Clinical Pharmacology of Integrase Inhibitors (INSTIs)

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- Janssen
- ViiV
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- Novartis
- Astellas
- Basilea
From a clinical viewpoint, at least three elements associated to INSTIs “advent” were found to be particularly impressing:

- Unprecedented virological response in Pts. with prior multiple failures and 3 class resistance (e.g. BENCHMRK Study)
- The fastest viral fall ever recorded
- Multiple superiority of INSTIs vs various comparators in non-inferiority clinical trials
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These were the best achievable results in treatment-experienced Pts with prior multiple failures before INSTIs were introduced:

**RESIST-2**

% with Undetectable VL (< 50 c/mL)

TORO 1&2: < 400 c/mL at wk 96

- **FUZEON+OB** = 661
- **OB** n = 334

ITT: DC or SW = F

34% 26%

Study week

Adapted from Arastéh et al. XVth IAC Bangkok, 2004, MoOrB1058

**POWER 1 and 2:**

HIV RNA < 50 copies/ mL at W. 48

- **DRV/RTV 600/100 mg BID**
  - 45%*
  - 46%*

- **Control**
  - 12%
  - 10%

*Cahn P, et al. CID 2006; 43: 1347-56

BENCHMRK-1 & -2 Combined Efficacy: Percent of Patients With HIV RNA <50 Copies/mL at Week 48 by Selected ARTs in OBT

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>443</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>228</td>
<td>34</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>44</td>
<td>89</td>
</tr>
<tr>
<td>Darunavir</td>
<td>22</td>
<td>68</td>
</tr>
<tr>
<td>+</td>
<td>45</td>
<td>80</td>
</tr>
<tr>
<td>-</td>
<td>23</td>
<td>57</td>
</tr>
</tbody>
</table>

After years of uncertainty, we had evidence that the < 50 copies HIV-RNA target was also achievable (to pretend) in Pts with extensive acquired resistance to 3 drug classes

David Cooper et al. CROI 2008; abstract 788. Reprinted with permission.
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- **Unprecedented virological response in Pts. with prior multiple failures and 3 class resistance** (e.g. BENCHMRK Study)
- **The fastest viral fall ever recorded**
- **Multiple superiority of INSTIs vs various comparators in non-inferiority clinical trials**
Viral fall: INSTIs

Markowitz M, et al.

Gallant JE, et al.

Min S, et al.


DTG

LPV/r

RAL

BIC

Bid

J Acquir Immune Defic Syndr 2006;43:509–515

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Integrate Inhibitors (IIs): main clinical trials

**Raltegravir (RAL)**
- **BENCHMARK**
- **SWITCHMREK**
- **STARTMREK**
- **ARDENT (ACTG 5257)**
- **QDMRK (QD vs bid)**

**Elvitegravir (ELV)**
- **Study 102 (vs EFV/FTC/TDF [atrilpa])**
- **Study 103 (vs ATV/r)**
- **STRATEGY - PI**
- **STRATEGY - NNRTI**
- **Study 109 vs F/TDF + 3rd drug**

**Dolutegravir (DGV)**
- **SPRING 1, 2 (vs RAL & EFV)**
- **SINGLE (vs)**
- **BICTEGRAVIR, treatment-naïve and switch studies**
- **SAILING (vs RAL, IIs-naïve pts)**
- **FLAMINGO (vs DRV/r)**

**Superiority:**
- ★★★ at week 48; ★★ at week 156; ★★★ > 100,000 c/mL at baseline; × not non-inf.
ADME

Absorption
Distribution
Metabolism
Elimination

Pharmacokinetic
Bioavailability
### INSTIs: food effect relative to fasting state

