The Integrase Inhibitor Drug Class: A Comparative Clinical Review

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Disclosure

• Gilead, ViiV/GlaxoSmithKline: Advisory board membership
• Janssen: Research support
Outline

• Discuss some advantages of integrase inhibitors vs other classes of agents and differences among drugs within the class
• Discuss some of the classic studies with the current integrase inhibitors in naïve and experienced patients
• Discuss some of newer data and provocative studies with drugs in this class
Mechanism of Action of Integrase Strand Transfer Inhibitors

Integrase Inhibitors block the strand transfer of HIV cDNA to cellular DNA.
DHHS, IAS-USA Guidelines: Recommended Regimens for First-line ART

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>• BIC/TAF/FTC</td>
<td>• BIC/TAF/FTC</td>
</tr>
<tr>
<td></td>
<td>• DTG/ABC/3TC</td>
<td>• DTG/ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>• DTG + (TAF or TDF)/FTC</td>
<td>• DTG + TAF/FTC</td>
</tr>
<tr>
<td></td>
<td>• EVG/COBI/(TAF or TDF)/FTC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RAL + (TAF or TDF)/FTC</td>
<td></td>
</tr>
</tbody>
</table>

- Recommendations may differ based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status
- Data are lacking for women of child-bearing age not using contraception
- IAS-USA now lists EVG/COBI/TAF/FTC and RAL + TAF/FTC as alternative regimens owing to their lower resistance barriers and, respectively, more drug interactions and higher pill burden[2]

## WHO Guidelines Updated

### Summary of Sequencing Options for First-, Second- and Third-Line ART Regimens for Adults (Including Pregnant Women and Adolescents) and Children

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Adults and adolescents (including women and adolescent girls who are of childbearing potential women or pregnant)</td>
<td>Two NRTIs + DTG</td>
<td>Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r)</td>
<td>Darunavir/ritonavir (DRV/r) + DTG + 1-2 NRTIs (if possible, consider optimization using genotyping)</td>
</tr>
<tr>
<td>Adults and adolescents (including women and adolescent girls who are of childbearing potential women or pregnant)</td>
<td>Two NRTIs + EFV</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Two NRTIs + DTG</td>
<td>Two NRTIs + (ATV/r or LPV/r)</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Two NRTIs + LPV/r</td>
<td>Two NRTIs + DRG</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Two NRTIs + NNRTI</td>
<td>Two NRTIs + DTG</td>
<td></td>
</tr>
</tbody>
</table>

Why do the Guidelines Prefer the Integrase Inhibitors?

<table>
<thead>
<tr>
<th></th>
<th>Integrase inhibitors</th>
<th>Protease inhibitors (DRV, ATV)</th>
<th>NNRTIs (EFV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potency</strong></td>
<td>• Potent (more)</td>
<td>• Potent</td>
<td>• Potent</td>
</tr>
<tr>
<td><strong>Time to suppression</strong></td>
<td>• Fastest</td>
<td>• Not bad</td>
<td>• Not bad</td>
</tr>
<tr>
<td><strong>Resistance</strong></td>
<td>• Low genetic barrier (1st generation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High genetic barrier (2nd generation)</td>
<td>• High genetic barrier when boosted</td>
<td>• Low genetic barrier</td>
</tr>
<tr>
<td><strong>Convenience</strong></td>
<td>• Once daily</td>
<td>• Once daily</td>
<td>• Once daily</td>
</tr>
<tr>
<td></td>
<td>• No food restrictions (except EVG/c)</td>
<td>• Taken with food</td>
<td>• Taken at bedtime</td>
</tr>
<tr>
<td><strong>Tolerability / toxicity</strong></td>
<td>• Well tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neural tube defects in pregnancy? (DTG)</td>
<td>• GI intolerance</td>
<td>• CNS intolerance, depression, suicidality</td>
</tr>
<tr>
<td></td>
<td>• Hyperbilirubinemia (ATV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic effects</strong></td>
<td>• None</td>
<td>• CV risk, hyperlipidemia, increases bone toxicity of TDF</td>
<td>• Hyperlipidemia</td>
</tr>
<tr>
<td><strong>Drug-drug interactions</strong></td>
<td>• Few</td>
<td>• Many, need the booster</td>
<td>• Some</td>
</tr>
</tbody>
</table>
Comparative Effectiveness of First-Line ARV regimens in Brazil

