Recent Trials of Second-Line ART: Lessons Learned & Applications to Clinical Practice

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Case

- 52-year-old cisgender man with longstanding HIV
- Viral load suppressed on rilpivirine/TAF/FTC for several years
- Prior ART: efavirenz/TDF/FTC
- Lapse in adherence following onset of COVID-19 pandemic
- Viral load rebound to 1,250 copies/mL
- Genotype: new E138K and M184V mutations
- *Which new ART regimen would you recommend?*
Background

• Following virologic failure of first-line ART, traditional practice was to aim for 3 fully active drugs in new regimen

• In areas without access to resistance testing, new regimen often included a boosted PI plus switch from TDF to AZT

• With widespread availability of dolutegravir, is this still the optimal strategy?

• As many countries roll out tenofovir DF-lamivudine-dolutegravir (“TLD”) as first-line ART, can it also be offered as empiric second-line ART?
DAWNING
Dolutegravir (DTG) vs. ritonavir-boosted lopinavir (LPV/r), each with two NRTIs, following virologic failure of first-line ART
DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure

DAWNING: Design

- **Design**
  - Open-label, randomized, phase 3b study performed in multiple countries in sub-Saharan Africa, South America, Central America, Asia, and Eastern Europe

- **Including Criteria**
  - Age ≥18 with HIV-1
  - Virologic failure after at least 6 months taking NNRTI plus 2 NRTIs (HIV RNA ≥400 copies/mL x 2)
  - No history of taking a boosted PI or INSTI
  - All had genotype resistance test at baseline
  - All received investigator-selected NRTIs (at least one fully active based on genotype)

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>DTG + 2 NRTIs (n = 312)</th>
<th>LPV/r + 2 NRTIs (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>37.5 (19-64)</td>
<td>38.7 (18-72)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>196 (63)</td>
<td>209 (67)</td>
</tr>
<tr>
<td>CD4 T cell count, mean (SD), log_{10} cells/mm^3</td>
<td>2.1 (0.5)</td>
<td>2.2 (0.4)</td>
</tr>
<tr>
<td>CD4 T cell count &lt;200 cells/mm^3</td>
<td>166 (53%)</td>
<td>151 (48%)</td>
</tr>
<tr>
<td>Mean HIV RNA, mean (SD), log_{10} copies/mL</td>
<td>4.2 (0.9)</td>
<td>4.2 (0.9)</td>
</tr>
<tr>
<td>HIV RNA &gt;100,000 copies/mL, n (%)</td>
<td>70 (22)</td>
<td>63 (20)</td>
</tr>
<tr>
<td>Duration of previous ART, median (IQR), weeks</td>
<td>86.4 (48.4-230.9)</td>
<td>90.9 (45.0-199.5)</td>
</tr>
<tr>
<td>Prior NNRTI: efavirenz</td>
<td>242 (78%)</td>
<td>242 (78%)</td>
</tr>
<tr>
<td>Prior NNRTI: nevirapine</td>
<td>70 (22%)</td>
<td>69 (22%)</td>
</tr>
<tr>
<td>Prior NNRTI: rilpivirine</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

## DAWNING: Results

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>NRTIs in new regimen</th>
<th>DTG + 2 NRTIs (n = 312)</th>
<th>LPV/r + 2 NRTIs (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF/FTC or TDF/3TC</td>
<td>132 (42%)</td>
<td>121 (39%)</td>
</tr>
<tr>
<td>AZT/3TC</td>
<td>128 (41%)</td>
<td>134 (43%)</td>
</tr>
<tr>
<td>TDF + AZT</td>
<td>36 (12%)</td>
<td>41 (13%)</td>
</tr>
</tbody>
</table>

**Fully susceptible NRTIs in new regimen**

<table>
<thead>
<tr>
<th>Fully susceptible NRTIs in new regimen</th>
<th>DTG + 2 NRTIs (n = 312)</th>
<th>LPV/r + 2 NRTIs (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;1</td>
<td>30 (10%)</td>
<td>36 (12%)</td>
</tr>
<tr>
<td>1 to 2</td>
<td>221 (71%)</td>
<td>212 (68%)</td>
</tr>
<tr>
<td>2</td>
<td>61 (20%)</td>
<td>64 (21%)</td>
</tr>
</tbody>
</table>

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure

DAWNING: Results

<table>
<thead>
<tr>
<th>Baseline Characteristics (NRTI Resistance Mutations)</th>
<th>DTG + 2 NRTIs (n = 312)</th>
<th>LPV/r + 2 NRTIs (n = 312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K65R</td>
<td>95 (30%)</td>
<td>92 (29%)</td>
</tr>
<tr>
<td>K70E</td>
<td>33 (11%)</td>
<td>37 (12%)</td>
</tr>
<tr>
<td>M184V/I only</td>
<td>77 (25%)</td>
<td>85 (27%)</td>
</tr>
<tr>
<td>M184V/I plus other major NRTI mutation</td>
<td>184 (59%)</td>
<td>167 (54%)</td>
</tr>
<tr>
<td>Other major NRTI mutation</td>
<td>90 (29%)</td>
<td>88 (28%)</td>
</tr>
<tr>
<td>Thymidine analog mutation (TAMs)</td>
<td>71 (23%)</td>
<td>81 (26%)</td>
</tr>
</tbody>
</table>

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure

DAWNING: Results

Virologic response at 48 weeks (intention-to-treat analysis), stratified by baseline viral load (VL)

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure

DAWNING: Results

Virologic response at 48 weeks, stratified by M184V and use of XTC (FTC or 3TC)

DTG vs LPV/r, each with two NRTIs, after first-line ART virologic failure
DAWNING: Results

