Simultaneity and adherence to multiple tablet regimens among patients starting once-daily atazanavir/ritonavir (ATV/r)-based therapy: the ANRS 134 - COPHAR 3 study

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for the ANRS 134 Study Group
Introduction

- Average adherence to boosted protease inhibitors-based antiretroviral therapy predicts virological suppression*

- Selective ritonavir nonadherence and dose-staggering may occur in recipients of boosted protease inhibitors (BPI)**

*Parienti JJ, Clin Infect Dis 2010
**Shuter J, HIV Clin Trial 2009
Objectives

• Assess simultaneity of drug intake for a once-daily 4-pill regimen including ritonavir

• Determine the relationships between
  – Adherence
  – Virological suppression among pts starting antiretroviral therapy
Methods

• HIV-infected pts starting QD MTR:
  – Atazanavir 150mg
  – Ritonavir 100 mg
  – Tenofovir/emtricitabine (245/200 mg)

• Prospective 3 MEMS caps computing:
  – Taking Compliance (TAC): % of taken doses
  – Correct Dosing (COD): % days w correct dosing/total
  – Timing Compliance (TIC):% of doses taken on time (± 3 hours)
Methods

• Data collected at W0, W4, W8, W12, W16 and W24:  
  → 5 periods of observation / pt

  P1  P2  P3  P4  P5

  W0  W4  W8  W12  W16  W24

• Dynamic Virological Suppression (DVS) defined as $\Delta$HIV RNA >1log every 4W or HIV RNA < 40 cp/mL *

• Longitudinal DVS was modeled by Logistic Mixed Models (Proc GLIMMIX in SAS)

*Gross R, AIDS 2001
### Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median [range]</td>
<td>36 [24-66]</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>29 (83)</td>
</tr>
<tr>
<td>Level of education, n (%)</td>
<td></td>
</tr>
<tr>
<td>High school, n (%)</td>
<td>30 (86)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>12 (34)</td>
</tr>
<tr>
<td>Alcohol &gt;4 times/week, n (%)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>AIDS, n (%)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Contamination route</td>
<td></td>
</tr>
<tr>
<td>Sexual, n (%)</td>
<td>34 (97)</td>
</tr>
<tr>
<td>CD4 &lt; 200</td>
<td>5 (14)</td>
</tr>
<tr>
<td>HIV RNA &gt; 100,000</td>
<td>10 (29)</td>
</tr>
</tbody>
</table>

![Graph showing Log10 HIV RNA and CD4 cells over time](image)

**N=35**
MEMS Adherence, %, median [Range]

<table>
<thead>
<tr>
<th>Medication</th>
<th>TAC</th>
<th>COD</th>
<th>TIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritonavir</td>
<td>100 [51-100]</td>
<td>98 [43-100]</td>
<td>87 [30-100]</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>100 [50-102]</td>
<td>95 [41-100]</td>
<td>86 [32-100]</td>
</tr>
<tr>
<td>TDF/EMT</td>
<td>100 [49-102]</td>
<td>98 [42-100]</td>
<td>86 [31-100]</td>
</tr>
</tbody>
</table>
Simultaneous intakes

3 simultaneous drug intakes within given interval

N=5252 events
Adherence and outcomes for 2 pts

- **A**: Atazanavir
- **B**: Tenofovir+emtricitabine
- **N**: Ritonavir

- **HIV RNA (Log10)**
- **CD4 (cell/mm³)**
- **Bilirubinemia (mmol/L)**

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**Graph A**
- Blue line: HIV RNA (Log10)
- Orange line: CD4 (cell/mm³)
- Dashed line: Bilirubinemia (mmol/L)

**Graph B**
- Green bars: Tx taken
- Red bars: Tx not taken
MEMS Adherence and DVS

<table>
<thead>
<tr>
<th>Adherence definition</th>
<th>Odds Ratio$</th>
<th>95% confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking compliance</td>
<td>1.7</td>
<td>[1.1 to 2.9]</td>
<td>0.04</td>
</tr>
<tr>
<td>Correct dosing</td>
<td>1.6</td>
<td>[1.1 to 2.5]</td>
<td>0.03</td>
</tr>
<tr>
<td>Timing compliance</td>
<td>1.4</td>
<td>[1.1 to 1.8]</td>
<td>0.02</td>
</tr>
</tbody>
</table>

$A$ value > 1 indicates an increased probability of DVS corresponding to +10% adherence
ROC curve and adherence cutoff
Limitations

• Follow-up is limited

• Results specific to the antiretroviral regimen and population studied

• The protocol may have induced better adherence (Hawthorne effect)
Conclusion

• Excellent simultaneity and high adherence in the absence of fixed dose regimen in naive HIV-infected subjects

Nevertheless,

• Average adherence (Timing compliance +/- 3 hours) appeared relevant to explain DVS
Acknowledgments

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- AARDEX: B. Vrijens

- Patients
- Investigators in each centre
- Pharmacists et pharmacologists

- Industry: BMS and Gilead for providing the drugs
- ANRS for supporting the study
Back-up SLIDES
Virological outcomes

*HIV RNA cp/mL among failers were: 152, 72, 59, 47 & 45