- **Objective**: Estimate the rates of virologic suppression in Brazilians starting antiretroviral therapy using different combinations.
- **Ministry of Health Database**
  - Started therapy January 2014 to June 2017
  - Had a follow-up viral load 180 days (+/- 90 days) from baseline
- **103,240 were included in the analyses**
- **Population Characteristics**
  - Age: 34 (26-43)
  - 67.6% were male
  - CD4: 394 (209-581) cells/mm³
  - VL: 38,057 copies/mL
  - Adherence: 96.2% (82.4%-100.0%)
- **Overall, 76.9% achieved a 6-month VL ≤50 copies/mL**
### Comparative effectiveness of first-line ARV regimens in Brazil

<table>
<thead>
<tr>
<th>Regimen</th>
<th>%</th>
<th>VS (%)</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC+TDF+DTG</td>
<td>7.2</td>
<td>85.2</td>
<td>1.42</td>
<td>(1.32-1.52)</td>
</tr>
<tr>
<td>3TC+TDF+EFV</td>
<td>74.0</td>
<td>78.0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3TC+AZT+LPV/r</td>
<td>4.9</td>
<td>67.2</td>
<td>0.59</td>
<td>(0.55-0.63)</td>
</tr>
<tr>
<td>3TC+TDF+ATV/r</td>
<td>4.6</td>
<td>71.3</td>
<td>0.67</td>
<td>(0.63-0.72)</td>
</tr>
<tr>
<td>3TC+AZT+EFV</td>
<td>3.5</td>
<td>72.9</td>
<td>0.94</td>
<td>(0.87-1.02)</td>
</tr>
<tr>
<td>3TC+TDF+LPV/r</td>
<td>2.0</td>
<td>63.7</td>
<td>0.54</td>
<td>(0.49-0.60)</td>
</tr>
<tr>
<td>Others</td>
<td>3.7</td>
<td>67.9</td>
<td>0.67</td>
<td>(0.62-0.73)</td>
</tr>
</tbody>
</table>

- Conclusion: Highest rate of virologic suppression with integrase inhibitors

Meireles MV, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0101.
Structure of Integrase Inhibitors

- **Raltegravir**
  - Binds to hydrophobic pocket in integrase
- **Elvitegravir**
  - Binds Mg++ in integrase
- **Dolutegravir**
- **Bictegravir**
  - Binds Mg++ in integrase
- **Cabotegravir**
  - Binds to hydrophobic pocket in integrase
Advantages and Disadvantages of HIV Integrase Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Raltegravir</th>
<th>Elvitegravir/cobicistat</th>
<th>Dolutegravir</th>
<th>Bictegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potency</td>
<td>• Potent</td>
<td>• Potent</td>
<td>• Potent</td>
<td>• Potent</td>
</tr>
<tr>
<td>Resistance</td>
<td>• Low genetic barrier</td>
<td>• Low genetic barrier</td>
<td>• High barrier • Active against virus resistant to 1st generation</td>
<td>• High barrier • Active, but not useable against virus resistant to 1st generation</td>
</tr>
<tr>
<td>Convenience</td>
<td>• Two tablets</td>
<td>• Only available as co-formulation</td>
<td>• Once daily</td>
<td>• Only available as co-formulation</td>
</tr>
<tr>
<td>Tolerability/toxicity</td>
<td>• Rare CPK elevation</td>
<td>• Increase in creatinine</td>
<td>• Increase in creatinine • insomnia /CNS intolerance</td>
<td>• Increase in creatinine</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td>• Few</td>
<td>• Many, due to booster</td>
<td>• Few</td>
<td>• Few</td>
</tr>
<tr>
<td>Cost (AWP/mo) in US</td>
<td>• $1667</td>
<td>• $3306 (Genvoya)</td>
<td>• $1842 • $3430 (Triumeq)</td>
<td>• $3520 (Biktarvy)</td>
</tr>
</tbody>
</table>
INSIGHTFUL TRIALS and COHORT STUDIES
## Dolutegravir Efficacy in ART-Naïve Patients

