Pharmacology of integrase inhibitors

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Content

• **INSTI pharmacology**
  – Metabolism
  – Impact on transporters
  – Forgiveness

• **Drug-drug interactions**
  – Antiretroviral
  – Non-antiretroviral
  – Communication
Apology
DRUG PHARMACOLOGY BASICS
Absorption from gut:
includes passive diffusion & diffusion or pumping via transporters

Distribution:
in plasma & other compartments; depends on molecule size, protein binding & other characteristics

Metabolism:
mainly liver & usually to less active/inactive 
affected by enzyme induction/inhibition, genetics, age, gender, liver disease

Excretion:
mainly renal (glomerular filtration, active tubular secretion) 
affected by age, transporter competition/inhibition
PK parameters

$$T_{1/2} \text{ (half life)} = \text{time taken for C max to drop in half}$$
It takes $$5 \times T_{1/2}$$ for a drug to be eliminated from the body.

AUC describes the total drug concentration over time.

$$AUC = \text{Area Under Curve}$$
PK parameters

IC50 = concentration required to inhibit 50% replication
IC95 = concentration required to inhibit 95% replication
The target drug level needs to be above the MEC to avoid resistance and not so high as to cause side effects.
PHARMACOLOGY OF INSTI
# Clinical Pharmacology Profile of InSTI

<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR</th>
<th>ELVITEGRAVIR</th>
<th>DOLUTEGRAVIR</th>
<th>BICTEGRAVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical dose</strong></td>
<td>400 mg BID OR 1200 mg QD</td>
<td>150 mg QD</td>
<td>50 mg QD</td>
<td>50 mg QD with FTC/TAF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boosted with cobi FTC/TDF or TAF</td>
<td>(INI-naïve), BID BID (INI-resistant)</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Excretion</strong></td>
<td>UGT1A1 renal elimination ~ 9%</td>
<td>CYP3A (major), UGT1A1/3 (minor), renal elimination ~7%</td>
<td>UGT1A1 (major), CYP3A (minor), renal elimination &lt;1%.</td>
<td>UGT1A1 and CYP3A (equal) renal elimination &lt;1%.</td>
</tr>
<tr>
<td><strong>Renal transporters</strong></td>
<td>Weak inhibition OCT2</td>
<td>COBI inhibits MATE-1</td>
<td>Inhibition of OCT2 &amp; MATE-1</td>
<td>Limited inhibition of OCT2 &amp; MATE-1</td>
</tr>
<tr>
<td><strong>Half Life $t_{1/2}$</strong></td>
<td>~9 hours</td>
<td>~12.9 hours (boosted)</td>
<td>~14 hours</td>
<td>~18 hours</td>
</tr>
<tr>
<td><strong>DDI Potential</strong></td>
<td>Least</td>
<td>Highest</td>
<td>Slightly greater than RAL</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Raltegravir OD vs BD

QDMRK
failure to achieve VL<50 mainly at high baseline VL in both arms also associated with lower Ctrough in the 800-mg-QD arm

Rizk ML at al. AAC 2012: 56(6): 3101-3106
Raltegravir 600mg vs 400mg

- 600mg has higher relative bioavailability vs 400 mg
  - likely due, at least in part, to improvements in tablet disintegration

- Once absorbed, both forms show similar pharmacokinetics:
  - Steady-state in around two days
  - Little to no accumulation with multiple doses

- Food had no clinically relevant effect on raltegravir exposure

ONCEEMRK
RAL 1200 OD non-inferior to 400 BD

It’s not just plasma half-life....

