Update on HIV Drug Resistance

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Learning Objectives
Upon completion of this presentation, learners should be better able to:

- Review resistance patterns to newest antiretroviral drugs
- Discuss implications of drug resistance on sequencing of antiretroviral regimens

Off-Label Disclosure
- Etravirine is not approved for use in treatment-naïve patients
Etravirine and Rilpivirine
Etravirine

- TMC125 identified through screening for activity against NNRTI-resistant viruses (K103N)
- In vitro passage experiments suggested high genetic barrier to resistance
- Known and novel NNRTI resistance mutations identified through in vitro passage experiments
  - L100I, Y181C, G190E, Y318F
  - V179I/F
- Data from DUET and phase 2 trials identified 17 clinically significant ETV resistance mutations
DUET-1 and -2: Etravirine resistance-associated mutations

- ETV mutations (n=17) weighted based upon impact on response (weight factor)$^1$:  
  - 3.0: Y181I/V  
  - 2.5: L100I, K101P, Y181C, M230L  
  - 1.5: V106I, V179F, E138A, G190S  
  - 1.0: V90I, A98G, K101E/H, V179D/T, G190A

- Most common resistance mutations emerging at ETV failure in DUET trials:  
  - V179F/I and Y181C/I$^2,3$

Phase 2 pilot study of ETR in treatment-naïve patients (SENSE)

- ART-naïve patients randomized to ETR (400 mg QD; N=79) or EFV (N=78) plus 2 NRTI

Gazzard et al AIDS 2011
### Table 2. Virological failures by treatment arm: HIV RNA levels and detection of genotypic resistance (IAS-USA or Bennett lists).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 48</th>
<th>FU</th>
<th>Resistance mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Etravirine arm (n=4)³</td>
</tr>
<tr>
<td>1</td>
<td>122 000</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>700</td>
<td>124</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>78 800</td>
<td>&lt;50</td>
<td>100, 104</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>178 000</td>
<td>&lt;50</td>
<td>85</td>
<td>68</td>
<td>&lt;50</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>118 000</td>
<td>&lt;50</td>
<td>114</td>
<td>&lt;50</td>
<td>50</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Efavirenz arm (n=7)</td>
</tr>
<tr>
<td>1</td>
<td>48 900</td>
<td>&lt;50</td>
<td>104</td>
<td>&lt;50</td>
<td>10700</td>
<td>Missing</td>
</tr>
<tr>
<td>2</td>
<td>3160</td>
<td>&lt;50</td>
<td>1350</td>
<td>240, 62</td>
<td>&lt;50, 73</td>
<td>Not amplified</td>
</tr>
<tr>
<td>3</td>
<td>397 000</td>
<td>123</td>
<td>111</td>
<td>&lt;50</td>
<td>81</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>3 810 000</td>
<td>107</td>
<td>129</td>
<td>56</td>
<td>&lt;50</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>240 000</td>
<td>&lt;50</td>
<td>&lt;50</td>
<td>2180</td>
<td></td>
<td>V106l + M184l</td>
</tr>
<tr>
<td>6</td>
<td>82 800</td>
<td>&lt;50</td>
<td>72</td>
<td>&lt;50</td>
<td>81600</td>
<td>K103N</td>
</tr>
<tr>
<td>7</td>
<td>412 000</td>
<td>33400</td>
<td>51 800</td>
<td>26 100</td>
<td></td>
<td>K103N + M184V + P225H</td>
</tr>
</tbody>
</table>

¹Gazzard et al AIDS 2011
DUET-1 and -2: Predictors of ETV Response and Resistance at Failure

Vingerhoets J et al. AIDS 2010
Rilpivirine (TMC278)

- Like etravirine, selected by screening for compounds active against viruses with K103N
- **Similar activity profile as etravirine**
  - Unaffected by K103N
  - Modest effect of Y181C
- **Slow to select resistance in vitro**

Azijn et al. Antimicrob Agents Chemother 2010
ECHO, THRIVE: Rilpivirine (TMC278) vs EFV in Treatment-Naive Patients

- Randomized, double-blind phase III trials

**Stratification by BL HIV-1 RNA < 100,000 vs ≥ 100,000 copies/mL, NRTI use**

Wk 48 primary analysis

Wk 96 final analysis

**ECHO** (N = 690)
- Treatment-naive,
- HIV-1 RNA ≥ 5000 copies/mL
- no NNRTI RAMs,
- susceptible to NRTIs

**THRIVE** (N = 678)

Rilpivirine 25 mg QD + TDF/FTC 300/200 mg QD (n = 346)

EFV 600 mg QD + TDF/FTC 300/200 mg QD (n = 344)

Rilpivirine 25 mg QD + 2 NRTIs† (n = 340)

EFV 600 mg QD + 2 NRTIs† (n = 338)

*THRIVE only. †Selected by investigator from ABC/3TC, TDF/FTC, ZDV/3TC.