### Randomized, Noninferiority Phase III Studies in ART-Naïve Patients

**Primary Endpoint:** HIV-1 RNA <50 c/mL at Week 48

<table>
<thead>
<tr>
<th>Regimen</th>
<th>SPRING-2  (Wk 96)</th>
<th>SINGLE (Wk 96)</th>
<th>FLAMINGO (Wk 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + 2 NRTI</td>
<td>332/411 (81%)</td>
<td>331/414 (80%)</td>
<td>194/242 (80%)</td>
</tr>
<tr>
<td>RAL + 2 NRTI</td>
<td>314/411 (76%)</td>
<td>203/419 (72%)</td>
<td>164/242 (68%)</td>
</tr>
<tr>
<td>DTG + ABC/3TC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EFV/TDF/FTC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG + 2 NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/r + 2 NRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- DTG was non-inferior to RAL in SPRING-2
- DTG demonstrated superiority to EFV/TDF/FTC (SINGLE) and DRV/r (FLAMINGO)
- No treatment-emergent resistance to DTG through 96 wks in SPRING-2, SINGLE, and FLAMINGO

PDFV = protocol-defined virologic failure.
SINGLE (DTG + ABC/3TC) vs EFV/TDF/FTC: Virologic Suppression <50 copies/mL

Week 96 adjusted difference in response (95% CI): +8.0% (+2.3% to +13.8%); P=0.006

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wk96 ∆ from BL</th>
<th>SE</th>
<th>Difference in response (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG + ABC/3TC QD (n=414)</td>
<td>325.3</td>
<td>10.5</td>
<td>44.0 (14.3, 73.6) P=0.004</td>
</tr>
<tr>
<td>EFV/TDF/FTC QD (n=419)</td>
<td>281.4</td>
<td>10.9</td>
<td></td>
</tr>
</tbody>
</table>

Walmsley S, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 543.
SINGLE (DTG + ABC/3TC) vs EFV/TDF/FTC: Resistance Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>DTG + ABC/3TC QD (n=414)</th>
<th>EFV/TDF/FTC QD (n=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI TE Major Mutations</td>
<td>0</td>
<td>1 (K65R)</td>
</tr>
<tr>
<td>NNRTI TE Major Mutations</td>
<td>0</td>
<td>6 (K101E, K103N, G190A)</td>
</tr>
<tr>
<td>INI-r TE Major Substitution</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Individuals Who Met Protocol Defined Virologic Failure Criteria

Walmsley S, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 543.
FLAMINGO Study (DTG vs DRV/r): HIV RNA <50 c/mL

No Emerging Resistance in Any Group

DTG:90%
DRV/r:83%

95% CI for Difference
Favors DRV/r Favors DTG

Test for superiority: \( P=0.025 \)

Results confirmed in per protocol analysis: 91% DTG versus 84% DRV/r, \( \Delta (CI) : 7.4 \ (1.4-13.3) \)

DTG showed superiority in high viral load and comparable efficacy independent of NRTI backbone through all VL strata.

Eligibility criteria: on first-line 2 NRTIs + NNRTI regimen for ≥6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs; at least 1 active NRTI

Stratification: by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)

Primary endpoint: proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)
DAWNING Study: Virologic Outcomes at Week 48

- Proportion of participants with HIV-1 RNA <50 c/mL at Week 48: DTG – 84% vs LPV/r – 70%; treatment difference [95% CI], 13.8% [7.3%-20.3%]; P<0.001 for superiority
- Virologic nonresponse at week 48: DTG – 30 (10%) LPV/r – 68 (22%)

Aboud M, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. THPEB040.
DAWNING STUDY:
Treatment Response by Sub-group

