Reducing Drug Regimens: Virological Perspective

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Higher survival in HIV-infected persons since the introduction of HAART (3DR)
...and a lower gap with the general population

La ausencia de factores de riesgo y comorbilidades influyen en las expectativas de vida

Cumulative survival for HIV-infected patients starting HAART and persons from the general population

Population group
- Control
- HIV+ only
- HIV+ with HIV risk factors*
- HIV+ with comorbidity**
- HIV+ with alcohol/drug abuse†

* Viral load >49 copies/mL, CD4 <200 cells/µL, AIDS-defining disease **as defined in the Charlson comorbidity index (CCI);
† Drug abuse reported as route of HIV transmission

Obel N et al. PLoS ONE 2011;6(7):e22698
Non-AIDS related diseases account for more than 50% of the deaths in HIV-infected persons.

AIDS: 49.6%

- Non-AIDS malignancy: 11.8%
- Non-AIDS infection: 8.2%
- CVD: 7.9%
- Violence/substance abuse: 7.8%
- Liver disease: 7.1%
- Respiratory disease: 1.6%
- Renal disease: 1.5%
- Other: 4.6%

N=1597

Inflammatory Markers Predict Mortality Independent of Nadir and Current CD4 count

Gut Epithelial Barrier Dysfunction

IDO-1 Induction

Monocyte Activation

Inflammation / Coagulation

Odds of Mortality
(4th vs. 1st Quartile)

Hunt, JID 2014
(see also: Tenorio, JID 2014)
SMART Study: Interrupting ART Increases the Risk of Heart Disease

No. at Risk

Years from Randomization

% with a Major CVD Event

Intermittent ART

Continuous ART

<table>
<thead>
<tr>
<th>Event</th>
<th>DC</th>
<th>VS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from CVD</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Non-fatal clinical MI</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Non-fatal silent MI</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>CAD requiring surgery for invasive procedure</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>All major CVD events</td>
<td>48</td>
<td>31</td>
</tr>
</tbody>
</table>

El-Sadr, NEJM, 2006
HIV infection contributes to the development of non AIDS events

Increase in Comorbidities

- Low CD4+ nadir
- Persistent Inflammation
- Cumulative Exposure to ART
- Coinfections (HBV, HCV, CMV, EBV y HPV)
- Ageing
- Life style (smoking, …)

Número de Fármacos: Evolución del TAR

1987
• First NRTI

1991–2
Two new NRTIs approved

1994
Dual NRTIs better than monotherapy

1994
Dual NRTIs better than monotherapy

• NNRTI + 2NRTIs
• PI/r + 2NRTIs
• II + 2NRTIs
• CCR5a + 2 NRTIs

• PI/r + NRTI
• PI/r + NNRTI
• PI/r + CCR5 inh
• PI/r + II
• II + 3TC
DRV-r en monoterapia no cumplió criterios de no inferioridad frente a DRV/r + 2 ITIAN (Monet, 144 sem)

Estudio PROTEA.
HIV-1 RNA in CSF samples at Week 48

HIV-1 RNA in CSF samples at Week 48 for patients undetectable at baseline (<40 copies/mL – not detected)

There were 2 patients with HIV-1 RNA <40 copies/mL (target detected) at baseline in the CSF. Both patients had HIV RNA <40 copies/mL (target not detected) at Week 48.
Proportion of patients with HIV-1 viral load < 50 copies/ml at all points from baseline to Week 96

<table>
<thead>
<tr>
<th></th>
<th>Darunavir/r monotherapy</th>
<th>Darunavir/r triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained virological control (viral load &lt; 50 copies/ml from baseline to week 96)</td>
<td>66/112 pts 59%</td>
<td>80/113 pts 71%</td>
</tr>
<tr>
<td>At least one viral load &gt; 50 copies/ml from baseline to week 96</td>
<td>46/112 pts 41%</td>
<td>33/113 pts 29%</td>
</tr>
</tbody>
</table>

Fisher exact test: p = 0.07
**EARNEST: Trial design**

**HIV positive adolescents / adults (n=1200)**
1st line NNRTI-based regimen >12m; > 90% adherence last 1m
Failure by WHO (2010) clinical, CD4 (VL-confirmed) or VL criteria

**RANDOMIZE**

- **PI + 2-3 NRTIs**
  (NRTIs according to local standard of care)

- **PI + RAL**
  (12 wk induction)

- **PI**
  (Monotherapy)

**FOLLOW-UP FOR 144 WEEKS**

**Primary outcome at week 96:**

*Good HIV disease control* — defined as all of:
- Alive and no new WHO4 events from 0-96 weeks AND
- CD4 cell count > 250 cells/mm³ at 96 weeks AND
- VL<10,000 c/ml OR >10,000 c/ml without PI res. mutations at 96 weeks
Los fracasos con monoterapia con IP/r provocan un mayor desarrollo de resistencias a IP que el tratamiento con IP/r + 2 ITIAN.
Note: assuming susceptible if VL<1000 c/ml at week 96; and using inverse probability weighting for VL>1000 c/ml with missing genotype at week 96 based on those with observed genotypes

