A Tale of Two Tenofovir: The Role of Tenofovir Alafenamide in the Management of Human Immunodeficiency Virus (HIV)

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LEARNING OBJECTIVES

1. Describe the incidence and prevalence of HIV in the United States and worldwide
2. Review the pathophysiology of HIV, including transmission, diagnosis, and stages of infection
3. Provide an overview of the history and current standards of HIV treatment
4. Identify patient populations in whom tenofovir alafenamide (TAF) should be utilized
BACKGROUND

Epidemiology
A. Statistics in the United States\textsuperscript{1-3}
   a. At the end of 2014, approximately 955,000 persons were living with HIV
   b. Populations with the highest rates of infections include:
      a. Persons aged 20-29 years (37% of diagnoses by age group in 2015)
      b. Persons living in southern states (50% of diagnoses by region in 2015)
      c. African Americans (45% of diagnoses by race in 2015)
      d. Male-to-male sexual contact (70% of diagnoses by risk group in 2015)
   c. The rate of diagnosis has decreased by 9% from 2010 to 2016\textsuperscript{4}
B. World prevalence\textsuperscript{4,5}
   a. At the end of 2016, there were an estimated 36.7 million persons living with HIV worldwide
      i. Approximately 53% are living in eastern or southern Africa
   b. During 2016, there were approximately 1.8 million new HIV diagnoses
      i. Southern and eastern Africa accounts for 43% of all new cases
   c. Rate of new infections in global population has decreased by 16% since 2010
      i. Decreased by 47% in children since 2010

Transmission\textsuperscript{6}

Table 1: Risk of Transmission by Route

<table>
<thead>
<tr>
<th>Route of Transmission</th>
<th>Risk per 10,000 Exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected blood transfusion</td>
<td>9,250</td>
</tr>
<tr>
<td>Receptive anal intercourse</td>
<td>138</td>
</tr>
<tr>
<td>Needle-sharing during IV drug use</td>
<td>63</td>
</tr>
<tr>
<td>Needle-stick</td>
<td>23</td>
</tr>
<tr>
<td>Insertive anal intercourse</td>
<td>11</td>
</tr>
<tr>
<td>Receptive penile-vaginal intercourse</td>
<td>8</td>
</tr>
<tr>
<td>Insertive penile-vaginal intercourse</td>
<td>4</td>
</tr>
</tbody>
</table>

A. Factors that may increase the risk of transmission:
   a. Presence of sexually transmitted diseases (STDs)
   b. Acute and late stages of HIV infection
   c. Elevated viral load
B. Factors that may decrease the risk of transmission:
   a. Condom use
   b. Male circumcision
   c. Antiretroviral treatment
   d. Pre-exposure prophylaxis (PrEP)

Diagnosis\textsuperscript{7}
A. Seroconversion
   a. Early detection of HIV infection relies on the host immune system to produce antibodies
      i. Eclipse period – time between infection and seroconversion; typically lasts around three weeks
      ii. HIV RNA is earliest marker of HIV which can be detected
      iii. p24 is the first antigen detected – utilized in the newest immunoassays
B. Types of HIV tests
   a. Antibody immunoassay
   b. Combination antigen and antibody immunoassay
   c. Nucleic acid test
      i. Has the earliest detection window, but is the most expensive
Stages of HIV infection

A. Stage 1: Acute HIV Syndrome
   a. Occurs within 2 to 4 weeks after infection
   b. Symptoms – occur in 50% of individuals
      i. GI disturbance
      ii. Fatigue
      iii. Fever
      iv. Headache
      v. Malaise
      vi. Sore throat
      vii. Swollen lymph glands
   c. Highly contagious due to profound viremia

B. Stage 2: Clinical Latency
   a. Virus is still present but replicating slowly
      i. CD4 count decreases slowly over time as the viral load increases
   b. Can last months to years
   c. Usually asymptomatic
   d. Patients can still transmit virus to others during this time
   e. With treatment, patients can remain latent for years

C. Stage 3: Acquired Immunodeficiency Syndrome (AIDS)
   a. Most severe stage
   b. Immune system is depleted, which puts patients at risk for opportunistic infections
   c. Viral load continues to increase
   d. Without treatment, patients have minimal survival past three years
   e. Common symptoms
      i. Chills
      ii. Fever
      iii. Sweats
      iv. Swollen lymph glands
      v. Weakness
      vi. Weight loss

D. HIV versus AIDS
   a. HIV is simply infection with the retrovirus
   b. AIDS occurs when the CD4 count is less than 200 cells/mL or when an opportunistic infection is present
      i. Uncontrolled HIV infection can lead to AIDS
      ii. Decreased CD4 count increases risk for opportunistic infections, such as:
         1. Kaposi’s sarcoma
         2. Mycobacterium avium complex infection (MAC)
         3. Pneumocystis jirovecii pneumonia (PCP)
         4. Thrush
         5. Toxoplasmosis encephalopathy (TE)
         6. Tuberculosis (TB)

Monitoring

A. Efficacy of treatment
   a. Plasma HIV RNA (viral load) – indicator of response to antiretroviral therapy (ART)
      i. Optimal viral suppression: undetectable HIV RNA
      ii. Treatment failure: HIV RNA > 200 copies/mL
   b. CD4 count – indicator of immune response to ART
      i. Shows need for opportunistic infection prophylaxis

B. Frequency of monitoring
   a. Every four to eight weeks following initiation or modification in therapy
   b. Every three months while on a stable, suppressive regimen
      i. May extend to six months after patient has been stable two years

C. Other tests that should be routinely monitored
   a. Metabolic panel
   b. Liver function tests
   c. Complete blood count with differential
   d. Urinalysis
   e. Fasting glucose or hemoglobin A1c
   f. Fasting lipid profile
HIV: human immunodeficiency virus; HAART: highly active antiretroviral therapy; CDC: Centers for Disease Control and Prevention; PCP: *Pneumocystis jirovecii* pneumonia; AIDS: acquired immunodeficiency syndrome; FDA: US Food and Drug Administration; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; CCR-5: C-C chemokine receptor type 5; INSTI: integrase strand inhibitor.

