Reduced Darunavir Dose Is as Effective in Maintaining HIV Suppression as the Standard Dose in Virologically Suppressed HIV-Infected Patients. The DRV600 Study.

José Moltó, Marta Valle, Elena Ferrer, Adrián Curran, José Ramón Santos, Silvana DiYacovo, Pere Domingo, Cristina Miranda, Mar Gutierrez, Bonaventura Clotet, and the DRV600 Study Group.
Background

• Current aim is to increase substantially the number of HIV+ patients on ART during the next decade.

• Meeting this goal in the setting of limited resources is challenging.

• Strategies aimed at maximizing ART efficiency
  – Use of generic drugs
  – Use of antiretrovirals which are cheaper to make
  – Improve synthesis of antiretrovirals
  – Dose optimization

Adapted from Hill et al
For several HIV-drugs, Phase 2 data showed no difference in efficacy between doses

Trend to select higher doses for Phase 3 and registration

**Pros**
- Maximize efficacy
- Drug-drug interactions

**Cons**
- Safety (i.e. AZT, ddI, d4T)
- Cost

Adapted from Hill et al
- 3-class experienced
- ≥ 1 PI mutation
- VL > 1000 copies/mL
- Investigator-selected PI(s) plus OBR (NRTIs ± ENF)
DRV/r Phase 2 trials: %HIV RNA >1 log reduction at Week 24, by dose and baseline DRV resistance

DRV FC <4 (sensitive)

DRV FC >4 (resistant)

Presented at the 12th Int. Workshop on Clin. Pharmacology of HIV Therapy, 13-15 April 2011, Miami, FL, USA

Haubrich et al AIDS 2007, 21: F11-F18
Hypothesis & Objectives

- **Hypothesis:** Lowering DRV daily-dose from 800 to 600mg QD in HIV+ patients with undetectable VL and no DRV RAM would maintain viral suppression while reducing costs associated with ART.

- **Objective:** To assess the efficacy, safety and economic impact of reducing DRV dose from 800mg to 600mg QD in virologically suppressed HIV-infected patients without evidence of PI resistance.
  - **PK sub-study** ..................... 14th IWCPHT 2013; P_25
  - **CSF sub-study** ..................... 15th IWCPHT 2014; P_46
Study endpoints
- The proportion of patients with HIV-1 RNA <50 c/mL at w48 (ITT).
  Non inferiority if lower limit of the 95% CI for $\delta < -15\%$, 80% power
- Changes in CD4+ T cell count
- Changes in DRV $C_{\text{trough}}$ in plasma
- The proportion of patients with AEs during follow-up
- The economic cost derived from ARV drugs
# Baseline characteristics & patient disposition

<table>
<thead>
<tr>
<th></th>
<th>DRV 800 n=50</th>
<th>DRV 600 n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>44.8 (10.5)</td>
<td>45.6 (10.8)</td>
</tr>
<tr>
<td><strong>Sex, male</strong></td>
<td>41 (82%)</td>
<td>40 (80%)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>24.9 (3.5)</td>
<td>25.3 (3.4)</td>
</tr>
<tr>
<td><strong>HCV antibody positive</strong></td>
<td>7 (14%)</td>
<td>13 (26%)</td>
</tr>
<tr>
<td><strong>CD4 cell count, cells/mm³</strong></td>
<td>591 (272)</td>
<td>523 (331)</td>
</tr>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>34 (68%)</td>
<td>32 (64%)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>16 (32%)</td>
<td>17 (34%)</td>
</tr>
<tr>
<td><strong>Protocol defined treatment failure at w48, n (%)</strong></td>
<td>3 (6%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Confirmed HIV RNA elevation</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exitus</td>
<td>-</td>
<td>1*</td>
</tr>
</tbody>
</table>

*Liver cirrhoses. Septic shock.
Results w48
Non inferiority of DRV/r 600/100 mg QD

94% 90% 96% 94%

% HIV-1 RNA <50 cp/mL

0 20 40 60 80 100

ITT  Observed data

50 50 49 48

95% CI for the difference

ITT: -4.0 (-12.9; 4.9)
Observed data: -2.2 (-9.6; 5.2)
Change in CD4+ T cell count from baseline

Δ CD4+T cells from BL (cells/mm3)

Weeks

DRV600

DRV800

p=0.415
Pharmacokinetics. DRV $C_{\text{trough}}$

![Graph showing DRV Ctrough over weeks with two lines representing DRV600 and DRV800 with p-value of 0.776.](image-url)
Safety

Drug-related AEs

<table>
<thead>
<tr>
<th></th>
<th>DRV 800 n=12</th>
<th>DRV 600 n=7</th>
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</thead>
<tbody>
<tr>
<td>Gastrointestinal disturbances</td>
<td>6</td>
<td>4</td>
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<tr>
<td>Dislipidemia</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Other &lt;5%</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

p=0.157

\[\Delta\text{Total cholesterol (mg/dL)}\]

\[\Delta\text{Triglycerides (mg/dL)}\]

p=0.284

p=0.157
## Cost-efficacy analysis

<table>
<thead>
<tr>
<th></th>
<th>Annual DRV cost per patient</th>
<th>Virologic response w48 (ITT)</th>
<th>Average annual DRV cost per patient with virologic response</th>
<th>Incremental cost per patient successfully treated</th>
<th>Patients successfully treated with DRV600 to have one free DRV600 a year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case</strong></td>
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<tr>
<td>DRV800</td>
<td>4,389 €</td>
<td>0.94</td>
<td>4,669 €</td>
<td>1,011 €</td>
<td>4</td>
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<tr>
<td>DRV600</td>
<td>3,292 €</td>
<td>0.9</td>
<td>3,658 €</td>
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<tr>
<td><strong>Best scenario</strong></td>
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<tr>
<td>DRV800</td>
<td>4,389 €</td>
<td>0.94</td>
<td>4,669 €</td>
<td>1,341 €</td>
<td>3</td>
</tr>
<tr>
<td>DRV600</td>
<td>3,292 €</td>
<td>0.989</td>
<td>3,329 €</td>
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<tr>
<td><strong>Worst scenario</strong></td>
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<td></td>
</tr>
<tr>
<td>DRV800</td>
<td>4,389 €</td>
<td>0.94</td>
<td>4,669 €</td>
<td>610 €</td>
<td>6</td>
</tr>
<tr>
<td>DRV600</td>
<td>3,292 €</td>
<td>0.811</td>
<td>4,059 €</td>
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Conclusions

- Compared with standard dose of 800mg QD, a DRV dose reduction to 600mg QD:
  - Provided **non-inferior efficacy** at w48 in suppressed HIV+ patients.
  - Resulted in **comparable darunavir PK** parameters
    - $C_{\text{trough}}$ well above the protein binding adjusted DRV IC$_{90}$ for wt strains
  - Had **comparable exposure/efficacy** in CSF
  - **Cost saving approx 1,000 € /pt-yr**
    - 4 pts on DRV600 qd = 1 free DRV600 qd
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