Dolutegravir-Lamivudine (Dovato)

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Last Updated: November 28, 2022
Dolutegravir-Lamivudine

Dose: 1 tablet once daily with or without food
Dolutegravir-Lamivudine

• **Indication**
  – Complete regimen for the treatment of HIV-1 (initial or maintenance ART) for adults or adolescents 12 years or older weighing at least 40 kg
  – Insufficient data for use in pregnancy

• **Class**
  – Dolutegravir: integrase strand transfer inhibitor (INSTI)
  – Lamivudine: nucleoside reverse transcriptase inhibitor (NRTI)

• **Dosing**
  – Fixed dose tablet: Dolutegravir 50 mg and Lamivudine 300 mg
  – 1 tablet once daily, with or without food
  – Not recommended in patients with renal impairment
  – Not recommended in patients with severe hepatic impairment (Child-Pugh C)

• **Common Adverse Effects (≥2%)**
  – Headache, nausea, diarrhea, insomnia, fatigue, anxiety, and dizziness
Dolutegravir-Lamivudine: Initial Antiretroviral Therapy

Baseline Requirements
- HIV RNA <500,000 copies/mL
- Hepatitis B surface antigen (HBsAg) negative
- Results from genotype known
HHS Antiretroviral Therapy Guidelines (September 21, 2022)
Dolutegravir-Lamivudine: Maintenance Antiretroviral Therapy

Initial Antiretroviral Therapy
3-Drug Regimen

Maintenance Antiretroviral Therapy
Dolutegravir-Lamivudine (2-Drug Regimen)

Requirements Prior to Switching
- HIV RNA <50 copies/mL for ≥6 months
- Hepatitis B surface antigen (HBsAg) negative
- No prior virologic failure
- No resistance to either maintenance drug
## Dolutegravir-Lamivudine

**Summary of Key Phase 3 Studies**

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<tr>
<th><strong>Trials in Treatment-Naïve Adults</strong></th>
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<tr>
<td>GEMINI-2: DTG-3TC versus DTG + TDF-FTC as Initial Therapy</td>
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</tbody>
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<table>
<thead>
<tr>
<th><strong>Switch Trials in Adults with Virologic Suppression</strong></th>
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</thead>
<tbody>
<tr>
<td>ASPIRE: Switch to DTG plus 3TC vs. 3-Drug Maintenance Regimen</td>
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<td>TANGO: Switch to DTG-3TC vs. 3- or 4-Drug Maintenance Regimen</td>
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<tr>
<td>SALSA: Switch to DTG-3TC vs. 3- or 4-Drug Maintenance Regimen</td>
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</tbody>
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**Abbreviations:** DTG-3TC = dolutegravir-lamivudine; DTG = dolutegravir; TDF-FTC = tenofovir DF-emtricitabine
Dolutegravir-Lamivudine
Trials in Treatment Treatment-Naïve Adults
DTG + 3TC versus DTG + TDF-FTC as Initial ART

GEMINI 1 and GEMINI 2: Week 48 Data
DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and GEMINI 2: Background

• **Background**
  - Two double-blind, multinational, noninferiority, randomized, controlled trials that compared initial ART of dolutegravir plus lamivudine (DTG + 3TC) versus dolutegravir plus tenofovir-DF-emtricitabine (DTG + TDF-FTC)

• **Enrollment Criteria**
  - Treatment-naïve adults
  - HIV RNA 1,000-500,000 copies/mL
  - No NRTI, INSTI, or major PI mutations
  - No chronic HBV
  - Not pregnant or breastfeeding

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and GEMINI 2: Results by Baseline HIV RNA Level

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

HIV RNA <50 copies/mL (%)

<table>
<thead>
<tr>
<th>Pooled Data</th>
<th>Baseline HIV RNA copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤100,000</td>
</tr>
<tr>
<td></td>
<td>&gt;100,000</td>
</tr>
<tr>
<td>Dolutegravir + Lamivudine</td>
<td>91/655/716</td>
</tr>
<tr>
<td>Dolutegravir + Tenofovir DF-Emtricitabine</td>
<td>91/526/576</td>
</tr>
<tr>
<td></td>
<td>92/129/140</td>
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</tbody>
</table>

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and GEMINI 2: Results by Baseline HIV CD4 Cell Count