Virologic response at 48 weeks, stratified by number of fully active NRTIs

Cases of virologic failure with emergent dolutegravir resistance

<table>
<thead>
<tr>
<th>HIV Subtype</th>
<th>Study NRTIs</th>
<th>Baseline HIV RNA (copies/mL)</th>
<th>HIV RNA at Virologic Failure (copies/mL)</th>
<th>Baseline NRTI RAM(s)</th>
<th>Emergent INSTI RAM(s)</th>
<th>Emergent NRTI RAM(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>TDF/FTC</td>
<td>461,000</td>
<td>2,464</td>
<td>M184V + K219K/E</td>
<td>G118R</td>
<td>D67N</td>
</tr>
<tr>
<td>C</td>
<td>AZT/3TC</td>
<td>1.2 million</td>
<td>454</td>
<td>M184V + K70E</td>
<td>Multiple</td>
<td>None</td>
</tr>
</tbody>
</table>

DTG arm: 11 participants met criteria for virologic failure (VF); 2 had emergent DTG resistance
LPV/r arm: 30 met criteria for VF; 3 emergent NRTI resistance, zero emergent PI resistance

• After 48 weeks, DTG plus 2 NRTIs showed superior efficacy compared to LPV/r plus 2 NRTIs following virologic failure on NNRTI plus 2 NRTIs

• Supports DTG + 2 NRTIs as second-line ART, even if only one NRTI fully active

• Limitations: open-label, baseline resistance testing performed (not generalizable to low-resource settings), use of LPV/r as comparator, use of TDF (not TAF)

• Outstanding questions: efficacy of TDF/FTC versus AZT/3TC in new regimen, efficacy and safety of switching in the absence of genotype

NADIA
Dolutegravir (DTG) vs. ritonavir-boosted darunavir (DRV/r), each with TDF/3TC or AZT/3TC, following virologic failure on first-line ART
DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure

NADIA: Design

- **Design**
  - Open-label, prospective, multicenter, two-by-two factorial, randomized, non-inferiority, 96-week trial conducted in Uganda, Kenya, and Zimbabwe

- **Including Criteria**
  - Age ≥12 with HIV-1
  - Virologic failure after at least 6 months taking NNRTI plus 2 NRTIs (HIV RNA ≥1,000 copies/mL twice)
  - No history of taking a boosted PI or INSTI
  - Nurse-led visits, standard of care visit frequency, emphasis on adherence counseling
  - No genotype at enrollment

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DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure

NADIA: Results

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>DTG (n = 235)</th>
<th>DRV/r (n = 229)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>33 (28-40)</td>
<td>35 (28-42)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>140 (59.6)</td>
<td>142 (62.0)</td>
</tr>
<tr>
<td>CD4 T cell count, median (IQR), cells/mm³</td>
<td>189 (58-388)</td>
<td>202 (84-357)</td>
</tr>
<tr>
<td>CD4 T cell count &lt;200 cells/mm³</td>
<td>125 (53.2)</td>
<td>113 (49.3)</td>
</tr>
<tr>
<td>Median HIV RNA (IQR), log₁₀ copies/mL</td>
<td>4.5 (3.9-5.1)</td>
<td>4.4 (3.8-5.1)</td>
</tr>
<tr>
<td>HIV RNA ≥100,000 copies/mL, n (%)</td>
<td>66 (28.1)</td>
<td>62 (27.1)</td>
</tr>
<tr>
<td>Duration of previous ART, median (IQR), years</td>
<td>3.6 (1.4-6.3)</td>
<td>3.7 (1.7-5.9)</td>
</tr>
<tr>
<td>K65R present at baseline</td>
<td>120 (52.6)</td>
<td>106 (47.1)</td>
</tr>
<tr>
<td>M184V/I present at baseline</td>
<td>196 (86.0)</td>
<td>195 (86.7)</td>
</tr>
</tbody>
</table>

DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure

NADIA: Results

Virologic response at 48 weeks (by intention-to-treat analysis)

![Bar chart showing virologic response at 48 weeks for DTG and DRV/r](chart.png)

DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure

NADIA: Results

Virologic response at 48 weeks, stratified by number of predicted active NRTIs

DTG vs DRV/r, each with TDF/3TC or AZT/3TC, after first-line ART virologic failure

NADIA: Results

Virologic response at week 48, stratified by NRTI backbone (TDF/3TC or AZT/3TC)

NADIA
Week 96 results presented at CROI 2022

- DTG + 2 NRTIs remained non-inferior to DRV/RTV + 2 NRTIs
- TDF/3TC now superior efficacy compared to AZT/3TC
- 9 cases of emergent DTG resistance (6 in AZT/3TC group, 3 TDF/FTC)
- Conclusions:
  - DTG + 2 NRTIs can be used as second-line ART, even if NRTIs predicted to have limited or no activity, but emergent DTG resistance may be a concern
  - DRV/r + 2 NRTIs has efficacy equivalent to DTG + 2 NRTIs in second-line treatment, without concern for resistance

Applications to Clinical Practice

• How should we apply these results to clinical practice?

  - DTG (or BIC) or DRV/r effective with <2 fully active NRTIs (e.g. with M184V); is this the end of AZT once and for all as part of HIV treatment?

  - Would you offer DTG (or BIC) plus TDF/FTC or TAF/FTC in the setting of M184V and K65R? Or M184V + TAMs? Are you comfortable if there is <1 active NRTI?

  - Cases of intermediate-to-high-level resistance to DTG occurred in NADIA; should this give us pause? Should we opt for DRV/r instead of DTG in certain scenarios?

• Returning to case, with M184V and viral load 1,250 copies/mL, which regimen would you recommend? What if the viral load were 12k copies? Or 100k copies?
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