USE OF BICTEGRAVIR/EMTRICITABINE/TENOFOVIR ALAFENAMIDE FOR THE TREATMENT OF HIV

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Financial Disclosure

“I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation”

Pharmacist Learning Objectives

- Identify the mechanism of action of each component of the new HIV combination medication bictegravir/emtricitabine/tenofovir alafenamide
- Evaluate patient specific factors to ensure safe use of the new HIV combination medication bictegravir/emtricitabine/tenofovir alafenamide

Technician Learning Objectives

- Identify the active ingredients of the antiretroviral combination medication discussed in this presentation
- Explain the correct dispensing and storage requirements for the new HIV combination medication bictegravir/emtricitabine/tenofovir alafenamide

Human Immunodeficiency Virus (HIV)

- Enveloped single stranded RNA virus
- Chronic condition that weakens the immune system by destroying CD4+ T cells, which fight disease and infection
- With appropriate antiretroviral therapy (ART), HIV can be controlled
  - Only 55% of people in the United States with HIV have suppressed viral loads
- As CD4+ T cells decline, a person is more susceptible to opportunistic infections
- May progress to acquired immunodeficiency syndrome (AIDS)

Epidemiology

- Contact with body fluids including:
  - Blood
  - Semen
  - Vaginal fluid
  - Rectal fluid
  - Breast milk
- Transmission through:
  - Sexual contact
  - Sharing needles/ contact with an HIV infected needle
  - Pregnancy, childbirth, or breast feeding

Pathophysiology
**Antiretroviral Therapy**

<table>
<thead>
<tr>
<th>Pharmacologic Category</th>
<th>Mechanism of Action</th>
<th>Common Side Effects</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry Inhibitor</td>
<td>Prevents binding and entry into the cell by binding to the transmembrane fusion protein gp41</td>
<td>Hypersensitivity reactions, injection site reactions, increased incidence of bacterial pneumonia</td>
<td>enfuviritide</td>
</tr>
<tr>
<td>Entry Inhibitor</td>
<td>Antagonist at chemokine receptor 5 (CCR5) co-receptor of the immune cell</td>
<td>Rash, hepatotoxicity, upper respiratory tract infection, cough</td>
<td>maraviroc</td>
</tr>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</td>
<td>Competitively inhibits the HIV reverse transcriptase enzyme and terminates synthesis of DNA chain; must be phosphorylated to active metabolites</td>
<td>Lactic acidosis, hepatic steatosis, peripheral neuropathy</td>
<td>abacavir, lamivudine, tenofovir</td>
</tr>
</tbody>
</table>

**Goals of Therapy**

- Maximally and durably suppress HIV RNA viral load
- Restore and preserve immunologic function
- Reduce HIV-associated morbidity and prolong the duration/quality of survival
- Prevent HIV transmission

**Antiretroviral Regimen for Treatment Naïve Patient**

- Two NRTIs and EITHER
  - An INSTI OR
  - A NNRTI OR
  - A PI with a pharmacokinetic enhancer (booster)
- For most patients an INSTI containing regimen is recommended
  - Highly effective, infrequent adverse effects, few drug-drug interactions
- Recommended NRTI combination option: emtricitabine-tenofovir alafenamide
  - Fewer bone and kidney toxicities compared with tenofovir disoproxil fumarate

**Biktarvy 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (Biktarvy®)**

- Approved: February 2018
- Indications:
  - Complete regimen for the treatment of HIV-1 in adults with no antiretroviral treatment history
  - To replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen for at least 3 months, with no history of treatment failure, and no known substitutions associated with resistance to components of Biktarvy®
- MOA:
  - Biktegravir = INSTI
  - Emtricitabine & tenofovir alafenamide= NRTIs
- Administration:
  - Take 1 tablet by mouth once daily with or without food
Contraindications
■ Co-administration with dofetilide and rifampin

Precautions
■ Immune reconstitution syndrome
■ New onset or worsening renal impairment
■ Lactic acidosis/severe hepatomegaly with steatosis
■ Severe acute exacerbation of hepatitis B in patients coinfected with HIV-1 and HBV

