HIV resistance update

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Badalona, Catalonia
• Transparency declaration

• I have served during the past 2 years as a consultant on advisory boards or participated in speakers’ bureaus or conducted clinical trials with BMS, Gilead, Janssen, Merck and ViiV.
HIV Replication Cycle: Targets for Antiretroviral Therapy

1. gp120
2. Fusion
3. Genomic RNA
4. Reverse Transcriptase
5. Unintegrated Linear DNA
6. mRNA
7. Protein Synthesis, Processing and Assembly
8. Budding
9. Mature HIV Virion

Integrase Inhibitors
Reverse Transcriptase Inhibitors
Fusion/Entry Inhibitors
CCR5 Antag
Principles of HIV treatment

Goal of therapy

Maximal, lifelong, continuous suppression of HIV replication
- Prevent resistance
- Promote immune recovery
- Prevent transmission

Regimen adherence considerations

Convenience

Patient Cost

Toxicity

Tolerability

Efficacy

When to start anti-retroviral therapy

Pre-requisites

- Patient readiness and willingness to adhere to treatment
- Support services
  - Education
  - Adherence

Treatment

All subjects with HIV infection:

- Acute or chronic HIV infection
- Any CD4 count
- Any VL (except EC?)
- Any age
- Hep B co-infection
- Hep C co-infection
- Opportunistic infection (delay perhaps in cryptococcal meningitis?)
- Pregnancy
Antiretroviral therapy, 26 years of continuous improvement, 28 drugs, 6 classes...

- **1981**: AIDS, 1st cases
- **1983**: HIV discovery
- **1981**: Zidovudine
- **1987**: Didanosine
- **1987**: Lamivudine
- **1987**: Stavudine

NNRTIs: Enfuvirtide, fosamprenavir, atazanavir
- **1996**: Lopinavir/r
- **1997**: Nevirapine, nelfinavir
- **1998**: Efavirenz, abacavir, amprenavir
- **1999**: Tipranavir
- **1999**: Maraviroc, raltegravir, darunavir

PIs: Emtricitabine, Tenofovir
- **2004**: Elvitegravir
- **2006**: Dolutegravir
- **2011**: Rilpivirine
- **2013**: Stribild

NNRTIs: Delavirdine
- **2002**: Saquinavir, ritonavir, indinavir

NRTIs: Zalcitabine
- **2012**: Trizivir*
- **2012**: Atripla*
- **2012**: Eviplera*

Integrase inhibitor: Maraviroc, raltegravir, darunavir

CCR5 inhibitor: Delavirdine

* STR (single tablet regimen)
Antiretroviral therapy, 26 years of continuous improvement, 15-28 drugs, 6 classes...

- NRTIs
- NNRTIs
- PIs
- Fusion inhibitor
- CCR5 inhibitor
- Integrase inhibitor

AIDS, 1st cases
LAV (HIV)

1981
1983
1987
1991
1992
1996
1997
1998
1999
2001
2002
2003
2004
2005
2007
2008
2012
2013
2014

- Didanosine
- Zalcitabine
- Stavudine, Lamivudine, saquinavir, ritonavir, indinavir
- Zidovudine

2002
2004
2008
2012
2013
2014

- Zidovudine
- Lamivudine
- Saquinavir, ritonavir, indinavir

2003
2005
2007
2010

- Trizivir*
- Atripla*
- Eviplera*
- Stribild*

* STR (single tablet regimen)
How to manage long term HIV control?

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<td>3 drugs required</td>
<td>How much viral potency and which drugs to maintained suppressed viremia?</td>
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<tr>
<td>4–5 log drop</td>
<td>How to individualize therapy to each individual? CD4 nadir, Activation status, Blood DNA (reservoirs)</td>
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Life Cycle and Pathogenesis of HIV

Viral Rebound After HAART Interruption

The Highest the BL VL
The longest it takes to VL<50 c/ml
Pivotal ART studies, VL <50 c/mL, 48 weeks ITT, by NRTIs

- GS-103 STIBILD (n=353)
- SPRING-2 DTG (n=242)
- QDMRK RAL BID (n=388)
- GS-102 STIBILD (n=348)
- SINGLE DTG (n=414)
- GS-103 ATV + RTV (n=355)
- STaR RPV (n=394)
- SPRING-2 RAL (n=169)
- STARTMRK RAL (n=281)
- THRIVE RPV (n=340)
- GS-102 ATRIPLA (n=352)
- ARTEMIS DRV + RTV (n=343)
- ECHO RPV (n=346)
- ECHO EFV (n=344)
- THRIVE EFV (n=538)
- STaR EFV (n=392)
- STARTMRK EFV (n=282)
- SINGLE EFV (n=419)
- GS 934 EFV (n=244)
- ARTEMIS LPV/r (n=346)
- CASTLE ATV + RTV (n=440)
- ABT 730 LPV/r qd (n=333)
- CASTLE LPV/r (n=443)
- ABT 730 LPV/r bid (n=331)
- GS-903 EFV (n=299)
- KLEAN FPV/r (n=434)
- KLEAN LPV/r (n=444)

EFV ZDV 3TC
006 Study
64%
Dec 1999

83.6%
In high BL
VL>100K

Modified from E Ribera
Resistance to ARVs
Two mechanisms of genetic evolution

1. **Rapid evolution through point mutations**
   - RT error rate: $\sim$1 per genome round
   - Replication rate: $10^9$-$10^{10}$ virus particles daily
   - *All possible mutations generated daily*

2. **Genetic evolution through recombination**
   - Recombination rate: 7-30 per genome round
High Mutation Rate
Approximately 1 substitution per genome per round

Recombination
Approximately 7–30 crossovers per genome per round

Rapid Replication
Approximately $10.3 \times 10^9$ virions per day
HIV genotyping

Separation of PBMCs from whole blood (Ficoll)

Amplification & sequencing

HIV genotyping

PR RT IN V3

Phenotypic interpretation of sequences

Geno2pheno [coreceptor]
### HIV mutation naming conventions

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<tr>
<th>First letter</th>
<th>Number</th>
<th>Last letter</th>
<th>Amino acid in wild-type target protein</th>
<th>Mutated codon</th>
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#### Examples:

- **L90M**: Leucine to methionine change at codon 90 of protease.
- **M184V**: Methionine to valine change at codon 184 of reverse transcriptase.
- **K219Q/E**: Lysine to glutamine or glutamate at codon 219 of reverse transcriptase.