Treatment Response by Subgroups

<table>
<thead>
<tr>
<th>HIV-1 RNA &lt; 50 c/mL, %</th>
<th>Overall</th>
<th>≤ 100,000</th>
<th>&gt; 100,000</th>
<th>2</th>
<th>&lt; 2</th>
<th>&lt; 200</th>
<th>&lt; 200</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84</td>
<td>89</td>
<td>64</td>
<td>84</td>
<td>84</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>DTG + 2 NRTIs</td>
<td>70</td>
<td>71</td>
<td>65</td>
<td>59</td>
<td>73</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>LPV/r + 2 NRTIs</td>
<td>84</td>
<td>89</td>
<td>64</td>
<td>84</td>
<td>80</td>
<td>88</td>
<td>72</td>
</tr>
</tbody>
</table>

Aboud M, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. THPEB040.
Dawning Study: Emergent Resistance Mutations

Confirmed virologic withdrawal criteria any time DTG 10 (3%), LPV/r 28 (9%)

<table>
<thead>
<tr>
<th>Resistance Analysis</th>
<th>DTG + 2 NRTIs (n=8)</th>
<th>LPV/RTV + 2 NRTIs (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NRTI</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>K70R</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>M184V</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>K219Q</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>K219E</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PI</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SAILING Study: DTG vs RAL after treatment failure

Design

HIV ART-experienced, INI-naive
HIV-1 RNA >400 c/mL
1:1 Randomization stratified by HIV-1 RNA (≤ or >50,000), DRV/r use and # of fully active drugs

Randomization

Week 24 planned interim

Week 48 primary analysis

DTG 50 mg QD +
RAL PBO + BR

RAL 400 mg BID +
DTG PBO + BR

BR, background regimen comprising at least 1 and no more than 2 active agents.
SAILING Study: DTG vs RAL
Primary Endpoint: HIV-1 RNA <50 c/mL at Week 48

- Virologic success: DTG 50 mg QD (n=354) 71%, RAL 400 mg BID (n=361) 64%
- Virologic non-response: DTG 20%, RAL 28%
- No W48 data: 9% for both groups

95% CI for difference
Favors RAL
Favors DTG
0.7 7.4 14.2

-20% -12% 0 20%
SAILING Study: DTG vs RAL

Protocol-Defined Virologic Failure

- Fewer PDVFs for DTG versus RAL by Week 48

<table>
<thead>
<tr>
<th></th>
<th>DTG 50 mg QD (N=354)</th>
<th>RAL 400 mg BID (N=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 16</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>10 (3%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Rebound</td>
<td>10 (3%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td><strong>Week 24</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>15 (4%)</td>
<td>35 (10%)</td>
</tr>
<tr>
<td>Rebound</td>
<td>14 (4%)</td>
<td>16 (4%)</td>
</tr>
<tr>
<td><strong>Week 48</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic non-response</td>
<td>21 (6%)</td>
<td>45 (12%)</td>
</tr>
<tr>
<td>Rebound</td>
<td>19 (5%)</td>
<td>26 (7%)</td>
</tr>
</tbody>
</table>
Impact of INSTI Mutations on Dolutegravir Susceptibility

Stay tuned for Charles Boucher’s presentation

DTG fold change at baseline in Viking by Integrase mutational Pathway
Eron et al JID 2013
GS-1489 Study (B/F/TAF vs DTG/ABC/3TC): Study Design and Baseline Characteristics

Treatment-Naive Adults
- HIV-1 RNA ≥ 500 copies/mL
- eGFR$_{CG}$ ≥ 50 mL/min
- HLA B*5701 negative
- Negative for chronic HBV

<table>
<thead>
<tr>
<th></th>
<th>B/F/TAF QD</th>
<th>DTG/ABC/3TC Placebo QD</th>
<th>DTG/ABC/3TC QD</th>
<th>B/F/TAF Placebo QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=314</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=315</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Primary Endpoint</td>
<td>96</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Age, median years (range)
- 31 (18–71) vs 32 (18–68)

Male, %
- 91 vs 90

Race/ethnicity, %
- Black or African descent: 36 vs 36
- Hispanic/Latino ethnicity: 23 vs 21

HIV-1 RNA, median log$_{10}$ c/mL (IQR)
- 4.42 (4.03, 4.87) vs 4.51 (4.04, 4.87)

