Don’t Break My HAART: Breaking Away from Triple Drug Therapies Among Virologically Suppressed HIV-1 Infected Patients

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Learning Objectives:

1. Identify management strategies to improve clinical outcomes in HIV-1 infection
2. Evaluate literature pertaining to the utility of dual antiretroviral maintenance therapy for HIV-1 infection
3. Identify appropriate patients in whom to consider a switch to dual therapy for the maintenance of virologic suppression
I) Human Immunodeficiency Virus (HIV)\(^1\)

**A) Genome**

i) Retrovirus: Ribonucleic acid (RNA) genome

ii) Lentivirus characterized by long incubation periods capable of producing a wide range of pathologies

**B) HIV-1 vs. HIV-2**

i) Type 1
   a) Increased virulence
   b) Majority of HIV infections globally

ii) Type 2
   a) Less infectious
   b) Immunodeficiency develops slowly
   c) Predominantly found in Sub-Saharan Africa
   d) Increased incidence of HIV-associated wasting syndrome
   e) Decreased response to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs)

**C) Viral structure**

![HIV structure](https://www.projectinform.org/wp-content/uploads/2016/05/HIV-Genome-2-688x535.jpg)

i) Lipid bilayer embedded with transmembrane and surface proteins
   a) Transmembrane fusion peptide = glycoprotein 41 (Gp41)
   b) Surface protein = glycoprotein 120 (Gp120)

ii) Nucleocapsid contains viral genome and three enzymes vital to HIV life cycle
   a) Reverse transcriptase: Transcribes viral RNA genome into complementary deoxyribonucleic acid (DNA)
   b) Integrase: Facilitates incorporation of pro-viral DNA into host cell genome
   c) Protease: Cleaves viral polypeptide into individual functional enzymes

**D) Host cell**

i) CD4 T lymphocyte
   a) Regulate immune response via activation of B-lymphocytes, cytotoxic T cells and macrophages
   b) Mediate the host defense against the following pathogens: bacteria, fungi, and protozoa
E) Acquisition of HIV infection

i) Attachment and cell entry
   a) HIV requires two binding events to enter the CD4 cell cytoplasm
      • HIV utilizes Gp120 to attach to CD4 receptor
      • Following attachment, Gp120 assumes a conformational change, allowing it to bind to chemokine coreceptors on the CD4 cell membrane (CCR5 and/or CXCR4)
   b) Binding of Gp120 to chemokine coreceptors enables fusion of viral and CD4 lipid membranes

ii) Transcription
   a) Once within the cytoplasm, viral RNA genome is transcribed into pro-viral DNA

iii) Integration
   a) Pro-viral DNA is transported from the cytoplasm into the host cell nucleus where it is incorporated into the host genome in preparation for viral replication
      • Viral integration requires: processing, joining, and post-integration repair
   b) Stable integration of pro-viral DNA into the human genome is essential for completing the HIV life cycle

iv) CD4 count decline following infection
   a) CD4 count and CD4% are both strong predictors of clinical disease progression
   b) CD4 count declines by approximately 50-80 cells/µL annually without antiretroviral therapy (ART)
   c) Degree of CD4 depletion correlates with development of opportunistic infection (OI)
   d) Immune response significantly impaired when CD4 cell count falls < 200 cells/µL or CD4% < 14%

II) Phases of HIV Infection*6

A) Acute HIV syndrome
   i) Initial stage of HIV infection
      a) Approximately 2–6 weeks after HIV infection
   ii) Wide dissemination of HIV particles and a rapid decrease in CD4 cell count
   iii) Seroconversion
      a) Host may experience short, flu-like illness as the immune system begins to produce anti-HIV antibodies
B) Clinical latency
   i) Asymptomatic stage of HIV infection
   ii) Immune response post-infection
      a) Anti-HIV antibodies are produced approximately 6-12 weeks after infection
      b) CD8 cytotoxic lymphocytes target and destroy HIV-infected CD4 cells
      c) Decrease in viral replication and CD4 cell turnover
      d) Duration of clinical latency phase is highly variable
         • Individuals may remain in clinical latency phase up to 10 years without ART

C) Acquired immune deficiency syndrome (AIDS)
   i) Final stage of HIV infection
   ii) Defined as: CD4 count < 200 cells/µL, CD4% < 14%, or development of an AIDS-defining condition (Table 1)
   iii) Without ART, individuals with HIV eventually develop progressive immunodeficiency marked by CD4 cell depletion and premature death
   iv) Life expectancy is approximately 3 years without ART

<table>
<thead>
<tr>
<th>Infection</th>
<th>Organism</th>
<th>Clinical Manifestation</th>
<th>At Risk Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jirovecii pneumonia (PCP)</td>
<td>Yeast</td>
<td>Pneumonia</td>
<td>CD4 &lt; 200 cells/ µL</td>
</tr>
<tr>
<td>Kaposi’s sarcoma</td>
<td>Virus</td>
<td>Skin cancer</td>
<td>CD4 &lt; 350 cells/ µL</td>
</tr>
<tr>
<td>Toxoplasmosis gondii encephalitis</td>
<td>Protozoa</td>
<td>Encephalitis</td>
<td>CD4 &lt; 100 cells/ µL</td>
</tr>
<tr>
<td>Mycobacterium avium complex (MAC)</td>
<td>Bacteria</td>
<td>Pulmonary manifestations</td>
<td>CD4 &lt; 50 cells/ µL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated disease</td>
<td></td>
</tr>
</tbody>
</table>

III) Historical Perspective of Antiretroviral Therapy (ART)⁴⁻¹⁵

A) HIV/AIDS epidemic within the United States (U.S.)
   i) June 1981: 5 cases of immunodeficiency syndrome (biopsy confirmed PCP)
   ii) July 1981: 26 cases of Kaposi’s sarcoma
   iii) August 1981: Centers for Disease Control and Prevention (CDC) begin tracking cases of Kaposi’s sarcoma and PCP
      a) Fall of 1981: 100 cases
      b) February 1983: 1,000 cases
      c) December 1983: 3,000 cases
      d) October 1995: 500,000 cases
         • AIDS becomes the leading cause of death among persons 25 to 44 years of age

B) Introduction of ART (Table 2)