#### AMINO ACIDS

- A: Alanine
- C: Cysteine
- D: Aspartate
- E: Glutamate
- F: Phenylalanine
- G: Glycine
- H: Histidine
- I: Isoleucine
- K: Lysine
- L: Leucine
- M: Methionine
- N: Asparagine
- P: Proline
- Q: Glutamine
- R: Arginine
- S: Serine
- T: Threonine
- V: Valine
- Y: Tyrosine
Update of the Drug Resistance Mutations in HIV-1: March 2013

Victoria A. Johnson, MD, Vincent Calvez, MD, PhD, Huldrych F. Günthard, MD, Roger Paredes, MD, PhD, Deenan Pillay, MD, PhD, Robert W. Shafer, MD, Annemarie M. Wensing, MD, PhD, and Douglas D. Richman, MD


IAS–USA is a not-for-profit, HIV clinical specialist–education organization. It is entirely different from and not affiliated with the International AIDS Society.
Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)

Multi-nRTI Resistance: 69 Insertion Complex (affects all nRTIs currently approved by the US FDA)

Multi-nRTI Resistance: 151 Complex (affects all nRTIs currently approved by the US FDA except tenofovir)

Multi-nRTI Resistance: Thymidine Analogue-Associated Mutations (TAMs; affect all nRTIs currently approved by the US FDA)
## Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont’d)

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Mutations in the Reverse Transcriptase Gene Associated With Resistance to Reverse Transcriptase Inhibitors (cont’d)

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

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Updates, user notes, and references available at www.iasusa.org.
## Mutations in the Protease Gene Associated With Resistance to Protease Inhibitors

### Atazanavir +/- ritonavir

|       | L   | G   | K   | L   | V   | L   | E   | M   | M   | G   | I   | F   | I   | D   | I   | I   | A   | G   | V   | I   | I   | N   | L   | I   |
|-------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 10    | 16  | 20  | 24  | 32  | 33  | 34  | 36  | 46  | 48  | 50  | 53  | 54  | 60  | 62  | 64  | 71  | 73  | 82  | 84  | 85  | 88  | 90  | 93  |

### Darunavir/ritonavir

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Mutations in the Envelope Gene Associated With Resistance to Entry Inhibitors

<table>
<thead>
<tr>
<th>Enfuvirtide</th>
<th>Maraviroc</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIIVQQNN</td>
<td></td>
</tr>
<tr>
<td>36 37 38 39</td>
<td></td>
</tr>
<tr>
<td>40 42 43</td>
<td></td>
</tr>
<tr>
<td>DVARHTD</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>ME</td>
</tr>
</tbody>
</table>

User Notes available at www.iasusa.org
## Mutations in the Integrase Gene Associated With Resistance to Integrase Strand Transfer Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Residue</th>
<th>Mutations</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>138, 140, 148</td>
<td>R263K with H51Y</td>
<td>Dramatic decrease in enzymatic activity and viral replication</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>138, 140, 143</td>
<td>R263K with H51Y</td>
<td>Dramatic decrease in enzymatic activity and viral replication</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>138, 140, 148</td>
<td>R263K with H51Y</td>
<td>Dramatic decrease in enzymatic activity and viral replication</td>
</tr>
</tbody>
</table>
Ongoing virus replication in the presence of suboptimal drug levels leads to the selection and ongoing evolution of drug-resistant mutants.
Risk of Resistance with Treatment Interruption

**Sub-therapeutic concentrations with selective pressure**

**Therapeutic concentration**

**NNRTI**

**NRTI #2**

**NRTI #1**

**Viral rebound**

**Stop Therapy**

**T1/2 (h)**
- NRTI: 1-6
- NNRTI: 6-55

**Drug concentrations**

**Time**

0-100

7-21 d

B.Clotet et al. AIDS 2001, 15:F19 ± F27
Off therapy resistant mutants lose the replicative advantage over wild-type virus and disappear from the dominant quasispecies, persisting as minority quasispecies and archived resistance.
Minority variants will remain hidden. Resistant virus is 10-20% of the population.
The HIV Hepatitis Guide

Resistance mutations

HIV
HBV
HCV

The Guide Contents

www.flsida.org/theguide

Editors: Bonaventura Clotet, Luis Menéndez-Arias
Jonathan M. Schapiro, Daniel Kurltzkes, David Burger
Jürgen Rockstroh, Vicente Soriano, Amalio Telenti, Francoise Brun-Vezinet, Anna Maria Geretti, Charles A. Boucher, Douglas D. Richman

MSD, GILEAD, Bristol-Myers Squibb
Aminoacid substitutions associated with resistance to HIV-1 reverse transcriptase inhibitors, protease inhibitors, and other drugs targeting virus maturation

- Located in transcriptase (RT)
- Located in protease (PR)
- Located in integrase (IN)

HIV resistance to integrase inhibitors
PR mutations

I50L

V3I

W6R

R8K

R8Q

L10F

L10I
**In vitro**


**In vivo**

Found in patients treated with atazanavir, and failing antiretroviral therapy. Usually associated with **A71V**. No evidence of cross-resistance with other PR inhibitors was found to be mediated by the
LOW-LEVEL VIREMIA
Intermittent viremia (Blip)

Plasma HIV RNA
(copies/mL)

Undetectable viremia
(standard assay)

Threshold
Persistent viremia (Low Level Viremia)

- Plasma HIV RNA (copies/mL)
- Threshold
- Undetectable viremia (standard assay)
Always worth trying to genotype at any detectable VL level

Table 2. HIV-1 genotyping resistance success rate according to different viremia levels