HIV-1 RNA >100,000 c/mL, %
- 17 vs 16

CD4 cell count, median cells/µL (IQR)
- 443 (299, 590) vs 450 (324, 608)

CD4 count <200 cells/µL, %
- 11 vs 10

Asymptomatic HIV infection, %
- 91 vs 91

eGFR$_{CG}$, median mL/min (IQR)
- 126 (108, 146) vs 123 (107, 144)

GS-1489 Study (B/F/TAF vs DTG/ABC/3TC): Results

Virologic Outcome

- **B/F/TAF non-inferior to DTG/ABC/3TC**
  - No resistance in either study arm
- Lipids not significantly different
- No drug-related renal events
- Significantly less nausea and minor adverse events with B/F/TAF

GS-1490 Study (B/F/TAF vs DTG + F/TAF): Study Design and Baseline Characteristics

Treatment-Naïve Adults
- HIV-1 RNA ≥500 copies/mL
- eGFR_{CG} ≥30 mL/min

<table>
<thead>
<tr>
<th></th>
<th>B/F/TAF (n=320)</th>
<th>DTG + F/TAF (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>33 (18–71)</td>
<td>34 (18–77)</td>
</tr>
<tr>
<td><strong>Male, %</strong></td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td><strong>Race/ethnicity, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African descent</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td><strong>Median HIV-1 RNA, log_{10} copies/mL (Q1, Q3)</strong></td>
<td>4.43 (3.95, 4.90)</td>
<td>4.45 (4.03, 4.84)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA &gt;100,000 copies/mL, %</strong></td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td><strong>Median CD4 cell count, cells/µL (Q1, Q3)</strong></td>
<td>440 (289, 591)</td>
<td>441 (297, 597)</td>
</tr>
<tr>
<td><strong>CD4 count &lt;200 cells/µL, %</strong></td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td><em><em>HBV</em>/HCV</em> coinfection, %**</td>
<td>3/2</td>
<td>2/2</td>
</tr>
<tr>
<td><strong>Median eGFR_{CG}, mL/min (Q1, Q3)</strong></td>
<td>120.4 (100.8, 141.8)</td>
<td>120.6 (102.8, 145.1)</td>
</tr>
</tbody>
</table>

GS-1490 Study (B/F/TAF vs DTG + F/TAF): Results

- Bictegravir non-inferior to dolutegravir
- Results consistent in sensitivity analyses
- No integrase resistance
- No difference in nausea

SINGLE (DTG + ABC/3TC vs EFV + TDF/FTC): Creatinine Profile Over Time

Pappa K, et al. 54th ICAAC; Washington, DC; September 5-9, 2014; Abst. H-647a.
DTG Discontinuation in Clinical Practice

- 387 patients started DTG (65 naïve) (median CD4 650/mm³)
- 16% stopped after a median of 78 days (range 5-327), 20% of naïves

Reason

- Sleep problems
- GI problem
- Psychiatric
- Fatigue
- Headache
- Stopped DTG alone
- Stopped ABC/3TC/DTG

DTG and Neural Tube Defects

Stay tuned for Rebecca Zash’s presentation now being given by Mauro Schechter

<table>
<thead>
<tr>
<th></th>
<th>No. of Infants with Defect</th>
<th>No. of Exposures</th>
<th>Percent with Defect</th>
<th>(95% CI)</th>
<th>Difference in Prevalence</th>
<th>(95% CI – Percentage Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-Positive</td>
<td>4</td>
<td>426</td>
<td>0.84</td>
<td>(0.37 to 2.4)</td>
<td>Reference</td>
<td>(–0.24 to –2.3)</td>
</tr>
<tr>
<td>HIV-Negative</td>
<td>14</td>
<td>11,300</td>
<td>0.12</td>
<td>(0.07 to 0.21)</td>
<td>–0.82</td>
<td>(–0.35 to –2.4)</td>
</tr>
<tr>
<td>Non-AIDS</td>
<td>0</td>
<td>2,812</td>
<td>0.00</td>
<td>(0.0 to 0.13)</td>
<td>–0.94</td>
<td>(–0.27 to –2.3)</td>
</tr>
<tr>
<td>DTG Started From</td>
<td>61</td>
<td>66,054</td>
<td>0.09</td>
<td>(0.07 to 0.12)</td>
<td>–0.85</td>
<td></td>
</tr>
</tbody>
</table>
NEWER DATA AND INTERESTING CONCEPTS
GEMINI 1 and 2: Study design