Figure 1: Timeline of HIV History and Treatment\(^{11,12}\)

- **1981-82**: CDC publishes reports describing an outbreak of PCP in Los Angeles and coins the term AIDS.
- **1984**: National Cancer Institute identifies HIV.
- **1987**: FDA approves first antiretroviral ZDV, an NRTI.
- **1988-94**: FDA approves additional NRTIs: ddI, ddC, d4T.
- **1995**: 3TC gains accelerated approval for use with ZDV; FDA approves first PI SQV.
- **1996**: FDA approves first NNRTI NVP.
- **1998**: FDA approves EFV and ABC; CDC releases the first guidelines for use of antiretroviral therapy.
- **1999**: TDF receives accelerated FDA approval; HAART becomes the standard of care.
- **2001**: FDA approves two NRTI combination tablets: Epzicom® (3TC/ABC) and Truvada® (FTC/TDF).
- **2003**: FDA approves Fuzeon® (T-20), ATV, and FTC.
- **2004**: FDA approves Selzentry® (MVC), a CCR-5 antagonist.
- **2006**: FDA approves first single tablet regimen Atripla® (EFV/FTC/TDF); Guidelines add FTC/TDF to ZDV/3TC as a preferred NRTI backbone.
- **2007**: FDA approves the first INSTI RAL; Guidelines add FTC/TDF to preferred regimens.
- **2008**: FDA approves Selzentry® (MVC), a CCR-5 antagonist; Guidelines add 3TC/ABC to preferred NRTI backbones.
- **2009**: FDA approves first single tablet regimen with an INSTI Stridob™ (EVG/c/FTC/TDF); Guidelines recommend treating all patients who test positive regardless of CD4 count.
- **2011**: FDA approves Complera® (RPV/FTC/TDF); Guidelines reclassify 3TC/ZDV as an alternative NRTI backbone.
- **2012**: FDA approves Triumeq® (DTG/3TC/ABC); Guidelines add all INSTI-containing regimens as preferred agents.
- **2013**: ATV-containing regimens move to alternate therapy options in the guidelines.
- **2014**: FDA approves DTG.
Improvements in Survival

A. Advancements in the understanding and treatment of HIV and opportunistic infections has increased the life expectancy of people living with HIV
   a. Before antiretrovirals, survival was limited, especially with presence of opportunistic infections
   b. Patients treated with mono- or dual-therapy in the early 1990s survived approximately eight years after diagnosis
   c. With the advent of HAART and therapy improvements over the years, patients now can survive at least 55 years after diagnosis

Guideline Recommendation Review

A. Since the first antiretroviral treatment guidelines were released in 1998, the recommendation has been to use a combination of three drugs
   a. Two NRTI “backbone”
   b. One agent from the following classes: INSTI, PI, NNRTI
B. FTC/TDF (Truvada) has been a preferred or recommended regimen since 2006
   a. At the end of 2014, there have been approximately 7.5 million patient years of TDF prescribed globally since approval in 2001
   b. The WHO lists EFV/FTC/TDF as the preferred regimen for adults and estimates more than 70% of patients are on this preferred regimen globally

COMPLICATIONS OF NRTI TREATMENT

Bone Toxicity

A. A decrease in bone mineral density (BMD) occurs with initiation of any antiretroviral regimen, but TDF is associated with the greatest change

Table 3: Evaluation of TDF Effects on BMD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoy JF, et al.</td>
<td>Randomized, multicenter study of a subpopulation of the START trial –</td>
<td>399 subjects, 83.7% on TDF. Greater BMD decreases seen in hip and spine with early ART initiation compared to deferred initiation. Greatest loss in spine was seen in the first 48 weeks then stabilized; hip declined steadily over 2 years.</td>
</tr>
<tr>
<td>START–BMD</td>
<td>compared changes in BMD between early ART initiation and deferred ART</td>
<td>initiation over 3 years.</td>
</tr>
<tr>
<td></td>
<td>initiation over 3 years.</td>
<td></td>
</tr>
<tr>
<td>Stellbrink HJ,</td>
<td>Randomized, open-label, multicenter study – evaluated changes in BMD</td>
<td>385 subjects. BMD loss was observed in both groups, but a statistically significant greater loss was seen in the EFV/FTC/TDF group. There was also an increased proportion of patients in the EFV/FTC/TDF group with a greater than 6% decrease in BMD from baseline.</td>
</tr>
<tr>
<td>et al. ASSERT</td>
<td>from baseline for treatment-naïve patients started on either EFV + 3TC/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABC or EFV/FTC/TDF over 48 weeks.</td>
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</tbody>
</table>