<table>
<thead>
<tr>
<th>Viremia ranges (copies/mL)</th>
<th>Overall N (% success)</th>
<th>B N (% success)</th>
<th>Non-B N (% success)</th>
<th>P&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12828 (96.4)</td>
<td>10212 (97.1)</td>
<td>2533 (96.1)</td>
<td>.683</td>
</tr>
<tr>
<td>50-200</td>
<td>769 (67.2)</td>
<td>583 (72.9)</td>
<td>139 (66.2)</td>
<td>.115</td>
</tr>
<tr>
<td>201-500</td>
<td>489 (88.1)</td>
<td>369 (90.0)</td>
<td>113 (86.7)</td>
<td>.330</td>
</tr>
<tr>
<td>501-1000</td>
<td>444 (93.2)</td>
<td>329 (94.5)</td>
<td>112 (92.0)</td>
<td>.328</td>
</tr>
<tr>
<td>10001-10000</td>
<td>2435 (97.3)</td>
<td>1967 (98.0)</td>
<td>456 (96.9)</td>
<td>.153</td>
</tr>
<tr>
<td>&gt;100000</td>
<td>4845 (99.2)</td>
<td>3969 (99.3)</td>
<td>867 (99.2)</td>
<td>.812</td>
</tr>
</tbody>
</table>

The success of the genotypic resistance test in plasma samples from HIV-1 infected patients was evaluated on the overall population with viremia >50 copies/mL (N=12828) and according to subtype (B vs. non-B), by stratifying for viremia ranges. The rate of genotyping success in patients with viremia <50 copies/mL was 17.5%.

<sup>6</sup> Potential differences in the rate of genotypic success in B and non-B subtypes were evaluated by Chi-squared test (corrected for the population size, as appropriate) or Fisher’s exact test, as appropriate. P values < 0.05 were considered as statistically significant.

Abbreviations: P, P value.
VF at 48wks after LLV for 6 months:
-22.7% (VL:50-199)
-24.2% (VL:200-499)
-58.9% (VL:500-999)
Prevalence of LLV

Table 2. Summary data on baseline characteristics, efficacy, and percent HIV RNA 50–400 copies/mL at Week 48 in first-line clinical trials of NNRTI-based HAART (n = 4,475)

<table>
<thead>
<tr>
<th>Trial [Ref]</th>
<th>Antiretrovirals used</th>
<th>CD4 count (cells/µL)</th>
<th>HIV RNA (log_{10} c/mL)</th>
<th>Summary 48-week efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRTI + third drug</td>
<td>n</td>
<td>HIV RNA &lt;50 (%)</td>
<td>HIV RNA 50–400 (%)</td>
</tr>
<tr>
<td>CNA3021 [28]</td>
<td>ABC/3TC + EFV</td>
<td>386</td>
<td>4.9</td>
<td>65% (7%)</td>
</tr>
<tr>
<td>CNA3024 [29]</td>
<td>ABC/3TC + EFV</td>
<td>324</td>
<td>4.6</td>
<td>69% (4%)</td>
</tr>
<tr>
<td>CNA3021 [28]</td>
<td>ABC/3TC + EFV</td>
<td>384</td>
<td>4.9</td>
<td>64% (7%)</td>
</tr>
<tr>
<td>Gilead 603 [30]</td>
<td>d4T/3TC + EFV</td>
<td>301</td>
<td>4.9</td>
<td>61% (6%)</td>
</tr>
<tr>
<td>FTC 301A [31]</td>
<td>FTC/ddI + EFV</td>
<td>286</td>
<td>4.9</td>
<td>78% (3%)</td>
</tr>
<tr>
<td>ACTG 5095 [24]</td>
<td>ZDV/3TC + EFV</td>
<td>765</td>
<td>4.9</td>
<td>83% (6%)</td>
</tr>
<tr>
<td>CNA3024 [29]</td>
<td>ZDV/3TC + EFV</td>
<td>325</td>
<td>4.8</td>
<td>69% (2%)</td>
</tr>
<tr>
<td>Gilead 934 [32]</td>
<td>TDF/FTC + EFV</td>
<td>254</td>
<td>5.0</td>
<td>70% (3%)</td>
</tr>
<tr>
<td>EPV 2001 [33]</td>
<td>ZDV/3TC + EFV</td>
<td>276</td>
<td>4.6</td>
<td>61% (2%)</td>
</tr>
<tr>
<td>EPV 2001 [33]</td>
<td>ZDV/3TC + EFV</td>
<td>276</td>
<td>4.7</td>
<td>59% (5%)</td>
</tr>
<tr>
<td>MERIT [34]</td>
<td>ZDV/3TC + EFV</td>
<td>361</td>
<td>4.9</td>
<td>69% (4%)</td>
</tr>
<tr>
<td>Gilead 603 [30]</td>
<td>TDF/3TC + EFV</td>
<td>299</td>
<td>4.9</td>
<td>82% (5%)</td>
</tr>
<tr>
<td>Gilead 934 [32]</td>
<td>TDF/FTC + EFV</td>
<td>255</td>
<td>5.0</td>
<td>60% (4%)</td>
</tr>
</tbody>
</table>

Mean (range) 278 (233–386) 4.9 (4.8–5.0) 71.5% (50–83%) 4.5% (2–7%)

Table 3. Summary data on baseline characteristics, efficacy, and percent HIV RNA 50–400 copies/mL at Week 48 in first-line clinical trials of boosted PI-based HAART (n = 3,608)