## Drug resistance in ECHO and THRIVE

<table>
<thead>
<tr>
<th></th>
<th>TMC278 N=686</th>
<th>EFV N=682</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure with resistance data, n</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td>No NNRTI(^1) or NRTI(^2) RAMs</td>
<td>29%</td>
<td>43%</td>
</tr>
<tr>
<td>Emergent(^\d) NNRTI(^1) RAMs</td>
<td>63%</td>
<td>54%</td>
</tr>
<tr>
<td>– Most frequent NNRTI RAM</td>
<td>E138K</td>
<td>K103N</td>
</tr>
<tr>
<td>Emergent(^\d) NRTI(^2) RAMs</td>
<td>68%</td>
<td>32%</td>
</tr>
<tr>
<td>– Most frequent NRTI RAM</td>
<td>M184I</td>
<td>M184V</td>
</tr>
</tbody>
</table>

- 31/62 (50%) of TMC278 failures were phenotypically resistant to TMC278
  - Of these, 90% were phenotypically cross-resistant to etravirine

Molina et al. Lancet. 2011
Cohen et al. Lancet 2011
Early emergence of M184I in patients receiving 3TC monotherapy

Schuurman et al J Infect Dis 1995
M184V is fitter than M184I

Larder et al. Science 1995
Replication capacity of E138K and M184I mutants in presence of ETV and/or 3TC

Replication capacity of E138K and M184I mutants in presence of RPV and 3TC

(A) 0.2 nM RPV

(B) 0.08 nM RPV + 8 μM 3TC

Hu & Kuritzkes 19th CROI, Seattle, WA 2012
Virion-associated RT activity of HIV-1 wild-type and mutant viruses

Elvitegravir
Primary Integrase Strand Transfer Inhibitor (INSTI) Resistance-Associated Mutations (RAMs)

### EVG Primary INSTI-RAMs

<table>
<thead>
<tr>
<th></th>
<th>IN</th>
<th>G</th>
<th>H</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir</td>
<td>66</td>
<td>92</td>
<td>97*</td>
<td>147</td>
</tr>
<tr>
<td>RAL Primary INSTI-RAMs</td>
<td>148</td>
<td>155</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### RAL Primary INSTI-RAMs

<table>
<thead>
<tr>
<th></th>
<th>IN</th>
<th>G</th>
<th>H</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>92</td>
<td>97*</td>
<td>143</td>
<td>148</td>
</tr>
<tr>
<td>155</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cross-study clinical development of INSTI-RAMs
*T97A may require additional mutations for resistance

Study Design 236-0102

Treatment naive (N = 700 planned)

- US & Puerto Rico
- Randomized 1:1
- Stratification by HIV-1 RNA (>100,000 c/mL)

Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48
- FDA snapshot analysis, 12% non-inferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5
Study Design 236-0103

Treatment naive (N = 700 planned)

- International
- Randomized 1:1
- Stratification by HIV-1 RNA (>100,000 c/mL)

Primary Endpoint: Proportion with HIV-1 RNA < 50 c/mL at Week 48
- FDA snapshot analysis, 12% non-inferiority margin
- HIV-1 RNA: Amplicor HIV-1 Monitor Test, version 1.5

DeJesus E, et al., CROI 2012; Seattle. Poster 627.
236-0102 and 236-0103: Results

Sax et al Lancet 2012; DeJesus et al Lancet 2012
**QUAD Virologic Failures with EVG Resistance show RAL Cross-resistance (>biological cut-off)**

<table>
<thead>
<tr>
<th>INSTI</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVG</td>
<td>&gt;198</td>
<td>149</td>
<td>111</td>
<td>54</td>
<td>51</td>
<td>44</td>
<td>36</td>
<td>36</td>
<td>28</td>
<td>23</td>
<td>5.6</td>
</tr>
<tr>
<td>RAL</td>
<td>28</td>
<td>6.2</td>
<td>3.8</td>
<td>6.0</td>
<td>12</td>
<td>3.6</td>
<td>3.0</td>
<td>11</td>
<td>3.3</td>
<td>8.7</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Biological Cut-Offs: EVG 2.5; RAL 1.5

Mead fold change value for EVG was >67-fold
Mean fold change value for RAL = 7.9-fold

