18th Conference on Retroviruses and Opportunistic Infections
Feb 27 – Mar 2, 2011
Hynes Convention center
Boston, MA, USA

UPDATE IN HIV DRUG RESISTANCE

Javier Martinez-Picado
HIV Drug Resistance

Drug Resistance
57 abstracts (5%)

1084 Abstracts

87 in 2010 (9%)
HIV Drug Resistance

**Oral Presentations:**
- Surveillance of **Transmitted** and **Acquired** HIV Drug Resistance Using WHO Surveys in RLS
- Drug Resistance and Minor Drug Resistant Variants in **iPrEx**
- Predicting the Impact of ART and **PrEP** with Overlapping Regimens on HIV Transmission and Drug Resistance in South Africa
- **DTG** in Subjects with HIV Exhibiting **RAL** Resistance: Functional Monotherapy Results of VIKING Study Cohort II

**Poster Sessions:**
112. Mechanisms of Resistance to **Novel Entry Inhibitors** (4)
113. Co-receptor Usage, Resistance to **CCR5 Inhibitors**, and Treatment Responses (5)
114. New Insights into **NNRTI** Resistance (5)
115. Novel Insights into **PI** Resistance (7)
116. Mechanisms of **Raltegravir** Resistance (3)
118. Resistance Profiles after **First-line Therapy** (3)
119. Is HIV Drug Resistance **Spreading**? (8)
125. Drug Resistance **Testing** (4)
140. HIV Drug Resistance and Tropism after Treatment Failure in **Children** (3)
151. Incidence and Prevention of **PMTCT**-associated Drug Resistance (4)
Drug Resistance and Minor Drug Resistant Variants in iPrEx

Liegler et al. Poster #97LB
PrPrEP with FTC/TDF provides additional protection against HIV–1 infection among MSM.
Selection for DR may occur if PrEP is used inconsistently

- RT mutations: K65R, K70E, M184V, and M184I
- qRT-PCR (allele-specific PCR; Lower limit of quantitation 0.5%)
- HIV– with pre-existing infection at enrollment were monitored longitudinally for drug resistance using population-based sequencing.

**Graph:**
- 22/43 (51%)
- 3/34 (9%)
Advances in PrEP

- 0/100 infections showed FTC or TDF resistance by population sequencing.
- 0/91 subjects were analyzed for minor variant DR.
- 0/33 in the TDF/FTC arm showed minor variant DR.
- 2/58 in the placebo arm: 1 subject at K65R (0.69%), and 1 at M184V (1.26%).
- Among those with pre-existing HIV-1 infection, M184V or I mutants that were detectable at seroconversion became undetectable by population sequencing 9 and 12 weeks after stopping FTC/TDF, and 36 weeks after stopping placebo.

- Minor variant DR was not detected in the active arm of the iPrEx study, consistent with low drug exposure in FTC/TDF PrEP failures.
- FTC resistance among those who started FTC/TDF with pre-existing infection waned rapidly after FTC/TDF was stopped.

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Resistance Profiles of FTC and 3TC in TDF-containing Regimens

Marcelin et al. Poster #617
Resistance Profiles after First-line Therapy

- Genotypic resistance analysis after first virologic failure of 880 pts on:
  - FTC/TDF (535)
  - 3TC+TDF (345) + EFV/PI/r

- Lower prevalence of M184V/I with FTC use
- No differences observed prevalence of NNRTI resistance (55 vs 62%) and PI mutations (6 vs 9%) for FTC vs. 3TC

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Resistance Profiles after First-line Therapy

WHY?

- Higher potency of FTC than 3TC
- Greater use of FTC in fixed-dose combinations
- The longer plasma and intracellular pharmacokinetics of FTC vs. 3TC.

