 140 picomolar in PBMC, Active across all tested subtypes, resistant variants low fitness
- Very long ½ life in RAT model – 9x above paEC_{95} 10 weeks after single injection

ANTIRETROVIRAL THERAPY – NEW STUDIES OF APPROVED AGENTS

SWORD-1 and SWORD-2  Phase III Study Design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Early switch phase</th>
<th>Late switch phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>DTG + RPV (N=513)</td>
<td>DTG + RPV</td>
<td>DTG + RPV</td>
</tr>
<tr>
<td>Week 52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 148</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inclusion criteria:
- On stable CAR >6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1 RNA <50 c/mL during the 12 months before screening
- HBV negative

Countries:
- Argentina
- Australia
- Belgium
- Canada
- France
- Germany
- Italy
- Netherlands
- Russia
- Spain
- Taiwan
- United Kingdom
- United States

Primary endpoint:
- Subjects with VL <50 c/mL at 48 weeks, snapshot (ITT-E snapshot)*

*10% non-inferiority margin for individual studies; 8% non-inferiority margin for pooled data.
**Snapshot Outcomes at Week 48 (Pooled)**

**Virologic outcomes**

- ** DTG + RPV (n=513) **
  - 95% (95% CI)
- ** CAR (n=511) **
  - 95% (95% CI)

**Adjusted treatment difference (95% CI)***

- 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

**Virologic success**

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV</th>
<th>CAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>486</td>
<td>485</td>
</tr>
</tbody>
</table>

**Virologic non-response**

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV</th>
<th>CAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%)</td>
<td>19</td>
<td>1</td>
</tr>
</tbody>
</table>

**Data pooled across SWORD-1 and SWORD-2.**

---

**ANRS 167 Lamidol Trial**

**July et al CROI 2017**

**METHODS**

- **Trial design**
  - Non-comparative open-label, single arm, multicenter trial with 2 phases:
    - **Phase 1** (8 weeks): third agent replaced by DTG 50 mg QD in combination with the current 2 NRTIs backbone
    - **Phase 2** (48 weeks): DTG 50mg + TMC 300mg QD for 48 weeks. Only patients with plasma HBV RNA (pVL) ≤ 50 c/mL at W8 were included in phase 2

- **CD4 nadir > 200 c/mL, first line ART (up to 2 modifications allowed provided no failure), previous wild-type genotype**
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 (1/12 vs 8/96, p=0.03). Endpoint > 200 c/mL
Comprehensive Assessment of Resistance Mutations Selected by Dolutegravir (DTG) in Subjects Failing DTG-Monotherapy after Switching from other Therapies (Redomo Study)