<table>
<thead>
<tr>
<th>Year</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>FDA approves the first antiretroviral agent, zidovudine</td>
</tr>
<tr>
<td></td>
<td>• Nucleoside monotherapy associated with virologic failure beyond 12 weeks</td>
</tr>
<tr>
<td>1992</td>
<td>FDA begins accelerated approval for HIV/AIDS related therapies</td>
</tr>
<tr>
<td></td>
<td>• Rapid access to multiple nucleosides</td>
</tr>
<tr>
<td></td>
<td>• Dual nucleoside therapy is introduced</td>
</tr>
<tr>
<td></td>
<td>o Use associated with transient virologic suppression in HIV infected individuals with high viral loads</td>
</tr>
<tr>
<td></td>
<td>o HIV incidence and mortality rates continue to rise</td>
</tr>
<tr>
<td>1995</td>
<td>FDA approves the first PI, saquinavir</td>
</tr>
<tr>
<td>1996</td>
<td>FDA approves the first NNRTI, nevirapine</td>
</tr>
</tbody>
</table>
C) Triple Therapy
   i) Coined “highly active antiretroviral therapy” (HAART)
   ii) Composed of 2 nucleoside reverse transcriptase inhibitors (NRTI) + 1 NNRTI or PI
   iii) INCAS Study: Introduced in 1996 by Montaner et al. at the 11th annual International AIDS Conference
      a) Triple therapy utilizing nevirapine + didanosine + zidovudine is associated with superior viral load suppression compared to dual therapy with zidovudine + didanosine or zidovudine + nevirapine
      b) HIV-1 RNA < 20 copies/mL at 52 weeks (51% vs. 12% vs. 0%; p < 0.001) respectively
   iv) HAART is incorporated into clinical practice
      a) HIV/AIDS-associated mortality declines for the first time since viral emergence
         • 73% decline in AIDS related OI
         • 70% decline in AIDS related death
      b) Life expectancy post-HIV infection increased from 9 years in 1995 to 23.6 years in 2002
         • With triple therapy resulting in longer lifespans, ageing patients with HIV experienced a reduction in deaths from OIs but an increase in mortality associated with chronic comorbidities (Table 3)

<table>
<thead>
<tr>
<th>Table 3: Mortality Associated with Chronic Comorbidities Among HIV-infected Persons in the U.S.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>Mortality Rate</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>18%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>18%</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>16%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>12%</td>
</tr>
<tr>
<td>GI disorders</td>
<td>11%</td>
</tr>
<tr>
<td>Infection</td>
<td>10%</td>
</tr>
<tr>
<td>Non-AIDS-related cancers</td>
<td>8%</td>
</tr>
</tbody>
</table>
Table 4: ART by Class

### Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acronym</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>ABC</td>
<td>• Inhibit reverse transcriptase conversion of viral RNA to pro-viral DNA</td>
<td>• Lactic acidosis</td>
</tr>
<tr>
<td>Tenofovir disoproxil fumarate</td>
<td>TDF</td>
<td>• Nucleos(t)ide analogue is incorporated into growing viral DNA strand causing early strand termination</td>
<td>• Hepatic steatosis</td>
</tr>
<tr>
<td>Tenofovir alafenamide fumarate</td>
<td>TAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>FTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine</td>
<td>3TC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine</td>
<td>DDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>AZT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine</td>
<td>D4T</td>
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</tbody>
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### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acronym</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine</td>
<td>RPV</td>
<td>• Inhibit reverse transcriptase conversion of viral RNA to pro-viral DNA</td>
<td>• Rash</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>EFV</td>
<td>• Blocks allosteric site on reverse transcriptase</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>NVP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>ETR</td>
<td></td>
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</table>

### Protease inhibitors (PIs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acronym</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>ATV</td>
<td>• Inhibit formation of mature virion particle by preventing proteolytic cleavage of viral polyprotein into individual functional proteins</td>
<td>• Hyperlipidemia</td>
</tr>
<tr>
<td>Darunavir</td>
<td>DRV</td>
<td></td>
<td>• Hyperbilirubinemia</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>LPV</td>
<td></td>
<td>• Lipohypertrophy</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>RTV</td>
<td></td>
<td>• GI intolerance</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>TPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>IDV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>NFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>FPV</td>
<td></td>
<td></td>
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<tr>
<td>Saquinavir</td>
<td>SQV</td>
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</tbody>
</table>
Integrase Strand Transfer Inhibitors (INSTI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acronym</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>DTG</td>
<td>• Inhibit insertion of pro-viral DNA into host genome</td>
<td>• Myopathy</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>RAL</td>
<td></td>
<td>• Insomnia</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>EVG</td>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Suicidality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hepatotoxicity</td>
</tr>
</tbody>
</table>

Cell Entry and Fusion Inhibitor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acronym</th>
<th>Mechanism</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>MCV</td>
<td>• Binds to active site on CCR5 co-receptor, inhibiting viral particles from entering CD4 cell</td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Requires CCR5 tropism assay to determine efficacy</td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>T-20</td>
<td>• Binds to Gp41, a glycoprotein on the surface of the HIV particle, and inhibits Gp41-mediated fusion of viral and CD4 cellular membranes</td>
<td>• Bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Injection site reactions</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic Enhancers/Boosters

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acronym</th>
<th>Mechanism</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobicistat</td>
<td>COBI</td>
<td>• Potent CYP3A4 inhibitor</td>
<td>Enhances systemic exposure of substrates</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>RTV</td>
<td>• Potent CYP3A4 and P-glycoprotein inhibitor</td>
<td>Enhances systemic exposure of substrates</td>
</tr>
</tbody>
</table>

V) Guideline Recommended Treatment Approach

A) Definition of adequate ART regimen
   i) At least 2, but preferably 3, fully active agents from different antiretroviral classes
      a) Regimens with less than 2 fully active agents are less likely to achieve virologic suppression and may promote resistance
      b) A fully active agent is one that is expected to have uncompromised antiviral activity based on patient’s treatment history (Hx) as well as current/past drug-resistance testing

B) Goals of ART
   i) Viral suppression
   ii) Restore or preserve immunologic function
   iii) Reduce HIV-associated morbidity/mortality
   iv) Prevent HIV transmission
   v) Improve quality of life
      a) Minimize drug-related toxicities
      b) Improve tolerability and convenience of ART
      c) Manage drug-drug and/or drug-disease interactions

C) Guideline recommended initial regimens for the general population with HIV (Table 5)
   i) Listed regimens have demonstrated high antiviral activity and favorable side effect profiles in clinical trials
   ii) Each regimen consists of two NRTIs and one integrase strand transfer inhibitor (INSTI)