Drug combinations which minimize drug resistance are important for developed countries, as well as, resource-limited settings where VL and resistance testing access is limited.
Predicting MVC Responses According to Absolute Number vs Proportion of CXCR-4 Using Virus among Treatment-experienced Patients

Heera et al. Poster #593
Co-receptor Usage, Resistance to CCR5 Inhibitors, and Treatment Responses

- pVL tend to experience rates of VF and the emergence of DR.
- Relevance of the absolute viral population size that is resistant to a given drug or drugs.

What is more important for predicting virologic responses to MVC?
- The number or the relative percentage of X4 virus?

Tx-experienced pts who participated in the combined MVC arms MOTIVATE or A4001029.
- The relative % of X4 virus was determined using UDS (454/Roche) + g2p.
- The absolute nº of X4 virus = pVL x %X4.
Co-receptor Usage, Resistance to CCR5 Inhibitors, and Treatment Responses

Figure 1. Distribution of CXCR4-using virus plasma HIV-1 RNA by percent at screening in TE patients in the unselected population. Patients with \( <2\% \) CXCR4-using virus respond to treatment with MVC. Patients with \( >20\% \) CXCR4-using virus are routinely identified by commonly used genotyping and not prescribed MVC.

Figure 2. Distribution of CXCR4-using virus by plasma HIV-1 RNA concentrations at screening in TE patients in the unselected population.
Co-receptor Usage, Resistance to CCR5 Inhibitors, and Treatment Responses

The amount of X4-virus predicts the % of responders to MVC in a continuous manner.
Either % or absolute amount of X4-virus can be used to dichotomise patients as R vs. NR

- ↓ pVL, ↑ CD4 counts at BL, ↑ active drugs, and ↓ viruses that are resistant to a component of a regimen are more likely to respond to a MVC-containing regimen.
Results from a Single Arm Study of DRV/r + RAL in Treatment-naïve HIV-1-infected Patients (ACTG A5262)

Taiwo et al. Poster #551
HIV-infected Men and Women, 18 years and older

ARV Naive

N=112

RAL 400 mg BID +
DRV 800 mg/RTV 100mg QD

Primary Endpoint: VL failure > 1000/ml at wk 12 or >0.5 log increase or > 50 at wk 24

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ART Outcomes

**Time to VF**

- **W24**: 17 VF (11 failed to suppress, 6 rebounded; cumulative % of VF = 16%)
- **W48**: 28 VF (11 additional rebounds; cumulative % of VF = 26%)

**Time to VF by BL pVL**

- Log Rank Test $p=0.0002$

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ART Outcomes

Virologic Efficacy HIV-1 RNA <200 and <50 copies/mL
(ITT analysis, missing/off study=ignored)

![Graph showing virologic efficacy over time]

- **Proportion**: 93%, 86%, 79%, 71%
- **Number of subjects**: 112, 110, 110, 107
- **Time (weeks)**: 0, 4, 12, 24, 36, 48

<table>
<thead>
<tr>
<th>N (%)</th>
<th>pVL</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (46%)</td>
<td>51 - 200</td>
</tr>
<tr>
<td>6 (21%)</td>
<td>201 - 1000</td>
</tr>
<tr>
<td>5 (18%)</td>
<td>&gt; 1000</td>
</tr>
<tr>
<td>4 (14%)</td>
<td>Missed</td>
</tr>
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</table>

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### ART Outcomes

#### Integrase Mutations at Virologic Failure*

<table>
<thead>
<tr>
<th>Baseline HIV RNA** (copies/mL)</th>
<th>Integrase Mutations at VF</th>
<th>Baseline Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>911,043</td>
<td>N155H</td>
<td></td>
</tr>
<tr>
<td>246,270</td>
<td>N155H/N</td>
<td></td>
</tr>
<tr>
<td>184,212</td>
<td>Q148K/Q, N155H/N</td>
<td></td>
</tr>
<tr>
<td>230,627</td>
<td>Q148Q/R, N155H/N</td>
<td></td>
</tr>
<tr>
<td>147,076</td>
<td>N155H/N</td>
<td>M41L</td>
</tr>
</tbody>
</table>

