HIV Drug Resistance Update 2007

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Outline

- Indications for resistance testing
- Epidemiology of drug resistance
- Risk of triple class resistance and failure in HIV positive patients
- Impact of drug resistance on survival
- Choice of initial ART and impact on resistance in cohort studies and clinical trials
- Using resistance testing to choose among ritonavir-boosted PIs in salvage (darunavir and tipranavir)
- Tropism testing and development of resistance to CCR5 antagonists
- Virologic predictors of failure to etravirine
- Virologic predictors of failure to HIV integrase inhibitors
When to Use Resistance Testing

<table>
<thead>
<tr>
<th></th>
<th>IAS-USA(^{[1]})</th>
<th>DHHS(^{[2]})</th>
<th>European(^{[3]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary/acute</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Postexposure prophylaxis</td>
<td>—</td>
<td>—</td>
<td>Recommend</td>
</tr>
<tr>
<td>Chronic, Rx naive</td>
<td>Consider(^{*})</td>
<td>Recommend</td>
<td>Strongly consider(^{*})</td>
</tr>
<tr>
<td>Failure</td>
<td>Recommend</td>
<td>Recommend</td>
<td>Recommend</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Recommend</td>
<td>—</td>
<td>Recommend(^{*})</td>
</tr>
<tr>
<td>Pediatric</td>
<td>—</td>
<td>—</td>
<td>Recommend(^{†})</td>
</tr>
</tbody>
</table>


Question 1

For which of the following classes of drugs has the prevalence of drug resistance in ARV-naive patients been highest in the US over the last 5 years?

a. NRTIs
b. NNRTIs
c. Pis
d. Entry inhibitors
For which of the following classes of drugs has the prevalence of drug resistance in ARV-naive patients been highest in the US over the last 5 years?

- a. NRTIs
- b. NNRTIs
- c. PIs
- d. Entry inhibitors

Primary Drug Resistance: March 2003 – October 2006

- Data from 409 sites in 11 states
- STD clinics (33.2%), counseling and testing centers (24.7%), private practices (7.8%), hospitals (6.8%), other/unknown (33.5%)
- Data from Colorado, Illinois, Louisiana, Maryland, Michigan, Massachusetts, Mississippi, North Carolina, Washington, South Carolina, Virginia

- Prevalence of Drug Resistance:
  - Any class: 10.4%
  - NRTIs: 3.5%
  - NNRTIs: 6.9%
  - PIs: 2.4%
  - ≥ 2 classes: 1.9%

Wheeler et al, 14th CROI, Los Angeles, 2007, Abstract 648
UK CHIC Study: Triple-Class Exposure and Failure

6 large HIV-treatment centers in southeast United Kingdom.

![Graph showing UK CHIC Study: Triple-Class Exposure and Failure](image)

Long-Term Risk of Developing Drug Resistance on HAART: UK CHIC Study


![Graph showing Long-Term Risk of Developing Drug Resistance on HAART: UK CHIC Study](image)

Overall risk of treatment failure: 38% over 6 years.
**Increased Disease Progression With Class-Wide Drug Resistance**

Cumulative Survival or Remaining Free of AIDS Events Stratified by Class-Wide Drug Resistance (CWDR)

n=623 patients failed HAART and underwent genotypic testing, then were followed for a median of 19 months (IQR 12-29). Multivariate Cox's model: increased risk of death was significantly associated with higher HIV RNA, prior AIDS, and detection of 3 CWR (hazard ratio 5.34 [95% CI 1.76-16.24]).