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NRTI</th>
<th>INSTI</th>
<th>Level of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF or TDF</td>
<td>FTC or 3TC</td>
<td>DTG</td>
<td>(AII) for TDF; (AII) for TAF</td>
</tr>
<tr>
<td>TAF or TDF</td>
<td>FTC</td>
<td>EVG/CObI</td>
<td>(AII) if HLA-B*5701 negative</td>
</tr>
<tr>
<td>TAF or TDF</td>
<td>FTC or 3TC</td>
<td>RAL</td>
<td>(AI) for TDF; (AII) for TAF</td>
</tr>
<tr>
<td>ABC</td>
<td>FTC or 3TC</td>
<td>DTG</td>
<td>(AI)</td>
</tr>
</tbody>
</table>

AI: Strong recommendation based on one or more randomized trials with clinical outcomes and/or validated laboratory endpoints
AII: Strong recommendation based on one or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes
D) Tenofovir/emtricitabine (TDF/FTC) remains the preferred dual NRTI backbone
   i) Recommended in 3 of the 4 preferred regimens for treatment naïve individuals
      a) Up to 80% of all treated patients living with HIV/AIDS are taking a tenofovir-containing regimen
   ii) Benefits of tenofovir/emtricitabine combination
      a) Potent antiviral activity
      b) Well tolerated
      c) Limited drug-drug interactions (DDIs)
      d) Co-formulated as a once daily pill (Truvada®)
      e) Anti-HBV activity
      f) Improved lipid parameters (TDF)
   iii) TDF warnings/precautions
      a) TDF-induced tubular toxicity
         • TDF is excreted in urine both by glomerular filtration and active tubular secretion
         • Co-administration of TDF with other drugs also eliminated by active tubular secretion increase TDF concentration via competitive inhibition
         • Accumulation of TDF depletes mitochondrial DNA within tubular cells leading to oxidative respiratory chain dysfunction and epithelial cell apoptosis
         • Nephrotoxicity may result in one of the following:
            (i) Slow progressive decline in creatinine clearance (CrCl) due to long term exposure
                1. CrCl < 30 ml/min requires intermittent dosing
            (ii) Drug-induced Fanconi Syndrome (rare)
                1. Dysfunctional transport within the proximal tubules leads to urinary wasting of solutes
               • See Appendix A for a summary of trials evaluating TDF-induced kidney injury
               • See Appendix B for risk factors associated with TDF-induced kidney injury
      b) TDF-induced decrease in bone mineral density (BMD)
         • TDF-induced impairment of tubular function leads to decreased 1α hydroxylation of vitamin D
            (i) Net effect lowers tubular reabsorption of vitamin D–binding protein
         • See Appendix C for a summary of trials evaluating TDF-induced bone density loss
   iv) TDF vs. TAF: Impact on renal function and bone mineralization
      a) TDF and TAF are both prodrugs of tenofovir diphosphate (TFV)
      b) When compared to TDF, TAF has shown greater distribution into lymphoid tissues, reducing systemic exposure of TFV by 86%
      c) TAF was found to have smaller increases in serum creatinine, less proteinuria, and smaller BMD declines when compared to TDF:
         • Change in serum creatinine (+0.08 vs. +0.11 mg/dL; p < 0.001)
         • Proteinuria (-3 vs. +20; p < 0.001)
         • Lumbar spine BMD decline (-1.30 vs. -2.86; p < 0.0001)
         • Total hip BMD decline (-0.66 vs. -2.95; p < 0.0001)
         • TAF contraindicated in CrCl < 30 ml/min

E) INSTIs emerge as the preferred third agent
   i) Recommended in all 4 guideline preferred regimens for treatment naïve individuals
      a) High virologic efficacy
         • Insertion of pro-viral DNA into the human genome is the final step in acquisition of persistent HIV infection
         • INSTIs associated with rapid and durable viral load suppression
            (i) Hoenigl et al. demonstrated INSTI-based regimens significantly reduced the time to viral suppression compared to boosted-PI based regimens (12 weeks vs. 24 weeks; p = 0.022)
b) High genetic barrier to resistance
   • First generation INSTIs, raltegravir and elvitegravir, share similar resistance profiles and a high degree of cross-resistance
   • Dolutegravir, a second generation INSTI, exhibits a high genetic barrier to resistance
     (i) In integrase-naive subjects with a Hx of virologic failure, dolutegravir exhibited lower rates of drug resistant mutations and higher rates of virologic suppression compared to raltegravir:
       1. Resistant mutations (1% vs. 4.7%; 95% CI -6.1% – -1.2%)
       2. Virologic suppression (71% vs. 64%; 95% CI 0.7 – 14.2)

c) Limited potential for DDIs
   • Raltegravir and dolutegravir bypass CYP450 system
     (i) metabolized via UDP-glucuronosyltransferase (UGT) pathway
   • Elvitegravir/cobicistat has greater potential for DDIs due to cobicistat’s CYP450 inhibition

d) Limited effects on lipid concentrations
e) Utility in patients with renal impairment

ii) INSTI warnings/precautions
a) Increased risk of depression/suicidality
   • Particularly in individuals with pre-existing psychiatric condition
b) Hepatotoxicity