B. Proposed mechanisms of bone loss with TDF
   a. Urinary phosphate wasting and renal osteodystrophy
   b. Increased bone turnover
      i. Elevated markers include serum type 1 procollagen N-terminal (P1NP), osteocalcin, and alkaline phosphatase
   c. Induced mitochondrial toxicity
C. Disease-state related risk factors for decreased BMD
   a. Low nadir CD4 counts at initiation of antiretroviral
   b. HIV-related immune activation increasing levels of inflammatory cytokines
Renal Toxicity\textsuperscript{27} 

A. Tenofovir is renally excreted by a combination of glomerular filtration and active tubular secretion via multidrug resistant protein 4 (MDRP-4) 
   a. Decreases creatinine clearance (CrCl) during the initial 48 weeks of treatment, and stabilizes thereafter 
   b. Found to increase urinary markers of tubule dysfunction 
      i. Albumin to creatinine ratio 
      ii. β2-microglobulin to creatinine ratio 
      iii. Protein to creatinine ratio 
      iv. Retinol binding protein to creatinine ratio 

B. Initial clinical trials of TDF did not show a significant occurrence of renal adverse events 
   a. Early trials excluded patients with baseline renal dysfunction 
   b. Case reports describing the occurrence of serious renal events (acute renal failure requiring dialysis, Fanconi’s syndrome, renal tubular dysfunction, progressive decline in renal function) were published following FDA approval 

Table 4: Evaluation of TDF Effects on Renal Function

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cooper RD, et al.\textsuperscript{28}</td>
<td>Meta-analysis comparing the change in renal function between TDF-containing regimens and non-TDF regimens, focusing on change in eCrCl.</td>
<td>10,899 subjects from 17 studies. Found TDF-containing ART regimens were associated with a greater loss in renal function compared to non-TDF regimens, as well as an increased risk for acute renal failure.</td>
</tr>
<tr>
<td>Goicoechea M, et al.\textsuperscript{29}</td>
<td>Subpopulation of a prospective, randomized trial which examined the change in eCrCl over 48 weeks in patients receiving a RTV-boosted PI + TDF, NNRTI + TDF, or non-TDF containing regimens.</td>
<td>146 subjects. Found that patients receiving RTV-boosted PI + TDF regimens had a greater decline in eCrCl at 48 weeks compared to those receiving NNRTI + TDF regimens.</td>
</tr>
<tr>
<td>Post FA, et al. ASSERT\textsuperscript{27}</td>
<td>Randomized, open-label, multicenter study – evaluated changes in eGFR and renal tubule markers from baseline for treatment-naïve patients started on either 3TC/ABC + EFV or EFV/FTC/TDF over 48 weeks.</td>
<td>385 subjects. No difference in eGFR was seen between the two groups, but a statistically significant increase in renal tubule markers was seen in the EFV/FTC/TDF group from baseline.</td>
</tr>
</tbody>
</table>

C. Possible risk factors for development of renal dysfunction with TDF\textsuperscript{30} 
   a. Co-administration of RTV-boosted PI\textsuperscript{29} 
   b. Co-administration of other nephrotoxic drugs 
   c. Older age 
   d. More advanced HIV-1 infection 
   e. Lower body mass 
   f. Baseline impaired renal function
TENOFOVIR ALAFENAMIDE (TAF)

Overview
A. Tenofovir alafenamide (TAF) first approved in November of 2015
   a. Gilead has released several combination tablets containing TAF
      i. November 2015: Genvoya® (EVG/c/FTC/TAF)
      ii. March 2016: Odefsey® (RVP/FTC/TAF)
      iii. April 2016: Descovy® (FTC/TAF)
B. Novel pro-drug of tenofovir
   a. Converted to the active form within peripheral blood mononuclear cells and other lymphatic tissues via hydrolysis
   b. Increased stability in plasma compared to TDF, resulting in a 90% reduction in circulating levels and dose
      i. Decreased levels proposed to decrease incidence of undesirable renal and bone effects associated with TDF
C. 2016 and 2017 HIV treatment guidelines
   a. Recommend FTC/TDF or FTC/TAF in preferred regimens
   b. Allow practitioners to switch between the two due to the favorable safety profile of TAF
   c. 2017 guidelines recommend TAF or ABC in patients who cannot receive TDF due to renal dysfunction or osteoporosis
D. Approved for patients with a CrCl of ≥ 30 mL/min (TDF requires dose adjustments at ≤ 50 mL/min)

Table 5: Use of TAF in Renal Impairment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post FA, et al.</td>
<td>Open-label, single-arm, multicenter cohort study of patients with a eCrCl of 30-69 mL/min evaluating changes in eCrCl and renal tubule markers after switch to EVG/c/FTC/TAF</td>
<td>242 subjects. At 48 and 96 weeks, there was no change in eCrCl after switch to EVG/c/FTC/TAF. There was a statistically significant improvement in renal tubule markers compared to baseline in patients who were previously on TDF-containing regimens.</td>
</tr>
</tbody>
</table>

E. Over the last three years, at several studies have compared TDF regimens to TAF regimens with regards to efficacy and safety

CLINICAL QUESTION

In an era with a safer alternative, should TDF still be used for long-term management of HIV infection in:
A. Treatment-naïve patients?
B. Treatment-experienced patients?
A. Trial overview