<table>
<thead>
<tr>
<th>Trial [Ref]</th>
<th>Antiretrovirals used</th>
<th>CD4 count (cells/µL)</th>
<th>HIV RNA (log_{10} c/mL)</th>
<th>Summary 48-week efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRTI + PI</td>
<td>n</td>
<td>HIV RNA &lt;50 (%)</td>
<td>HIV RNA 50–400 (%)</td>
</tr>
<tr>
<td>ARTEMIS [35]</td>
<td>TDF/FTC + DRV/r</td>
<td>343</td>
<td>4.9</td>
<td>64% (3%)</td>
</tr>
<tr>
<td>ARTEMIS [35]</td>
<td>TDF/FTC + LPV/r</td>
<td>346</td>
<td>4.8</td>
<td>78% (7%)</td>
</tr>
<tr>
<td>HEAT [36]</td>
<td>TDF/FTC + LPV/r</td>
<td>286</td>
<td>4.8</td>
<td>67% (4%)</td>
</tr>
<tr>
<td>HEAT [36]</td>
<td>ABC/3TC + LPV/r</td>
<td>276</td>
<td>4.9</td>
<td>66% (7%)</td>
</tr>
<tr>
<td>KLEAN [37]</td>
<td>ABC/3TC + LPV/r</td>
<td>444</td>
<td>5.1</td>
<td>71% (8%)</td>
</tr>
<tr>
<td>ABT-663 [38]</td>
<td>d4T/3TC + LPV/r</td>
<td>326</td>
<td>5.0</td>
<td>67% (8%)</td>
</tr>
<tr>
<td>CASTLE [25]</td>
<td>TDF/FTC + LPV/r</td>
<td>443</td>
<td>5.0</td>
<td>76% (5%)</td>
</tr>
<tr>
<td>SOLO [39]</td>
<td>ABC/3TC + FPV/r</td>
<td>173</td>
<td>4.8</td>
<td>69% (13%)</td>
</tr>
<tr>
<td>KLEAN [37]</td>
<td>ABC/3TC + FPV/r</td>
<td>434</td>
<td>5.1</td>
<td>73% (7%)</td>
</tr>
<tr>
<td>CASTLE [25]</td>
<td>TDF/FTC + ATV/r</td>
<td>440</td>
<td>5.0</td>
<td>78% (8%)</td>
</tr>
<tr>
<td>BMS-089 [40]</td>
<td>d4T/3TC + ATV/r</td>
<td>95</td>
<td>4.8</td>
<td>75% (11%)</td>
</tr>
</tbody>
</table>

Mean (range) 204 (166–228) 4.9 (4.8–5.1) 73.3% (67–84%) 7.3% (3–13%)

Causes and Consequences of Incomplete HIV RNA Suppression in Clinical Trials
Anton Pozniak,1 Ravindra K. Gupta,2 Deenan Pillay,3 Jose Arribas,4 and Andrew Hill1
Management

– Guidelines: threshold of virological failure
  • 50 copies/ml (FR, EUR)
  • 200 copies/ml (USA)

– Therapeutic interventions
  • Change treatment according to resistance data
  • Change antiretroviral to more potent, different diffusion
  • Simplification
  • Intensification (different from residual viramia with pVL < 50 copies/ml)

⇒ Identification of the cause of LLV may help the kind of intervention
HIGH GENETIC BARRIER AND LOW RISK FOR RESISTANCE
OK04 trial: maintenance with LPV/r monotherapy

**A5257 Study Design**

HIV-infected patients, ≥18 yr, with no previous ART, VL ≥ 1000 c/mL at US Sites

- Randomized 1:1:1 to Open Label Therapy
  - Stratified by screening HIV-1 RNA level (≥ vs < 100,000 c/mL), A5260s metabolic substudy participation, cardiovascular risk

- ATV 300 mg QD + RTV 100mg QD + FTC/TDF 200/300 mg QD
- RAL 400 mg BID + FTC/TDF 200/300 mg QD
- DRV 800 mg QD + RTV 100 mg QD + FTC/TDF 200/300 mg QD

Study Conclusion 96 weeks after final participant enrolled

Follow-up continued for 96 weeks after randomization of last subject (range 2-4 years) regardless of status on randomized ART

*With the exception of RTV, all ART drugs were provided by the study*
Cumulative Incidence of Virologic or Tolerability Failure

Difference in 96 wk cumulative incidence (97.5% CI)

- **ATV/r vs RAL**
  - 15% (10%, 20%)
- **DRV/r vs RAL**
  - 7.5% (3.2%, 12%)
- **ATV/r vs DRV/r**
  - 7.5% (2.3%, 13%)

*Consistent results seen with TLOVR at a 200 copies/ml threshold*
Resistance to Study Agents

1809 Participants

295 Virologic Failures

1 Baseline Missing
56 VF Failed to Amplify

ATV/r

- 75/94 VF
- Available
- 9 Any Resistance (1.5% of ATV/r)
- 5 isolated M184V
- 1 integrase mutation
- 2 T69D/T215AI
- 1 K70N + M184V

RAL

- 65/85 VF
- Available
- 18 Any Resistance (3% of RAL)
- 7 isolated M184V
- 1 isolated integrase mutation
- 7 integrase + M184V
- 3 integrase + M184V + K65R

DRV/r

- 99/115 VF
- Available
- 4 Any Resistance (<1% of DRV/r)
- 3 isolated M184V
- 1 integrase mutation

*Stanford University Genotypic Resistance Interpretation Algorithm V 6.3.1
Dual therapy with Lopinavir/ Ritonavir (LPV/r) and Lamivudine (3TC) is non-inferior to standard triple drug therapy in Naïve HIV-1 infected subjects: 48-week results of the GARDEL Study.

ClinicalTrials.gov: # NCT01237444

Pedro Cahn on behalf of the GARDEL study group
Study design

Phase III, randomized, international, controlled, open-label study

- Study included adult patients from Argentina, Chile, Mexico, Peru, Spain, US.

**DT:**
LPV/r 400/100mg BID
+ 3TC 150 mg BID
(n=217)

**TT:**
LPV/r 400/100mg BID
+ 3TC or FTC and a third investigator-selected NRTI in fixed-dose combination
(n=209)

**Stratified by screening**
HIV-1 RNA
(≤ or > 100,000 copies/mL)

ARV- naive patients,
≥18 years
HIV-1 RNA
>1000 copies/ml
No IAS-USA defined NRTI or PI resistance at screening*
(N = 426)

*Defined as ≥ 1 major or ≥ 2 minor LPV/r mutations*

LPV major mutations include the following mutations: V32I; I47V/A; L76V; V82A/F/T/S

**Wk 24**
interim analysis

**Wk 48**
primary endpoint
Viral load <50 copies/mL at week 48 (ITTe)

(p = 0.171, difference +4.6% [Cl_{95%}: -2.2% to +11.8%])
Viral load <50 copies/mL at week 48 (ITTe), baseline VL > 100.000 copies/mL

(p = 0.145, difference +9,3% [CI95%:-2.8% to +21.5%])
CD4 increase from BL to W48