c) Myopathy

VI) ART Considerations

A) HIV/hepatitis B virus (HBV) co-infection
   i) Estimated at 5 - 10% of the HIV-infected population in the United States
   ii) Persons with HIV/HBV coinfection and detectable viremia of both viruses are at increased risk of progression to cirrhosis, decompensated liver disease, and the development of hepatocellular carcinoma (HCC)
   iii) All patients should be assessed for HBV coinfection prior to ART initiation
      a) HBV reactivation may occur upon initiation of ART lacking anti-HBV activity
      b) Initial testing should include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total hepatitis B core antibody (anti-HBc)
      c) HBV reactivation should be considered in HBsAg-positive and anti-HBs-positive patients who experience elevated LFTs upon initiation of ART
   iv) The following are recommended for HIV/HBV co-infection (HBsAg positive)
      a) Quantitative serum HBV DNA testing to distinguish between active/inactive disease
   v) HIV/HBV co-infected individuals should receive a fully suppressive ART regimen that includes 2 agents with anti-HBV activity
      a) TDF, TAF, FTC, and 3TC are the only agents with anti-HBV activity
         • ART should include TDF or TAF in combination with FTC or 3TC
      b) Entecavir should be used in addition to a fully suppressive ART regimen in those unable to tolerate TAF or TDF
         • Entecavir and 3TC share overlapping pathways to HBV resistance (rtM204 mutation), it is unknown whether entecavir + 3TC or FTC will provide greater benefit than entecavir alone
         • Avoid 3TC or FTC as the only HBV-active agent in ART as HBV mutations can emerge rapidly when these drugs are used without a second drug active against HBV
   vi) HBV reactivation may occur upon discontinuation of ART with anti-HBV activity
      a) Discontinuation of ART active against HBV may cause hepatocellular damage and reactivation of HBV
      b) HBV reactivation should be considered in individuals who experience elevated LFTs upon discontinuation of ART
B) HLA-B*5701 allele
   i) Abacavir requires HLA-B*5701 genotype testing prior to initiation
      a) Use is contraindicated in HLA-B*5701-positive individuals due to the risk of an immune mediated
         hypersensitivity reaction
      b) HLA-B*5701 allele occurs at approximately 5% frequency in European populations, 1% in Asian
         populations, and less than 1% in African populations
      c) Symptoms include: Rash, nausea/vomiting, respiratory distress, and/or death

C) Metabolic abnormalities
   i) Compared to the general population, HIV infected adults are at increased risk of age-related chronic
      diseases
      a) HIV-infection stimulates a state of chronic inflammation, increasing the risks for the following:
         atherosclerotic cardiovascular disease (ASCVD), chronic obstructive pulmonary disease (COPD), and
         metabolic disorders
      b) ART related toxicities further compound the risk of ASCVD
         • Protease inhibitors, as a class, have been shown to adversely affect lipid and metabolic parameters
            (i) Use associated with lipohypertrophy, body-fat redistribution, hyperlipidemia, hypertriglyceridemia,
                insulin resistance, and an increased risk of MI

VII) Therapeutic Definitions

A) Virologic suppression
   i) Plasma RNA < 50 copies/mL

B) Virologic blip
   i) A single, transient increase in viral load > 50 copies/mL, in a patient who was previously suppressed
   ii) Does not necessitate an immediate change in ART
   iii) Possible causes include either other infections (e.g., influenza, herpes, etc.) or recent vaccinations

C) Virologic failure
   i) Two consecutive HIV RNA levels ≥ 200 copies/mL after 24 weeks on ART
   ii) Follow-up viral load must be at least 2-3 months after initial viral load to be considered diagnostic
   iii) Patients will require resistance testing followed by a change in ART regimen

D) Low-level viremia
   i) HIV RNA < 200 copies/mL
   ii) Risk of emerging resistance is believed to be relatively low
   iii) Patients do not require a change in ART regimen
   iv) Monitor HIV RNA every 3 months to assess the need for changes in ART in the future

E) Immune non-responders
   i) Immune non-responders are patients whose CD4 counts fail to rise appropriately on therapy, despite a
      suppressed viral load – “immunological discordance”
   ii) Patients do not require a change in ART regimen

F) Latent HIV Reservoir
   i) Despite effective ART, HIV often persists in a stable reservoir within resting CD4 cells
      a) Latently infected CD4 cells do not actively produce viral particles
      b) Latent HIV reservoirs can be found throughout the body (brain, lymph nodes, blood, and digestive tract)
      c) The reservoir persists even in patients on long-term ART who have no detectable viremia
   ii) Reservoir serves as a permanent archive for all wild-type and drug-resistant viruses that have circulated at
       significant levels
VIII) Clinical Question

A) Can maintenance of virologic suppression be achieved with dual therapy?

IX) Reasons to Consider Dual Therapy

A) Minimize drug-drug and/or drug-disease interactions
B) Improve tolerability of ART
C) Minimize cumulative drug exposure and reduce the risk of long-term drug toxicities

X) Goal of Dual Therapy

A) Maintain virologic suppression without jeopardizing future treatment options
B) FDA advises a noninferiority margin of 4% for virologic failure analysis