- **Eligibility criteria**
  - ≤10 days of prior ART
  - No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
  - No HBV infection or need for HCV therapy
GEMINI 1 and 2: Snapshot Outcomes at Week 48

Virologic outcome

Adjusted treatment difference (95% CI)a

GEMINI-1
- DTG + 3TC (N=356)
- DTG + TDF/FTC (N=358)

GEMINI-2
- DTG + 3TC (N=360)
- DTG + TDF/FTC (N=359)

HIV-1 RNA <50 c/mL, %

Virologic success
- GEMINI-1: DTG + 3TC (90), DTG + TDF/FTC (93)
- GEMINI-2: DTG + 3TC (93), DTG + TDF/FTC (94)

Virologic nonresponse
- GEMINI-1: DTG + 3TC (4), DTG + TDF/FTC (2)
- GEMINI-2: DTG + 3TC (2), DTG + TDF/FTC (6)

No virologic data
- GEMINI-1: DTG + 3TC (6), DTG + TDF/FTC (4)
- GEMINI-2: DTG + 3TC (5), DTG + TDF/FTC (4)

Adjusted treatment difference (95% CI)a

- GEMINI-1: DTG + TDF/FTC - DTG + 3TC
  - Percentage point difference: -6.7
  - 95% CI: (-10.0, -3.4)

- GEMINI-2: DTG + TDF/FTC - DTG + 3TC
  - Percentage point difference: -4.3
  - 95% CI: (-7.7, -0.9)

Cahn P, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0106LB.
GEMINI 1 and 2: Results

Snapshot Analysis by Visit: Pooled ITT-E Population

HIV-1 RNA <50 c/mL, %

-20 0 20 40 60 80 100

Study week

-4 0 4 8 12 16 20 24 28 32 36 40 44 48

DTG + 3TC (n=716)
DTG + TDF/FTC (n=717)

Cahn P, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0106LB.
GEMINI 1 and 2: Pooled Outcomes at Week 48

**Snapshot Analysis**

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA, c/mL</th>
<th>DTG + 3TC</th>
<th>DTG + TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100,000</td>
<td>91/94</td>
<td>92/90</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>93/93</td>
<td>79/93</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline CD4+ cell count, cell/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤200</td>
</tr>
<tr>
<td>&gt;200</td>
</tr>
</tbody>
</table>

**TRDF Analysis**

<table>
<thead>
<tr>
<th>Baseline HIV-1 RNA, c/mL</th>
<th>DTG + 3TC</th>
<th>DTG + TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤100,000</td>
<td>98/98</td>
<td>99/97</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>138/149</td>
<td>140/153</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline CD4+ cell count, cell/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤200</td>
</tr>
<tr>
<td>&gt;200</td>
</tr>
</tbody>
</table>

- DTG + 3TC CD4 <200 Snapshot non-response (n=13): 1 CVW, 3 with VL >50 in window (2 of 3 re-suppressed), 2 discontinued due to AE (TB, Chagas disease), 2 protocol violations, 2 lost to follow-up, 1 withdrew consent, 1 withdrew to start HCV treatment, 1 change in ART (incarcerated)
- DTG + TDF/FTC < 200 Snapshot non-response (n=4): 1 investigator discretion, 1 withdrew consent, 1 lost to follow-up, 1 VL >50 (re-suppressed)

Cahn P, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0106LB.
GEMINI 1 and 2: Results

- Low rates of virologic withdrawals were observed at Week 48
- No resistance mutations