**Resistance Testing and Clinical Outcomes**

- **HIV Outpatient Study (HOPS) cohort**
  - Resistance testing in ART-experienced patients (n=1056)
  - No resistance testing in ART-experienced patients (n=3130)

- **Resistance testing associated with**
  - White
  - <40 years old
  - Privately insured
  - Lower CD4+
  - Higher HIV RNA

- In MV analysis, those with resistance testing had a 59% reduced risk of death

Transmitted Drug Resistance: A Global Concern

Transmitted Drug Resistance (Any Class)

Prevalence (%) of Transmitted Drug Resistance

- Europe 2002/2003 (n=1083)
  - 9.1%
- Spain 1997-2006 (n=358)
  - 12.6%
- France 2003-04 (n=323)
  - 12.3%
- Germany 2000-05 (n=831)
  - 9.0%
- Portugal 2003 (n=178)
  - 8.4%
- UK 2004-06 (n=239)
  - 7.1%
- USA 2003 (n=317)
  - 10.0%


- Madrid cohort
  - Patients initiating antiretroviral therapy
- From 2000-2006, there was a significant decline in the proportion of patients:
  - Meeting criteria for resistance testing (HIV RNA >1000 copies/mL) (P<0.0001)
  - With therapeutic failure (sustained HIV RNA >1000 copies/mL after 6 months of HAART) (P<0.0001)
- Declines may be due to greater efficacy of new regimens

Incidence (%) of HIV RNA >1000 Copies/mL and First Therapeutic Failures

<table>
<thead>
<tr>
<th>Year</th>
<th>HIV RNA &gt;1000 Copies/mL</th>
<th>First Therapeutic Failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>14.4</td>
<td>100</td>
</tr>
<tr>
<td>2001</td>
<td>10.7</td>
<td>61.2</td>
</tr>
<tr>
<td>2002</td>
<td>11.1</td>
<td>57.3</td>
</tr>
<tr>
<td>2003</td>
<td>10.2</td>
<td>56.6</td>
</tr>
<tr>
<td>2004</td>
<td>7.8</td>
<td>62.3</td>
</tr>
<tr>
<td>2005</td>
<td>4.6</td>
<td>38.1</td>
</tr>
<tr>
<td>2006</td>
<td>3.4</td>
<td>43.9</td>
</tr>
</tbody>
</table>

n values: total number of patients treated.

Hernandez R, et al. 8th ICDTHIV; 2006; Glasgow, United Kingdom. Abstract P212.
Transmitted drug resistance

- Studies report prevalence of drug resistance in ARV-naïve patients:
  - Newly infected (11–15%)
  - Newly diagnosed (7–11%)
- Persistence of transmitted resistant virus in 14 patients
  - NNRTI resistance in 10/14 patients (median follow-up 2.1 years)
  - Resistant virus persistently detectable in 13/14 patients
  - Mean time to first detectable wt/resistant mixture was 103 weeks (95% CI: 49–216 weeks)
- Response to therapy in patients with transmitted resistance (AIEDRP Cohort)
  - NNRTI (n=67), PI (n=18), NRTI (n=25): some with MDR virus
  - 45% (38/84) failed to suppress, best response in those receiving >2 active drugs (p=0.01)

Little S, et al. 14th CROI, Los Angeles 2007, #60

PREPARE Study: Drug Resistance in US Treatment-Naïve Patients

IAS-USA Defined Resistance Mutations

- 2000 (n=251)
- 2003 (n=405)
- 2001 (n=411)
- 2004 (n=522)
- 2002 (n=205)
- 2005 (n=546)

Question 2: Virologic failure with which of the following regimens is likely to lead to multi-class resistance?

a. zidovudine, lamivudine, abacavir
b. tenofovir, emtricitabine, lopinavir/ritonavir
c. zidovudine, lamivudine, efavirenz
d. tenofovir, emtricitabine, efavirenz
**Emergence of drug resistance after first line combination therapy in the Swiss cohort study**

- Combination ARV therapy started Jan 1999 – Dec 2005 (n=1323)
  - Boosted PI (n=518)
  - NNRTI (n=805)
- Viral failure by third agent: in previously suppressed patients or HIV RNA >500 c/mL after more than 180 days of treatment
  - Boosted PI (n=4.6%)
  - NNRTI (n=5.6%)
  - No difference by regimen for virologic failure, but more discontinuations for adverse events with boosted PIs