*Successful Integrase genotyping in 25/28 patients

- All HIV RNA > 100,000 copies/mL.
- No PI resistance mutations in 23 patients with genotypic results

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Fitness Interactions of RPV and 3TC/FTC Resistance Mutations—A Possible Explanation for the Association of E138K and M184I in Clinical Trials

Hu et al. Poster #594
New Insights into NNRTI Resistance

Pooled W48 safety and efficacy results from the ECHO and THRIVE Phase III trials comparing TMC278 vs efavirenz in Tx-naïve HIV-1-infected patients

![Graph showing virologic failure rates with NNRTI RAMs](image)

- Among TMC278 VFs with emerging NNRTI RAMs, 46%, 31% and 23% had 1, 2, or 3 NNRTI RAMs, respectively, at failure
- Non-clade B VFs (n=13, including 8 clade C) did not exhibit any distinctive pattern of NNRTI RAMs

*Not present at screening or baseline and present at time of failure while on treatment
*Occurring in ≥5.0% of VF with available resistance data

Eron J, et al. 50th ICAAC 2010; Abstract H-1810

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New Insights into NNRTI Resistance

Why E138K/M184I is frequently observed in patients with virologic failure of RPV in phase 3 clinical trials?

TMC 125
Etravirine

TMC 278
Rilpivirine

Cross-resistance
ETR-RPV

Susceptibility to ETV (as a surrogate for RPV)

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New Insights into NNRTI Resistance

The combination E138K/M184I confers a relative replication advantage and higher levels of resistance to ETV and 3TC as compared to the E138K/M184V double-mutant.
DTG in Subjects with HIV Exhibiting RAL Resistance: Functional Monotherapy Results of VIKING Study Cohort II

Eron et al. Poster #151LB
New HIV and HCV Antiviral Agents, Prevention, and ARV Strategies

- Current or historic RAL-failures with evidence of RAL-resistance
- At least 3 ART-class resistant (includes INI)
- Subjects receive DTG 50mg QD (Cohort I), 50mg BID (Cohort II)
- Cohort II subjects must have ≥1 fully active ART in OBR

Allocated to one of two groups based on genotype at screen to ensure broad sensitivity range

<table>
<thead>
<tr>
<th>Q148H/K/R + one or more secondary resistance mutations*</th>
<th>N~ 10 (cohort II)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional MonoTx Phase</strong></td>
<td>Replace RAL with DTG or add, if RAL already stopped</td>
</tr>
<tr>
<td><strong>Continuation Phase</strong></td>
<td>DTG + OBR</td>
</tr>
<tr>
<td>All other mutations (including codon 148 single mutation)**</td>
<td>N~ 10 (cohort II)</td>
</tr>
</tbody>
</table>

*Q148H/K/R plus changes in L74 and/or E138 and/or G140
**N155H and Y143H pathways or Q148H/K/R single mutants

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## Virologic Response by Mutational Pathway

<table>
<thead>
<tr>
<th></th>
<th>DTG 50mg QD (N=27)</th>
<th>DTG 50mg BID (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects: 1° endpoint *</td>
<td>21/27 (78%)</td>
<td>23/24 (96%)</td>
</tr>
<tr>
<td>With Q148 +≥1</td>
<td>3/9 (33%)</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>With other pathways</td>
<td>18/18 (100%)</td>
<td>12/13 (92%)</td>
</tr>
<tr>
<td>All subjects: &lt;400 c/mL</td>
<td>11/27 (41%)</td>
<td>13/24 (54%)</td>
</tr>
</tbody>
</table>

*Primary endpoint: <400c/mL and/or ≥ 0.7log decline
New HIV and HCV Antiviral Agents, Prevention, and ARV Strategies