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Low fat Meal</th>
<th>Moderate fat meal</th>
<th>High fat meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL 400 mg</td>
<td>AUC - 46%</td>
<td>AUC + 13%</td>
<td>AUC + 200%</td>
</tr>
<tr>
<td></td>
<td>$C_{12}$ =</td>
<td>$C_{12}$ + 66%</td>
<td>$C_{12}$ + 40%</td>
</tr>
<tr>
<td></td>
<td>$C_{max}$ - 52%</td>
<td>$C_{max}$ + 5%</td>
<td>$C_{max}$ + 200%</td>
</tr>
<tr>
<td>RAL 1200 mg</td>
<td>AUC - 42%</td>
<td>AUC + 1.9%</td>
<td>AUC + 1.9%</td>
</tr>
<tr>
<td></td>
<td>$C_{24}$ - 16%</td>
<td>$C_{24}$ - 12%</td>
<td>$C_{24}$ - 12%</td>
</tr>
<tr>
<td></td>
<td>$C_{max}$ - 52%</td>
<td>$C_{max}$ - 28%</td>
<td>$C_{max}$ - 28%</td>
</tr>
<tr>
<td>ELV</td>
<td>AUC + 36%</td>
<td>AUC + 9%</td>
<td>AUC + 9%</td>
</tr>
<tr>
<td></td>
<td>$C_{max}$ + 22%</td>
<td>$C_{max}$ + 56%</td>
<td>$C_{max}$ + 56%</td>
</tr>
<tr>
<td>DTG</td>
<td>AUC + 33%</td>
<td>AUC + 41%</td>
<td>AUC + 66%</td>
</tr>
<tr>
<td></td>
<td>$C_{max}$ + 46%</td>
<td>$C_{max}$ + 52%</td>
<td>$C_{max}$ + 13%</td>
</tr>
<tr>
<td>BIC</td>
<td>AUC + 24%</td>
<td></td>
<td>AUC + 24%</td>
</tr>
<tr>
<td></td>
<td>$C_{max}$ + 13%</td>
<td>$C_{max}$ + 13%</td>
<td>$C_{max}$ + 13%</td>
</tr>
</tbody>
</table>

Medications containing polyvalent cations (Ca++, Mg++), including laxatives, antacids *decrease* the absorption of INSTIs.
## INSTIs: T/2, Protein binding and Clearance

### INSTIs: No clinical/pharmacological data available on Child-Pugh C stage of liver disease. No dose adjustments required for milder disease stages (Child-Pugh A & B)

<table>
<thead>
<tr>
<th>INSTI</th>
<th>T/2 (hours)</th>
<th>Protein binding</th>
<th>% clearance (urine)</th>
<th>% clearance (faeces)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAL</td>
<td>9.0</td>
<td>83%</td>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(9 unch. + 23 glucuronide)</td>
<td></td>
</tr>
<tr>
<td>ELV/COBI</td>
<td>12.9</td>
<td>98-99%</td>
<td>6.7</td>
<td>94.8</td>
</tr>
<tr>
<td>DTG</td>
<td>14.0</td>
<td>&gt; 99%</td>
<td>32</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(&lt;1 unch. + 18.9 glucuronide)</td>
<td></td>
</tr>
<tr>
<td>BIC</td>
<td>17.3</td>
<td>&gt; 99%</td>
<td>35</td>
<td>60.3</td>
</tr>
</tbody>
</table>

**DOLUTEGRAVIR**

CrCl < 30mL/min:
- AUC - 40%
- C\text{max} - 23%
- C\text{24} - 43%

**BICTEGRAVIR**

CrCl <30mL/min: not recommended
**METABOLISM OF INTEGRASE STRAND TRANSFER INHIBITORS (INSTIs)**

- **Raltegravir**
- **Dolutegravir**
- **Elvitegravir**
- **Bictegravir**

**Substrates (S)**

- OATP1B1
- OATP1B3
- OCT2
- CYP2C9
- UGT (++ 1A1)

**Inducers (ind)**

- CYP3A4
- MATE1
- BCRP

**Inhibitors (inh)**

- Pgp

**Symbols**

- **S** = substrate
- **ind** = inducer
- **inh** = inhibitor
The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects

Table 1. Statistical comparison of metformin PK parameters with and without dolutegravir