- BSL
- W4
- W12
- W24
- W36
- W48

DT + 227 cells/mm³
TT + 217 cells/mm³

p = 0.625
Protocol-Defined Virologic Failure and Emergent Resistance Mutations

PDVF: 2 measurements of HIV-1 RNA at least 1 week apart
- >400 copies/mL at week 24
- > 50 copies/mL at week 48

Emergent resistance mutations, in samples successfully amplified:
- DT: 2 out of 5 both M184V
- TT: 0 out of 8

<table>
<thead>
<tr>
<th>Number of patients, n (%)</th>
<th>DT (N=214)</th>
<th>TT (N=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed virological failures</td>
<td>10 (4.6 %)</td>
<td>12 (5.9 %)*</td>
</tr>
<tr>
<td>HIV-1 RNA at failure (copies/ml) (median-IQR)</td>
<td>236 (183-17,687)</td>
<td>1027 (123-4,880)</td>
</tr>
<tr>
<td>Never suppressed</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Rebounders</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Primary PI RAMs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI RAMs (M184V)</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*p=0.72
Our results demonstrate that DT with LPV/r+3TC was non-inferior to triple therapy after 48 weeks of treatment, regardless of baseline viral load.

The DT regimen tended to have better safety and tolerability.

Virologic failure, occurring at similarly low levels in both treatment arms, did not result in PI resistance development, preserving a wide range of drugs for 2nd line ARV therapy.

These results suggest that a dual LPV/r+3TC regimen warrants further clinical research and consideration as a potential therapeutic option for ARV naïve subjects.
Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study

Bonaventura Clotet, Judith Feinberg, Jan van Lunzen, Marie-Aude Khuong-Josses, Andrea Antinori, Irina Dumitru, Vadim Pokrovskiy, Jan Fehr, Roberto Ortiz, Michael Saag, Julia Harris, Clare Brennan, Tamio Fujiwara, Sherene Min, on behalf of the ING114915 Study Team

Summary

Background Dolutegravir has been shown to be non-inferior to an integrase inhibitor and superior to a non-nucleoside reverse transcriptase inhibitor (NNRTI). In FLAMINGO, we compared dolutegravir with darunavir plus ritonavir in individuals naive for antiretroviral therapy.

Methods In this multicentre, open-label, phase 3b, non-inferiority study, HIV-1-infected antiretroviral therapy-naive adults with HIV-1 RNA concentration of 1000 copies per mL or more and no resistance at screening were randomly assigned (1:1) to receive either dolutegravir 50 mg once daily or darunavir 800 mg plus ritonavir 100 mg once daily with investigator-selected tenofovir–emtricitabine or abacavir–lamivudine. Randomisation was stratified by screening HIV-1 RNA (≤100 000 or >100 000 copies per mL) and nucleoside reverse transcriptase inhibitor (NRTI) selection. The primary endpoint was the proportion of patients with HIV-1 RNA concentration lower than 50 copies per mL (Food and Drug Administration [FDA] snapshot algorithm) at week 48 with a 12% non-inferiority margin. This trial is registered with ClinicalTrials.gov, NCT01449929.

Findings Recruitment began on Oct 31, 2011, and was completed on May 24, 2012, in 64 research centres in nine countries worldwide. Of 595 patients screened, 484 patients were included in the analysis (242 in each group). At week 48, 217 (90%) patients receiving dolutegravir and 200 (83%) patients receiving darunavir plus ritonavir had HIV-RNA of less than 50 copies per mL (adjusted difference 7.1%, 95% CI 0.9–13.2), non-inferiority and on pre-specific secondary analysis dolutegravir was superior (p=0.025). Confirmed virological failure occurred in two (<1%) patients in each group; we recorded no treatment-emergent resistance in either group. Discontinuation due to adverse events of stopping criteria was less frequent for dolutegravir (four [2%] patients) than for darunavir plus ritonavir (ten [4%] patients) and contributed to the difference in response rates. The most commonly reported (≥10%) adverse events were diarrhoea (dolutegravir 41 [17%] patients vs darunavir plus ritonavir 70 [29%] patients), nausea (39 [16%] vs 43 [18%] and headache (37 [15%] vs 24 [10%]). Patients receiving dolutegravir had significantly fewer low-density lipoprotein values of grade 2 or higher (11 [2%] vs 36 [7%]; p=0.0001).

Interpretation Once-daily dolutegravir was superior to once-daily darunavir plus ritonavir. Once-daily dolutegravir in combination with fixed-dose NRTIs represents an effective new treatment option for HIV-1-infected treatment-naive patients.

Funding ViiV Healthcare and Shionogi & Co.
Viral fitness cost prevents HIV-1 from evading dolutegravir drug pressure

Thibault Mesplède¹, Peter K Quashie¹,², Nathan Osman¹, Yingshan Han¹, Diane N Singhroy¹,³, Yolanda Lie⁴, Christos J Petropoulos⁴, Wei Huang⁴ and Mark A Wainberg¹,²,³*

Abstract

Background: Clinical studies have shown that integrase strand transfer inhibitors can be used to treat HIV-1 infection. Although the first-generation integrase inhibitors are susceptible to the emergence of resistance mutations that impair their efficacy in therapy, such resistance has not been identified to date in drug-naïve patients who have been treated with the second-generation inhibitor dolutegravir. During previous in vitro selection study, we identified a R263K mutation as the most common substitution to arise in the presence of dolutegravir with H51Y arising as a secondary mutation. Additional experiments reported here provide a plausible explanation for the absence of reported dolutegravir resistance among integrase inhibitor-naïve patients to date.

Results: We now show that H51Y in combination with R263K increases resistance to dolutegravir but is accompanied by dramatic decreases in both enzymatic activity and viral replication.

Conclusions: Since H51Y and R263K may define a unique resistance pathway to dolutegravir, our results are consistent with the absence of resistance mutations in antiretroviral drug-naïve patients treated with this drug.

