Doravirine

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Disclosures

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Doravirine Basics

• **Medication**
  - Oral, once daily, non-nucleoside reverse transcriptase inhibitor (NNRTI)

• **Administration**
  - Few drug-drug interactions, can give with proton pump inhibitors, and no food requirements

• **With Renal Impairment**
  - No adjustment with mild, moderate, or severe renal impairment

• **With Hepatic Impairment**
  - No dose adjustment for Child-Pugh A or B; insufficient data for C

• **Pregnancy**
  - Insufficient data for use in pregnancy

• **Common Adverse Effects** (≥5%)
  - Nausea, dizziness, headache, fatigue, diarrhea, abdominal pain, abnormal dreams
Doravirine

100 mg

NNRTI

Dose: 1 tablet once daily with or without food
Doravirine: NNRTI Mechanism of Action

Illustration: Cognition Studio, Inc. and David H. Spach, MD
Doravirine: Key Studies
Key Doravirine Studies

• DRIVE FORWARD
• DRIVE AHEAD
• DRIVE SHIFT
Doravirine + 2 NRTIs vs. Darunavir + Ritonavir + 2 NRTIs
DRIVE FORWARD: Design

• **Design**
  – Randomized, double-blind, phase 3 study comparing doravirine plus 2 NRTIs with darunavir, boosted with ritonavir, in combination with 2 NRTIs as initial antiretroviral therapy

• **Inclusion Criteria**
  – Antiretroviral-naïve adults
  – HIV RNA ≥1,000 copies/mL
  – No resistance to any study drug

• **Regimens** (all once daily)
  – Doravirine (100 mg) + 2 NRTIs
  – Darunavir (800 mg) + Ritonavir (100 mg) + 2 NRTIs

Doravirine + 2 NRTIs vs. Darunavir + Ritonavir + 2 NRTIs
DRIVE FORWARD: 48 Week Results

Week 48 Virologic Response (Intention-to-Treat Analysis)

Doravirine-TDF-3TC versus Efavirenz-TDF-FTC as Initial Therapy

DRIVE AHEAD: Design

- **Design**
  - Randomized, double-blind, phase 3 study comparing fixed dose doravirine-tenofovir DF-lamivudine with fixed dose efavirenz-tenofovir DF-emtricitabine as initial antiretroviral therapy

- **Inclusion Criteria**
  - Antiretroviral-naïve adults
  - HIV RNA ≥1,000 copies/mL
  - No resistance to any study drug

- **Regimens**
  - Doravirine-TDF-3TC (100/300/300 mg) daily
  - Efavirenz-TDF-FTC (600/300/200 mg) daily

Week 48 Virologic Response (Observed Failure)

Doravirine-TDF-3TC versus Efavirenz-TDF-FTC as Initial Therapy
DRIVE AHEAD: 48 Week Results

HIV RNA <50 copies/mL (%)

- All: 88.7 (Doravirine-TDF-Lamivudine), 88.8 (Efavirenz-TDF-Emtricitabine)
- ≤100,000 copies/mL: 90.6 (Doravirine-TDF-Lamivudine), 91.1 (Efavirenz-TDF-Emtricitabine)
- >100,000 copies/mL: 81.2 (Doravirine-TDF-Lamivudine), 80.8 (Efavirenz-TDF-Emtricitabine)

Switch to Doravirine-TDF-3TC versus Continued Baseline Regimen

DRIVE SHIFT: Design

• **Design**
  - Open-label, non-inferiority trial
  - Adults with suppressed HIV RNA while taking 2 NRTIs plus anchor drug, randomized (2:1) to immediately switch to fixed-dose doravirine-tenofovir-DF-lamivudine or continue the baseline regimen with delayed switch at 24 weeks

• **Inclusion Criteria**
  - Adults with suppressed HIV RNA ≥6 months
  - No history of virologic failure

• **Baseline Regimen**
  - 2 NRTIs + (boosted protease inhibitor, boosted elvitegravir, or NNRTI)

**Immediate Switch**
Doravirine-TDF-3TC (n = 447)

**Delayed Switch**
Baseline Regimen to Week 24, then Doravirine-TDF-3TC (n = 223)

Switch to Doravirine-TDF-3TC versus Continued Baseline Regimen

DRIVE SHIFT: Baseline Antiretroviral Regimens

<table>
<thead>
<tr>
<th>Anchor Agent, n (%)</th>
<th>Immediate Switch (n = 447)</th>
<th>Delayed Switch (n = 223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PI</td>
<td>316 (70.7)</td>
<td>156 (70.0)</td>
</tr>
<tr>
<td>Darunavir</td>
<td>166 (37.1)</td>
<td>82 (36.8)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>96 (21.5)</td>
<td>43 (19.3)</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>54 (12.1)</td>
<td>31 (13.9)</td>
</tr>
<tr>
<td>Elvitegravir-cobicistat</td>
<td>25 (5.6)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>106 (23.7)</td>
<td>55 (24.7)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>78 (17.4)</td>
<td>36 (16.1)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>17 (3.8)</td>
<td>12 (5.4)</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>11 (2.5)</td>
<td>7 (3.1)</td>
</tr>
</tbody>
</table>