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

<table>
<thead>
<tr>
<th>Baseline CD4 Count (cells/mm$^3$)</th>
<th>Pooled Data</th>
<th>&gt;200</th>
<th>≤200</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir + Lamivudine</td>
<td>655/716</td>
<td>605/653</td>
<td>50/63</td>
</tr>
<tr>
<td>Dolutegravir + Tenofovir DF-Emtricitabine</td>
<td>669/717</td>
<td>618/662</td>
<td>51/55</td>
</tr>
</tbody>
</table>

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results

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

<table>
<thead>
<tr>
<th></th>
<th>Dolutegravir + Lamivudine</th>
<th>Dolutegravir + Tenofovir DF-Emtricitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL (%)</td>
<td>91/655/716</td>
<td>93/669/717</td>
</tr>
<tr>
<td></td>
<td>90/320/356</td>
<td>93/332/358</td>
</tr>
<tr>
<td></td>
<td>93/335/360</td>
<td>94/337/359</td>
</tr>
</tbody>
</table>

### GEMINI 1 and 2 Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DTG + 3TC (n = 716)</th>
<th>DTG + TDF-FTC (n = 717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>32 (26-40)</td>
<td>33 (26-42)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>113 (16)</td>
<td>98 (14)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>480 (67)</td>
<td>497 (69)</td>
</tr>
<tr>
<td>Black or African American, n (%)</td>
<td>99 (14)</td>
<td>76 (11)</td>
</tr>
<tr>
<td>CD4 cell count, mean (SD)</td>
<td>462 (219.2)</td>
<td>461.3 (213.1)</td>
</tr>
<tr>
<td>CD4 count ≤200 cells/mm³, n (%)</td>
<td>63 (9)</td>
<td>55 (8)</td>
</tr>
<tr>
<td>HIV RNA (log₁₀ copies/mL)</td>
<td>4.42 (0.66)</td>
<td>4.45 (0.65)</td>
</tr>
<tr>
<td>≤100,000 copies/mL, n (%)</td>
<td>576 (80)</td>
<td>564 (79)</td>
</tr>
<tr>
<td>&gt;100,000 copies/mL, n (%)</td>
<td>140 (20)</td>
<td>153 (21)</td>
</tr>
</tbody>
</table>

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results

Week 48 Changes in Renal Function

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results

Week 48 Changes in Markers of Renal Proximal Tubulopathy

![Bar chart showing changes in markers of renal proximal tubulopathy at Week 48 compared to baseline.](image)

- **Protein to creatinine (g/moL)**: 0.87 (DTG + Lamivudine) vs. 1.03 (DTG + Tenofovir DF-Emtricitabine)
- **Retinol-binding protein to creatinine (μg/mmoL)**: 0.93 vs. 1.11
- **β-2 microglobulin to creatinine (μg/mmoL)**: 0.92 vs. 1.31

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results

Week 48 Changes in Serum Bone Biomarkers

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Conclusions

Interpretation: “The non-inferior efficacy and similar tolerability profile of dolutegravir plus lamivudine to a guideline-recommended three-drug regimen at 48 weeks in ART-naive adults supports its use as initial therapy for patients with HIV-1 infection.”
DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and GEMINI 2: Week 96 Data
DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results by Baseline HIV RNA Level

Week 96 Virologic Response (Intention-to-Treat Analysis)

<table>
<thead>
<tr>
<th>Baseline HIV RNA copies/mL</th>
<th>Pool Data</th>
<th>≤100,000</th>
<th>&gt;100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL (%)</td>
<td>86/716</td>
<td>87/576</td>
<td>84/140</td>
</tr>
<tr>
<td></td>
<td>90/717</td>
<td>90/564</td>
<td>86/153</td>
</tr>
</tbody>
</table>

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results by Baseline CD4 Cell Count

Week 96 Virologic Response (Intention-to-Treat Analysis)

**GEMINI 1 and 2: Results by Baseline CD4 Cell Count**

<table>
<thead>
<tr>
<th>Baseline CD4 Count (cells/mm³)</th>
<th>Pooled Data</th>
<th>&gt;200</th>
<th>≤200</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA &lt;50 copies/mL (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir + Lamivudine</td>
<td>86/716</td>
<td>88/573</td>
<td>68/43</td>
</tr>
<tr>
<td>Dolutegravir + Tenofovir DF-Emtricitabine</td>
<td>90/717</td>
<td>90/653</td>
<td>48/63</td>
</tr>
</tbody>
</table>