XI) Literature Review

A) Previous literature evaluating dual therapy in virologically suppressed HIV-1 infected patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Design</th>
<th>Population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAL-GESIDA</td>
<td>Darunavir/r + lamivudine vs.</td>
<td>Open-label, randomized, multi-center,</td>
<td>N = 249</td>
<td>DUAL-GESIDA met non-inferiority for the primary endpoint of HIV RNA &lt; 50 copies/mL but was not powered to detect non-inferiority for the secondary endpoint of virologic failure: • HIV RNA &lt; 50 copies/mL darunavir/r + lamivudine vs. darunavir/r + 2 NRTIs (88.9% vs. 92.7%; 95% CI -11.0 – 3.4) • Virologic failure (3% vs. 2%) One patient allocated to the darunavir/r + 2 NRTI group developed non-signature PI resistance associated mutations (L10I, A71T, L76W) Darunavir/r + lamivudine associated with a significant increase in total and LDL cholesterol in patients receiving TDF at baseline: • Total cholesterol (p&lt; 0.001) • LDL (p = 0.01)</td>
</tr>
<tr>
<td></td>
<td>darunavir/r + 2 NRTIs</td>
<td>non-inferiority clinical trial</td>
<td>• HIV RNA &lt; 50 copies/mL ≥ 6 months (mean 23 months) • HBV negative • No Hx of ART failure or drug resistant mutations</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-inferiority margin = 12%</td>
<td>• Required 128 participants per arm to achieve 80% power • Duration = 48 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N = 249</td>
<td></td>
</tr>
<tr>
<td>ATLAS-M</td>
<td>Atazanavir/r + lamivudine vs.</td>
<td>Open-label, randomized, multi-center,</td>
<td>N = 266</td>
<td>ATLAS-M met non-inferiority for the primary endpoint of HIV RNA &lt; 50 copies/mL but was not powered to detect non-inferiority for the secondary endpoint of virologic failure: • HIV RNA &lt; 50 copies/mL at 48 weeks (90.6% vs. 83.9%; 95% CI -1.5 – 14.9; p = 0.113) • HIV RNA &lt; 50 copies/mL at 96 weeks (77.8% vs. 65.6%; 95% CI -2 – 23.2) • Virologic failure (1.5% vs. 6.8%; p = 0.056) Atazanavir/r + lamivudine increased the risk of hypertriglyceridemia and hyperbilirubinemia • Hypertriglyceridemia (7.6% vs. 1.6%; p = 0.027) • Hyperbilirubinemia (59.6% vs. 35.8%; p = 0.001) Atazanavir/r + 2 NRTI was associated with a significant decline in GFR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Non-inferiority margin = 12%</td>
<td>• Duration = 96 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug Combination</td>
<td>Study Design</td>
<td>Participants</td>
<td>Results</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **OLE**              | Lopinavir/r + lamivudine vs.      | Open-label, randomized, multi-center, non-inferiority clinical trial         | N = 239      | - Change in eGFR (5 vs. -3; p<0.001)  
- No participants developed drug resistant mutations  
- OLE met non-inferiority for the primary endpoint of HIV RNA < 50 copies/mL but was not powered to detect non-inferiority for the secondary endpoint of virologic failure:  
  - HIV- RNA < 50 copies/mL lopinavir/r + lamivudine vs. lopinavir/r + 2 NRTI (87.8% vs. 86.6%; 95% CI -9.6 – 7.3; p=0.92)  
  - Virologic failure (5% vs. 5%)  
One participant allocated to the Lopinavir/r + lamivudine group developed NRTI drug resistant mutations (103Asn, 184Val):  
  - Hx of non-adherence to antiretroviral treatment with tenofovir, lamivudine, and efavirenz before entering the study  
  - Retrospective analysis of a saved sample showed 103Asn, 184Val, and 181Cys present at baseline  
Lopinavir/r + lamivudine was associated with a significant increase in total and LDL cholesterol:  
  - Total cholesterol (p=0.019)  
  - LDL cholesterol (p=0.008)  
Lopinavir/r + lamivudine associated with a significant increase in eGFR when compared to triple therapy (p=0.003)                                                                                     |
|                      | lopinavir/r + 2 NRTIs             |                                                                               |              |                                                                                                                                                                                                                                                                                                                                 |
|                      |                                   |                                                                               |              |                                                                                                                                                                                                                                                                                                                                 |
| **ARNS 167 LAMIDOL** | Dolutegravir + lamivudine        | Open label, single arm, multi-center pilot                                  | N = 104      | 97% of participants remained virologically suppressed                                                                                                                                  |
|                      |                                   |                                                                               |              |                                                                                                                                                                                                                                                                                                                                 |
| **HARNESS**          | Atazanavir/r + raltegravir vs.    | Open-label, randomized, multi-center, non-inferiority pilot                  | N = 109      | Atazanavir/r + raltegravir associated with higher rates of virologic failure and treatment discontinuation:  
  - HIV- RNA < 50 copies/mL (69.4% vs. 86.5%)  
  - Treatment discontinuation (77.8% vs. 86.5%)  
2 participants allocated to the atazanavir/r + raltegravir arm developed resistant mutations:  
  - INSTI drug resistant mutations (Y143C, N155H)  
  - PI and INSTI resistant mutations (L10V, G16Q, L33F, P39Q, M46L, G48V, Q58E, I62V, L63I/T, I64L, A71V, I72V, V77I, V82A, T91S, I93L) and (F121Y) |
|                      | Atazanavir/r + TDF/FTC            |                                                                               |              |                                                                                                                                                                                                                                                                                                                                 |
B) Current literature evaluating dual therapy in virologically suppressed HIV-1 infected patients

**SALT Trial**

**Objective**

Evaluate the efficacy of dual therapy with atazanavir/ritonavir plus lamivudine (ATV/r+3TC) vs. triple therapy with ATV/r plus 2 nucleos(t)ides for the maintenance of virologic suppression

**Study Design**

- Open-label, randomized, multi-center, non-inferiority clinical trial

**Methods**

- Participants randomized in a 1:1 fashion to receive ATV/r+3TC or ATV/r+2 nucleos(t)ides
  - Dual therapy arm:
    - 30 days of triple therapy with ATV/r + 2 nucleos(t)ides before switching to dual therapy with ATV/r + 3TC
    - Transition phase designed to prevent induction of ATV/r by EFV or NVP
  - Triple therapy arm:
    - ATV/r + TDF/FTC
    - ATV/r + ABC/3TC
    - ATV/r + AZT/3TC
- Virologic failure:
  - Two consecutive (≥ 14 days but < 30 days apart) HIV-1-RNA ≥ 50 copies/mL
  - Missing patients and changes in any study drug were also considered failures
- Non-adherence:
  - Adherence < 90% determined utilizing pill counts and a medication adherence questionnaire
- Non-inferiority margin = 12%
- Duration 96 weeks

**Inclusion Criteria**

- Age ≥ 18 years
- HIV RNA < 50 copies/mL ≥ 6 months
- Negative HBV surface antigen

**Exclusion Criteria**

- Switch in ART in previous 4 months before screening
- Hx of resistant mutations
- Previous Hx of ART failure

**Primary Endpoint**

- HIV-1 RNA < 50 copies/mL at 48 weeks

**Secondary Endpoints**

- HIV-1-RNA < 50 copies/mL at 96 weeks
- Virologic failure
- Viral load blip
- Change in CD4 T-cell count from baseline

**Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ATV/r + 3TC N=140</th>
<th>ATV/r + 2NUCs N=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (range)</td>
<td>45 (38–52)</td>
<td>42 (36–48)</td>
</tr>
<tr>
<td>Female sex</td>
<td>44 (31%)</td>
<td>32 (22%)</td>
</tr>
<tr>
<td>Previous AIDS-defining illness</td>
<td>37 (26%)</td>
<td>35 (24%)</td>
</tr>
<tr>
<td>Baseline CD4 count, cells/μL (range)</td>
<td>579 (397–770)</td>
<td>614 (443–796)</td>
</tr>
<tr>
<td>Duration of ART prior to randomization, months (range)</td>
<td>39.4 (26.7–62.3)</td>
<td>40.5 (22.3–67.2)</td>
</tr>
<tr>
<td>Duration of viral load &lt; 50 copies/mL pre-randomization, months (range)</td>
<td>27 (16–51)</td>
<td>29 (15–58)</td>
</tr>
<tr>
<td>Baseline NRTI Backbone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>119 (83%)</td>
<td>116 (81%)</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>21 (15%)</td>
<td>25 (16%)</td>
</tr>
<tr>
<td>Baseline 3rd-agent class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>47 (33%)</td>
<td>46 (32%)</td>
</tr>
<tr>
<td>Ritonavir-boosted PI</td>
<td>92 (64%)</td>
<td>94 (66%)</td>
</tr>
</tbody>
</table>

