Dolutegravir (DTG, Tivicay)

- Clinical Trial Data and Resistance
- Prescribing Information
- Drug Interactions
Clinical Trial Data and Resistance
# Dolutegravir Phase 3 Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment History</th>
<th>Comparison</th>
<th>Response Rates &amp; Key Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPRING-2</td>
<td>Naïve</td>
<td>Dolutegravir QD vs. Raltegravir</td>
<td>• Non-inferior (88% vs. 85%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dolutegravir resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Similar safety</td>
</tr>
<tr>
<td>SINGLE</td>
<td>Naïve</td>
<td>Dolutegravir QD vs. Efavirenz</td>
<td>• Superior (88% vs. 81%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No dolutegravir resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Fewer discontinuations</td>
</tr>
<tr>
<td>SAILING</td>
<td>&gt;2-class ARV</td>
<td>Dolutegravir QD vs. Raltegravir</td>
<td>• Superior (71% vs. 64%)</td>
</tr>
<tr>
<td></td>
<td>resistance</td>
<td></td>
<td>• Less virological failure and resistance</td>
</tr>
<tr>
<td>VIKING-3</td>
<td>Integrase</td>
<td>Single-arm, Dolutegravir BID</td>
<td>• 64% virological suppression</td>
</tr>
<tr>
<td></td>
<td>resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SAILING: Dolutegravir vs. Raltegravir in Treatment-Experienced Individuals

Study Design

Protocol
- Randomized, double-blind, double-dummy, phase 3 study
- HIV-infected adults with HIV RNA $\geq 400$ copies x2 or $\geq 1,000$ copies x1, plus resistance to at least 2 ARV classes, plus at least 1-2 active drugs

Dolutegravir 50 mg QD + OBT + Placebo (n = 354)

Raltegravir 400 mg BID + OBT + Placebo (n = 361)

Key Results:
- Week 48 % with VL <50 favored dolutegravir: 71% vs. 64% (P=0.030)
- Difference greatest in those with high viral loads or not using boosted darunavir
- Fewer virological failures and emergent resistance mutations in dolutegravir arm
- Adverse events similar; small increases in serum Cr seen in dolutegravir arm

Urine Formation

Glomerular Filtration

Proximal Tubule

Tubular Reabsorption

Loop of Henle

Distal Tubule

Tubular Secretion

Collecting Tubule

Dolutegravir Cobicistat

Inhibit tubular secretion of creatinine by blocking OCT2 transporter

Creatinine Clearance

- Estimated: Cockcroft-Gault
- Actual: Iohexol clearance

Excretion
VIKING-3: Dolutegravir in Treatment-Experienced Individuals with Integrase Resistance

**Study Design**

- **Protocol**
  - HIV-infected adults with VL $\geq$500 copies
  - Resistance to raltegravir or elvitegravir, plus resistance to at least 2 additional ARV classes

**Key Results:**
- Day 8 mean VL change from baseline: -1.43 log copies
- % with VL <50 copies at 24 weeks: 64%
- 4% discontinued due to adverse events

VIKING-3: Dolutegravir 24-week response by baseline integrase RAM

% with VL <50 copies at 24 weeks

- All patients
- N155H
- Y143C/H/R
- Q148H/R + G140A/S
- Q148H/R + >2 secondary

Integrase resistance-associated mutations (RAM’s)
Dolutegravir Response

- Multivariate analysis identified two factors highly associated with decreased response to dolutegravir:
  1) **Q148 + >2 secondary mutations**
  2) **Higher baseline fold change**

### Review of Integrase Resistance

<table>
<thead>
<tr>
<th>Raltegravir</th>
<th>Elvitegravir</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>N155H</td>
<td>N155H</td>
<td>Q148 + secondary mutations (G140A/S, E138E/K, etc)</td>
</tr>
<tr>
<td>Q148H/R/K</td>
<td>Q148H/R/K</td>
<td></td>
</tr>
<tr>
<td>Y143R/H/C</td>
<td>E92Q</td>
<td></td>
</tr>
</tbody>
</table>

- **Raltegravir**
  - N155H
  - Q148H/R/K
  - Y143R/H/C
- **Elvitegravir**
  - N155H
  - Q148H/R/K
  - E92Q
- **Dolutegravir**
  - Q148 + secondary mutations (G140A/S, E138E/K, etc)
Prescribing Information and Drug Interactions
Prescribing Information

- 50 mg tabs
  - QD if treatment-naïve or integrase-naïve
  - BID if integrase resistance (confirmed or suspected)
  - BID with potent CYP3A4/UGT1A1 inducers (efavirenz, tipranavir/ritonavir, fosamprenavir/ritonavir, rifampin)
- With or without food
- Most common SE’s: diarrhea, nausea, headache, insomnia

Dolutegravir Tablets

Raltegravir

Dolutegravir
# Drug Interactions: ARV’s

<table>
<thead>
<tr>
<th>ARV</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz, boosted fosamprenavir or</td>
<td>↓Dolutegravir</td>
<td>-Treatment-naïve or integrase-naïve: dolutegravir BID</td>
</tr>
<tr>
<td>boosted tipranavir</td>
<td></td>
<td>-Integrase resistance: avoid</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>↓Dolutegravir</td>
<td>Avoid</td>
</tr>
<tr>
<td>Etravirine</td>
<td>↓Dolutegravir</td>
<td>Avoid unless also giving boosted darunavir,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>boosted atazanavir or boosted lopinavir</td>
</tr>
<tr>
<td>Boosted darunavir, boosted lopinavir,</td>
<td>No clinically significant effect</td>
<td>No adjustment needed</td>
</tr>
<tr>
<td>rilpivirine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Drug Interactions: Non-ARV’s

<table>
<thead>
<tr>
<th>Medication</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine, phenytoin, phenobarbital, carbamazepine, St. John’s Wort</td>
<td>↓Dolutegravir</td>
<td>Avoid</td>
</tr>
<tr>
<td>Cation-containing antacids or laxatives (sucralfate, oral Fe, oral Ca) or</td>
<td>↓Dolutegravir</td>
<td>Dolutegravir should be administered 2 hours before</td>
</tr>
<tr>
<td>buffered medications</td>
<td></td>
<td>or 6 hours after</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↓Dolutegravir</td>
<td>Dolutegravir BID</td>
</tr>
<tr>
<td>Metformin</td>
<td>↑Metformin</td>
<td>Close monitoring, consider metformin dose adjustment</td>
</tr>
<tr>
<td>Dofelitide</td>
<td>↑Dofelitide</td>
<td>Avoid</td>
</tr>
<tr>
<td>Boceprevir, telaprevir, prednisone, rifabutin, omeprazole</td>
<td>No significant effect</td>
<td>No adjustment needed</td>
</tr>
</tbody>
</table>
Summary

• Dolutegravir is a potent, next-generation integrase inhibitor available for treatment-naïve or experienced patients
• Active against most cases of integrase resistance (exception: Q148 + >2 secondary mutations or higher dolutegravir fold-change)
• Once-daily unless integrase resistance or coadministration with a potent CYP inducer
• Overall well-tolerated with high barrier to resistance
Coming Soon…

- FLAMINGO - dolutegravir vs. boosted darunavir in treatment-naïve individuals
- The “Tri Pill” – abacavir-lamivudine-dolutegravir