HIV Integrase Genotypic and Phenotypic Changes at day 11

- 15* paired viral isolates (day 1 & day 11) evaluated
- 0/15 subjects substitution identified in 572 in-vitro passage
- 3/15 subjects virus had additional RAL associated mutations detectable at day 11
  - In all 3 cases, substitutions were mixture with WT aa at Day 11
  - All 3 subjects achieved Tx success ($\geq 0.7 \log_{10} c/mL$ reduction from BL)
  - Two subjects have DTG susceptibility change of 3- and 5-fold as compared to BL

*Viral load too low to analyze genotype and phenotype in remaining isolates at Day 11

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New HIV and HCV Antiviral Agents, Prevention, and ARV Strategies

**VIKING Study Conclusions**

- A better response rate for the primary endpoint at day 11 was observed (23/24, 96%) in DTG 50mg BID
  - All 11 subjects in BID with Q148+ secondary mutations responded (compared with 3/9 in QD).
  - A significantly larger reduction in viral load was observed at day 11 in BID (-1.76) vs. QD (-1.45).
- DTG 50mg BID has been selected for Phase 3 INI-resistant study.
Minority HIV-1 Drug Resistance Mutations and the Risk of Initial ART Failure: A Systematic Review and Pooled Analysis

Li et al. Poster #614
Novel Resistance Mechanisms, Assays, and Interpretations

Kaplan-Meier curves for the % of patients without VF by the presence of minority HIV-1 drug-resistant variants

![Kaplan-Meier curves for minority HIV-1 drug-resistant variants](image)

- Minority variants not detected
- Minority variants detected

\[ p < 0.001 \]

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Novel Resistance Mechanisms, Assays, and Interpretations

<table>
<thead>
<tr>
<th>Group vs. no MV</th>
<th>HR</th>
<th>95% CI</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MV</td>
<td>2.6</td>
<td>1.9–3.5</td>
<td>985</td>
</tr>
<tr>
<td>Any MV (multivariate)*</td>
<td>2.3</td>
<td>1.7–3.3</td>
<td>769</td>
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<table>
<thead>
<tr>
<th>MV Type</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>NRTI MV</td>
<td>1.6 (0.1–17.7)</td>
</tr>
<tr>
<td>NNRTI MV</td>
<td>2.6 (1.9–3.5)</td>
</tr>
<tr>
<td>EFV</td>
<td>2.6 (1.9–3.5)</td>
</tr>
<tr>
<td>NVP</td>
<td>2.7 (0.7–10.3)</td>
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<table>
<thead>
<tr>
<th>MV / Adherence</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MV / Any Adh</td>
<td>ref (ref)</td>
</tr>
<tr>
<td>MV / Adh ≥95%</td>
<td>1.5 (0.98–2.3)</td>
</tr>
<tr>
<td>MV / Adh &lt;95%</td>
<td>5.1 (3.6–7.2)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>MV %</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>2.2 (1.6–3.1)</td>
</tr>
<tr>
<td>≥1%</td>
<td>5.0 (2.4–10.3)</td>
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<table>
<thead>
<tr>
<th>MV copy #</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9 copies</td>
<td>1.8 (0.9–3.8)</td>
</tr>
<tr>
<td>10–99 copies</td>
<td>2.2 (1.5–3.2)</td>
</tr>
<tr>
<td>100–999 copies</td>
<td>3.0 (2.0–4.5)</td>
</tr>
<tr>
<td>≥1000 copies</td>
<td>4.1 (2.5–6.8)</td>
</tr>
</tbody>
</table>

* Multivariate analysis included adherence, ethnicity, CD4 count, and HIV-1 RNA levels

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Novel Resistance Mechanisms, Assays, and Interpretations

- Minority HIV-1 DRM, and NNRTI mutations in particular, significantly increase the risk of VF of initial ART.
- This elevated risk was seen even in those with a high rate of medication adherence.
Questions are guaranteed in life; Answers aren't.