Keywords: HIV integrase, Dolutegravir, Resistance to antiretrovirals, Viral fitness, Strand-transfer assay
Drugs with high genetic barrier like boosted PIs and Dolutegravir (integrase inhibitor) are not associated with the emergence of resistance at treatment failure in naïve patients.
TREATMENT OF MDR VIRUS
DUET study design and major inclusion criteria

- Plasma VL >5000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historic genotype
- ≥3 primary PI mutations at screening
- In DUET-1, patients were recruited from Thailand, Australia, Europe and the Americas
- DUET-1 and DUET-2 differed only in geographic location; pooled analysis was prespecified

*BR = DRV/r with optimized NRTIs and optional ENF

RAM = resistance-associated mutation
Patients with VL <50 copies/mL at Week 48 (ITT-TLOVR)

**DUET-1**
- ETR + BR (n=304)
- Placebo + BR (n=308)

Responders (%) ± 95% CI

```
0 2 4 8 12 16 20 24 32 40 48
```

```
p<0.0001†
```

```
60% 39%
```

**Pooled DUET-1 and DUET-2**
- ETR + BR (n=599)
- Placebo + BR (n=604)

Responders (%) ± 95% CI

```
0 2 4 8 12 16 20 24 32 40 48
```

```
61% 40%
```

*Pooled DUET data included for comparison; †Logistic regression test for responder rate difference.
Emerging DRV mutations in virological rebounders

Every active drug protects the whole regimen

- The most frequently emerging DRV RAMs in both arms were V32I and I54L
## Etravirine Weighted Score

<table>
<thead>
<tr>
<th>Mutation</th>
<th>MGRM Weight</th>
<th>TBTC Weight</th>
<th>Enhanced Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>V90I</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A38G</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>L100I</td>
<td>4</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>K101E</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>K101H</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>K101P</td>
<td>4</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
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Comparison of NNRTI mutations conferring resistance to etravirine in 3 Weighted scores.

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<th>Tibotec</th>
<th>Monogram</th>
<th>Stanford</th>
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<td>Y318F</td>
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</tr>
</tbody>
</table>

Mutations not included do not grant points in any score. Blank spaces indicate mutations that do not grant points in that specific score.

Llibre JM. CID 2010; 50:872–881

Stanford
> 10 meaningful
> 60 resistance
Tibotec
Monogram
>4
Minority Drug Resistance Mutations Associated with the NNRTI Mutation K103N in ARV-naïve and NNRTI Treated HIV-1 Infected Patients

33 plasma samples with only K103N in bulk genotyping and pVL>4.5 log c/ml.

- 13 naive pts with transmitted primary resistance.
- 20 pts with VF to NVP or EFV.

Ultradeep pyrosequencing (454 Life Sciences) encompassing the first 240 RT residues.

**Naives.**
- 6/13 had ≥ 1 RT DRM.
- 1(7.7%) had a known ETR DRM.
- 1 V90I (1.4%*) (1 point TBT)

**Failures to NVP or EFV.**
- 14/20 had ≥ 1 RT DRM.
- 9 (45%) had a known ETR DRM
- 3 G190A (4.9%, 5.4%, 3.2%)
- 3 V90I (8.2%, 1.9%, 10%)
- 2 G190S (4.8%, 3.1%)
- 2 Y181C (3.5%, 7.0%)
- 2 K101E (3-8%, 4.0%)
- 2 L100I (32%, 14%)
- 1 V179D (3.4%)
- 1 V106I (1.0%)

**Conclusion.**
Pts with K103N acquired after 1st gen NNRTI failure (but not naïves with transmitted DRM) commonly have additional ETR DRM minority variants.

Varguese V. IHDRW Florida 2009. #122.
High rate of virologic success with raltegravir plus etravirine and darunavir/ritonavir in treatment-experienced patients with multidrug-resistant virus: Results of the ANRS 139 TRIO trial

Y. Yazdanpanah 1, C. Fagard 2, D. Descamps 3, A.M. Taburet 4, B. Roquebert 3, I. Tschope 2, C. Katlama 5, G. Pialoux 6, C. Jacomet 7, C. Piketty 8, D. Bollens 9, J.-M. Molina 10, G. Chene 2 and the ANRS 139 TRIO Trial Group

1 Tourcoing Hospital, Tourcoing, France; 2 INSERM U897, Bordeaux, France; 3 Bichat-Claude Bernard Hosp, Paris, France; 4 Kremlin Bicetre Hosp, Paris, France; 5 Pitie-Salpetriere Hosp, Paris, France; 6 Tenon Hosp, Paris, France; 7 Clermont-Ferrand Hosp, Clermont-Ferrand, France; 8 Georges Pompidou Hosp, Paris, France; 9 Saint-Antoine Hosp, Paris, France; 10 Saint-Louis Hosp, Paris, France

Results from other studies on 3 new and/or fully active drugs in treatment experienced patients with MDR virus:

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<tr>
<th>Drug Combinations</th>
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<th>N = 103</th>
<th>N = 80</th>
<th>N = 109</th>
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<tr>
<td>RAL + DRV/r + ENF</td>
<td>89%</td>
<td>77%</td>
<td>71%</td>
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<td>RAL + GSS=2</td>
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<tr>
<td>RAL + PSS=2</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ETR + DRV/r + ENF</td>
<td>60%</td>
<td>68%</td>
<td>73%</td>
<td>82%</td>
</tr>
<tr>
<td>ETR + PSS=2</td>
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<td></td>
</tr>
<tr>
<td>RAL + DRV/r + ETR</td>
<td>90%</td>
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Efficacy similar to that reported for ARV-naive patients

- % pts with HIV RNA < 50 cp/ml

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<th>Study</th>
<th>Arm</th>
<th>N</th>
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<th>24 wks</th>
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<td>Benchmark 1&amp;2</td>
<td>RAL+DRV/r+ENF</td>
<td>74</td>
<td>89%</td>
<td>60%</td>
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<tr>
<td>Duet 1</td>
<td>RAL+GSS=2</td>
<td>74</td>
<td>77%</td>
<td>68%</td>
</tr>
<tr>
<td>Duet 2</td>
<td>RAL+PSS=2</td>
<td>66</td>
<td>71%</td>
<td>73%</td>
</tr>
<tr>
<td>Trio</td>
<td>ETR</td>
<td>80</td>
<td>73%</td>
<td>82%</td>
</tr>
</tbody>
</table>

- HIV-1 RNA was below 50 copies/ml in 88% (95% CI 82;94) of patients at W96.
- Mean change of HIV-1 RNA from baseline to week 48 and week 96 was at -2.4 log_{10} copies/ml (SD: 0.8) and -2.3 log_{10} copies/ml (SD: 0.9), respectively.
- Mean change of CD4+ cell count from baseline to week 48 and week 96 was +130 cells/mm³ (SD: 140) and +179 (SD: 191), respectively (Figure 1).