*One patient in RAL/PI with intermediate/high level resistance to TDF had moved to 3TC TDF ALV at week 4 due to rash
DTG Monotherapy RCT Stopped Due to Failures

- 8/77 Monotherapy >50 by week 48
- 6/8 Genotype amplified
- 3/6 INI resistance
- 1 each 155H, 263K, 230R
- DSMB stopped study
- Authors recommend against DTG monotherapy
- Combined analysis of 3 cohorts*
  - 11/178 (6.1%) VF
  - 3.9% INI resistance
  - 148R/H (3), 155H (2), 118R (2)

*Blanco JI, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 42
FV con DTG-mono

Número de pacientes controlados en las 3 cohortes: 10.440

DTG-bi-triterapia: 1.082 (10%)

DTG-monoterapia: 122 (1,17%)

Fracaso virológico:

- DTG-mono: 11 (9%; IC 95%: 6-18%)
- DTG-bi-triterapia: 64 (6%; IC 95%: 5-7%)

Valor exacto de Fisher:

- p=0,17
- Razón de VF mono: 1,58 (IC 95%: 0,73-3,13)

SALT Trial
Switching to ATV/r+3TC vs. Standard ATV/r+2NRTIs is safe and effective

95% CI for the difference

Favors ATV/r+2NUC(t)s  Favors ATV/r+3TC

-4.8%  5.2%  15.2%

Non-inferiority, $\Delta = -12\%$

Pérez Molina JA. Lancet Infectious Diseases 2016
PADDLE: Dolutegravir + Lamivudine for Treatment-Naive Pts

- Open-label, single-arm phase IV exploratory trial
- 18/20 pts achieved HIV-1 RNA < 50 c/mL at Wk 48
  - 1 pt committed suicide (deemed unrelated to study drugs)
  - 1 pt experienced PDVF at Wk 36 (BL HIV-1 RNA > 100,000 c/mL); resuppressed HIV-1 RNA without ART change by discontinuation visit (Wk 52)
  - 3 other pts with BL HIV-1 RNA > 100,000 c/mL suppressed at Wk 48

110 Subjects
- No Hx of failure, No Hep B
- 8 week Switch to 2NRTI+DTG
- 40 Weeks FU on DTG/3TC
- 1 x VF (no resistance)
- 4 SAE
  - Suicidal ideation
  - CK elevation post exercise
  - Grade 4 Depression
  - Acute Hep C
Dolutegravir + Rilpivirine for Maintenance of Suppression: Snapshot Outcomes at Week 48.

DTG+RPV is non-inferior to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48.

Llibre J, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 44LB.
Existe la replicación vírica persistente en tejidos

N=8, time on HAART with undetectable HIV RNA 2.8 – 12 years

Existe replicación vírica persistente en tejidos

Significance

We show that HIV continues to replicate in the lymphatic tissues of some individuals taking antiretroviral regimens considered fully suppressive, based on undetectable viral loads in peripheral blood, and that one mechanism for persistent replication in lymphatic tissues is the lower concentrations of the antiretroviral drugs in those tissues compared with peripheral blood. These findings are significant because they provide a rationale and framework for testing the efficacy of new agents and combinations of drugs that will fully suppress replication in lymphatic tissues. More suppressive regimens could improve immune reconstitution, as well as provide the effective regimens needed for functional cure and eradication of infection.
Variable penetration of ARV in tissue

Lymph Nodes

- HIV copies/gram tissue
- emtricitabine (fmol/10^6 cells)
- tenofovir (fmol/10^6 cells)
- atazanavir (ng/ml)
- Therapeutic concentrations of drugs

Fletcher, 19th CROI, Seattle 2012
Variable penetration of ARV in tissue

Ongoing viral replication and subtherapeutic ART concentrations in lymph nodes

Fletcher, PNAS 2014
(see also Lorenzo-Redondo, Nature 2016)
Persistent HIV–1 replication maintains the tissue reservoir during therapy

Ramon Lorenzo-Redondo1*, Helen R. Fryer2*, Trevor Bedford3, Eun-Young Kim1, John Archer4, Sergei L. Kosakovsky Pond5†, Yoon-Seok Chung6, Sudhir Penugonda1, Jeffrey G. Chipman7, Courtney V. Fletcher8, Timothy W. Schacker9, Michael H. Malim10, Andrew Rambaut11, Ashley T. Haase12, Angela R. McLean2 & Steven M. Wolinsky1

Lymphoid tissue is a key reservoir established by HIV–1 during acute infection. It is a site associated with viral production, storage of viral particles in immune complexes, and viral persistence. Although combinations of antiretroviral drugs usually suppress viral replication and reduce viral RNA to undetectable levels in blood, it is unclear whether treatment fully suppresses viral replication in lymphoid tissue reservoirs. Here we show that virus evolution and trafficking between tissue compartments continues in patients with undetectable levels of virus in their bloodstream. We present a spatial and dynamic model of persistent viral replication and spread that indicates why the development of drug resistance is not a foregone conclusion under conditions in which drug concentrations are insufficient to completely block virus replication. These data provide new insights into the evolutionary and infection dynamics of the virus population within the host, revealing that HIV–1 can continue to replicate and replenish the viral reservoir despite potent antiretroviral therapy.