<table>
<thead>
<tr>
<th>Plasma Metformin PK Parameter</th>
<th>GLS mean Metformin Alone (Period 1)</th>
<th>Metformin + DTG (Period 2)</th>
<th>GLS mean ratio (90% CI) Metformin + DTG vs. Metformin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (DTG 50 mg QD)</td>
<td>n = 15</td>
<td>n = 14</td>
<td>1.66 (1.53, 1.81)</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.932</td>
<td>1.55</td>
<td></td>
</tr>
<tr>
<td>AUC(0-τ) (hr*µg/mL)</td>
<td>6.83</td>
<td>12.2</td>
<td>1.79 (1.65, 1.93)</td>
</tr>
<tr>
<td>Cohort 2 (DTG 50 mg BID)</td>
<td>n = 15</td>
<td>n = 14</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.845</td>
<td>1.878</td>
<td>2.11 (1.91, 2.33)</td>
</tr>
<tr>
<td>AUC(0-τ) (hr*µg/mL)</td>
<td>6.49</td>
<td>15.9</td>
<td>2.45 (2.25, 2.66)</td>
</tr>
</tbody>
</table>

**BICTEGRAVIR and METFORMIN**

Coadministration increased metformin Cmax and AUC by 28% and 39% due to inhibition of renal OCT2 and MATE1 transporters by bictegravir.

By Tomislav Meštrović  www.news-medical.net/.../Metformin-Overdosage

The minimum reported lethal dose was found in a 42 year-old patient who had a blood metformin level of **188 µg/ml** (e.g. therapeutic range level is usually between **0.5–2.5 µg/ml**).
**UGT1A1 only**

**RALTEGRAVIR**

**UGT1A1 + CYP3A4**

**DOLUTEGRAVIR**

**BICTEGRAVIR**

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### Drug Interactions

<table>
<thead>
<tr>
<th>Drug metabolizing enzymes</th>
<th>BIC</th>
<th>RIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A</td>
<td>Substrate</td>
<td>Inducer</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Substrate</td>
<td>Inducer</td>
</tr>
</tbody>
</table>

---

**RIFAMPICIN and INSTIs**

- **DTG 50 mg QD**
- **DTG 50 mg BID**
- **DTG 50 mg BID + RIF 600 mg QD**

Results: BIC IQ in HIV-Infected Patients in Phase 3 (n=1193) B/F/TAF qd vs B/F/TAF bid + RIF qd

- Mean IQ: 16.1
- Mean IQ: 3.2

Individual patients may fall below the paEC50 = 152 ng/mL

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**Graphs and Data**

- DTG concentration (µg/mL) vs Time after dose (hours)
- Raltegravir Plasma Concentration, nM vs Time, hrs
**RAL + Rifabutin:**
- Cmax: +39%
- AUC: +19%
- Ctrough: -20%

**ELV/COBI + Rifabutin**
- **ELV:**
  - AUC: -21%
  - Cmin: -67%
  - Cmax: -20%
- **COBI:**
  - Cmin: -66%

- **25-O-desacetyl-rifabutin:**
  - AUC: +525%
  - Cmin: +394%
  - Cmax: +384%

**INSTIs and Rifabutin**

**DTG + Rifabutin**
- DTG 50 mg QD
- DTG 50 mg QD + rifabutin 300 mg QD

**BIC* + Rifabutin**
- Bictegravir:
  - AUC: -38%
  - Cmin: -56%
  - Cmax: -20%

* Pgp induction by Rifabutin may decrease TFV exposure
TDM of DTG intakers was reviewed:

- 141 patients on DTG but not Valproate: median 557 ng/mL, (IQ 290-1135 ng/mL)
- 7 patients taking DTG and Valproate: median 68 ng/mL, (IQ 37-148 ng/mL) p<0.001
Coadministration has not been studied but based on metabolism and clearance a clinically relevant drug interaction is unlikely. Valproate is mainly glucuronidated by UGTs 1A6, 1A9 and 2B7 and metabolized by CYP2C9 and CYP2C19. Dolutegravir is not expected to inhibit or induce CYP450 or UGT enzymes at clinically relevant concentrations.