**Figure 2:** Treatment-naïve – EVG/c/FTC/TDF versus EVG/c/FTC/TAF


**Figure 3:** Treatment-experienced – FTC/TDF → FTC/TAF


**Figure 4:** Treatment-experienced – TDF regimen → EVG/c/FTC/TAF


# Treatment-Naïve

## Table 5: Trials 1a & 1b – EVG/c/FTC/TDF versus EVG/c/FTC/TAF\(^{35,36}\)

<table>
<thead>
<tr>
<th><strong>Overview</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
<td>To compare the efficacy, renal toxicity, and bone toxicity of tenofovir alafenamide versus tenofovir disoproxil fumarate in treatment naïve patients with HIV at 48 and 144 weeks</td>
</tr>
</tbody>
</table>
| **Trial design** | Two non-inferiority, randomized, double-blind, multicenter, active-controlled, phase 3 trials  
• One conducted at 134 sites in North America, Europe, Australia, Japan, and Thailand  
• One conducted at 128 sites in North America, Europe, and Latin America  
• Randomization occurred between January 22, 2013, to November 4, 2013  
• Patients from both trials continued to be followed through week 144 of treatment |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • Age ≥ 18 years  
• Diagnosed with HIV-1  
• No previous antiretroviral treatment  
• HIV-1 RNA ≥ 1000 copies/mL  
• eCrCl ≥ 50 mL/min  
• Genotype screening showing sensitivity to EVG, FTC, and TFV | • Positive hepatitis B surface antigen  
• Positive hepatitis C antibody  
• New AIDS-defining illness within 30 days of screening |
| **Intervention** | 1:1 randomization to the following groups:  
• TAF Group: EVG/c/FTC/TAF + placebo  
• TDF Group: EVG/c/FTC/TDF + placebo |
| **Endpoints** |  |
| **Primary Endpoint** | • Proportion of patients who had plasma HIV-1 RNA less than 50 copies/mL at week 48  
• Treatment failures included patients lost to follow-up and those who discontinued the study drug for any reason in the modified intent-to-treat population analyzed |
| **Secondary Endpoints** | • Proportion with plasma HIV-1 RNA less than 20 copies/mL  
• Percentage change from baseline in CD4 count  
• Safety  
• Percentage change from baseline in hip and spine BMD  
• Change from baseline in serum creatinine  
• Treatment-emergent proteinuria via percentage change from baseline in:  
  • Urine retinol binding protein to creatinine ratio  
  • Urine β2-microglobulin to creatinine ratio  
  • Urine protein to creatinine ratio  
  • Urine albumin to creatinine ratio |
| **Statistical Analysis** |  |
| • Non-inferiority margin set at 12%; one-sided α of 0.025  
• Sample size of 840 patients provided at least 95% power to establish non-inferiority assuming an overall treatment response rate of 85%  
• Appropriate tests were used to secondary endpoints |
| **Results** |  |
| **Baseline Characteristics** | 866 randomized to TAF group, 867 randomized to TDF group  
• Similar between the two groups  
• Gender: 15% female  
• Ethnicity: 56/57% white  
• Similar rates of retention through week 144  
• TAF: 85% (729)  
• TDF: 82% (694) |
### Endpoints

#### 48-Week Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF % (n) n = 866</th>
<th>TDF % (n) n = 867</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 50 copies/mL</td>
<td>92% (800)</td>
<td>90% (784)</td>
<td>-0.7 – 4.7%</td>
<td>---</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 20 copies/mL</td>
<td>84.4%</td>
<td>84%</td>
<td>-3 – 3%</td>
<td>0.83</td>
</tr>
<tr>
<td>Increase in CD4 count</td>
<td>230 (SD 177.3)</td>
<td>211 (SD 170.7)</td>
<td>3 – 36 cells/mL</td>
<td>0.024</td>
</tr>
<tr>
<td>Virologic failure with resistance</td>
<td>0.8% (7)</td>
<td>0.6% (5)</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

#### 144-Week Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF % (n) n = 866</th>
<th>TDF % (n) n = 867</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 50 copies/mL</td>
<td>84.2% (729)</td>
<td>80% (694)</td>
<td>0.6 – 7.8%</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 20 copies/mL</td>
<td>81.1%</td>
<td>75.8%</td>
<td>1.5 – 9.2%</td>
<td></td>
</tr>
<tr>
<td>Increase in CD4 count</td>
<td>326 (SD 215.3)</td>
<td>305 (SD 204.5)</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Virologic failure with resistance</td>
<td>1.4% (12)</td>
<td>1.4% (12)</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

### Safety

#### 48-Week Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF n = 866</th>
<th>TDF n = 867</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip bone density</td>
<td>-0.66 (SD 3.26)</td>
<td>-2.95% (SD 3.41)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Spine bone density</td>
<td>-1.3% (SD 3.08)</td>
<td>-2.86 (SD 3.25)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>eCrCl</td>
<td>-6.2 mL/min</td>
<td>-11.2 mL/min</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine retinol binding protein to creatinine ratio</td>
<td>+9</td>
<td>+51</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urine β2-microglobulin to creatinine ratio</td>
<td>-32</td>
<td>+24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio</td>
<td>-3</td>
<td>+20</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urine albumin to creatinine ratio</td>
<td>-5</td>
<td>+7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Other side effects which occurred at similar rates between the two groups, included: diarrhea, nausea, headache, upper respiratory tract infection
- Number of patients who discontinued study drug due to serious adverse events deemed related to the study drug:
  - TAF: 7 (0.8%), 0 due to renal adverse events
  - TDF: 11 (1.3%), 4 due to renal adverse events
<table>
<thead>
<tr>
<th>Endpoint Change from Baseline</th>
<th>TAF n = 866</th>
<th>TDF n = 867</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip bone density</td>
<td>-0.75%</td>
<td>-3.36%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spine bone density</td>
<td>-0.92%</td>
<td>-2.95%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>eCrCl</td>
<td>-1.6 mL/min</td>
<td>-7.7 mL/min</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% of participants with ≥ 25% decrease in CrCl from baseline</td>
<td>17.6%</td>
<td>33.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine retinol binding protein to creatinine ratio</td>
<td>+34.8</td>
<td>+111</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine β2-microglobulin to creatinine ratio</td>
<td>-25.7</td>
<td>+53.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio</td>
<td>-10.5</td>
<td>+25.2</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Other side effects which occurred at similar rates between the two groups, included: diarrhea, nausea, headache, upper respiratory tract infection
- Number of patients who discontinued study drug due to serious adverse events deemed related to the study drug:
  - TAF: 11 (1.3%), 0 due to renal adverse events
  - TDF: 29 (3.3%), 12 due to renal adverse events