We conclude that continued virus production from infected cells in lymphoid tissue sanctuary sites, where drug concentrations are not fully suppressive, can continue to replenish the viral reservoir and traffic to blood or lymphoid tissue

Effects on Mucosal Immunity of First-Line ART With EFV vs. MRV vs. MRV+RAL in combination with FTC/TDF

In the duodenum, the quadruple regimen resulted in:
- greater CD8+ T-cell density decline
- greater normalization of mucosal CCR5+CD4+ T-cells
- increase of the naïve/memory CD8+ T-cell ratio
- greater decline of sCD14 levels
- greater decline of duodenal HIV DNA levels
Variable penetration of ARV in tissue

Drug distribution to colon

Colon/Plasma Concentrations

Drug distribution to duodenum

Duodenum/Plasma Concentrations

La monoterapia con IP/r se asocia con una mayor replicación vírica persistente

García F. JIAS 2014.
Suboptimal cART Adherence is Associated with Higher Levels of Inflammation Despite HIV Suppression.

Porcentaje de diferencia en la concentración sérica de los biomarcadores (ajustado por edad, VHC, hipertensión, raza y tabaquismo).

<table>
<thead>
<tr>
<th>Abreviaturas</th>
<th>Estimado</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>11,2%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>14,8%</td>
<td>0,008</td>
</tr>
<tr>
<td>CRP</td>
<td>21,1%</td>
<td>0,006</td>
</tr>
<tr>
<td>IL-2</td>
<td>14,4%</td>
<td>0,022</td>
</tr>
<tr>
<td>IL-10</td>
<td>11,1%</td>
<td>0,023</td>
</tr>
<tr>
<td>IL-6</td>
<td>11,6%</td>
<td>0,014</td>
</tr>
</tbody>
</table>

Abreviaturas: BAFF, factor activador de las células B; CCL, quimioquinas C-C ligando; CXCL quimioquinas CXC ligando; GM-CSF, factor estimulante de granulocitos y macrófagos; IFN-γ, interferón gamma; IL, interleucina; sCD14, CD14 soluble; sCD27, CD27 soluble; sgp130, glicoproteína soluble 130; sIL-2Rα, receptor soluble IL-2; sIL-6R, receptor soluble IL-6; sTNF-R2, receptor soluble del factor de necrosis tumoral; TNF-α, factor de necrosis tumoral α; CRP, proteína C reactiva.
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<table>
<thead>
<tr>
<th>Biomarker</th>
<th>&lt;85% vs 100% (4-d)</th>
<th>85-99% vs. 100% (4-d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimado</td>
<td>$p$</td>
</tr>
<tr>
<td>TNF-α</td>
<td>9,9%</td>
<td><strong>0,001</strong></td>
</tr>
<tr>
<td>IFN-γ</td>
<td>17,0%</td>
<td>0,012</td>
</tr>
<tr>
<td>CRP</td>
<td>21,9%</td>
<td>0,019</td>
</tr>
<tr>
<td>IL-2</td>
<td>20,3%</td>
<td><strong>0,011</strong></td>
</tr>
<tr>
<td>IL-10</td>
<td>12,6%</td>
<td><strong>0,035</strong></td>
</tr>
<tr>
<td>IL-6</td>
<td>16,3%</td>
<td><strong>0,010</strong></td>
</tr>
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Conclusiones

- **Desde el punto de vista clínico:**
  - La monoterapia (con IP/r o dolutegravir) no demuestra la no inferioridad respecto al tratamiento con tres fármacos
  - La biterapia (con IP/r o dolutegravir) es no inferior al tratamiento triple

- **Desde el punto de vista virológico:**
  - **Resistencias:**
    - La monoterapia (con IP/r o dolutegravir) se puede asociar con el desarrollo de resistencias
    - La biterapia (con IP/r o dolutegravir) no parece asociarse con el desarrollo de resistencia
  - **Persistencia de replicación vírica e inflamación secundaria:**
    - La reducción del número de fármacos pudiera asociarse a una replicación residual en tejidos que condicionara inflamación persistente y el desarrollo secundario de comorbilidades
    - Se debería evaluar este aspecto antes de adoptar la reducción del número de fármacos como una estrategia de rutina clínica