**Conclusion**
- ARV efficacy similar for all groups but more resistance emerged with NNRTI-based regimens

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**Resistance emergence, on therapy, at time of failure (ACTG 5142)**

<table>
<thead>
<tr>
<th></th>
<th>LPV/RTV + 2 NRTIs (n = 253)</th>
<th>EFV + 2 NRTIs (n = 250)</th>
<th>LPV/RTV + EFV (n = 250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed VF,* n</td>
<td>94</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>Genotypic assays, n</td>
<td>52</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>NRTI mutations, n (%)</td>
<td>8 (15)</td>
<td>11 (33)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>• M184I/V, n</td>
<td>7</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>• K65R, n</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>NNRTI mutations, n (%)</td>
<td>2 (4)</td>
<td>16 (48)</td>
<td>27 (69)</td>
</tr>
<tr>
<td>• K103N, n</td>
<td>0</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>Major PI mutations,† n</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mutations in 2 classes, n</td>
<td>2</td>
<td>10</td>
<td>2</td>
</tr>
</tbody>
</table>

*Defined as early: lack of suppression by 1 log₁₀ or rebound before Week 32; or late: failure to suppress to < 200 copies/mL or rebound after Week 32.
†Q30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, 90M.

Update on Genotypic Resistance Development in GS 934 Study

FTC/TDF + EFV (n=244)  
ZDV/3TC + EFV (n=243)  
\( p=0.02^{b} \)

<table>
<thead>
<tr>
<th>Genotyped</th>
<th>Any Resistance</th>
<th>EFV-R</th>
<th>M184V/I</th>
<th>K65R</th>
<th>TAMs</th>
<th>Wild Type</th>
</tr>
</thead>
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<td></td>
<td>19</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>21</td>
<td>13</td>
<td>10</td>
<td>0</td>
<td>6</td>
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</tr>
</tbody>
</table>

mITT population - N=22 pts with baseline NNRTI resistance excluded

a. Confirmed ≥ 400 copies/mL after week 8 or at discontinuation. Genotyping of 2 on ZDV/3TC failed for technical reasons.  
b. Fisher’s exact test

McColl D, et al. 11th EACS; Madrid, Spain; October 24-27, 2007. PS3.1/08.

Clinical cut-offs for genotypic scores

Genotype scores defined for RTV-boosted PIs in treatment-experienced subjects:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resistance mutations</th>
<th>Genotypic cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPV/RTV</td>
<td>L10I/R/V/F, L33F, M36I, M46I/L, I54M/L/T/V, I62V, L63P, A71I/L/V/T, G73A/C/F/T, V82A/F/S/T, I84V, L90M</td>
<td>&lt; 4</td>
</tr>
</tbody>
</table>

2. Pellegrin I, et al. ibid, H-1059;  
New r/PI Monogram Phenotype Clinical Cutoffs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lower Value Fold Change</th>
<th>Upper Value Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/RTV</td>
<td>&lt; 5.2</td>
<td>&lt; 5.2</td>
</tr>
<tr>
<td>FPV/RTV</td>
<td>&lt; 4.0</td>
<td>&gt; 11</td>
</tr>
<tr>
<td>LPV/RTV</td>
<td>&lt; 9.0</td>
<td>&gt; 55</td>
</tr>
<tr>
<td>SAQ/RTV</td>
<td>&lt; 2.3</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>TPV/RTV</td>
<td>&lt; 2.0</td>
<td>&gt; 8.0</td>
</tr>
<tr>
<td>DRV/RTV</td>
<td>&lt; 10.0</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