Demographic and key baseline characteristics were well matched across treatment groups
## Results

<table>
<thead>
<tr>
<th></th>
<th>ATV/r + 3TC N=133</th>
<th>ATV/r + 2NUCs N=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt; 50 copies/mL at 48 weeks</td>
<td>110 (83%)</td>
<td>104 (78%)</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt; 50 copies/mL at 96 weeks</td>
<td>99 (74.4%)</td>
<td>99 (73.9%)</td>
</tr>
<tr>
<td>Viral load blip not leading to treatment interruption</td>
<td>20 (15%)</td>
<td>23 (17%)</td>
</tr>
<tr>
<td>2 non-consecutive viral load blips not leading to treatment interruption</td>
<td>4 (3%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Virologic failure at 48 weeks</td>
<td>6 (4%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Virologic failure at 96 weeks</td>
<td>10 (7.5%)</td>
<td>7 (5.2%)</td>
</tr>
<tr>
<td>NRTI (M184V) and PI (L63P) resistant mutations</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Change in CD4 count, cells/μL</td>
<td>+19</td>
<td>+18</td>
</tr>
<tr>
<td>Adherence to study drug</td>
<td>128 (96%)</td>
<td>125 (93%)</td>
</tr>
</tbody>
</table>

1 Post randomization triple therapy arm: TDF/FTC = 75.6%; ABC/3TC = 23.8%; AZT/3TC = <1%
2 A single, transient increase in VL > 50 copies/mL followed by a subsequent return < 50 copies/mL

### Safety

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>ATV/r + 3TC N=140</th>
<th>ATV/r + 2NUCs N=141</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>99 (70.7%)</td>
<td>99 (70.2%)</td>
</tr>
<tr>
<td>Mean change in triglyceride from baseline1</td>
<td>+12.1%</td>
<td>-6.2% (p &lt; 0.003)</td>
</tr>
<tr>
<td>Grade 3-4 AE2</td>
<td>99 (70.7%)</td>
<td>99 (70.2%)</td>
</tr>
<tr>
<td>Hyperbiliurbinemia</td>
<td>91 (65%)</td>
<td>93 (65.9%)</td>
</tr>
<tr>
<td>Increased liver function tests (LFTs)</td>
<td>3 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>3 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>AEs leading to withdrawal from the study</td>
<td>7 (5%)</td>
<td>10 (7.1%)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

1Denotes statistical significance
2Severe or life-threatening AE

### Author’s Conclusion

Dual treatment with ritonavir-boosted atazanavir plus lamivudine is safe, effective, and well tolerated treatment strategy for patients with virologically suppressed HIV-1 infection. The long-term global efficacy was favorable and did not lead to the emergence of resistant mutations.

### Reviewer’s Critique

**Strengths**
- 96-week follow-up: longer than the 48 weeks seen in similar trials
- Majority of participants allocated to triple therapy were on TDF/FTC based regimens pre-and post-randomization
- Objective measure to assess adherence: pill count
- 30-day run in to decrease DDIs and establish tolerability

**Limitations**
- Not powered to detect 4% non-inferiority for rate of virologic failure
- Open-label design
- Small sample size

### Take Home

83% of participants allocated to the dual therapy arm maintained virologic suppression. This was enough to meet the pre-defined non-inferiority margin for the primary endpoint of virologic suppression. Rate of confirmed virologic failure was higher in the dual therapy arm. SALT was not powered to detect the more stringent noninferiority margin for virologic failure analysis. Dual therapy with atazanavir/ritonavir plus lamivudine was however, associated with a significant increase in triglycerides.
SWORD Studies

SWORD-1 and SWORD-2: Regimen switch to dolutegravir + rilpivirine from current antiretroviral regimen in HIV-1 infected and virologically suppressed adults

Objective
Evaluate the efficacy and safety of dual therapy with dolutegravir + rilpivirine (DTG + RPV) vs. triple therapy for maintenance of virologic suppression

Study Design
• Open label, randomized, multi-center, non-inferiority studies

Methods
• Participants randomized in a 1:1 fashion to receive DTG + RPV or continue with current ART
• Virologic failure
  o HIV-1-RNA ≥ 50 copies/mL and a second confirmatory VL ≥ 200 copies/mL
• Virologic success pre-defined non-inferiority margin of 8%
• Virologic failure complementary analysis pre-defined non-inferiority margin of 4% to maintain consistency with FDA guidelines
• Duration 48 weeks

Inclusion Criteria
• Age ≥ 18 years
• HIV RNA < 50 copies/mL for ≥ 12 months
• No previous ART failure
  o Defined as HIV-1 RNA ≥ 400 copies/mL after initial suppression < 50 copies/mL
• No more than one viral blip in the previous 12 months before screening
  o Defined as HIV RNA > 50 copies/mL but < 200 copies/mL
• No switch in ART in previous 6 months pre-screening
• Negative HBV surface antigen

Exclusion Criteria
• Hx of PI, INSTI, NRTI, or NNRTI resistance-associated mutation
• Hx of INSTI R263K resistance - associated substitution
• Severe hepatic impairment (Child-Pugh C)
• Anticipated need to receive hepatitis c virus (HCV) treatment during the study period
• Substantial suicidality risk (determined by the site investigator)
• QT interval ≥ 450 msec
• Pregnancy or breastfeeding

Primary Endpoint
• Participants with HIV-1 RNA < 50 copies/mL at 48 weeks

Secondary Endpoints
• Virologic failure
• Change in CD4 T-cell count from baseline

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV</th>
<th>Current ART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=513</td>
<td>N=511</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>43 (21-79)</td>
<td>43 (22-76)</td>
</tr>
<tr>
<td>Age ≥ 50 years</td>
<td>147 (29%)</td>
<td>142 (28%)</td>
</tr>
<tr>
<td>Female Sex</td>
<td>120 (23%)</td>
<td>108 (21%)</td>
</tr>
<tr>
<td>Baseline CD4 count, cells/μL (range)</td>
<td>611 (3-1774)</td>
<td>638 (9-1671)</td>
</tr>
<tr>
<td>≤ 500 cells/μL</td>
<td>165 (32%)</td>
<td>149 (29%)</td>
</tr>
<tr>
<td>Baseline TDF use</td>
<td>374 (73%)</td>
<td>359 (70%)</td>
</tr>
<tr>
<td>Baseline 3rd-agent class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI1</td>
<td>275 (54%)</td>
<td>278 (54%)</td>
</tr>
<tr>
<td>Ritonavir-boosted PI2</td>
<td>133 (26%)</td>
<td>136 (27%)</td>
</tr>
<tr>
<td>INSTI3</td>
<td>105 (20%)</td>
<td>97 (19%)</td>
</tr>
<tr>
<td>Median duration of ART prior to randomization, months (range)</td>
<td>51 (8-221)</td>
<td>53 (9-270)</td>
</tr>
</tbody>
</table>