**Author’s Conclusion**

48-weeks: Treatment with a coformulated tablet including TAF was non-inferior with more favorable bone and renal effects than treatment with the same formulation with TDF.

144-weeks: Continued treatment with TAF coformulated with EVG/c/FTC demonstrated continued viral suppression and a more favorable safety profile compared to TDF.

**Strengths**

- Large study population
- Power set and met
- Appropriate non-inferiority margin
- Utilized standard evaluation of efficacy for HIV medications
- Only difference between intervention was TDF or TAF
- Long follow-up period – nearly three years of data
- Utilized similar markers to assess renal and bone toxicity which were used previously for TDF

**Limitations**

- Funded by Gilead Sciences
- Not powered to assess safety endpoints or any endpoints past initial 48-weeks
- Cannot generalize to treatment-experienced patients or those with baseline renal dysfunction

**Take Home**

After three years of treatment, the TAF-containing regimen is associated with decreased bone and renal toxicity compared to the TDF-containing regimen while maintaining efficacy in suppression of HIV viral load in treatment-naïve patients.
### Treatment-Experienced

#### Table 6: Trials 2a & 2b – FTC/TDF → FTC/TAF\(^{37,38}\)

<table>
<thead>
<tr>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
</tr>
<tr>
<td>To assess the safety and efficacy of fixed-dose combination FTC with TAF in virologically suppressed patients switched from FTC with TDF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized, double-blind, active-controlled phase 3 trial from 78 sites in North America and Europe</td>
</tr>
<tr>
<td>Randomization occurred between May 6, 2011, and September 11, 2014</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥ 18 years</td>
</tr>
<tr>
<td>• Virologically suppressed (HIV-1 RNA &lt; 50 copies/mL) for at least 6 months</td>
</tr>
<tr>
<td>• On regimens containing fixed-dose FTC and TDF</td>
</tr>
<tr>
<td>• eCrCl &gt; 50 mL/min</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1:1 randomization to the following groups:</td>
</tr>
<tr>
<td>o TAF group: switch to received fixed-dose FTC/TAF with the same third agent as the original regimen + placebo</td>
</tr>
<tr>
<td>▪ Ritonavir-boosted PI: TAF 10 mg + FTC 200 mg</td>
</tr>
<tr>
<td>▪ Other third agents: TAF 25 mg + FTC 200 mg</td>
</tr>
<tr>
<td>o TDF group: continue same regimen of fixed-dose FTC/TDF with third agent + placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Proportion of patients with plasma HIV-1 RNA &lt; 50 copies/mL at week 48</td>
</tr>
<tr>
<td>o Treatment failures included patients lost to follow-up and those who discontinued the study drug for any reason.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Percentage change in hip and spine BMD</td>
</tr>
<tr>
<td>• Change from baseline in serum creatinine</td>
</tr>
<tr>
<td>• Proportion of patients with HIV-1 RNA &lt; 20 copies/mL</td>
</tr>
<tr>
<td>• Change from baseline in CD4 cell count</td>
</tr>
<tr>
<td>• Proteinuria via percentage change from baseline in:</td>
</tr>
<tr>
<td>▪ Urine retinol binding protein to creatinine ratio</td>
</tr>
<tr>
<td>▪ Urine β2-microglobulin to creatinine ratio</td>
</tr>
<tr>
<td>▪ Urine protein to creatinine ratio</td>
</tr>
<tr>
<td>▪ Urine albumin to creatinine ratio</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-inferiority margin set at 10%</td>
</tr>
<tr>
<td>• One-sided α set at 0.025</td>
</tr>
<tr>
<td>• A sample size of 660 patients provided 95% power to establish non-inferiority assuming an 87% response rate for both groups at week 48</td>
</tr>
<tr>
<td>• Appropriate tests were used to assess secondary endpoints</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 333 randomized to the TAF group, 330 randomized to the TDF group</td>
</tr>
<tr>
<td>• Similar characteristics between the two groups</td>
</tr>
<tr>
<td>o Median age: 49 years</td>
</tr>
<tr>
<td>o Gender: 14% (TAF) and 16% (TDF) women</td>
</tr>
<tr>
<td>o Race: 73% (TAF) and 77% (TDF) white</td>
</tr>
<tr>
<td>o Third agent: 47% (TAF) and 45% (TDF) boosted protease inhibitors</td>
</tr>
<tr>
<td>• Similar rates of retention through week 96</td>
</tr>
<tr>
<td>o TAF: 93.4% (311)</td>
</tr>
<tr>
<td>o TDF: 91.5% (302)</td>
</tr>
</tbody>
</table>