<table>
<thead>
<tr>
<th>Potential Interaction</th>
<th>Dolutegravir</th>
<th>Valproate</th>
</tr>
</thead>
</table>

VPA significantly up-regulated CYP3A4 mRNA in primary hepatocytes and augmented the effect of rifampicin.

Coadministration has not been studied but based on metabolism and clearance a clinically relevant drug interaction is unlikely. Valproate is mainly glucuronidated by UGTs 1A6, 1A9 and 2B7 and metabolized by CYP2C9 and CYP2C19.

VPA is metabolized through glucuronidation by several UGT enzymes (such as UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15), through β-oxidation in mitochondria and, to a lesser extent, through cytochrome P450.

http://www.hiv-druginteractions.org/

Drug Metab Dispos. 2007 Jul;35(7):1032-41

However, a small case series study has reported a ~80-90% decrease in dolutegravir AUC when coadministered with valproate. The mechanism of the interaction is unclear but could possibly involve protein binding displacement and chelation with magnesium contained in the excipients of slow release valproate formulations.

UGT enzymes (such as UGT1A3, UGT1A4, UGT1A6, UGT1A8, UGT1A9, UGT1A10, UGT2B7, and UGT2B15), through cytochrome P450.
7 apr 2018
Roma 0  Fiorentina 2

10 apr 2018
Roma 3  Barcelona 0

Fiorentina  Barcelona

?
No data are available. However, based on the results of recent matches between Roma and Fiorentina and Roma and Barcelona, the final score should be:

Fiorentina 5  Barcelona 0
INSTIs Clinical Pharmacodynamics
Treatment interruption

Lopinavir half-life: 5-6 hours

Efavirenz half-life: 45 hours

Time of residual effective Pk exposure
25/242 (10%) Patients underwent virological failure

Few Patients stop to take drug/s soon after enrollment and fail

Some Patients adhere suboptimally, and a proportion of them fail

In this subgroup, further to specific regimen properties (e.g. intrinsic potency, forgiveness...), the probability of failure might also depend upon some co-factors (e.g. high BL HIV-RNA, low CD4+ cell counts, HCV co-infection)

In ITT analysis of clinical trials (before INSTIs release), there seemed to be a tendency to better virological outcome in case of drugs with longer elimination half-life.

<table>
<thead>
<tr>
<th>Study</th>
<th>Virological response (&lt;50 copies/mL)</th>
<th>Half-life (T/2, hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTG 5142</td>
<td>EFV + 2N/NtRTIs</td>
<td>45</td>
</tr>
<tr>
<td>(144 weeks)</td>
<td>LPV/r + 2N/NtRTIs</td>
<td>5-6</td>
</tr>
<tr>
<td>ARTEMIS</td>
<td>DRV/r + TDF/FTC</td>
<td>10-15</td>
</tr>
<tr>
<td>(96 weeks)</td>
<td>LPV/r + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>CASTLE</td>
<td>ATV/r + TDF/FTC</td>
<td>8.6-15</td>
</tr>
<tr>
<td>(96 weeks)</td>
<td>LPV/r + TDF/FTC</td>
<td></td>
</tr>
<tr>
<td>ARTEN</td>
<td>NVP + TDF/FTC</td>
<td>25-30</td>
</tr>
<tr>
<td>(48 weeks)</td>
<td>ATV/r + TDF/FTC</td>
<td>8.6-15</td>
</tr>
<tr>
<td>ACTG 5202</td>
<td>TDF/FTC + EFV or ATV/r</td>
<td>80%</td>
</tr>
<tr>
<td>(48 weeks)</td>
<td>ABV/3TC + EFV or ATV/r</td>
<td>75%</td>
</tr>
</tbody>
</table>