<table>
<thead>
<tr>
<th>Variable, n (%)</th>
<th>GEMINI 1</th>
<th>GEMINI 2</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DTG + 3TC (N=356)</td>
<td>DTG + TDF/FTC (N=358)</td>
<td>DTG + 3TC (N=360)</td>
</tr>
<tr>
<td>CVW</td>
<td>4 (1)</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Treatment-emergent resistance</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Cahn P, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0106LB.
Dolutegravir + lamivudine provided comparable maintenance of viral suppression
  - Rare viral blips (n=1)
• Virologic failure (n=1 in each arm)
  - No emergence of resistance at virologic failure
• CD4 gain was similar between the 2 arms
• Both regimens were well tolerated over 48 weeks
  - Discontinuation due to adverse events (n=1, dual therapy)
  - Similar changes in total cholesterol, LDL-C, triglycerides, and creatinine clearance
• Fully powered randomized trial ongoing
  – TANGO studies

SWORD: Dolutegravir + Rilpivirine for Maintenance of Suppression

Phase III, Randomized, Multicenter, Open-label, Parallel-Group, Non-Inferiority Studies

**Screening**
- VL <50 c/mL on INI, NNRTI, or PI + 2 NRTIs

**Early Switch Phase**
- DTG + RPV (N=513)
- CAR (N=511)

**Late Switch Phase**
- DTG + RPV

**Continuation Phase**
- DTG + RPV

**Inclusion Criteria**
- On stable CAR ≥6 months before screening
- 1st or 2nd ART with no change in prior regimen due to VF
- Confirmed HIV-1RNA <50 c/mL during the 12 months before screening

**Primary endpoints at 48 weeks:**
- Subjects with VL <50 c/mL (ITT-E snapshot)

**Countries**
- Argentina
- Australia
- Belgium
- Brazil
- Canada
- China
- Czech Republic
- Denmark
- Estonia
- France
- Germany
- Greece
- Italy
- Japan
- Korea
- Latvia
- Lithuania
- Luxembourg
- Netherlands
- New Zealand
- Norway
- Poland
- Portugal
- Singapore
- Spain
- Sweden
- Switzerland
- Taiwan
- Thailand
- United States
- United Kingdom

Llibre J, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 44LB.
DTG+RPV is non-inferior to CAR with respect to snapshot in the ITT-E population (<50 c/mL) at Week 48.
LATTE-2: Study Design

**Induction period**
- CAB 30 mg + ABC/3TC for 20 weeks

**Maintenance period**
- CAB 400 mg IM + RPV 600 mg IM Q4W (n=115)
- CAB 600 mg IM + RPV 900 mg IM Q8W (n=115)
- CAB 30 mg + ABC/3TC PO QD (n=56)

**Day 1**
- Randomization 2:2:1

**Week 32**
- Primary analysis
- Dosing regimen selection

**Week 48**
- Analysis
- Dosing regimen confirmation

CAB loading dose at Day 1 (800 mg)
CAB loading doses at Day 1 (800 mg) and Week 4 (600 mg)

LATTE-2 Study: Efficacy

Virologic Outcomes

HIV-1 RNA <50c/mL, %

- CAB + RPV LA Q8W (n=115)
- CAB + RPV LA Q4W (n=115)
- CAB + NRTIs PO (n=56)

Virologic Success

- CAB + RPV LA Q8W: 94%
- CAB + RPV LA Q4W: 87%
- CAB + NRTIs PO: 84%

Virologic Non-Response

- CAB + RPV LA Q8W: 4%
- CAB + RPV LA Q4W: 0%
- CAB + NRTIs PO: 2%

No Virologic Data

- CAB + RPV LA Q8W: 2%
- CAB + RPV LA Q4W: 13%
- CAB + NRTIs PO: 14%

Treatment Differences (95% CI)

- Q8W IM: -0.6 to 10.0%
- Q4W IM: -8.4 to 14.4%

INSPIRING study: Phase IIIb, DTG vs EFV in HIV-Tb Co-infection

Phase IIIb, randomized, multicenter, open-label, non-comparative, active-controlled, parallel-group study

- HIV/TB co-infected ART-naive adults
- HRZE (2 months) → HR (4 months)
  - DTG (50 mg BID) + 2 NRTIs (n=69)
  - EFV (600 mg QD) + 2 NRTIs (n=44)
- HR (4 months) → DTG dose switch
  - 2 weeks post-completion of TB treatment
  - Primary endpoint at Week 48: % <50 copies/mL (modified Snapshot)