- Once the INSTI it binds to the integrase enzyme & the speed the drug unbinds = dissociation half-life

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Dissociation of INSTI from Wild-type IN-DNA Complexes*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By Exponential Decay</td>
</tr>
<tr>
<td></td>
<td>Apparent $t_{1/2}$ (hr) [**]</td>
</tr>
<tr>
<td>BIC</td>
<td>135 ± 20 [na]</td>
</tr>
<tr>
<td>DTG</td>
<td>79 ± 13 [71]</td>
</tr>
<tr>
<td>RAL</td>
<td>14 ± 3 [8.8]</td>
</tr>
<tr>
<td>EVG</td>
<td>3.6 ± 0.7 [2.7]</td>
</tr>
</tbody>
</table>

* White K et al. CROI 2017
Impact of food on drug absorption

• Food may have no effect or may change the rate or extent of drug absorption by following mechanisms:
  – Altered pH
  – Altered gastric emptying
  – Stimulation of gastro-intestinal secretions
  – Altered drug bioavailability
  – Increased blood flow
  – Competition for transporters
  – Increased viscosity of gastric contents
  – Complex formation between drug & food components
Why is this important?

- Counselling patients
- Utilising data to alter exposure:
  - Overcoming resistance
  - Managing side effects
Impact of food on elvitegravir (as Stribild)

<table>
<thead>
<tr>
<th>N=24</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$AUC_{\text{last}}$ (ng·hr/ml)</th>
<th>$AUC_{\text{inf}}$ (ng·hr/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted</td>
<td>1490 (40.3)</td>
<td>15600 (40.2)</td>
<td>16400 (38.6)</td>
</tr>
<tr>
<td>Light Meal</td>
<td>1760 (31.5)</td>
<td>20400 (28.0)</td>
<td>21100 (27.5)</td>
</tr>
<tr>
<td>HC/HF Meal</td>
<td>2230 (27.1)</td>
<td>28000 (22.6)</td>
<td>28800 (21.6)</td>
</tr>
</tbody>
</table>

GMR (90% CI) %

<table>
<thead>
<tr>
<th>Light Meal vs. Fasted</th>
<th>122 (108, 138)</th>
<th>136 (121, 154)</th>
<th>134 (119, 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC/HF Meal vs. Fasted</td>
<td>156 (138, 176)</td>
<td>191 (170, 216)</td>
<td>187 (166, 210)</td>
</tr>
<tr>
<td>HC/HF Meal vs. Light Meal</td>
<td>128 (114, 145)</td>
<td>140 (124, 158)</td>
<td>139 (123, 157)</td>
</tr>
</tbody>
</table>

References

German P. 49th ICAAC 2009; poster A1-1300
Impact of food on elvitegravir (as Stribild)

In the presence of integrase resistance, DTG should preferably be taken with food to enhance exposure (particularly with Q148)

Food effect may vary with formulation: example of bictegravir

Forgiveness

• Tail studies very informative
• Achieve steady state, stop then monitor drug levels
• Dolutegravir & elvitegravir in healthy volunteers:
  – \([\text{DTG}] > \text{IC90}\) in 100% of subjects after 36 & 48 h and in 94% after 60 & 72 h
  – \([\text{EVG}] > \text{IC95}\) in 100% of subjects at 24 h, 65% at 36 h, 0% after 48 h
Renal transporters

May result in reduced uptake from blood

May result in reduced excretion

Yombi JC et al. AIDS 2014, 28:621–632
Two main consequences?

- Impact on creatinine secretion
- Impact on drug secretion
Renal Transporters and Creatinine Clearance

**Creatinine**

Inhibition by:
- Rilpivirine
- Dolutegravir
- Bictegravir

Renal tubular cell

OCT2

**Creatinine**

Inhibition by:
- Dolutegravir
- Bictegravir

MATE1

Blood to Urine: Active Tubular Secretion

Slide courtesy of Marta Boffito; adapted from Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724
DRUG-DRUG INTERACTIONS
Mechanisms of drug interactions

**ABSORPTION**
- Chelation
- pH effects
- Gut enzymes & transporters

**HEPATIC CLEARANCE**
- Enzymes/transporters
- Liver disease
- Pharmacogenetics

**RENAL CLEARANCE**
- Renal transporters
- Renal disease

UGT1A1*28 polymorphism increases [RAL] which correlates with fatigue
Pharmacokinetic consequences of drug-drug interactions