Dolutegravir
### VIKING study results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort I, DTG 50 mg Once Daily (n = 27)</th>
<th>Cohort II, DTG 50 mg Twice Daily (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy at day 11</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary end point, no. (%)</td>
<td>21 (78)</td>
<td>23 (96)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA level, log_{10} copies/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>4.40 (0.79)</td>
<td>4.38 (0.74)</td>
</tr>
<tr>
<td>Day 11, mean (SD)</td>
<td>2.94 (1.01)</td>
<td>2.62 (0.78)</td>
</tr>
<tr>
<td>Change from baseline, mean (SD)</td>
<td>−1.45 (0.77)</td>
<td>−1.76 (0.54)</td>
</tr>
<tr>
<td>Model-adjusted change, mean (SD)</td>
<td>−1.45 (0.08)</td>
<td>−1.76 (0.09)</td>
</tr>
<tr>
<td>Adjusted treatment difference, mean (95% CI)</td>
<td></td>
<td>−0.32 (−0.57 to −0.06)(^b)</td>
</tr>
<tr>
<td><strong>Efficacy at week 24</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA load, copies/mL, no. (%)(^c)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>11 (41)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>&lt;400</td>
<td>14 (52)</td>
<td>20 (83)</td>
</tr>
</tbody>
</table>

\(^a\) Model adjusted for age, gender, race, at-risk group, previous baseline HIV-RNA load, prior ARV exposure, and randomized arm

\(^b\) Model adjusted for age, gender, race, at-risk group, and randomized arm

\(^c\) Model adjusted for age, gender, race, at-risk group, prior ARV exposure, randomized arm, and baseline HIV-RNA load
SAILING study design

HIV-1 ART-experienced, INI-naive
HIV-1 RNA >400 c/mL\(^a\)
1:1 Randomization
Stratified by HIV-1 RNA
(≤ or >50,000), DRV/r use and # of fully active drugs

Randomized Phase

DTG 50 mg QD +
RAL PBO + BR

RAL 400 mg BID +
DTG PBO + BR

Randomization

Week 24
Planned Interim

Week 48

\(^a\) At Screening and a second consecutive test >400 c/mL within 4 months prior to Screening (if Screening HIV-1 RNA >1000 c/mL, no additional HIV-1 RNA assessment was needed)
PBO, placebo; BR, background regimen

Pozniak et al, 20\(^{th}\) CROI, 2013; Abstract, 179LB
SAILING study results

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 24.

Week 24 adjusted difference in response (95% CI):
+9.7 in favor of DTG (3.1%, 15.9%); P=0.003

*Adjusted difference based on stratified analysis adjusting for Baseline HIV-1 RNA (≤50,000 c/mL vs >50,000 c/mL), DRV/r use without primary PI mutations and Baseline PSS (2 vs <2)
SINGLE study design

Primary endpoint:
Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis,
-10% non-inferiority margin with pre-specified tests for superiority

Secondary endpoints:
Tolerability, long-term safety, immunologic, health outcome and viral resistance

Walmsley et al ICAAC 2012
**SINGLE: primary endpoint analysis**

- **DTG 50mg + ABC/3TC QD** was statistically superior to **TDF/FTC/EFV** at week 48 (primary endpoint).
- Subjects receiving **DTG + ABC/3TC** achieved virologic suppression faster than **TDF/FTC/EFV**, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (TDF/FTC/EFV; p<0.0001)

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**WK 48 difference in response (95% CI):**
+7.4% (+2.5% to +12.3%); p=0.003
### SINGLE: Resistance at virologic failure

<table>
<thead>
<tr>
<th></th>
<th>DTG 50mg +ABC/3TC QD (N=414)</th>
<th>TDF/FTC/EFV (N=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with PDVF</td>
<td>18 (4%)</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>PDVF genotypic pop.</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>PDVF Genotypic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RT Results at Bas.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and PDVF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI tmt-emergent</td>
<td>0</td>
<td>1(K65R)</td>
</tr>
<tr>
<td>major mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI tmt-emergent</td>
<td>0</td>
<td>4 (K101E, K103N, G190A)*</td>
</tr>
<tr>
<td>major mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDVF Genotypic</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>(IN Results at Bas.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and PDVF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INI-r tmt-emergent</td>
<td>0**</td>
<td>0</td>
</tr>
<tr>
<td>major substitution</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* n=1 with K101E, n=1 with K103N, n=1 with G190A and n=1 with K103N+G190A

**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility
Implications for ART sequencing*

- Etravirine unlikely to be useful as “salvage” NNRTI following rilpivirine failure
  - Impact of E138K on efavirenz and nevirapine uncertain
- Raltegravir and elvitegravir cannot be used sequentially
- Dolutegravir likely to be active in setting of limited raltegravir and elvitegravir resistance
- Utility of raltegravir and elvitegravir after initial dolutegravir failure uncertain

*Opinion of Daniel R. Kuritzkes, MD, expert.