Defining the scenario in year 2008

Q1. When & how to start?. Planning for life
Q2. When & how to switch?
Q3. Optimal use of old & new drugs. Role of strategic trials?
Q4. How to avoid repeating irreversible mistakes mostly in poor resource settings

Jose M Gatell
Hospital Clinic. Barcelona. Spain
gatell0@attglobal.net
ANTIRETROVIRAL THERAPY

VL

ART

blib

failure

salvage ART

100000

50

50-90%

30-70-90%
<table>
<thead>
<tr>
<th></th>
<th>no.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial therapy</strong></td>
<td>378</td>
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<td>333</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 10000 copies</td>
<td>352</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3130</td>
<td>100</td>
</tr>
</tbody>
</table>
Getting older with HIV

ACTIVE PATIENTS. H. CLINIC. BARCELONA

YEAR

PERCENTAGE

< 50 yr.

>50 yr.

- Graph showing the percentage of active patients over the years, comparing those over 50 years old and those under 50 years old.
• Significant reduction in mortality for HIV-infected patients over this period (P<0.001; ?² test for trend), but not for the general population (P<0.936; ?² test for trend)
HIV-1 infected adults with CD4 cell count > 500/mm$^3$ on long-term ARV therapy reach same mortality rates as the general population

- Standardized mortality ratio (SMR) in 2435 HIV-infected adults, according to cumulated time spent with CD4 cell count between 350 and 499 /mm$^3$ and > 500 /mm$^3$, after the time of truncation $\$$.  

ANRS CO8 APROCOCOPILOTE and ANRS CO3 AQUITAINE cohorts, 1997-2005

\[
\begin{array}{c|c|c|c|c|c|c|c|c|c|c|c}
\text{Time of truncation after initiation of cART (years)} & 0 & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
\text{SMR (CI)} & & & & & & & & & & \\
\end{array}
\]

- truncation : the time period taken into account starts 1, 2, 3, … years after initiation of cART

HIV-1: Clinical treatment. ART

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HIV-1: Clinical treatment. ART

Q1. When & how to start?. Planning for life

Earlier. All patients vs. special situations?
Clinical end points: non-AIDS events
Long term tolerance/convenience

How to start with “old” drugs/combinations
Role of new drugs. Added value vs. higher costs
Novel ART treatment strategies

Intermittent therapy

SMART: study design

participants with CD4+ > 350 cells/mm³

Virologic Suppression (VS) strategy
use of ART to maintain viral load as low as possible throughout follow-up

n = 3000

Drug Conservation (DC) strategy
stop or defer ART until CD4+ < 250; then episodic ART based on CD4+ cell count to increase counts to > 350

n = 3000

plan: 910 primary endpoints, 8 years average follow-up

findings (Jan 06): 164 primary endpoints, 14 months average follow-up, 2% lost to follow-up
## Novel ART treatment strategies

### Intermittent therapy

#### SMART: event rates

<table>
<thead>
<tr>
<th>Event</th>
<th>DC group</th>
<th>VS group</th>
<th>HR (DC/VS) [95% CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint: OD or death</strong></td>
<td>120</td>
<td>47</td>
<td>2.6 [1.9, 3.7]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>55</td>
<td>30</td>
<td>1.8 [1.2, 2.9]</td>
<td>0.007</td>
</tr>
<tr>
<td>Serious OD</td>
<td>13</td>
<td>2</td>
<td>6.6 [1.5, 29]</td>
<td>0.01</td>
</tr>
<tr>
<td>Non-serious OD</td>
<td>63</td>
<td>18</td>
<td>3.6 [2.1, 6.1]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major CVD, renal and hepatic events</td>
<td>65</td>
<td>39</td>
<td>1.7 [1.1, 2.5]</td>
<td>0.009</td>
</tr>
<tr>
<td>Grade 4 events</td>
<td>173</td>
<td>148</td>
<td>1.2 [0.9, 1.5]</td>
<td>0.13</td>
</tr>
<tr>
<td>Grade 4 event or death</td>
<td>205</td>
<td>164</td>
<td>1.3 [1.03, 1.6]</td>
<td>0.03</td>
</tr>
</tbody>
</table>
# Novel ART treatment strategies

## Intermittent therapy

**SMART:** OD and non-OD death by CD4+ count

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. of patients</th>
<th>Rate DC</th>
<th>VS</th>
<th>Relative Risk (95% CI)</th>
<th>P-Value Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatal and non-fatal OD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>20</td>
<td>1.5</td>
<td>1.1</td>
<td>1.4</td>
<td>0.06</td>
</tr>
<tr>
<td>450-549</td>
<td>22</td>
<td>2.5</td>
<td>0.5</td>
<td>4.7</td>
<td></td>
</tr>
<tr>
<td>550-649</td>
<td>13</td>
<td>2.0</td>
<td>0.4</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>650+</td>
<td>40</td>
<td>2.2</td>
<td>0.4</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td><strong>Non-OD death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>350-449</td>
<td>22</td>
<td>1.7</td>
<td>1.1</td>
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<td>13</td>
<td>1.5</td>
<td>0.9</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>650+</td>
<td>25</td>
<td>1.0</td>
<td>0.6</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