1. Increased exposure to one/both drugs
   - Risk of toxicity

2. Decreased exposure to one/both drugs
   - Lack of efficacy
Inhibition of hepatic CYP: increased systemic exposure

A. Drug alone

B. Drug + inhibitor

Inhibitor blocks the function of the CYP enzyme

AUC 2

Concentration

Time

AUC 5

Concentration

Time

Drug

CYP

Cobicistat & ritonavir
Perpetrator vs victim

• Any individual drug can be one or the other, or both
• Example = dolutegravir
  – **Perpetrator:** increased metformin concentrations
  – **Victim:** concentrations reduced by cations
  – **Victim:** of strong enzyme inducers

Adapted from Back DJ & Kiser J. ICAAC September 2014.
Effect of DTG on metformin

Dose adjustment of metformin may be considered

<table>
<thead>
<tr>
<th>Regimen</th>
<th>$C_{\text{max}}$ (µg/mL)</th>
<th>$AUC_{0-\tau}$ (µg·h/mL)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + DTG (50 mg q24h) vs metformin alone</td>
<td>1.66 (1.53, 1.81)</td>
<td>1.79 (1.65, 1.93)</td>
<td>1.09 (0.954, 1.24)</td>
</tr>
<tr>
<td>Metformin + DTG (50 mg q12h) vs metformin alone</td>
<td>2.11 (1.91, 2.33)</td>
<td>2.45 (2.25, 2.66)</td>
<td>1.14 (1.00, 1.29)</td>
</tr>
</tbody>
</table>

Values shown are GLS mean ratio (90% CI)

Zong et al 2014
Chelation of InSTI by polyvalent cations

Mean DTG concentration (µg/mL) vs Time (h)

- DTG alone
- DTG + antacid
- DTG + antacid 2 hours later

Patel et al 2011
Impact of moderate/strong UGT1A1 and/or CYP3A4 inducers on DTG

<table>
<thead>
<tr>
<th>Co-administered drug</th>
<th>n</th>
<th>DTG dose studied</th>
<th>DTG C\text{r} or C\text{24} GLS mean ratio (90% CI)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPV/r 700/100 mg BID</td>
<td>12</td>
<td>50 mg QD</td>
<td>0.51 (0.41–0.63)</td>
<td>DTG 50 mg BID should be given</td>
</tr>
<tr>
<td>TPV/r 500/200 mg BID</td>
<td>16</td>
<td>50 mg QD</td>
<td>0.24 (0.21–0.27)</td>
<td>DTG 50 mg BID should be given</td>
</tr>
<tr>
<td>DRV/r 600/100 mg BID</td>
<td>15</td>
<td>30 mg QD</td>
<td>0.62 (0.56–0.69)</td>
<td>No DTG dose adjustment required</td>
</tr>
<tr>
<td>EFV 600 mg QD</td>
<td>12</td>
<td>50 mg QD</td>
<td>0.25 (0.18–0.34)</td>
<td>DTG 50 mg BID should be given</td>
</tr>
<tr>
<td>ETR 200 mg BID</td>
<td>15</td>
<td>50 mg QD</td>
<td>0.12 (0.09–0.16)</td>
<td>DTG 50 mg BID should be given</td>
</tr>
<tr>
<td>Rifampin 600 mg QD</td>
<td>11</td>
<td>50 mg BID</td>
<td>0.28 (0.23–0.34)</td>
<td>DTG 50 mg BID should be given</td>
</tr>
<tr>
<td>Rifabutin 300 mg QD</td>
<td>9</td>
<td>50 mg QD</td>
<td>0.70 (0.57–0.87)</td>
<td>No DTG dose adjustment required</td>
</tr>
<tr>
<td>CBZ 100 mg BID</td>
<td>14</td>
<td>50 mg QD</td>
<td>0.274 (0.24–0.31)</td>
<td>DTG 50 mg BID should be given</td>
</tr>
</tbody>
</table>

The GLS ratio values in red signify that in these cases, C\text{r} for DTG is reduced significantly below 75% (the lower boundary of a clinically significant alteration in DTG exposure)
### ARVs and interaction potential