Figure 1. Mean change in HIV-1 RNA and CD4+ from baseline, ANRS 139 TRIO

Figure 2. Median change in lipid parameters, ANRS 139 TRIO
Resistances Impacting Dolutegravir

- Raltegravir (RAL) signature mutations at Y143, Q148, and N155 arise at virologic failure
  - Continuing treatment with RAL may lead to the addition of 2° mutations or pathway evolution (eg, N155H to Y143 or Q148)

- With respect to dolutegravir (DTG) FC, there are 2 general RAL-resistant genotypic populations
  - No or minimal increase in DTG FC for viruses with 143 mutational pathway, 155 mutational pathway, 148 single mutation
  - Variable to high increase in DTG FC for viruses with 148 plus secondary mutations
Deep sequencing in HIV clinical management

Roger Paredes, MD, PhD
HIV Unit & IrsiCaixa AIDS Research Institute
Hospital Universitari Germans Trias i Pujol
Badalona, Catalonia, Spain
HIV RESISTANCE STEMS FROM THE HUGE ABILITY OF THE VIRUS TO GENERATE DIVERSITY

Population level

Individual level

Population Sequencing Offers a summary of nucleotides present in >20% of virus population
Clinical Indications

- Naive
  - NNRTIs
  - PIs
- ART Experienced
- Tropism
Clinical Indications

- Naive
  - NNRTIs
  - PIs
- ART Experienced
- Tropism
INCLUSION
- Cohort or case-control studies
- that evaluated the effects of low-frequency HIV-1 NRTI and NNRTI DRMs on the rate of virologic failure
- in treatment-naive adults
- receiving an initial NNRTI-based ART.

EXCLUSION
- No comparison group
- No treatment outcome data
- Focused solely on primary infection
- Cross-sectional design

Low-Frequency HIV-1 Drug Resistance Mutations and Risk of NNRTI-Based Antiretroviral Treatment Failure
A Systematic Review and Pooled Analysis

Jonathan Z. Li, MD
Roger Parende, MD, PhD
Heather J. Ribault, PhD
Exegenea S. Svanoevaia, PhD
Kari J. Matsuura, MD
Michael J. Konik, MD
Kathy Huqpler Hullbeck, PhD
Melanie Baldwin, PhD
Marion R. Jakobson, PhD, Me
Anna Maria Geretti, MD, PhD
Redolana Thirabour, MD, PhD
Laix Obstrell, MD, PhD
Bernard Macquessier, PharmD, PhD
Jeffrey A. Johnson, PhD
Michael D. Miller, PhD
Daniel H. Kosttikes, MD

CENO210 TESTS FOR HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) DRUG RESISTANCE-ASSOCIATED MUTATIONS AMPLIFICATION AND POPULATION SEQUENCING TECHNIQUES THAT DETECT RESISTANCE-ASSOCIATED MUTATIONS PRESENT IN AT LEAST 15% TO 25% OF THE VACCINE POPULATION. USING THESE TRADITIONAL ASSAYS, THE PREVALENCE OF TRANSMITTED DRUG RESISTANCE MUTATIONS IS ESTIMATED TO BE BETWEEN 8% AND 16% AMONG HIV-1 INFECTED PERSONS IN NORTH AMERICA AND EUROPE. THESE ASSAYS FALI TO DETECT THE PRESENCE OF LOW-FREQUENCY, OR MINORITY, DRUG RESISTANCE MUTATIONS WITHIN THE POPULATION OF HIV-1 QUASISPRESSES IN AN INFECTED INDIVIDUAL. COMPARED WITH STANDARD POPULATION-SEQUENCING, A NUMBER OF ULTRASENSITIVE ASSAYS, INCLUDING ALLELE-SPECIFIC PCR AND DEEP SEQUENCING, CAN DETECT MUTATIONS IN PATIENTS WITH HIGHLY VARIABLE VIREMIA. IN THIS SERIES OF STUDIES, WE HAVE DEVELOPED A PROTOCOL FOR TESTING PAIRED THERAPEUTIC SAMPLES FROM PATIENTS RECEIVING ART AND STUDYING THE CORRELATION BETWEEN DRUG RESISTANCE MUTATIONS AND TREATMENT OUTCOME.
**PREVALENCE & OUTCOMES**

**Figure 2.** Kaplan-Meier Curves for Proportion of Patients Without Virologic Failure by Presence of Drug-Resistant HIV-1 Minority Variants

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<td>1000</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>1250</td>
<td>7</td>
</tr>
</tbody>
</table>

*P < .001*
## ADHERENCE & THRESHOLD

%MVxVL = mutational load

| Minority variant and adherence | No minority variant and any adherence | Any minority variant | | Adherence ≥95% | 35 | 138 | 73 | 617 | 1.5 (0.98-2.3) | | Adherence <95% | 63 | 138 | 79 | 617 | 5.1 (3.6-7.2) | | No minority variant | | Adherence ≥95% | 1 [Reference] | | Adherence <95% | 43 | 231 | 386 | 4.0 (2.8-5.8) | | Any minority variant | Adherence ≥95% | 35 | 43 | 73 | 386 | 3.1 (1.9-5.0) | | Adherence <95% | 63 | 43 | 79 | 386 | 10.6 (6.9-16.4) | | Minority variant, % | | <1 | 91 | 209 | 154 | 781 | 2.2 (1.6-3.1) | | ≥1 | 18 | 209 | 30 | 781 | 5.0 (2.4-10.3) | | <0.5 | 86 | 107 | 143 | 654 | 2.2 (1.6-3.0) | | ≥0.5 | 14 | 107 | 32 | 654 | 5.2 (2.8-9.8) | | Minority variant copies, No. | 1-9 | 8 | 148 | 15 | 720 | 1.8 (0.9-3.8) | | 10-99 | 41 | 148 | 71 | 720 | 2.2 (1.5-3.2) | | 100-999 | 35 | 148 | 55 | 720 | 3.0 (2.0-4.5) | | ≥1000 | 20 | 148 | 38 | 720 | 4.1 (2.5-6.8) |
Clinical Indications