---

Favours DC favours VS
4. Evidence above 350 CD4’s. The guidelines

EACS June, 2008

- Risk benefit shifted toward earlier treatment
- Clinical benefit of:
  - Suppressing HIV replication
  - Maintaining CD4’s above 500

- cART >350 CD4’s:
  - Hep C & B reinfection
  - Pregnant women
  - HIV seronegative partner

Near 100% of the population
Hospital Clinic. Initial ART, N= 1886
CD4 Counts Are Low at Start of HAART

2003–2005

• 42 countries
• 176 sites
• 33 008 patients

Rates of most common OIs

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Mycobact. TB</th>
<th>NH lymphoma</th>
<th>HIV wasting</th>
<th>CMV</th>
<th>PCP</th>
<th>Total OI events</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL&lt;500c</td>
<td>9 (11%)</td>
<td>16 (20%)</td>
<td>6 (8%)</td>
<td>2 (3%)</td>
<td>8 (10%)</td>
<td>80</td>
</tr>
<tr>
<td>VL=500c</td>
<td>29 (10%)</td>
<td>29 (10%)</td>
<td>32 (11%)</td>
<td>30 (10%)</td>
<td>11 (4%)</td>
<td>295</td>
</tr>
<tr>
<td>VL=500nc</td>
<td>20 (12%)</td>
<td>14 (8%)</td>
<td>16 (10%)</td>
<td>8 (5%)</td>
<td>20 (12%)</td>
<td>165</td>
</tr>
</tbody>
</table>
Comparison of 903 vs 934
Total limb fat

Data on file, Gilead Sciences.
STARTMRK – Percent of Patients With HIV RNA <50 copies/mL (95% CI) (Non-Completer = Failure)

Percent of Patients with HIV RNA <50 Copies/mL

Number of Contributing Patients

- Raltegravir 400 mg b.i.d.*: 281, 279, 281, 279, 281, 279, 278, 280, 280
- Efavirenz 600 mg q.h.s.*: 282, 282, 282, 282, 281, 282, 280, 281

*In combination with TDF/FTC
**STARTMRK – Change From Baseline in Fasting Serum Lipids Week 48**

**Lipid-Lowering Rx**

<table>
<thead>
<tr>
<th></th>
<th>RAL* # (%)</th>
<th>EFV * # (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added Rx</td>
<td>3 (1)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Increased Rx</td>
<td>4 (1)</td>
<td>4 (1)</td>
</tr>
</tbody>
</table>

*In combination with TDF/FTC

‡p<0.001
Pacientes activos y tratados

![Graph showing the number of patients over years]

- **Active**
- **Treated**

Years: 1985 to 2007

Number of patients: 0 to 3500
HIV-1: Clinical treatment. ART

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Q2. When & how to switch?

Stable and virologically suppressed patients still on suboptimal drugs/combinations

Failing patients: Always, planning for 100% response, selection and interpretation of resistance and tropism tests
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</tr>
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</table>

Hospital Clinic. Barcelona. 2007
Effect of Previous AZT Exposure on Total Limb Fat

Week 48 Change in Limb Fat by Years of Previous Exposure to AZT

- Median Changes in Limb Fat (kg)
  - Truvada: n=20, p=0.014
  - Combivir: n=18, p=0.13

- Comparison:
  - < 3 Years: 6.20
  - ≥ 3 Years: 3.68

- Median Baseline Limb Fat:
  - < 3 Years: 4.01
  - ≥ 3 Years: 5.41

- DEXA sub-study treated analysis set and sub-set of Whole Body Fat composition

- Median Baseline Limb fat

G Moyle, et al., CROI 2008; Poster #938
Salvage Antiretroviral Therapy

Dangerous situation

50-90%

30-70-90%
Acumulación de NAMs en estudio CNA-3005

Número de pacientes en %

Semanas de tratamiento tras fracaso virológico

Melby T. 8th CROI 2001. Abstract 448
Cohorte SCOPE: Riesgo de Cambio Tardío en la Terapia Antirretroviral Estable

- Pacientes con experiencia en Tratamiento (n=106)
  - ART estables durante ≥120 días
  - HIV-RNA >1000 c/ml
  - ≥1 resistencia por mutación
  - Pruebas de resistencia realizadas cada 4 meses

- Aparición de nuevas mutaciones a 1 año
  - Alguna mutación: 44%
  - NAM: 23%
  - IP: 18%