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results

Week 96 Changes in Renal Function

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Results

Week 96 Changes in Serum Bone Biomarkers

<table>
<thead>
<tr>
<th>Bone Biomarker</th>
<th>Dolutegravir + Lamivudine</th>
<th>Dolutegravir + Tenofovir DF-Emtricitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone-specific alkaline phosphatase</td>
<td>0.29</td>
<td>2.36</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>0.27</td>
<td>4.21</td>
</tr>
<tr>
<td>Procollagen 1 N-terminal propeptide</td>
<td>11.00</td>
<td>23.70</td>
</tr>
<tr>
<td>Type 1 collagen C-telopeptide</td>
<td>0.10</td>
<td>0.24</td>
</tr>
</tbody>
</table>

DTG + 3TC versus DTG + TDF-FTC as Initial ART
GEMINI 1 and 2: Week 96 Conclusion

Conclusion: “Consistent with 48-week data, dolutegravir + lamivudine demonstrated long-term, non-inferior efficacy vs dolutegravir + tenofovir disoproxil fumarate/emtricitabine without increased risk of treatment emergent resistance, supporting its use in treatment-naive HIV-1–infected individuals.”

Dolutegravir-Lamivudine

Switch Studies in Adults with Virologic Suppression
Switch to DTG + 3TC versus Continued 3-Drug ART

ASPIRE
Switch to DTG + 3TC versus Continued 3-Drug Antiretroviral Therapy

ASPIRE: Background

- **Background**: Open-label, multicenter, pilot randomized trial that enrolled persons with suppressed HIV RNA levels and compared switch to 2-drug regimen versus continuing standard 3-drug antiretroviral therapy

- **Inclusion Criteria**:
  - Adults (age >18 years) with HIV
  - HIV RNA <50 copies/mL at least twice over 48 weeks
  - Screening HIV RNA <20 copies/mL
  - Taking any 3-drug ART regimen
  - No history of virologic failure
  - No known NRTI or INSTI resistance mutations
  - No chronic HBV
  - CrCl ≥50 mL/min

**Switch Group**
Dolutegravir + Lamivudine (n = 44)

**Continue Group**
Continue 3-drug ART (n = 45)

Switch to DTG + 3TC versus Continued 3-Drug Antiretroviral Therapy

ASPIRE: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Combined Group Study Population (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (IQR)</td>
<td>47 (38-54)</td>
</tr>
<tr>
<td>Male, %</td>
<td>88</td>
</tr>
<tr>
<td>White, %</td>
<td>60</td>
</tr>
<tr>
<td>Black or African American, %</td>
<td>38</td>
</tr>
<tr>
<td>Hispanic ethnicity, %</td>
<td>15</td>
</tr>
<tr>
<td>CD4 count, cells/mm³, median (IQR)</td>
<td>680 (498-927)</td>
</tr>
<tr>
<td>Time on ART, years, median (IQR)</td>
<td>5.7 (3.7-7.5)</td>
</tr>
<tr>
<td>Pre-randomization INSTI, %</td>
<td>37</td>
</tr>
<tr>
<td>Pre-randomization PI, %</td>
<td>33</td>
</tr>
<tr>
<td>Pre-randomization NNRTI, %</td>
<td>30</td>
</tr>
</tbody>
</table>

Switch to DTG + 3TC versus Continued 3-Drug Antiretroviral Therapy

ASPIRE: Results at 24 & 48 Weeks

Week 24 & 48 Virologic Responses (Intention-to-Treat Analysis)

One virologic failure occurred in the dolutegravir + lamivudine arm; no resistance mutations detected.

Conclusion: “In this randomized pilot clinical trial, dolutegravir plus lamivudine was noninferior to continuation of standard 3-drug maintenance antiretroviral therapy. There was no emergence of drug resistance in the participant who experienced virologic failure while receiving dolutegravir plus lamivudine.”
Switch to Dolutegravir-Lamivudine versus Continued TAF-Based 3-Drug ART

TANGO
Switch to DTG-3TC versus Continued TAF-Based Baseline Regimen

TANGO: Design

- **Design**: Open-label, non-inferiority trial in adults with suppressed HIV RNA while taking a 3- or 4-drug tenofovir alafenamide (TAF)-based regimen, randomized to switch to fixed-dose dolutegravir-lamivudine (DTG-3TC) or continue the baseline regimen.