Coakley, 46th ICAAC, 2006, Abstract H-995

TPV and DRV Mutations and Phenotypic Cut-offs

Similarities and Differences in Key Mutations

<table>
<thead>
<tr>
<th>Drug</th>
<th>10V</th>
<th>13V</th>
<th>20VRV</th>
<th>33F</th>
<th>35G</th>
<th>36I</th>
<th>43T</th>
<th>46L</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV</td>
<td>11I</td>
<td></td>
<td></td>
<td>32I</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33F</td>
<td></td>
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</tr>
</tbody>
</table>

TPV

<table>
<thead>
<tr>
<th>47V</th>
<th>54A/M/V</th>
<th>58E</th>
<th>69K</th>
<th>74P</th>
<th>82L/T</th>
<th>83D</th>
<th>84V</th>
<th>89V</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>

DRV

<table>
<thead>
<tr>
<th>47V</th>
<th>50V</th>
<th>54L/M</th>
<th>73S</th>
<th>76V</th>
<th>82L/T</th>
<th>83D</th>
<th>84V</th>
<th>89V</th>
</tr>
</thead>
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</tbody>
</table>

Assay/ Cutoff | PhenoSense: FC for Reduced Activity | PhenoSense: FC for No Response | VircoTYPE: FC for Maximal Response | VircoTYPE: FC for Minimal Response |
<table>
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<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>TPV</td>
<td>≥ 2</td>
<td>≥ 8</td>
<td>&lt; 1.2</td>
<td>≥ 5.4</td>
</tr>
<tr>
<td>DRV</td>
<td>≥ 10</td>
<td>≥ 90</td>
<td>&lt; 3.4</td>
<td>≥ 96.9</td>
</tr>
</tbody>
</table>

Phenotypic and genotypic determinants of darunavir resistance

- Combined analysis of POWER 1, 2, 3
  - DRV/RTV 600 mg/100 mg BID +
  - OBR arms at Week 24; n=377
  - Phenotype by Antivirogram®
- Fold-change in EC50 strongest predictor of Week 24 outcome
  - Clinical cut-offs established at <10-fold, >40-fold
- Mutations associated with decreased response include
  - V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V
- Viruses with >3 DRV resistance mutations had median IC50 >10-fold

Weighing the mutations associated with a diminished response to darunavir

- Estimated increase in FC
  - < 2
  - 2 to 3
  - 3 to 4
  - > 4

- Mutations
  - V11I
  - I54L
  - G73S
  - L89V
  - V32I
  - L33F
  - I47V
  - I54M
  - L76V
  - I84V
  - I50V

Determined by multiple regression analyses of the 1,405 screening samples from the POWER 1, 2 and 3 studies
TITAN: Subgroup and resistance analyses

- New PI mutations: 21% of DRV and 36% of LPV failures
- New NRTI mutations: 14% of DRV and 27% of LPV failures

Subgroup analyses at Week 48

<table>
<thead>
<tr>
<th>HIV RNA</th>
<th>DRV</th>
<th>LPV</th>
<th>Difference</th>
<th>p (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 c/mL LPV FC ≤ 40</td>
<td>70%</td>
<td>60%</td>
<td>10%</td>
<td>0.013*</td>
</tr>
<tr>
<td>&lt;50 c/mL LPV FC ≤ 10</td>
<td>70%</td>
<td>63%</td>
<td>7%</td>
<td>0.07*</td>
</tr>
<tr>
<td>&lt;400 c/mL &lt; 6 LPV mutations</td>
<td>91%</td>
<td>85%</td>
<td>6%</td>
<td>Not done</td>
</tr>
<tr>
<td>≥6 LPV mutations</td>
<td>86%</td>
<td>41%</td>
<td>45%</td>
<td>Not done</td>
</tr>
</tbody>
</table>

De Meyer S, et al. 4th IAS, Sydney 2007, #WEPEB038

*p (non-inferiority) <0.001
Higher response rates were observed at Week 48 in the PREZISTA/r arm compared to the LPV/r arm regardless of the number of PREZISTA RAMs at baseline. The virologic response to LPV/r was already reduced (response <75% of the overall response) in patients with 2 PREZISTA RAMs at baseline.