Renal Impairment
■ Concentrations in patients with severe renal impairment with CrCl <30 ml/min
  • No dose adjustment in patients with CrCl ≥30 ml/min

Hepatic Impairment
■ Concentrations in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) impairment
  • Has not been studied and is not recommended in patients with severe impairment (Child-Pugh Class C)

Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Bictegravir (BIC)</th>
<th>Emtricitabine (FTC)</th>
<th>Tenofovir Alafenamide (TAF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% bound to plasma proteins</td>
<td>&gt;99</td>
<td>&lt;4</td>
<td>~80</td>
</tr>
<tr>
<td>Half life (hours)</td>
<td>17.3</td>
<td>10.4</td>
<td>0.51</td>
</tr>
<tr>
<td>Major route of elimination</td>
<td>Metabolism</td>
<td>Glomerular filtration and active tubular secretion</td>
<td>Metabolism</td>
</tr>
<tr>
<td>% of dose excreted in urine</td>
<td>35</td>
<td>70</td>
<td>&lt;1</td>
</tr>
<tr>
<td>% of dose excreted in feces</td>
<td>60.3</td>
<td>13.7</td>
<td>31.7</td>
</tr>
</tbody>
</table>

Pharmacokinetics
■ Bictegravir inhibits cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE 1) in vitro
  - May increase concentrations of dofetilide
■ Bictegravir is a substrate of CYP3A4 and UGT1A1
  - Medications that inhibit CYP3A4 may increase plasma concentrations of bictegravir
  - Medications that induce CYP3A4 may decrease plasma concentrations of bictegravir
■ Tenofovir alafenamide is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP)

Storage
■ Keep the container tightly closed
■ Dispense only in original container

Lactation
• Breast feeding is not recommended to avoid risking postnatal transmission of HIV-1 infection

Pregnancy
• Pregnancy exposure registry monitoring outcomes
• Bictegravir and tenofovir alafenamide use during pregnancy has not been evaluated
• Emtricitabine
  • No difference in overall risk of major birth defects
  • Rate of miscarriage was not reported

Cost
• $117.83 per tablet
• 30-days supply: $3,534.90

Objectives
■ Primary Outcome:
  - Proportion of participants who had plasma HIV-1 RNA of <50 copies/ml at week 48
■ Efficacy Endpoint:
  - CD4 count from baseline at week 48

Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomized, double-blind, multicenter, phase 3, non-inferiority trial

Treatment Groups

- Fixed-dose combination bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg + 2 placebos OR
- Dolutegravir 50 mg in combination with co-formulated emtricitabine 200 mg and tenofovir alafenamide 25 mg + placebo

Randomization was stratified by:
- HIV-1 RNA (≤100,000 copies/ml, >100,000 to ≤400,000 copies/ml, or >400,000 copies/ml)
- CD4 count (<50 cells/μL, 50 to 199 cells/μL, or ≥200 cells/μL)
- Region (USA or outside USA)

Design

- Randomized 1:1, double-blind, multicenter, active-controlled, non-inferiority phase 3 trial
- 126 outpatient centers in 10 countries
- Treated for 144 weeks
- Study visits at day 1, weeks 4, 8, 12 and then every 12 weeks through week 144
- Laboratory analysis at each visit: HIV-1 RNA, CD4 count, complete or symptom directed physical examinations

Inclusion

- Adults ≥ 18 years with previously untreated HIV-1 infection
- HIV-1 RNA levels ≥ 500 copies/ml
- eGFR ≥ 30 ml/min
- Virological resistance testing showing sensitivity to emtricitabine and tenofovir

Exclusion

- Opportunistic illness indicating stage 3 HIV diagnosed within 30 days prior to screening
- Decompensated cirrhosis (ascites, variceal bleeding, encephalopathy)
- Current alcohol or substance use that may interfere with compliance
- Females pregnant or breastfeeding