1The most commonly reported NNRTI at baseline was efavirenz
2The most commonly reported protease inhibitor at baseline was darunavir/r
3The most commonly reported INSTI at baseline was raltegravir

Demographic and key baseline characteristics were well matched across treatment groups
### Results

<table>
<thead>
<tr>
<th></th>
<th>DTG + RPV</th>
<th>Current ART</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA &lt; 50 copies/mL</td>
<td>486 (95%)</td>
<td>485 (95%)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic failure</td>
<td>3 (&lt;1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>NNRTI (K101K/E) resistant mutations(^1)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
<tr>
<td>Change in CD4 cell count from baseline, cells/μL</td>
<td>+28</td>
<td>+22</td>
</tr>
<tr>
<td>Discontinued due to AE or death</td>
<td>17 (3%)</td>
<td>3 (&lt;1%)</td>
</tr>
</tbody>
</table>

\(^1\) One participant on DTG + RPV with confirmed poor adherence developed an NNRTI resistance associated substitution (K101K/E) with no loss in rilpivirine susceptibility (1.2-fold change). Participant was able to achieve viral load < 50 copies/mL again after re-establishing adherence; No INSTI resistance–associated mutations were identified.

### Safety

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>DTG + RPV N=513</th>
<th>Current ART N=511</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>395 (77%)</td>
<td>364 (71%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>49 (10%)</td>
<td>50 (10%)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (8%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24 (5%)</td>
<td>37 (7%)</td>
</tr>
<tr>
<td>Neuropsychiatric AEs</td>
<td>26 (5%)</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>AEs leading to withdrawal from the study</td>
<td>17 (3%)</td>
<td>3 (&lt;1%)</td>
</tr>
<tr>
<td>CNS AEs leading to withdrawal</td>
<td>9 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Deaths(^1)</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

\(^1\) Two deaths. Both unrelated to study drug. DTG+RPV Kaposi’s Sarcoma (N=1), current ART Lung cancer (N=1).

### Authors’ Conclusion

Dual therapy with dolutegravir plus rilpivirine provides an efficacious alternative to guideline-preferred triple drug regimens in patients with virologically suppressed HIV-1 infection without histories of resistance.

### Reviewer’s Critique

**Strengths**
- Largest study population for dual therapy
- Non-inferiority margins more stringent than the 12% used in previous trials: 10% for individual studies, 8% for pooled analysis, and 4% for virologic failure analysis
- Conducted midpoint futility analysis to ensure participants were not receiving suboptimal therapy
- High recruitment of commonly under-represented subpopulations (age ≥ 50 years, female sex)
- Strict reporting of adverse events: Volunteered by the participant, identified by investigator questioning participant, physical examination, or via laboratory analysis
- Robust follow up data collection

**Limitations**
- Open label design
- Subjective measure to assess adherence: Patient reported questionnaire
- Will require follow up studies to assess long-term efficacy beyond 48 weeks
- Baseline criteria did not assess the following:
  - Pre-ART CD4 count
  - Pre-ART viral load (VL)
  - Pre-randomization duration of VL < 50 copies/mL

### Take Home

Dual therapy with dolutegravir + rilpivirine was non-inferior to triple therapy for the maintenance of virologic suppression. 95% of participants across both treatment groups maintained virologic suppression. Dolutegravir + rilpivirine was not associated with an increased risk of drug resistant mutations or metabolic effects. Dolutegravir + rilpivirine was associated with a non-significant increase in neuropsychiatric adverse events.
II) Summary of Evidence

A) Clinical trials excluded patients with a history of treatment failure, drug resistant mutations, or HIV/HBV co-infection
B) Providers should have full access to patient’s ART history and any previous genotypic and phenotypic drug resistance
   i) Providers should use this information to determine drugs likely to have full vs. partial activity
C) If there is uncertainty about prior resistance, it would not be advisable to switch to dual therapy

III) Recommendations

A) Dual therapy with dolutegravir + rilpivirine may be considered among virologically suppressed HIV-1 infected individuals who require a change in ART due to toxicity. The following criteria must be met prior to switching to dual therapy:
   i) On stable ART
   ii) HIV RNA < 50 copies/mL
   iii) Unable to tolerate daily tenofovir administration
      a) TDF: CrCl < 30ml/min or osteoporosis diagnosis
      b) TAF: CrCl < 30ml/min
   iv) Unable to tolerate abacavir-containing ART
      a) HLA-B*5701 positive
   v) HBV negative
      a) Dolutegravir + rilpivirine has no activity against HBV
   vi) No Hx of INSTI or NNRTI failure
   vii) No Hx of INSTI or NNRTI resistance-associated mutation
   viii) Stable mental health evaluation
B) Although dual therapy with boosted-PI based regimens met non-inferiority for virologic suppression, these trials were not designed to detect the more stringent 4% noninferiority margin for virologic failure analysis recommended by the FDA. Furthermore, boosted-PI regimens have been associated with an increased risk of metabolic side effects making them a less favorable option than dolutegravir + rilpivirine
   i) Dual therapy utilizing boosted-PI based regimens may be considered in the following patient population:
      a) On stable boosted-PI regimen ≥ 6 months
      b) HIV RNA < 50 copies/mL for ≥ 6 months
      c) Unable to tolerate daily tenofovir administration
         • TDF: CrCl < 30ml/min or osteoporosis diagnosis
         • TAF: CrCl < 30ml/min
      d) Unable to tolerate abacavir-containing ART
         • HLA-B*5701 positive
      e) HBV negative
      f) No Hx of PI or NRTI failure
      g) No Hx of PI or NRTI resistance-associated mutation
C) Suggested post-switch monitoring
   i) Patients should be evaluated more closely for several months following modification of ART before resuming previous monitoring schedule
      a) Adherence and tolerability
         • Clinic visit or phone call 2 weeks post switch
         • Dolutegravir + rilpivirine must be taken with a meal for full absorption
      b) Efficacy and response to treatment
         • HIV RNA 4-8 weeks post switch to assess efficacy
            (i) Ensure HIV RNA remains < 50 copies/mL
      c) Routine laboratory testing within 3 months
References