* Intracellular triphosphate active moiety

T/2 – related forgiveness

*p=0.3312 p<0.0001

Di Perri. G.teaching material, 2015
The reason why, inspite of similar or much shorter T/2, INSTIs tend to overcome other “third drugs” in terms of forgiveness is likely to be multifactorial:

- Better tolerability leading to **better adherence**;

- Greater absolute **intrinsic potency**; due to the **magnitude** of the IQ (inhibitory quotient), even with relatively short T/2, the residual drug concentration is still enough to guarantee anti-HIV activity for a relatively long time (e.g. DGV);

- **Longer residency time on target** (Pk lesser predictive of PD as a variable associated to antiretroviral activity);

- **Faster viral load reduction** *(possibly associated to longer time to viral regrowth)*; at any time point, any episode of missing drug intake takes place with a lower viral load and the chance of a measureable viral regrowth is less likely with INSTIs, particularly in the first weeks of therapy (provided that treatment is resumed);
ACTG 5202 interim results: time to first safety event (High viral load stratum at DSMB action)

As-treated analysis of patients receiving first NRTI backbone

ABC/3TC vs. TDF/FTC: primary virologic endpoint (High viral load stratum at DSMB action)

ABC/3TC vs. TDF/FTC with

- EFV: HR 2.46 (95% CI 1.20, 5.25)
- ATV/r: HR 2.22 (95% CI 1.19, 4.14)

Sax et al. NEJM 2009;361:2230

Similar Efficacy of INSTIs (RAL or DTG) + ABC/3TC or TDF/FTC, Even for High BL VL

- In SPRING-2, similar efficacy with ABC/3TC or TDF/FTC + RAL or DTG, including with high BL HIV-1 RNA*

*Pooled data from both INSTIs.

RELATIONSHIP BETWEEN DTG TROUGH CONCENTRATION AND VIRAL LOAD REDUCTION

DTG is associated with a well characterised, predictable exposure-response relationship.

Phase IIa, dose-ranging, placebo-controlled, 10-day monotherapy study:
- Placebo
- 2 mg QD
- 10 mg QD
- 50 mg QD

Model fit: $E_{\text{max}} = -2.6, IC_{50} = 0.036 \mu g/mL$

Day 11 log_{10} viral load change from baseline:
- $-3.5$
- $-3.0$
- $-2.5$
- $-2.0$
- $-1.5$
- $-1.0$
- $-0.5$
- $0.0$
- $0.5$
- $1.0$

Subjects with HIV-1 RNA <50 c/mL are represented by orange-bordered circles.
Open circles with lines denote mean standard deviation.

A patient taking the 2 mg dose underwent virologic suppression in 10 days!!

DTG is associated with a well characterised, predictable exposure-response relationship.

c/mL, copies/mL; $E_{\text{max}}$, maximum effect; RNA, ribonucleic acid

Adapted from Min S, et al. AIDS 2011; 25:1737–45
...invading the pocket natively occupied by the proviral DNA extensity...

...chelating the metallic cations indispensable for the integrase catalytic activity...

....invading the pocket natively occupied by the proviral DNA extensity.....
Dolutegravir (S/GSK1349572) Exhibits Significantly Slower Dissociation than Raltegravir and Elvitegravir from Wild-Type and Integrase Inhibitor-Resistant HIV-1 Integrase-DNA Complexes

Hightower KE, et al.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2011, p. 4552–4559