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Bictegravir (n=320)</th>
<th>Dolutegravir (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>33 (27-46)</td>
<td>34 (27-46)</td>
</tr>
<tr>
<td>Sex, men</td>
<td>280 (88%)</td>
<td>288 (89%)</td>
</tr>
<tr>
<td>Race, white</td>
<td>183 (57%)</td>
<td>195 (60%)</td>
</tr>
<tr>
<td>Region, USA</td>
<td>193 (60%)</td>
<td>193 (59%)</td>
</tr>
<tr>
<td>HIV-1 RNA concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100,000 to ≤400,000 copies/ml</td>
<td>54 (17%)</td>
<td>41 (13%)</td>
</tr>
<tr>
<td>&gt;400,000 copies/ml</td>
<td>12 (4%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Median creatinine clearance (ml/min)</td>
<td>120.4</td>
<td>120.6</td>
</tr>
</tbody>
</table>

Baseline Demographics

<table>
<thead>
<tr>
<th>CD4 count (cells/μL)</th>
<th>Bictegravir (n=320)</th>
<th>Dolutegravir (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>15 (5%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>≥50 to &lt;200</td>
<td>29 (9%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>≥200 to &lt;350</td>
<td>67 (21%)</td>
<td>77 (24%)</td>
</tr>
<tr>
<td>≥350 to &lt;500</td>
<td>91 (28%)</td>
<td>94 (29%)</td>
</tr>
<tr>
<td>≥500</td>
<td>118 (37%)</td>
<td>120 (37%)</td>
</tr>
</tbody>
</table>

Statistical Methods

- Noninferiority assessed with 95% CI for the difference in virological response rates, with a non-inferiority margin of -12%
  - Mantel Haenszel proportion
- Assuming a response rate of 91% at week 48 in both groups, a sample size of 600 patients would achieve a power of 90% to detect noninferiority at a one-sided alpha of 0.025
- Primary endpoint analyzed by intention to treat (ITT) and per-protocol
- Change in CD4 count from baseline at week 48
  - Analysis of variance model (ANOVA)
Primary Outcome: HIV-1 RNA < 50 copies/ml

- Bictegravir regimen was non-inferior to the dolutegravir regimen
  - 286 (89.4%) of 320 participants vs. 302 (92.9%) of 325 participants
  - Difference -3.5%, 95% CI (-7.9 to 1.0)
  - P= 0.12, for superiority
- Per-protocol analysis
  - 279 (99%) of 282 participants and 296 (99.7%) of 297 participants
  - Difference -0.7%, 95% CI (-2.6 to 1.2)
  - P= 0.33, for superiority

Efficacy Endpoint

- Mean change in CD4 count at week 48
  - 180 cells/μL for bictegravir group and 201 cells/μL for dolutegravir group
  - P=0.10
- Viral resistance testing
  - 12 participants met criteria: 7 bictegravir, 5 dolutegravir
  - No treatment emergent resistance identified


Safety

<table>
<thead>
<tr>
<th></th>
<th>Bictegravir (n=320)</th>
<th>Dolutegravir (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>40 (13%)</td>
<td>40 (12%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (12%)</td>
<td>39 (12%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>25 (8%)</td>
<td>29 (9%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>22 (7%)</td>
<td>31 (10%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (6%)</td>
<td>26 (8%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16 (5%)</td>
<td>14 (4%)</td>
</tr>
</tbody>
</table>


Strengths

- Appropriate comparator used
- ITT and per-protocol analysis provided the same conclusion
- Used FDA snapshot algorithm to standardize study
- Randomized controlled trial
- Double-blind prevents bias

Limitations

- Large number of participants had a CD4 count ≥ 500 cells/μL and HIV-1 RNA < 100,000 at baseline
- Demographics: men, white, USA, CrCl > 100ml/min
- Gilead Sciences, Inc. funded the study


Author’s Conclusion

- Bictegravir group showed non-inferior efficacy to the dolutegravir group
- No study participant discontinued treatment due to lack of efficacy
- No drug resistance found
- Discontinuations due to adverse effects occurred rarely in both groups and none occurred in more than one participant


Personal

- Possible new treatment option for treatment naïve patients
- Convenient regimen that promotes adherence
- Well tolerated
- Need further studies to attain more data for those with HIV-1 RNA >100,000 and CD4 count <500 cells/μL
Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults in HIV-1: 48 week results of a randomized, double-blind, multicenter, active-controlled, phase 3, non-inferiority trial