TLOVR, time-to-loss of virologic response; VF, virologic failure; LPV, lopinavir; PI, protease inhibitor; RAM, resistance-associated mutation


DUET 1 and 2: Virologic response (<50 c/mL) in etravirine arms by BL mutations at Week 24

- 13 BL resistance-associated mutations (RAMs) associated with a decreased response to ETR:
  - V90I
  - A98G
  - L100I
  - V106I
  - K101E/P
  - V179D/F
  - G190A/S
  - Y181C/I/V

- If >3 mutations present, response similar to PBO
- Note: 14% had ≥3 ETR RAMs

Katlama C, et al. 4th IAS, Sydney 2007, #WESS204:2
Effect of Y 181C on Etravirine Response Rates in DUET 1 and 2

- Y181C is a common mutation conferring resistance to currently available NNRTIs
- The TMC125 response rate is not compromised when Y181C is present, with either 0 or 1 other TMC125 RAM
- When Y181C is present with two or more TMC125 RAMs (13% of all patients), response rates were substantially reduced

Katlama C, et al. 4th IAS, Sydney 2007, #WESS204:2

Baseline NNRTI resistance: Predictive of virologic failure

- Retrospective analysis of 138 ART-naïve pts from study CNA30024 (ABC/3TC + EFV vs ZDV/3TC + EFV)
- ~50% of study population experienced virologic failure (HIV RNA >50 c/mL) during the study
- Standard genotypic sequencing identified 4 patients with baseline resistance (K103N, Y181C, M184V)
- Using ultrasensitive assays, baseline samples re-evaluated for K103N, Y181C, M184V present at frequencies below detection level of standard sequencing
- Ultrasensitive testing found 8 additional samples with K103N, Y181C, M184V; all 12 patients experienced virologic failure during the study

Johnson J, et al 15th IHDRW, Sitges 2006, #69
HIV-1 Entry Inhibitors

CD4 binding → Coreceptor binding → Virus-cell fusion

- gp41
- gp120
- V3 loop
- CD4
- TNX-355
- CCR5/CXCR4 (R5/X4)
- CCR5 antagonists
  - Maraviroc
  - Vicriviroc
- CXCR4 antagonists
  - Enfuvirtide

Cell membrane

Figure adapted from Doms R, et al. Genes Dev. 2000;14:2677-2688.

Question 3: Which of the following patients is least likely to have R5-tropic HIV?

- a. ARV naive patient with CD4 count of 50
- b. ARV naive patient with CD4 count of 200
- c. ARV experienced patient with CD4 count of 50
- d. ARV experienced patient with CD4 count of 200
Question 3: Which of the following patients is least likely to have R5-tropic HIV?

a. ARV naive patient with CD4 count of 50
b. ARV naive patient with CD4 count of 200
c. ARV experienced patient with CD4 count of 50
d. ARV experienced patient with CD4 count of 200

Tropism Profile in SCOPE and HOMER Cohorts are Influenced by CD4 Counts and by Treatment Status

* Tropism profiles in treatment naïve and experienced groups are distinct

Hunt et al., JID, 2006, 194:926-30
Summary: Monogram Tropism Assay

<table>
<thead>
<tr>
<th>Assay Attribute</th>
<th>Current Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnaround time</td>
<td>16 days</td>
</tr>
<tr>
<td>Minor variant detection</td>
<td>100% at 10% mixture</td>
</tr>
<tr>
<td></td>
<td>85% at 5% mixture</td>
</tr>
<tr>
<td>Viral load sensitivity</td>
<td>≥ 1,000 copies/mL (&gt; 95%)</td>
</tr>
<tr>
<td>Assay failure rate</td>
<td>5% (n = 23,000)</td>
</tr>
</tbody>
</table>