<table>
<thead>
<tr>
<th></th>
<th>DG V</th>
<th>RAL</th>
<th>ELV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WT</strong> Diss. Time (T/2)</td>
<td>71 h</td>
<td>8.8 h</td>
<td>2.7 h</td>
</tr>
<tr>
<td>FC EC50</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DG V</th>
<th>RAL</th>
<th>ELV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Y143R</strong> Diss. Time (T/2)</td>
<td>42 h</td>
<td>1.1 h</td>
<td>1.7 h</td>
</tr>
<tr>
<td>FC EC50</td>
<td>1.4</td>
<td>16</td>
<td>1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DG V</th>
<th>RAL</th>
<th>ELV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Q148H</strong> Diss. Time (T/2)</td>
<td>5.2 h</td>
<td>0.2 h</td>
<td>0.2 h</td>
</tr>
<tr>
<td>FC EC50</td>
<td>0.97</td>
<td>13</td>
<td>7.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<th>DG V</th>
<th>RAL</th>
<th>ELV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N155H</strong> Diss. Time (T/2)</td>
<td>9.6 h</td>
<td>0.6 h</td>
<td>0.4 h</td>
</tr>
<tr>
<td>FC EC50</td>
<td>0.99</td>
<td>8.4</td>
<td>25</td>
</tr>
</tbody>
</table>

- **DG V** Dolutegravir
- **RAL** Raltegravir
- **ELV** Elvitegravir

**Much shorter exposure of replicating virions to drugs**

**Dead Bugs Don’t Mutate: Susceptibility Issues in the Emergence of Bacterial Resistance**

Charles W. Stratton

*Emerging Infectious Diseases 2009; 9: 10-16.*

Based on the n. of mutations required to significantly decrease activity, INSTIs should not differ too much from NNRTIs

<table>
<thead>
<tr>
<th>Week</th>
<th>20 mg</th>
<th>50 mg</th>
<th>75 mg</th>
<th>100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>20/32 (63)</td>
<td>29/31 (94)</td>
<td>35/51 (69)</td>
<td>46/51 (90)</td>
</tr>
<tr>
<td>48</td>
<td>46/51 (90)</td>
<td>47/51 (94)</td>
<td>46/51 (90)</td>
<td>47/51 (90)</td>
</tr>
<tr>
<td>96</td>
<td>42/53 (79)</td>
<td>45/51 (88)</td>
<td>46/51 (88)</td>
<td>36/50 (72)</td>
</tr>
<tr>
<td>Any</td>
<td>7 (13)</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>NR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rebound</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

The much faster action of INSTIs contributes substantially to their genetic barrier.
Therapeutic (genetic) barrier of INSTIs

Overall low rate of resistance emergence at W48 in ARV-naive trials:

- **RAL 400 mg** 1 tablet bid: 0% to 1.4%
  SPRING-2, STARTMRK, ONCEMRK

- **RAL 600 mg** 2 tablets qd: 0.8%
  ONCEMRK

- **DTG**: 0% to 0.2%
  ARIA, SPRING-2, SINGLE, FLAMINGO

- **EVG/c**: 0% to 2%
  ARIA, WAVES, Study 102, Study 103

Some Clinical PK update on INSTIs
The investigators measured intracellular integrase inhibitor concentrations in samples from PBMCs and mononuclear cells from lymph nodes, ileum, and rectum from 34 patients, 11 taking dolutegravir, 17 elvitegravir, and 6 raltegravir with TDF, TAF, or abacavir plus FTC or 3TC.
Dolutegravir **PK** and NP symptoms

- Higher DTG Ctrough in patients with symptoms
- High DTG Ctrough in patients discontinuing (1719 ng/mL)
- Symptoms disappearance with DTG every other day (in a low BMI patient)

Dolutegravir (50 mg QD)

Elvitegravir/COBI (150/150 mg QD)

Raltegravir

Bictegravir (75 mg QD)

400 mg bid

1200 mg QD
ONCEMRK

• 802 pts randomized (2:1)
  – RAL 1200 mg QD + TDF/FTC
  – RAL 400 mg BID + TDF/FTC

• RAL QD non-inferior to RAL BID
  VL <40: 88.9% vs. 88.3%

Wk 48 VL<40 (Snapshot)

Primary endpoint (NC=F; snapshot) at Week 48:
% HIV RNA <40 c/mL: 88.9% for QD and 88.3% for BID; Δ 0.5 (-4.2, 5.2)
% HIV RNA <50 c/mL (NC=F): 89.9% for QD and 90.2% for BID; Δ -0.4 (-4.9, -4.0)