*Most common NRTI backbone in both arms: TDF/FTC (73.8% in immediate switch, 69.1% in delayed switch)*

Switch to Doravirine-TDF-3TC versus Continued Baseline Regimen

DRIVE SHIFT: Results

Week 48 Doravirine-TDF-3TC vs Week 24 Baseline Regimen (FDA snapshot)

## Summary of Phase 3 Doravirine Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRIVE-FORWARD¹</td>
<td>Treatment-Naïve</td>
<td>Doravirine + 2 NRTIs is non-inferior to Darunavir + Ritonavir + 2 NRTIs</td>
</tr>
<tr>
<td>DRIVE-AHEAD²</td>
<td>Treatment-Naïve</td>
<td>Doravirine-TDF-3TC is non-inferior to Efavirenz-TDF-FTC</td>
</tr>
<tr>
<td>DRIVE-SHIFT³</td>
<td>Treatment-Experienced</td>
<td>Immediate or delayed switch to Doravirine-TDF-3TC is non-inferior to baseline ART</td>
</tr>
</tbody>
</table>

Doravirine is Weight Neutral

• Weight gain over 96 weeks was low with doravirine use\(^1\)

• Two clinical trials looking into switch to doravirine after weight gain
  – \(^2\)Do IT (A5391): Doravirine for Persons With Excessive Weight Gain on INSTIs and TAF
  – \(^3\)DeLiTE: Can INSTI-associated Weight Gain be Halted or Reversed With a Switch to DOR/3TC/TDF?

• Consider doravirine in persons who have experienced or are hesitant about the potential of antiretroviral-related weight gain

Source
\(^2\)DO IT: https://clinicaltrials.gov/ct2/show/NCT04636437
\(^3\)DeLiTE: https://clinicaltrials.gov/ct2/show/NCT04665375
Doravirine: Resistance
Doravirine *In Vitro* Resistance Pathways with HIV Subtype B

Doravirine: Development of Drug Resistance with Virologic Failure

• Available data suggest doravirine has high genetic barrier to resistance\(^1\)

• In four doravirine clinical trials <1% of participants experienced treatment failure with doravirine resistance\(^1\)

• With virologic failure on doravirine in clinical trials, the most prevalent treatment-emergent mutations were at positions 106 (V106A/I/M) and 227 (F227C/L)\(^2,3\)

Source
## Impact of Doravirine Resistance

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Resistance Associated Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V106A</td>
</tr>
<tr>
<td>Doravirine</td>
<td>High-Level</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>

Source: Stanford Resistance Database
Doravirine Activity with Prior NNRTI Virologic Failure Resistance

- Common mutations K103N and G190A have no impact on doravirine
- DRIVE BEYOND study showed good virologic response with doravirine-TDF-3TC in 10 persons with baseline K103N or G190A
- Single mutations with V106A, Y188L, G190E, or M230L confer high-level resistance to doravirine
- Avoid doravirine with mutations that confer intermediate or high-level resistance

Source
Impact of NNRTI RAMs on Doravirine

<table>
<thead>
<tr>
<th>Source: Stanford Resistance Database</th>
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<table>
<thead>
<tr>
<th>No Impact on Doravirine</th>
<th>K103N; G190A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential Low-level Doravirine Resistance</td>
<td>K101P; E138K; Y181C</td>
</tr>
<tr>
<td>Low-level Doravirine Resistance</td>
<td>K101E; Y181C; K103N + Y181C; H221Y</td>
</tr>
<tr>
<td>Intermediate-level Doravirine Resistance</td>
<td>L100I + K103N; V106M; P225H; F227L; Y318F</td>
</tr>
<tr>
<td>High-level Doravirine Resistance</td>
<td>V106A; Y188L; G190E; M230L</td>
</tr>
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</table>
Doravirine: Summary

• Oral, once-daily NNRTI available alone or in a fixed dose combination
• Typically used in treatment experienced or to address ART weight gain
• Most common treatment emergent mutations were V106I and F227L
• Retains full activity with a K103N and G190A mutations
• Well-tolerated with few drug-drug interactions
• Can take with or without food and can take with proton pump inhibitors
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