Co-receptor tropism switches in drug-resistant virus

- Viremic patients (SCOPE Cohort) on stable ARV with tropism assessed q4 months (n=76)
  - Median HIV RNA $3.8 \log_{10} \text{c/mL}$, CD4= 241 cells/uL
- Baseline Tropism
  - R5 only- 52 (68%)
  - DM 22 (29%)
  - X4 only 2 (3%)
- Longitudinal tropism
  - R5 to DM (12%) over 1 yr (3 with low X4 RLU, 1 R5 to DM to R5)
  - DM to R5 (11%) over 1 yr
  - DM to X4 only (8%)
- Increased risk of R5 to DM in those CCR5Δ32 (n=3)

Hunt P et al CROI 2007, Los Angeles Abstract #619
Switches in Tropism from Screening to Baseline Visits in MOTIVATE, ACTG 5211 and MERIT Studies

- Of 1049 subjects in MOTIVATE 1 and 2 studies, 8% changed tropism from screening visit to baseline (approximately 4 – 6 weeks)

- In this group, response to maraviroc treatment was consistent with the results of study A4001029 in subjects with D/M tropic virus

- In ACTG 5211, of 118 subjects screened R5, subsequently 10% to D/M; again virologic response was inferior in those who switched tropism as compared with majority of patients who did not switch tropism

- In naïve patients (MERIT Study), incidence of tropism switch from screening to baseline only 4 – 5%

**CCR5 antagonist resistance**

**Phenotypic resistance**¹

- Decreased maximum percentage inhibition in U87 cells (eg, Monogram assay)

- *In vitro* selected resistant virus often cross-resistant to other CCR5 inhibitors

- Shift in IC₅₀ in PBMC MOTIVATE 1 and 2 MVC failures²

- ~65% with dual/mixed tropic virus with phenotypic resistance

- 4/12 who had R5 only at failure had phenotypic resistance
  - No specific amino acid pattern changes

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Role of HIV Integrase

Viral DNA synthesis

Step 1: Assembly of PIC on viral DNA in nucleoprotein complex

Nuclear membrane

Host DNA

Nuclear entry

Step 2: Processing of 3' ends by PIC

Strand transfer

Gap repair

Mature provirus

Step 3a: Target DNA binding

Step 3b: Concerted target DNA cleavage and joining


Integrase inhibitor resistance mutations

RAL resistance

- Initial in vivo data from Phase III studies\(^1,2\)
- Virologic rebound in 16% RAL (32/41 showed integrase changes) vs 51% in control arm
- Two mutually exclusive pathways to resistance:

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>N155H</td>
<td>E92Q, V151I, T97A, G163K, L74M</td>
</tr>
<tr>
<td>Q148K/R/H</td>
<td>G140S/A, E138K</td>
</tr>
</tbody>
</table>

- “Next-generation”\(^3\) inhibitor?: MK2048 active in vitro despite primary resistance mutations
- Note: Concern for cross-resistance to RAL identified by in vitro fold change\(^3\)

Elvitegravir resistance

- Elvitegravir (GS-9137) resistance mutations in vitro\(^4\)
- Two pathways identified:

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>T66I</td>
<td>F121Y, S153Y, R263K</td>
</tr>
<tr>
<td>E92Q</td>
<td>S147G, H51Y, E157Q</td>
</tr>
</tbody>
</table>

1. Cooper D, et al. 14th CROI, Los Angeles 2007, #105aLB,
2. Steigbigel R, et al. ibid, #105aLB,
3. Wai, IBID # 87,
4. Jones, #627
**Conclusions**

- Drug resistance may become less common in patients with good adherence as more potent, well tolerated drugs are available
- Clinical trials continue to provide new data about drug combinations that are less likely to select for resistance
- Commercially available assays have poor sensitivity for resistance to minority quasispecies (<10% of population)
- Viral tropism is a new predictor of response to R5 antagonists
- New assays for integrase and R5 inhibitors will be needed to assess for the development of resistance to these new classes