• For subgroup with BL HIV RNA >100,000 c/mL:
  % HIV RNA <40 c/mL (OF): 86.7% for QD and 83.8% for BID; Δ 2.9 (-6.5, 14.1)
  CD4 (cells/mm³) increase (OF): 232 for QD and 234 for BID; Δ -2 (-31, 27)

Comparative PHARMACOKINETICS

Subgroup Analyses from ONCEMRK, a Phase 3 Study of Raltegravir 1200 mg Once Daily vs RAL 400 mg Twice Daily, in Combination with Tenofovir/Emtricitabine, in Treatment-Naïve HIV-1 Infected Subjects: Results

### HIV RNA < 40 c./mL

<table>
<thead>
<tr>
<th></th>
<th>400 mg BID</th>
<th>1200 mg QD</th>
<th>BID</th>
<th>QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>93.6 (251)</td>
<td>94.2 (501)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline HIV RNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 100,000 c/mL</td>
<td>97.7 (177)</td>
<td>97.2 (358)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100,000 c/mL</td>
<td>83.8 (74)</td>
<td>86.7 (143)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 500,000 c/mL</td>
<td>95.8 (237)</td>
<td>95.2 (479)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 500,000 c/mL</td>
<td>57.1 (14)</td>
<td>72.7 (22)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

|                  |          |            |     |      |
| Baseline CD4+ count |        |            |     |      |
| < 200 cells/uL    | 87.9 (33)| 85.1 (67)  |     |      |
| > 200 cells/uL    | 94.5 (218)| 95.6 (434)|     |      |

The time to achieve virological undetectability and the rate of success at 48 weeks are pre-HAART viremia dependent.

<table>
<thead>
<tr>
<th>Pre-HAART viremia ranges (copies/mL)</th>
<th>No.</th>
<th>Median Time (95% CI) to achieve VS (weeks)</th>
<th>Probability of VS at 48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500K</td>
<td>135</td>
<td>23 (21-25)</td>
<td>84%</td>
</tr>
<tr>
<td>300K - 500K</td>
<td>102</td>
<td>22 (21-24)</td>
<td>93%</td>
</tr>
<tr>
<td>100K - 300K</td>
<td>273</td>
<td>18 (17-20)</td>
<td>93%</td>
</tr>
<tr>
<td>30K - 100K</td>
<td>229</td>
<td>15 (14-16)</td>
<td>98%</td>
</tr>
<tr>
<td>&lt;30K</td>
<td>235</td>
<td>10 (9-11)</td>
<td>99%</td>
</tr>
</tbody>
</table>

P<0.001 at log-rank test

Are we happy with this?
Infections with a high bacterial density at the initiation of antibiotic therapy may present a therapeutic problem, including a higher risk for the emergence of resistance due to the larger number of bacteria present and the **higher probability of having at least one resistant bacterial cell within a large initial inoculum (CFUo)**

A higher bacterial inoculum might correspond to a high BL viral load, and the sooner you get rid of it the lower is the chance of selecting resistant mutants.... So a quicker action does contribute to the genetic barrier...

Dose Ranging and Fractionation of Intravenous Ciprofloxacin against *Pseudomonas aeruginosa* and *Staphylococcus aureus* in an In Vitro Model of Infection


<table>
<thead>
<tr>
<th>Organism and regimen</th>
<th>Peak/MIC (0-8 h)</th>
<th>T &gt; MIC (0-8 h)</th>
<th>T &gt; MIC (0-24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. aeruginosa</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 mg TID</td>
<td>4.2</td>
<td>7.5</td>
<td>23</td>
</tr>
<tr>
<td>600 mg bid</td>
<td>6</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>1200 mg QD</td>
<td><strong>11</strong></td>
<td>8</td>
<td>13</td>
</tr>
</tbody>
</table>

The same total daily dose

Regrowth without Resistance

Regrowth with Resistance
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