C'è un nuovo paradigma per la tollerabilità?

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Time lines of antiretroviral development

1987 – first NRTI approved
1987 – Zidovudine (AZT)
1991 – Didanosine (ddI)
1992: Zalcitabine
1994 – Stavudine
1995 – lamivudine, hard gel saquinavir
1996 – nevirapine, ritonavir, indinavir
1997 – delavirdine, nelfinavir, soft gel saquinavir
1998 – abacavir, efavirenz
1999 – amprenavir
2000 – lopinavir/ritonavir
2001 – tenofovir
2003 – enfuvirtide, atazanavir, emtricitabine, fosamprenavir
2005 – tipranavir
2006 – darunavir
2007 – maraviroc
2008 – raltegravir
2011 – rilpivirine
2012 – elvitegravir /cobicistat* / emtricitabine/ tenofovir
2013 – dolutegravir

* CYP3A inhibitor no antiretroviral activity

Cause di *switch* per *long-term toxicity*

- da nucleosidici timidinici e ddI
- da EFV per tossicità neurologica (metabolica)
- da PI per tossicità metabolica (renale, cardiovascolare)
- da ABC per rischio cardiovascolare
- da TDF per tossicità metabolica (rene-osso)

E gli inibitori dell’integrasì?
**Mean odds ratio (95% CrI) of AEs and discontinuation due to AEs: Dolutegravir vs other ‘third’ drugs.**

<table>
<thead>
<tr>
<th>DTG compared to</th>
<th>Adverse Events N = 11 studies</th>
<th>Discontinuation due to AEs N = 18 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>0.58 (0.33, 0.94)*</td>
<td>0.24 (0.10, 0.49)*</td>
</tr>
<tr>
<td>DRV/r</td>
<td>1.06 (0.66, 1.61)</td>
<td>0.45 (0.18, 0.93)*</td>
</tr>
<tr>
<td>EFV</td>
<td>0.57 (0.38, 0.81)*</td>
<td>0.26 (0.14, 0.43)*</td>
</tr>
<tr>
<td>EVG/c</td>
<td>0.77 (0.41, 1.34)</td>
<td>0.38 (0.15, 0.79)*</td>
</tr>
<tr>
<td>LPV/r</td>
<td>0.54 (0.29, 0.89)*</td>
<td>0.21 (0.09, 0.40)*</td>
</tr>
<tr>
<td>RAL</td>
<td>1.11 (0.79, 1.53)</td>
<td>0.87 (0.37, 1.77)</td>
</tr>
<tr>
<td>RPV</td>
<td>0.79 (0.44, 1.30)</td>
<td>0.74 (0.33, 1.42)</td>
</tr>
</tbody>
</table>

*Significant comparisons are in bold with an asterisk.

doi:10.1371/journal.pone.0105653.t002

Dolutegravir: AEs by Treatment Subgroup.
(A) Grade 2 to 4 Drug-related AEs. (B) AEs Leading to Withdrawal

Koteff et al. 8° IAS conference, Vancouver July 2015 #TUPEB261
Population Pharmacokinetic Analysis and Pharmacogenetics of Raltegravir in HIV-Positive and Healthy Individuals

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The objectives of this study were to characterize raltegravir (RAL) population pharmacokinetics in HIV-positive (HIV⁺) and healthy individuals, identify influential factors, and search for new candidate genes involved in UDP glucuronosyltransferase (UGT)-mediated glucuronidation. The pharmacokinetic analysis was performed with NONMEM. Genetic association analysis was performed with PLINK using the relative bioavailability as the phenotype. Simulations were performed to compare once- and twice-daily regimens. A 2-compartment model with first-order absorption adequately described the data. Atazanavir, gender, and bilirubin levels influenced RAL relative bioavailability, which was 30% lower in HIV⁺ than in healthy individuals. UGT1A9*3 was the only genetic variant possibly influencing RAL pharmacokinetics. The majority of RAL pharmacokinetic variability remains unexplained by genetic and nongenetic factors. Owing to the very large variability, trough drug levels might be very low under the standard dosing regimen, raising the question of a potential relevance of therapeutic drug monitoring of RAL in some situations.
## Tolerability Failure - ARDENT
Toxicity Associated Discontinuation of randomized ART*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ATV/r n = 605</th>
<th>RAL n = 603</th>
<th>DRV/r N = 601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any toxicity discontinuation</td>
<td>95 (16%)</td>
<td>8 (1%)</td>
<td>32 (5%)</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>25</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Jaundice/Hyperbilirubinemia</td>
<td>47</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other hepatic toxicity</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Metabolic toxicity</td>
<td>6</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Renal toxicity (all nephrolithiasis)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal chem/heme (excl. LFTs)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other toxicity</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* Participants allowed to switch therapy for intolerable toxicity
ACTG 5257: Mean changes from baseline in metabolic outcomes

Ofotokun et al. CID 2015;60:1842-51
Cumulative probability of metabolic syndrome, by treatment group.

Ofotokun et al. CID 2015;60:1842-51
Relative changes in metabolic parameters for dolutegravir versus third agents of interest