<table>
<thead>
<tr>
<th>Higher potential</th>
<th>Moderate Potential</th>
<th>Low Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boosted PIs (r or cobi)</strong></td>
<td><strong>Rilpivirine</strong></td>
<td><strong>Raltegravir</strong></td>
</tr>
<tr>
<td>Perpetrators – enzyme and transporter Inhibition</td>
<td>Victim of enzyme inhibition and induction. Also absorption.</td>
<td>Victim of few induction and absorption interactions</td>
</tr>
<tr>
<td>Victim - absorption (ATV); induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EVG/cobi</strong></td>
<td><strong>Maraviroc</strong></td>
<td>Most NRTIs</td>
</tr>
<tr>
<td>Perpetrators – enzyme and transporter inhibition</td>
<td>Victim of enzyme inhibition and induction.</td>
<td>Some transporter mediated</td>
</tr>
<tr>
<td>Victim - absorption; induction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Efavirenz, nevirapine, etravirine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perpetrators – enzyme and transporter induction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Slide courtesy of Marta Boffito*
BIC Drug–Drug Interaction Profile

- **Perpetrator?** Low potential (OCT2/metformin)
- **Victim?** Low potential (or moderate?)
  - INSTIs are affected by cation-containing antacids
    - BIC administration with antacids should be staggered (± 2 hours)
    - Fasted administration 2 hours before or 2 hours after antacid resulted in a decrease in BIC exposures of 13% and 52%, respectively
  - BIC is a substrate of CYP3A4 and UGT1A1
    - Inhibition of both CYP3A4 and UGT1A1 needed for substantial increase in exposure
    - Potent induction reduces exposure to a clinically significant extent

Zhang, et al. CROI 2017
# Acid-reducing drugs & cations

<table>
<thead>
<tr>
<th></th>
<th>RALTEGRAVIR (ISENTRESS)</th>
<th>ELVITEGRAVIR (Stribild &amp; Genvoya)</th>
<th>DOLUTEGRAVIR (Tivicay, Triumeq &amp; Juluca)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTACIDS e.g.</strong></td>
<td>Do not take aluminium or magnesium antacids. Calcium antacids are OK if you are on TWICE A DAY raltegravir &amp; do not need to be spaced</td>
<td>Can be taken if at least 4 hours apart from your HIV meds</td>
<td>Take your HIV meds 2 hours before or 6 hours after antacids, multivitamins or calcium supplements.</td>
</tr>
<tr>
<td><strong>MULTIVITAMINS</strong></td>
<td>Can only be taken if you are on TWICE A DAY raltegravir &amp; at least 6 hours apart</td>
<td></td>
<td>If you have any resistance to dolutegravir you should NOT take these – your clinician will advise you</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>Can only be taken if you are on TWICE A DAY raltegravir &amp; at least 4 hours apart</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[https://www.hiv-druginteractions.org/checker](https://www.hiv-druginteractions.org/checker) accessed 21st May 2018
## ART & contraception

Coloured boxes: European SPC advice; grey boxes: my opinion NR = not recommended

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>DMPA(^a)</th>
<th>Implanon(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAL</strong></td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>DTG</strong></td>
<td>No dose adjustment(^*)</td>
<td>Likely fine</td>
<td>Likely fine</td>
</tr>
<tr>
<td><strong>Stribild &amp; Genvoya</strong></td>
<td><strong>NG</strong>: AUC ↑126%, Cmin ↑167%, Cmax ↑108%</td>
<td>Likely fine</td>
<td>Likely fine</td>
</tr>
<tr>
<td></td>
<td><strong>EE</strong>: AUC ↓25%, Cmin ↓44%, Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At least 30mcg EE. If prog other than norgestimate, use alternative(^c)</td>
<td>Likely fine</td>
<td>Likely fine</td>
</tr>
<tr>
<td><strong>BIC</strong></td>
<td>Small increases in ethinyl oestradiol &amp; norgestimate</td>
<td>Likely fine</td>
<td>Likely fine</td>
</tr>
</tbody>
</table>

\(^a\) DMPA: clearance = hepatic blood flow, inducers unlikely to impact efficacy  
\(^b\) Implanon: failures on EFV & AED; SPC says efficacy may be affected by enzyme inducers  
\(^c\) Long-term effects of substantial increases in progesterone exposure are unknown  

*no impact on LH or FSH
COMMUNICATION
Dear Doctor,

RE: Mr X

I saw this gentleman with HIV.....he is on Stribild. Please note there is a risk of drug interactions (see footer). He needs an annual flu vaccination and a pneumococcal vaccine.