- Naive
  - NNRTIs
  - PIs
- ART Experienced
- Tropism
Clinical Indications

Naive

- NNRTIs
- PIs

ART Experienced

Tropism
CASE-CONTROL SUBANALYSIS OF THE CASTLE STUDY

Results

148 Samples Sent for UDS

53 VF
33 Subtype B
20 Non-subtype B

51 with UDS data
32 Subtype B
19 Non-subtype B

2 with no UDS data

95 VS
57 Subtype B
38 Non-subtype B

90 with UDS data
54 Subtype B
36 Non-subtype B

5 with no UDS data
PREVALENCE OF RESISTANCE – castle study

DRUG RESISTANCE BY ARM

Clinical Indications

- Naive
  - NNRTIs
  - PIs
- ART Experienced
- Tropism
Clinical Indications

- Naive
  - NNRTIs
  - PIs
- ART Experienced
- Tropism
IMPROVED PREDICTION OF SALVAGE ANTIRETROVIRAL THERAPY OUTCOMES USING ULTRASENSITIVE HIV-1 DRUG RESISTANCE TESTING

Christian Pou,¹,²* Marc Noguera-Julián,¹,²,³* Susana Pérez-Álvarez,¹,² Federico García,⁴ Rafael Delgado,⁵ David Dalmau,⁶,⁷ Miguel Álvarez-Tejado,⁸ Dimitri Gonzalez,⁹ Chalom Sayada,⁹ Natalia Chueca,⁴ Federico Pulido,⁵ Laura Ibañez,⁶ Cristina Rodríguez,¹,² Maria Casadellà,¹,² José R. Santos,²,¹⁰ Lidia Ruiz,¹,² Bonaventura Clotet,¹,²,³,¹⁰ Roger Paredes¹,²,³,¹⁰

Accepted CID 2014
Background

- ARV-experienced subjects with MDR HIV-1 are our most difficult-to-treat patients and could highly benefit from more precise resistance evaluations.

- Failure to suppress viral replication with subsequent salvage ART might result in exhaustion of treatment options and increased mortality.

- The clinical relevance of ultrasensitive genotyping in treatment-experienced individuals remains largely unexplored.

- Does ultrasensitive HIV-1 drug resistance genotyping provide better predictions of virological outcomes to salvage ART in treatment-experienced subjects relative to Sanger sequencing?
Study Design

- Retrospective, multicentre, cohort study
  - Can Ruti, H12 Octubre Madrid, San Cecilio Granada, Mutua Terrassa
- Funded by the CDTI, MICINN
- Clinicaltrials.gov ID: NCT01346878

Inclusion

- ART-experienced
- HIV-1-infected adults who initiated salvage ART including, at least, one PI/r, RAL or ETR
- >1 mL of plasma available for genotypic resistance testing with HIV-1 RNA levels ≥ 5,000 copies/mL within 48 weeks before treatment change (baseline)
KM: GSS & virological failure (HIVdb. Stanford database)
KM: GSS & virological failure (ANRS)

454-GSS ANRS

Sanger-GSS ANRS

Log-Rank=0.004

Log-Rank=0.129

Number at risk:
- 454-GSS <3: O 44, 19, 11, 11, 11, 11, 2

Number at risk:
- Sanger-GSS <3: O 49, 23, 14, 14, 14, 14, 3
- Sanger-GSS ≥3: ● 82, 45, 32, 20, 20, 20, 20
KM: GSS & virological failure (REGA)
Cox hazards regression - MULTIV

Differences according to number of active drugs

<table>
<thead>
<tr>
<th></th>
<th>454 model</th>
<th>Sanger model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>454-GSS (HIVdb)</td>
<td></td>
<td></td>
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<tr>
<td>≥3</td>
<td>1</td>
<td>(1.4, 14.2)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>4.4</td>
<td>(1.3, 14.2)</td>
</tr>
<tr>
<td>Sanger-GSS (HIVdb)</td>
<td></td>
<td></td>
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<tr>
<td>≥3</td>
<td>1</td>
<td>(0.9, 2.0)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>0.9</td>
<td>(0.4, 2.0)</td>
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<tr>
<td>Centre</td>
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<tr>
<td>01</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>1.9</td>
<td>(0.7, 5.6)</td>
</tr>
<tr>
<td>03</td>
<td>3.8</td>
<td>(0.6, 23.9)</td>
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<tr>
<td>04</td>
<td>0.7</td>
<td>(0.2, 3.2)</td>
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<tr>
<td>Baseline HIV-1 RNA (copies/mL)</td>
<td></td>
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<tr>
<td>&lt;100,000</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥100,000</td>
<td>2.7</td>
<td>(0.9, 7.5)</td>
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<tr>
<td>Calendar year at TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per each additional year</td>
<td>0.9</td>
<td>(0.7, 1.1)</td>
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<tr>
<td># previous ARV drugs</td>
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<tr>
<td>Per each additional drug</td>
<td>1.2</td>
<td>(1.0, 1.4)</td>
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<tr>
<td>Time between genotypic test and TC</td>
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</tr>
<tr>
<td>Per each additional month</td>
<td>1.1</td>
<td>(1.0, 1.3)</td>
</tr>
</tbody>
</table>

Similar results with ANRS and REGA

4.4 times more risk of failure
Conclusions

• Ultrasensitive HIV-1 genotyping predicts salvage ART outcomes better than Sanger sequencing.

• A Genotypic Sensitivity Score (GSS) <3 by 454 is an independent predictor of virological failure to salvage ART.

• Ultrasensitive HIV-1 drug resistance testing may improve salvage ART outcomes.
Moltes gràcies

Thank you for your attention