- **Inclusion Criteria**
  - Adults with suppressed HIV RNA >6 months
  - Taking 3- or 4-drug TAF-based ART
  - No history of virologic failure
  - No major NRTI resistance; no INSTI resistance
  - No hepatitis B or C

- **Regimens**
  - Dolutegravir-lamivudine (50/300mg) daily
  - TAF-based 3- or 4-drug baseline regimen

**Switch Group**
Dolutegravir-Lamivudine  
(n = 369)

**Continue Baseline Regimen Group**
TAF-Based 3- or 4-Drug Regimen  
(n = 372)

Switch to DTG-3TC versus Continued TAF-Based Baseline Regimen

**TANGO: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dolutegravir-Lamivudine (n = 369)</th>
<th>TAF-Based ART (n = 372)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>40 (20-74)</td>
<td>39 (18-73)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>25 (7)</td>
<td>33 (9)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>297 (81)</td>
<td>289 (78)</td>
</tr>
<tr>
<td>African American/African, n (%)</td>
<td>50 (14)</td>
<td>58 (16)</td>
</tr>
<tr>
<td>CD4 cell count &lt;500, n (%)</td>
<td>98 (27)</td>
<td>74 (20)</td>
</tr>
<tr>
<td>CD4 cell count ≥500, n (%)</td>
<td>271 (73)</td>
<td>298 (80)</td>
</tr>
<tr>
<td>Months on ART, median (range)</td>
<td>33.8 (7.1-201.2)</td>
<td>35.1 (7.0-160.8)</td>
</tr>
<tr>
<td>Baseline third agent class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSTI</td>
<td>289 (78)</td>
<td>296 (80)</td>
</tr>
<tr>
<td>NNRTI</td>
<td>51 (14)</td>
<td>48 (13)</td>
</tr>
<tr>
<td>PI</td>
<td>29 (8)</td>
<td>28 (8)</td>
</tr>
</tbody>
</table>

Switch to DTG-3TC versus Continued TAF-Based Baseline Regimen
TANGO: Results at Week 48

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

- Confirmed withdrawal for virologic failure: 0 in DTG/3TC arm, 1 in TAF-based ART arm
- No new resistance mutations occurred
- 4 with baseline M184V/I in DTG/3TC arm (by proviral genotype) suppressed at week 48

Switch to DTG-3TC versus Continued TAF-Based Baseline Regimen
TANGO: Results at Week 48

Week 48 Changes in Renal Function (Plasma/Serum Markers)

Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Results at Week 48

Week 48 Changes in Markers of Proximal Tubulopathy (Urine Tests)

Conclusion: “Dolutegravir-lamivudine was noninferior in maintaining virologic suppression vs a TAF-based regimen at week 48, with no virologic failure or emergent resistance reported with DTG/3TC, supporting it as a simplification strategy for virologically suppressed people with HIV-1.”

Switch to DTG-3TC versus Continued TAF-Based Baseline Regimen

TANGO: 144 Week Results

Week 144 Virologic Response (ITT-Exposed)

Conclusion: “The 2-drug regimen dolutegravir-lamivudine was non-inferior in maintaining virologic suppression vs a tenofovir alafenamide-based regimen at Week 48, with no virologic failure or emergent resistance reported in the dolutegravir-lamivudine group, supporting its use as a simplification strategy for virologically suppressed people living with HIV-1.”

Switch to DTG-3TC versus Continued 3- or 4-Drug ART
SALSA
Switch to DTG-3TC versus Continued 3- or 4-Drug Regimen

SALSA: Design

- **Design:** Open-label, non-inferiority trial in adults with suppressed HIV RNA while taking a 3- or 4-drug regimen, randomized to switch to fixed-dose dolutegravir-lamivudine (DTG-3TC) or continue baseline regimen

- **Inclusion Criteria**
  - Adults with suppressed HIV RNA ≥6 months
  - No history of virologic failure
  - No major NRTI resistance; no INSTI resistance
  - No Hepatitis B or C

- **Regimens**
  - Dolutegravir-lamivudine (50/300mg) daily
  - 3- or 4-drug baseline regimen

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**Switch Group**

Dolutegravir-Lamivudine  
(n = 246)

**Continue Baseline Regimen Group**

3- or 4-Drug Regimen  
(n = 247)

Switch to DTG-3TC versus Continued 3- or 4-Drug Regimen
SALSA: 48 Week Results

Week 48 Virologic Response ITT-Exposed (Snapshot Analysis)

Conclusion: “Switching to dolutegravir-lamivudine was non-inferior to continuing current antiretroviral regimen for maintaining virologic suppression at Week 48 with no observed resistance, supporting the efficacy, good safety, and high barrier to resistance of dolutegravir-lamivudine.”
Acknowledgments

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