Your sincerely

Dr L Waters

Blurb about vaccinations and drug interactions in general – I’m sure no-one actually bothers to read it so that’s why I type important interactions in myself. I wonder if you’ll read this? Will you??
What we do now

• GP and referral letter templates a section at the top of the letter which we delete as appropriate:
  – Please note there is a significant risk of drug-drug interactions between HIV therapy and other drugs, e.g:
  – Ritonavir/cobicistat is a potent inhibitor of CYP3A4; important interactions include simvastatin (risk of rhabdomyolysis) and several inhaled/intranasal/injected steroids such as fluticasone and triamcinolone (risk of iatrogenic Cushing’s)
  – Rilpivirine has significant interactions with acid-reducing agents; PPI are contra-indicated; H2A and antacids require careful dose spacing
Patient information

• If you find yourself repeating the same messages

Make an information card!!
### Patient Information Card

**Elvitegravir**
- **Aluminium** or Magnesium***
- Calcium***
- Iron**
- Multivitamins
  - Take with care: Take 4 hours before or after elvitegravir
  - Discuss use with Doctor or Pharmacist
  - Can be found in antacids
  - Can be found in supplements
  - Can be found in antacids and supplements

**Atazanavir**
- Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole, Rabeprazole (Proton pump inhibitors)
- Clindamycin, Flibanserin, Nanilide (H2 receptor antagonists)
- Articid (e.g., anything containing aluminium hydroxide, magnesium carbonate, magnesium trisilicate, magnesium hydroxide, calcium carbonate, sodium bicarbonate)
  - Take with care: Take 1 hour before or 2 hours after elvitegravir
  - Discuss use with Doctor or Pharmacist
  - Can be found in antacids
  - Can be found in supplements
  - Can be found in antacids and supplements

**Rilpivirine**
- Aticid (e.g., anything containing aluminium hydroxide, magnesium carbonate, magnesium trisilicate, magnesium hydroxide, calcium carbonate, sodium bicarbonate)
  - Take with care: Take 12 hours before or 4 hours after rilpivirine
  - Discuss use with Doctor or Pharmacist
  - Can be found in antacids
  - Can be found in supplements
  - Can be found in antacids and supplements

**Dolutegravir**
- Aluminium*** or Magnesium***
- Calcium***
- Iron**
- Multivitamins
  - Take with care: Take 2 hours before or 6 hours after dolutegravir
  - Discuss use with Doctor or Pharmacist
  - Can be found in antacids
  - Can be found in supplements
  - Can be found in antacids and supplements

**Rilpivirine**
- Antacids (e.g., anything containing aluminium hydroxide, magnesium carbonate, magnesium trisilicate, magnesium hydroxide, calcium carbonate, sodium bicarbonate)
  - Take with care: Take 2 hours before or 4 hours after rilpivirine

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**Important information about your medication**

You have been prescribed a medication that interacts with some common supplements and medications. Taking these tablets or liquids can result in your medication not working as effectively. Some of these are prescribed and others can be purchased over the counter from a pharmacy.

Supplements that may cause a problem include aluminium, magnesium, calcium, iron, sodium bicarbonate. This list is not an exhaustive list. Please check any other supplements with your doctor or pharmacist.

It may be clear from the name of the product what the ingredients are. For example, iron (ferrous sulphate, ferrous gluconate, ferrous fumarate).

However, for some products you will need to read the list of ingredients. For example, Antacids (Gaviscon, Tums, Ranitidin, Milk of Magnesia).
Conclusions

• Understanding pharmacology important

• The main clinical implications:
  – Food advice
  – Advice about late/missed doses
  – Drug-drug interactions

• Ensure advice to patients and other health care professionals is:
  – Clear
  – Accessible
  – Relevant
Acknowledgements

• Marta Boffito – Queen of PGP
Thank you!

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