Objectives

- **Primary Outcome:**
  - Proportion of participants with plasma HIV-1 RNA of ≥ 50 copies/ml at week 48
- **Efficacy Endpoints:**
  - Change in CD4 count from baseline to week 48


Treatment Groups

- Co-formulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg + placebo
- Fixed-dose, combination dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg + placebo


Design

- Randomized 1:1, double-blind, multicenter, active-controlled, non-inferiority, phase 3 trial
- 96 outpatient centers in 9 countries
- Treated for 48 weeks then were able to participate in an open-label extension phase for an additional 96 weeks
- Study visits at baseline, week 4, 8, 12, 36, 48, and every 12 weeks thereafter if participating in open-label extension
- Laboratory analysis at each visit: CD4 counts, renal function, HIV-1 RNA


Inclusion

- eGFR ≥ 50 ml/min
- No documented or suspected resistance to emtricitabine, tenofovir, dolutegravir, abacavir, or lamivudine
- HIV RNA <50 copies/ml at screening
- Currently on a stable regimen for ≥3 months before screening with HIV-1 RNA ≤50 copies/ml for ≥3 months before screening
- Currently receiving dolutegravir, abacavir, and lamivudine

Exclusion

- Decompensated cirrhosis (Ascites, variceal bleeding, encephalopathy)
- Current alcohol or substance use that may interfere with compliance
- Acute hepatitis in 30 days prior to study entry
- Chronic hepatitis B infection
- Females breastfeeding or pregnant

Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Bictegravir (n=282)</th>
<th>Dolutegravir (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>47 (21-71)</td>
<td>45 (20-70)</td>
</tr>
<tr>
<td><strong>Sex, men</strong></td>
<td>247 (88%)</td>
<td>252 (90%)</td>
</tr>
<tr>
<td><strong>Race, white</strong></td>
<td>206 (73%)</td>
<td>202 (73%)</td>
</tr>
<tr>
<td><strong>eGFR (ml/min)</strong></td>
<td>101</td>
<td>101</td>
</tr>
<tr>
<td><strong>CD4 count (cells/μL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500</td>
<td>227 (80%)</td>
<td>205 (73%)</td>
</tr>
<tr>
<td><strong>Time on regimen before study drug dosing (years)</strong></td>
<td>1.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Statistical Methods

- Non-inferiority established if the upper bound of 95% CI for the difference between the groups is <4%
  - Using an unconditional exact method with two inverted one-sided tests
- Assuming that 2% of participants in each group would have HIV-RNA of ≥ 50 copies/ml at week 48, a sample size of 520 participants would achieve 90% power to detect non-inferiority at a one-sided alpha of 0.025
- Primary endpoint analyzed by intention to treat (ITT) and per-protocol
- Change in CD4 count from baseline at week 48
  - Analysis of variance model (ANOVA)

Primary Outcome: HIV-1 RNA ≥ 50 copies/ml

- Bictegravir regimen was non-inferior to the dolutegravir regimen
  - 3 (1%) of 282 participants vs. 1 (<1%) of 281 participants
  - Difference 0.7%, 95% CI (-1.0 to 2.8)
  - P=0.62, for superiority
- Per-protocol analysis
  - 1 (<1%) of 257 participants vs. 0 (0%) of 256 participants
  - Difference 0.4%, 95% CI (-1.1 to 2.2)
  - P=1.00, for superiority

Efficacy Endpoint

- Mean change in CD4 count from baseline to week 48
  - Decreased by 31 cells/μL in bictegravir group and increased by 4 cells/μL in the dolutegravir group
  - Difference -35 cells/μL, 95% CI (-67 to -3), p=0.031
- After adjusting for baseline CD4 count, changes were not significant
  - Difference -21 cells/μL, 95% CI (-51 to 9), p=0.18
- Viral resistance testing
  - 5 participants met criteria: 3 bictegravir, 2 dolutegravir
  - No virological resistance developed

Safety

<table>
<thead>
<tr>
<th></th>
<th>Bictegravir (n=282)</th>
<th>Dolutegravir (n=281)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (2%)</td>
<td>8 (3%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Abnormal dreams</td>
<td>1 (&lt;1%)</td>
<td>5 (2%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (&lt;1%)</td>
<td>3 (1%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Treatment related adverse event</td>
<td>23 (8%)</td>
<td>44 (16%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Strengths