- 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

<table>
<thead>
<tr>
<th>#</th>
<th>In code</th>
<th>Prior IsSTI</th>
<th>without VF</th>
<th>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-GRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>B001</td>
<td>None</td>
<td>768</td>
<td>&lt;37</td>
<td>330 (8)</td>
<td>146(10)</td>
<td>1393(18)</td>
<td>98% (PC)</td>
<td>8</td>
<td>330</td>
<td>8</td>
<td>330</td>
</tr>
<tr>
<td>1</td>
<td>B002</td>
<td>RAL</td>
<td>0 (LLV)</td>
<td>86</td>
<td>80 (16)</td>
<td>171 (18)</td>
<td>122 (32)</td>
<td>3228 (48)</td>
<td>98% (PC)</td>
<td>16</td>
<td>80</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>B003</td>
<td>None</td>
<td>312</td>
<td>&lt;37</td>
<td>26180 (20)</td>
<td>6014 (22)</td>
<td>10560 (28)</td>
<td>98% (PC)</td>
<td>20</td>
<td>26180</td>
<td>28</td>
<td>6014</td>
</tr>
<tr>
<td>3</td>
<td>B004</td>
<td>RAL</td>
<td>12</td>
<td>249</td>
<td>123 (12)</td>
<td>1350 (24)</td>
<td>22170 (25)</td>
<td>82% (PC)</td>
<td>0</td>
<td>123</td>
<td>32</td>
<td>22170</td>
</tr>
<tr>
<td>4</td>
<td>B007</td>
<td>EGV</td>
<td>240</td>
<td>&lt;37</td>
<td>57 (52)</td>
<td>51 (64)</td>
<td>&lt;37 (88)</td>
<td>100% (PC)</td>
<td>52</td>
<td>57</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>B008</td>
<td>None</td>
<td>480</td>
<td>&lt;50</td>
<td>190 (32)</td>
<td>1350 (36)</td>
<td>40000 (40)</td>
<td>88% (PC)</td>
<td>32</td>
<td>190</td>
<td>36</td>
<td>1350</td>
</tr>
<tr>
<td>6</td>
<td>M001</td>
<td>RAL</td>
<td>232</td>
<td>21</td>
<td>55 (2)</td>
<td>168 (13)</td>
<td>239 (15)</td>
<td>60% (SQ)</td>
<td>0</td>
<td>55</td>
<td>16</td>
<td>239</td>
</tr>
<tr>
<td>7</td>
<td>M002</td>
<td>None</td>
<td>228</td>
<td>&lt;20</td>
<td>538 (24)</td>
<td>11000 (28)</td>
<td>100% (SQ)</td>
<td>24</td>
<td>538</td>
<td>29</td>
<td>11000</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>C001</td>
<td>EGV</td>
<td>20</td>
<td>&lt;50</td>
<td>306 (24)</td>
<td>583 (28)</td>
<td>100% (SQ)</td>
<td>24</td>
<td>306</td>
<td>24</td>
<td>306</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>B005</td>
<td>RAL, EGV</td>
<td>432</td>
<td>&lt;37</td>
<td>179 (13)</td>
<td>71 (14)</td>
<td>56 (16)</td>
<td>98% (PC)</td>
<td>13</td>
<td>179</td>
<td>14</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>B006</td>
<td>None</td>
<td>172</td>
<td>&lt;37</td>
<td>355 (72)</td>
<td>1355 (76)</td>
<td>1397 (80)</td>
<td>100% (PC)</td>
<td>72</td>
<td>355</td>
<td>76</td>
<td>355</td>
</tr>
</tbody>
</table>

Median (IQR): 236 (186-402) 20 (11-28) 190 (102-343) 29 (20-34) 330 (181-3682)

ANTIRETROVIRAL THERAPY – RESISTANCE

Low Prevalence of Drug Resistance with Modern Agents – Davy et al CROI 2017

Figure 1. Prevalence of resistance among patients in care by calendar year.
Among 685 patients initiating ART 2007-2014 and still in care in 2015, we observed the following resistance profile in 2015:
- any class: 21% (95% CI 17%, 24%)
- NNRTI: 17% (14%, 20%)
- NRTI: 6% (4%, 8%)
- PI: 2% (1%, 4%)
- 2 or more classes: 5% (3%, 7%)
- 3 or more classes: 1% (0%, 2%)

Figure 2. Prevalence of resistance among patients with virologic failure by calendar year.
ARS Question #3
In sub-Saharan Africa pre-treatment antiretroviral drug resistance is:

1. Uncommon (< 5%) of treatment naïve patients
2. Occurring at similar rates to the US but with frequent NRTI and NNRTI resistance
3. Occurring at similar rates to the US but like the US mostly NNRTI resistance with a single mutation
4. Very common (> 20%) of treatment naïve patients
5. Unsure

Pretreatment Drug Resistance in TASP trial

- Prevalence of PDR in TASP
- Distribution of Drug Resistance Mutations per ARV class in all ART-naive

- PDR prevalence ~9% in both recently- and chronically infected participants
- 2x more low-level variants detected with NGS
- NNRTI mostly compromised by PDR, but NRTIs are still active

Derache A et al. CROI 2017 – abstract # 43

HIV AND COMPLICATIONS
The Association between Cardiovascular Disease and Contemporarily used Protease Inhibitors

Baseline Characteristics

The Large Gap Between Statin Eligibility and Prescription in the NA-ACCORD

Figure 1: Trends in statin treatment gap (the difference between those indicated according to ATP III and prescribed statins), 2001-2013
ARS Question #4
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)

HIV AND CURE
CROI 2017
Update From Seattle

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Professor of Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

New York, New York, February 24, 2017

Acknowledgements

- Beatriz Grinsztejn
- Jean-Michel Molina
- Bach-Yen Nguyen
- Keri Altoff
- Mark Wainberg
- David Piontkowsky
- Sonia Napravnik
- Thibaut Dany
- Chuck Hicks
- Jintanat Ananworanich

CROI 2017
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New York, New York, February 24, 2017