Inclusion criteria:
- HIV-1 RNA ≥1000 copies/mL and CD4+ ≥50 cells/mm³
- Pulmonary, pleural, or lymph node tuberculosis with RIF-sensitive MTB confirmed by culture or GeneXpert
- RIF-containing TB treatment started up to a maximum of 8 weeks before randomization and no later than the screening date

DTG:EFV 3:2 randomization stratified by:
- Screening plasma HIV-1 RNA ≥100,000 or <100,000 copies/mL
- Screening CD4+ ≥100 or <100 cells/mm³

Dooley K, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0206.

aDuration of continuation phase of TB treatment according to local guidelines (up to 7 months in some countries)
INSPIRING study: DTG vs EFV in HIV-Tb Co-infection

FDA Snapshot Outcomes at Week 48

<table>
<thead>
<tr>
<th>n (%)</th>
<th>DTG (n=69)</th>
<th>EFV (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic success (HIV-1 RNA &lt;50 copies/mL)</td>
<td>52 (75)</td>
<td>36 (82)</td>
</tr>
<tr>
<td>Virologic nonresponse</td>
<td>6 (9)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Data in window not &lt;50 copies/mL</td>
<td>0</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Discontinued for other reason while not &lt;50 copies/mL</td>
<td>6 (9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1 (2)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Change in ART</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No virologic data</td>
<td>11 (16)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Discontinued because of AE or death</td>
<td>0</td>
<td>2 (5)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Discontinued for other reasons</td>
<td>11 (16)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3 (7)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Missing data during window but on study</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>DTG: discontinued for other reasons while not <50 copies/mL: 3 lost to follow-up; 2 withdrawal of consent; 1 pregnancy.
<sup>b</sup>EFV: discontinued for other reasons while not <50 copies/mL: 1 lost to follow-up.
<sup>c</sup>EFV: discontinued due to AE: 1 EFV hypersensitivity; 1 increased gamma-glutamyltransferase.
<sup>d</sup>DTG: No virologic data/Discontinued for other reasons: 7 lost to follow-up; 2 pregnancies; 1 physician decision; 1 withdrawal of consent.
<sup>e</sup>EFV: No virologic data/Discontinued for other reasons: 2 lost to follow-up; 1 withdrawal of consent (patient relocated).

Dooley K, et al. AIDS 2018; Amsterdam, the Netherlands; July 23-27, 2018; Abst. TUAB0206.
## INSPIRING study: TB- and Non–TB-Associated Immune Reconstitution Inflammatory Syndrome (IRIS)

### Participants with events sent to adjudication committee for TB-associated IRIS

| Met criteria for TB-associated IRIS | 9 (13) | 12 (27) |
| Possibly met criteria for TB-associated IRIS | 4 (6)\(^a\) | 4 (9)\(^b\) |

### Participants with events sent to adjudication committee for non–TB-associated IRIS

| Met criteria for non–TB-associated IRIS | 2 (3) | 3 (7) |
| Possibly met criteria for non–TB-associated IRIS | 1 (1)\(^c\) | 0 |
| 1 (1)\(^d\) | 0 |

### Treatment outcomes

<table>
<thead>
<tr>
<th>n (%)</th>
<th>DTG (n=69)</th>
<th>EFV (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Success</strong></td>
<td>61 (88)</td>
<td>40 (91)</td>
</tr>
<tr>
<td><strong>Treatment failure</strong></td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Died</strong></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Not evaluated / Lost to follow-up</strong></td>
<td>8 (12)</td>
<td>3 (7)</td>
</tr>
</tbody>
</table>

\(^{a, b, c, d}\) Grade 1, 2 \(\times\) Grade 2, and 1 \(\times\) Grade 3. \(^{a, b, c, d}\) Grade 2 (IRIS and strongyloidiasis; also experienced TB-associated IRIS). \(^{a, b, c, d}\) Grade 1 (herpes zoster).
Conclusions

• Integrase inhibitors have transformed the treatment landscape
• We have excellent drugs in the class (some are more excellent than others)
• A lot more to come