- Met power for primary outcome of the study
- ITT and per-protocol analysis provided the same conclusion
- Used FDA snapshot algorithm to standardize study
- Randomized controlled trial
- Double-blind prevents bias

Weaknesses

- Demographics: men, white, CD4 count
- Study population reasonably healthy
- Gilead Sciences, Inc. funded the study
- Could not assess acceptability or palatability of decreased tablet size with bictegravir regimen due to double-blind, active-controlled study
Author's Conclusion

Switching to bictegravir, emtricitabine, and tenofovir alafenamide maintained high efficacy rates and was non-inferior to remaining on dolutegravir, abacavir, and lamivudine.

- No emergence of drug resistance
- Well tolerated regimen

Personal Conclusions

- Bictegravir group reliably continued to suppress HIV-1 RNA when switch from a stable regimen
- Bictegravir continued to sustain immunologic function
- Patient’s has less treatment related adverse events with bictegravir group

In Conclusion

- bictegravir 50 mg/ emtricitabine 200 mg/ tenofovir alafenamide 25 mg (Biktarvy®) has shown effectiveness and non-inferiority to several established HIV-1 regimens when treating HIV-1 naïve patients and switching from a stable HIV regimen
- Well tolerated overall
- Provides an option for switching therapy to a preferred regimen
- No trials available that evaluate use in a patient that is not well controlled on a HIV regimen or has encountered previous resistance.

References

- Biktarvy (bictegravir/ emtricitabine/ tenofovir alafenamide) [package insert]. Foster City, CA: Gilead Sciences, Inc., 2018 Feb
- Pharmacist Post-test Question

Which of the following components is correctly matched with its mechanism of action?

a. bictegravir (Integrase Strand Transfer Inhibitor – INSTI)
b. emtricitabine (Non-Nucleoside Reverse Transcriptase Inhibitor - NNRTI)
c. tenofovir alafenamide (Protease Inhibitor – PI)
d. tenofovir alafenamide (Integrase Strand Transfer Inhibitor - INSTI)

Pharmacist Post-test Question

Which of the following patients should NOT initiate therapy with the new HIV combination medication bictegravir/ emtricitabine/ tenofovir alafenamide?

a. A 39 year-old female who has no history of resistance with any component of Biktarvy®
b. A 67 year-old male who received confirmation of a negative hepatitis B blood test
c. A 55 year-old man with liver impairment (Child-Pugh Class A)
d. A 25 year-old woman with a CrCl of 28 ml/min who uses 2 forms of contraceptive
Pharmacist Post-test Question

Which of the following patients should NOT initiate therapy with the new HIV combination medication bictegravir/emtricitabine/tenofovir alafenamide?

a. A 39 year-old female who has no history of resistance with any component of Biktarvy®

b. A 67 year-old male who received confirmation of a negative hepatitis B blood test

c. A 55 year-old man with liver impairment (Child-Pugh Class A)

d. A 25 year-old woman with a CrCl of 28 ml/min who uses 2 forms of contraceptive

Technician Post-test Question

Name the active ingredients and trade name of the new combination medication discussed in this presentation

a. dolutegravir, emtricitabine, tenofovir alafenamide

b. bictegravir, emtricitabine, tenofovir disoproxil fumarate

c. dolutegravir, emtricitabine, tenofovir disoproxil fumarate

d. bictegravir, emtricitabine, tenofovir alafenamide

Technician Post-test Question

Name the active ingredients and trade name of the new combination medication discussed in this presentation

a. dolutegravir, emtricitabine, tenofovir alafenamide

b. bictegravir, emtricitabine, tenofovir disoproxil fumarate

c. dolutegravir, emtricitabine, tenofovir disoproxil fumarate

d. bictegravir, emtricitabine, tenofovir alafenamide

Technician Post-test Question

How is this combination product dispensed?

a. In blister packs

b. In its original container

c. Repackaged in a new bottle

d. In a medication box organization system

Technician Post-test Question

How is this combination product dispensed?

a. In blister packs

b. In its original container

c. Repackaged in a new bottle

d. In a medication box organization system