---

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### Endpoints

#### 48-Week Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF % (n) n = 333</th>
<th>TDF % (n) n = 330</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 50 copies/mL</td>
<td>94% (314)</td>
<td>93% (307)</td>
<td>-2.5 – 5.1%</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 20 copies/mL</td>
<td>92% (305)</td>
<td>91% (300)</td>
<td>-3.7 – 5.1%</td>
</tr>
<tr>
<td>Median increase in CD4 count</td>
<td>20 cells/µL</td>
<td>21 cells/µL</td>
<td>---</td>
</tr>
<tr>
<td>Virolologic failure with resistance</td>
<td>0.003% (1)</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

#### 96-Week Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF % (n) n = 333</th>
<th>TDF % (n) n = 330</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 50 copies/mL</td>
<td>88.6% (295)</td>
<td>89.1% (294)</td>
<td>-5.3 – 4.4%</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median increase in CD4 count</td>
<td>44 cells/µL</td>
<td>33 cells/µL</td>
<td>---</td>
</tr>
<tr>
<td>Virolologic failure with resistance</td>
<td>0.003% (1)</td>
<td>0</td>
<td>---</td>
</tr>
</tbody>
</table>

### Safety

#### 48-Week Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF n = 866</th>
<th>TDF n = 867</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone Density</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip bone density</td>
<td>+1.527%</td>
<td>-0.206%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spine bone density</td>
<td>+1.135%</td>
<td>-0.152%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Renal Function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>-0.08 mg/dL (SD 0.238)</td>
<td>-0.04 mg/dL (SD 0.126)</td>
<td>0.005</td>
</tr>
<tr>
<td>eCrCl</td>
<td>+8.4 mL/min</td>
<td>+2.8 mL/min</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Renal Protein Markers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine retinol binding protein to creatinine ratio</td>
<td>-16%</td>
<td>+18%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urine β2-microglobulin to creatinine ratio</td>
<td>-40%</td>
<td>+22%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urine protein to creatinine ratio</td>
<td>-15%</td>
<td>+8%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Urine albumin to creatinine ratio</td>
<td>-8%</td>
<td>+12%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Safety</td>
<td>96-Week Results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td><strong>TAF</strong>&lt;br&gt;n = 866</td>
<td><strong>TDF</strong>&lt;br&gt;n = 867</td>
<td><strong>p-value</strong></td>
</tr>
<tr>
<td>Bone Density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip bone density</td>
<td>+1.9%</td>
<td>-0.3%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Spine bone density</td>
<td>+2.2%</td>
<td>-0.2%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Renal Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>eCrCl</strong></td>
<td>+10 mL/min</td>
<td>+4 mL/min</td>
<td>---</td>
</tr>
<tr>
<td>Renal Protein Markers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine retinol binding protein to creatinine ratio</td>
<td>+42.6</td>
<td>-4.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine β2-microglobulin to creatinine ratio</td>
<td>+46.8</td>
<td>-29.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

- Other side effects which occurred at similar rates between the two groups, included: upper respiratory tract infection, diarrhea, headache, nasopharyngitis
- Number of patients who discontinued study drug due to serious adverse events deemed related to the study drug:
  - TAF: 2 (1%), 0 due to renal adverse events
  - TDF: 3 (1%), 1 due to renal adverse events

**Author’s Conclusion**

- **48-weeks:** Switching from regimens containing fixed-dose FTC/TDF to fixed-dose FTC/TAF was associated with maintenance of virological suppression with non-inferior virological efficacy and overall tolerability, along with improvement in markers of renal and bone toxicity
- **96-weeks:** The combination of FTC and TAF has the potential to be an important NRTI backbone in the treatment of patients with HIV, and the flexibility to be combined with a variety of third agents with safety advantages over FTC/TDF.

**Strengths**

- Power set and met
- Appropriate non-inferiority margin
- Utilized standard evaluation of efficacy for HIV medications
- Long-term follow-up (almost two years) of the same patient populations allows for continued comparison
- Provides insight for clinical decision making for treatment-experienced patients on TDF-containing regimens
- Utilized similar markers to assess renal and bone toxicity which were used previously for TDF

**Limitations**

- Funded by Gilead Sciences
- Specific details of previous regimens were not reported
- Not powered to assess safety endpoints or any endpoints past 48-weeks

**Take Home**

Switching patients currently on a TDF-containing regimen to a TAF-containing regimen does not compromise efficacy and results in improvement in BMD and renal markers through 96-weeks of treatment

**Table 7: Trial 3 – TDF Regimen → EVG/c/FTC/TAF**

<table>
<thead>
<tr>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
</tr>
<tr>
<td><strong>Trial design</strong></td>
</tr>
</tbody>
</table>
  - Recruited HIV-1 infected adults from previous Gilead clinical studies
  - Randomization occurred between April 12, 2013, through April 3, 2014 |
**Trial Design**

**Inclusion Criteria**
- Age ≥ 18 years
- Virologically suppressed (HIV-1 RNA < 50 copies/mL)
- On one of four regimens containing fixed-dose FTC and TDF:
  - EVG/c/FTC/TDF
  - ATV/c + FTC/TDF
  - EFV/FTC/TDF
  - ATV/r + FTC/TDF
- eCrCl > 50 mL/min