XIV) Appendices

Appendix A: Trials evaluating TDF-induced Kidney Injury (Table 7)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallant JE et al.</td>
<td>Prospective study evaluating TDF’s effect on creatinine clearance (CrCl)</td>
<td>N = 658</td>
<td>1 year</td>
<td>TDF associated with significantly greater decline in CrCl (-13.3 ml/min vs. -7.5ml/min; p = 0.005)</td>
</tr>
<tr>
<td>Scherzer R et al.</td>
<td>Retrospective study evaluating TDF’s effects on proteinuria, eGFR, and progression to chronic kidney disease (CKD)</td>
<td>N = 10,841</td>
<td>5.5 years</td>
<td>Each year of TDF-exposure increased the risk of proteinuria and CKD:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 4,303 with TDF exposure</td>
<td></td>
<td>• Proteinuria (HR 1.3; 95% CI 1.22-1.37; p&lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 6,538 controls</td>
<td></td>
<td>• CKD (HR 1.33; 95% CI 1.18-1.51; p&lt;0.0001)</td>
</tr>
<tr>
<td>Montenegro-Chu MO et al.</td>
<td>Retrospective study evaluating effect of TDF on progression to advanced stages of CKD in patients with and without baseline renal impairment</td>
<td>N = 230</td>
<td>10 years</td>
<td>TDF-exposure was associated with an increased risk of CKD progression:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 111 with TDF exposure</td>
<td></td>
<td>• Progression from CKD-1 to CKD-2 (48.8% vs. 23.7%; p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 119 controls</td>
<td></td>
<td>• Progression from CKD-1 to CKD-3 (5.8% vs. 0.0%; p = 0.028)</td>
</tr>
</tbody>
</table>

Table 7: Summary of Trials Evaluating TDF-induced Kidney Injury

Appendix B: Risk factors for TDF-induced nephrotoxicity (Table 8)

### Table 8: Risk Factors for TDF-Induced Nephrotoxicity

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-existing renal dysfunction</td>
<td>17.4</td>
<td>p = 0.018</td>
</tr>
<tr>
<td>Concomitant use of nephrotoxic medications</td>
<td>2.40</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Advanced age</td>
<td>1.05</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Advanced HIV-infection</td>
<td>0.46 for each additional WHO stage</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

Appendix C: Trials evaluating TDF-induced decrease in BMD (Table 9)

### Table 9: Summary of Trials Evaluating TDF-induced Bone Density Loss

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective</th>
<th>Population</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASSERT Study</strong>42</td>
<td>Prospective trial evaluating the effects of TDF/FTC + EFV vs. ABC/3TC + EFV on BMD and markers of bone mineral turnover</td>
<td>N = 385</td>
<td>48 weeks</td>
<td>Participants allocated to TDF/FTC + EFV experienced greater BMD declines at total hip and lumbar spine (LS): • Total hip (-3.6% vs. -1.9%; p &lt; 0.001) • LS (-2.4% vs. -1.6%; p = 0.036) • BMD loss ≥ 6% more common with TDF/FTC • Hip = 13% vs. 3% • Spine = 15% vs. 5% • Decrease in LS BMD stabilized at 24 weeks • Decrease in hip BMD ongoing through week 48 • Osteopenia or osteoporosis was not reported</td>
</tr>
<tr>
<td><strong>START Bone Mineral Density Sub-study</strong>43</td>
<td>Retrospective trial evaluating effects of immediate vs. deferred ART initiation on BMD</td>
<td>N = 399</td>
<td>2.2 years</td>
<td>Immediate ART initiation resulted in greater BMD declines at femoral neck, total hip, and lumbar spine • Femoral neck (–3% vs. –1.4%; 95% CI –2.6 to –0.8; p &lt; 0.001) • Total hip (–2.5% vs. –1.0%; 95% CI –2.2 to –0.8; p &lt; 0.001) • Lumbar spine (–1.9% vs. –0.4%; 95% CI –2.2 to –1.0; p &lt; 0.001) • BMD declines were greatest in the first year of ART</td>
</tr>
</tbody>
</table>

Appendix D: Recommended initial therapy based on specific clinical scenarios (Table 10)

### Table 10: Recommended Initial Therapy Based on Specific Clinical Scenarios

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Avoid</th>
<th>Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count &lt; 200 cells/µL</td>
<td>• RPV-based regimens</td>
<td>• DRV/r + DTG</td>
</tr>
<tr>
<td>HIV RNA &gt; 100,000 copies/mL</td>
<td>• RPV-based regimens</td>
<td>• DRV/r + DTG</td>
</tr>
<tr>
<td></td>
<td>• DRV/r + DTG</td>
<td>• ABC or TAF</td>
</tr>
<tr>
<td></td>
<td>• ABC/3TC + EFV or ATV</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>• TDF and ATV</td>
<td>• ABC or TAF</td>
</tr>
<tr>
<td>Liver impairment</td>
<td>• NVP, ATV, ABC, DRV, NFV, SQV, TPV, DTG, EVG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FPV and IDV require dose adjustments</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>• TDF</td>
<td>• ABC or TAF</td>
</tr>
<tr>
<td>Psychiatric condition</td>
<td>• EFV and RPV</td>
<td>• ABC or TAF</td>
</tr>
<tr>
<td></td>
<td>• Monitor patients on INSTI based regimens</td>
<td></td>
</tr>
<tr>
<td>HIV-associated dementia</td>
<td>• EFV</td>
<td>• DTG or DRV</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>• ABC and LPV</td>
<td>• DTG, RAL, or RPV</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>• PIs, EFV, EVG, or TAF</td>
<td>• DTG, RAL, RPV, or TDF</td>
</tr>
<tr>
<td>HIV/HBV co-infection</td>
<td></td>
<td>• See section VIII of handout</td>
</tr>
<tr>
<td>TB treatment</td>
<td>• TAF with any rifamycin containing regimen</td>
<td>• EFV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RAL requires dose adjustments</td>
</tr>
</tbody>
</table>