Figure 5. BENCHMRK-1 & -2 Combined Efficacy\(^\dagger\)
Percent of Patients with HIV RNA <50 copies/mL at Week 48 by PSS. Based on Upper and Lower cutoffs

<table>
<thead>
<tr>
<th>PSS</th>
<th>N</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSS = 0 (Based on lower cutoff)</td>
<td>65</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>2</td>
</tr>
<tr>
<td>PSS = 0 (Based on upper cutoff)</td>
<td>33</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>PSS = 1 (Based on lower cutoff)</td>
<td>137</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>29</td>
</tr>
<tr>
<td>PSS = 1 (Based on upper cutoff)</td>
<td>71</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>13</td>
</tr>
<tr>
<td>PSS ≥ 2 (Based on lower cutoff)</td>
<td>221</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>108</td>
<td>48</td>
</tr>
<tr>
<td>PSS ≥ 2 (Based on upper cutoff)</td>
<td>313</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>153</td>
<td>43</td>
</tr>
</tbody>
</table>

\(^\dagger\)Virologic failures carried forward

[Graph showing comparison between Raltegravir + OBT and Placebo + OBT]
Combined Efficacy* (1) – % Patients with HIV RNA < 400 copies/mL at Week 16 by Selected ARTs in OBT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Efficacy Data</td>
<td>447</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>230</td>
<td>43</td>
</tr>
<tr>
<td>Efficacy by ARTs in OBT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>44</td>
<td>98</td>
</tr>
<tr>
<td>+</td>
<td>23</td>
<td>87</td>
</tr>
<tr>
<td>+</td>
<td>42</td>
<td>90</td>
</tr>
<tr>
<td>-</td>
<td>24</td>
<td>63</td>
</tr>
<tr>
<td>-</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>+</td>
<td>47</td>
<td>55</td>
</tr>
<tr>
<td>-</td>
<td>191</td>
<td>74</td>
</tr>
<tr>
<td>-</td>
<td>90</td>
<td>29</td>
</tr>
</tbody>
</table>

+ : First Use in OBT
- : No Use in OBT

* Virological failures carried forward
HIV-1: Clinical treatment. ART

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Pharma companies focus on short term safety & non inferiority over gold standard

Strategic trials: resources, regulations
Treatment success and failure

Success: only significant difference: EFV vs NVP+EFV, p< 0.001

Failure component: (whichever comes first)

- change Rx
- disease progression
- virologic
- success

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NVP-od</td>
<td>29.1</td>
</tr>
<tr>
<td></td>
<td>11.4</td>
</tr>
<tr>
<td>NVP-bd</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>18.9</td>
</tr>
<tr>
<td>EFV</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>15.3</td>
</tr>
<tr>
<td>NVP+EFV</td>
<td>34.5</td>
</tr>
<tr>
<td></td>
<td>16.3</td>
</tr>
</tbody>
</table>

Frank van Leth
NEVIRAPINE, EFAVIRENZ, OR ABACAVIR FOR SIMPLIFICATION OF EFFECTIVE PROTEASE INHIBITOR-BASED ANTI RETROVIRAL THERAPY

(The NEV/EFA/ABA Study)

1 yr / 3 yr Martinez et al NEJM, 2003 / CROI, 2006
**NEV/EFA/ABA Study**

**Proportion of non-failing patients**

ITT analysis ("conservative")

Failures: death, AIDS, or detectable viral load

*generalized Log-rank test, P=0.020*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Patients</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>155</td>
<td>140</td>
<td>110</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>156</td>
<td>140</td>
<td>110</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>149</td>
<td>121</td>
<td>98</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>
**ACTG 5142: Outcomes at Week 96 (ITT)**

- **EFV + 2 NRTIs** superior to **LPV/r + 2 NRTIs** in primary endpoints of
  - Time to virologic failure ($P = .006$)
  - Time to regimen completion ($P = .02$)
- **Protocol-defined threshold for significance:** $P < .016$

HIV-1: Clinical treatment. ART

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REPUBLIQUE DU SENEGAL
MINISTERE DE LA SANTE
REGION MEDICALE DE LOUIS
DISTRICT SANITAIRE DE TOLL
CENTRE DE SANTE DE RO TOLL
BP 30
TEL: 963 31 09
FAX: 963 55 65
HIV-1: Clinical treatment. ART

Q4. How to avoid repeating irreversible mistakes mostly in poor resource settings

Lipoatrophy

Accumulation of resistance mutations

Clinical monitoring
1. Prevention
   Classical plus non-classical methods (circumcision)

2. Treatment
   Role of new drugs in naive patients?
   Most patients are virologically suppressed.
   Role of simplification?
   Goal of salvage therapy is < 50 copies/ml

3. General medical care in “old” patients

4. Supportive measures: mental health, nutrition...