**Intervention**
- 2:1 randomization to the following groups:
  - TAF group: switched to single-tablet containing EVG/c/FTC/TAF
  - TDF group: continue one of the original regimens, listed above

**Endpoints**

**Primary Endpoint**
- Proportion of patients with plasma HIV-1 RNA < 50 copies/mL at week 48

**Secondary Endpoints**
- Proportion of patients with HIV-1 RNA < 20 copies/mL
- Change from baseline in CD4 cell count
- Percentage change in hip and spine BMD
- Change from baseline in serum creatinine
- Proteinuria via percentage change from baseline in:
  - Urine retinol binding protein to creatinine ratio
  - Urine β2-microglobulin to creatinine ratio
  - Urine protein to creatinine ratio
  - Urine albumin to creatinine ratio

**Statistical Analysis**
- Non-inferiority margin set at -12%
- One-sided α set at 0.025
- A sample size of 1436 patients provided greater than 99% power to establish non-inferiority assuming a 90% response rate for both groups at week 48
- Appropriate tests were used for secondary endpoints

**Results**

**Baseline Characteristics**
- 959 randomized to the TAF group, 477 randomized to the TDF group
- Similar characteristics between the two groups
  - Median age: 40 years
  - Gender: 11% (TAF) and 10% (TDF) women
  - Race: 68% (TAF) and 66% (TDF) white
  - Exception: Hispanic or Latino ethnic origin (TAF 26%, TDF 17%; p = 0.006)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF, % (n) n = 959</th>
<th>TDF, % (n) n = 477</th>
<th>Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 50 copies/mL</td>
<td>97% (932)</td>
<td>93% (444)</td>
<td>1.6 – 6.7%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA ≤ 20 copies/mL</td>
<td>94% (897)</td>
<td>90% (431)</td>
<td>0.1 – 6.3%</td>
<td>---</td>
</tr>
<tr>
<td>Median increase in CD4 count</td>
<td>35 cells/µL (SD 165)</td>
<td>24 cells/µL (SD 156)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Virologic failure with resistance</td>
<td>0.001% (1)</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

1Patient was re-suppressed to < 50 copies/mL 4 weeks later without a change in treatment
### Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TAF, % (n)</th>
<th>TDF, % (n)</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVG/COBI/FTC/TDF</td>
<td>98% (301/306)</td>
<td>97% (149/153)</td>
<td>-1.9 – 3.9%</td>
</tr>
<tr>
<td>EVF/FTC/TDF</td>
<td>96% (241/251)</td>
<td>90% (112/125)</td>
<td>0.5 – 12.3%</td>
</tr>
<tr>
<td>ATV/r or c + FTC/TDF</td>
<td>97% (390/402)</td>
<td>92% (183/199)</td>
<td>0.9 – 9.2%</td>
</tr>
</tbody>
</table>

### Safety

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Change from Baseline</th>
<th>TAF, % (n)</th>
<th>TDF, % (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip bone density</td>
<td>+1.47%</td>
<td>-0.34%</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Spine bone density</td>
<td>+1.56%</td>
<td>-0.44%</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean serum creatinine (Excluding EFV)</td>
<td>-0.4 µmol/L</td>
<td>+2.9 µmol/L</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (EFV only)</td>
<td>+9.2 µmol/L¹</td>
<td>+1.77 µmol/L</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>eCrCl (Excluding EFV)</td>
<td>+1.2 mL/min</td>
<td>-3.7 mL/min</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Urine retinol binding protein to creatinine ratio</td>
<td>-33.4%</td>
<td>+18.1%</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Urine β2-microglobulin to creatinine ratio</td>
<td>-52.3%</td>
<td>+18.7%</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Urine protein to creatinine ratio</td>
<td>-20.9%</td>
<td>+9.6%</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Urine albumin to creatinine ratio</td>
<td>-17.9%</td>
<td>+8.5%</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

¹Consistent with the established COBI effect on inhibition of serum creatinine excretion when initiating

- Other side effects which occurred at similar rates between the two groups, included: upper respiratory tract infection, diarrhea, nasopharyngitis, headache
- Number of patients who discontinued study drug due to serious adverse events deemed related to the study drug:
  - TAF: 9 (1%), 2 due to renal adverse events
  - TDF: 12 (3%), 5 due to renal adverse events
- Greater median increase in total cholesterol, HDL, LDL, and triglycerides in the TAF group compared to the TDF group (p< 0.001). However, minimal differences were seen in the total cholesterol to HDL ratio between the two groups (p = 0.004)

### Author’s Conclusion

Virologically suppressed HIV-1 infected patients who switched to a TAF-containing regimen maintained virological suppression at a statistically higher rate at 48 weeks with significant improvements in bone and renal safety

### Strengths

- Large sample size with high power to detect a difference
- Appropriate non-inferiority margin
- Utilized standard evaluation of efficacy for HIV medications
- Utilized similar markers to assess renal and bone toxicity which were used previously for TDF

### Limitations

- Funded by Gilead Sciences
- Open-label study
- Not powered to assess safety endpoints

### Take Home

Patients who are taking one of the four studied regimens containing FTC/TDF can switch to EVG/c/FTC/TAF with an improvement in efficacy and the potential for improvement in renal and bone safety compared with those who continue on their original TDF-containing regimen
EVIDENCE SUMMARY

Treatment-naïve
A. TAF containing regimens are safer with similar efficacy to TDF-containing regimens

Treatment-experienced
A. Switching to TAF-containing regimens from TDF-containing regimens maintains efficacy and results in improvement in markers of renal and bone toxicity historically associated with TDF
B. EVG/c/FTC/TAF offers superiority over some older regimens containing EFV or boosted ATV

RECOMMENDATIONS

A. Treatment-naïve patients
   a. TAF-containing regimens preferred over TDF-containing regimens
      i. Currently, there is not enough evidence available to recommend FTC/TAF over 3TC/ABC regimens
   b. Patient specific factors to consider:
      i. Genotypic resistance profile
      ii. Renal dysfunction: guidelines recommend TAF or ABC-containing regimens
      iii. Pre-existing osteopenia or osteoporosis: guidelines recommend TAF or ABC-containing regimens
      iv. Cost of TAF-containing medications

B. Treatment-experienced patients
   a. Whether to switch or not depends on the patient’s current regimen
      i. Patients on a TDF single tablet regimen with an identical TAF single tablet regimen available should be switched to TAF as soon as feasible
      ii. Patients on co-formulated FTC/TDF (Truvada®) should be switched to co-formulated FTC/TAF (Descovy®) as soon as feasible
      iii. Patients on regimens which do not contain TDF should not be switched at this time
         1. Currently, there is not enough evidence available to recommend FTC/TAF over 3TC/ABC regimens
      iv. Patients with moderately impaired renal function (CrCl ≥ 15 mL/min) or decreased BMD
         1. If patients are on a TDF-containing regimen, they should be switched as soon as feasible
         2. If patients are not on a TDF-containing regimen, switching to a TAF-containing regimen is not recommended at this time due to lack of evidence
   b. Other patient specific factors to consider
      i. Ability to take multiple tablets a day
      ii. Genotypic resistance profile
      iii. Cost of TAF-containing regimen compared to current regimen

C. Global perspective
   a. The WHO lists EFV/FTC/TDF as their preferred regimen
   b. TAF may not be preferred in regions with limited resources
      i. For regions where TAF-containing single tablet regimens are accessible, reasonable to recommend these over TDF if cost permits
   c. TDF has historically been one of the most widely distributed HIV medications to these regions, so it is currently still preferred due to its cost, ease of access, and recognizability

FUTURE CONSIDERATIONS

A. TDF patent expiring December 2017
   a. Generic versions could provide a more cost-effective alternative when combined with other generic NRTIs
   b. TAF patent will expire December 2022

B. Additional single tablet regimens containing TAF will likely be released
REFERENCES


density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results


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APPENDICES

A. Important abbreviations

General Abbreviations
1. AIDS: acquired immune deficiency syndrome
2. ART: antiretroviral therapy
3. BMD: bone mineral density
4. CDC: Centers for Disease Control and Prevention
5. DNA: deoxyribonucleic acid
6. eCrCl: estimated creatinine clearance
7. eGFR: estimated glomerular filtration rate
8. FDA: US Food & Drug Administration
9. GI: gastrointestinal
10. HAART: highly active antiretroviral therapy
11. HIV: human immunodeficiency virus
13. PEP: post-exposure prophylaxis
14. RNA: ribonucleic acid
15. WHO: World Health Organization

Classes of Antiretrovirals
1. INSTI: integrase strand inhibitor
2. NRTI: nucleoside reverse transcriptase inhibitor
3. NNRTI: non-nucleoside reverse transcriptase inhibitor
4. PI: protease inhibitor

Antiretroviral Agents
Entry Inhibitors
1. MVC: maraviroc (Selzentry®)

Fusion Inhibitors
1. T-20: enfuvirtide (Fuzeon®)

Brand Names of Antiretrovirals
Single tablet regimens
1. Atripla® (EFV/FTC/TDF)
2. Triumeq® (DTG/3TC/ABC)
3. Genvoya® (EVG/c/FTC/TAF)
4. Striolland® (EVG/c/FTC/TF)
5. Complera® (RPV/FTC/TDF)
6. Odefsey® (RPV/FTC/TAF)

Antiretroviral Agents (continued)
INSTIs
1. DTG: dolutegravir (Tivicay®)
2. EVG: elvitegravir (Vitekta®)
3. RAL: raltegravir (Isentress®)

NNRTIs
1. EFV: efavirenz (Sustiva®)
2. NVP: nevirapine (Viramune®)
3. RPV: rilpivirine (Edurant®)

NNRTIs
1. 3TC: lamivudine (Epivir®)
2. ABC: abacavir (Ziagen®)
3. d4T: stavudine (Zerit®)
4. ddC: zalcitabine (Hivid®)
5. ddf: didanosine (Videx®)
6. FTC: emtricitabine (Emtriva®)
7. TAF: tenofovir alafenamide (Vemlidy®)
8. TDF: tenofovir disoproxil fumarate (Viread®)
9. ZDV: zidovudine (Retrovir®)

PIs
1. ATV: atazanavir (Reyataz®)
2. DRV: darunavir (Prezista®)
3. RTV or /r: ritonavir (Norvir®)
4. SQV: saquinavir (Invirase®)

CYP-450 Inhibitor (Booster)
1. COBI or /c: cobicistat

Combination tablets
1. Combivir® (3TC/ZDV)
2. Descovy® (FTC/TAF)
3. Epzicom® (3TC/ABC)
4. Truvada® (FTC/TDF)