When to okay Tivicay®:
Is the latest HIV agent just another “me too” drug?

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In collaboration with Centro San Vicente Clinic
PGY1 Community Pharmacy Resident

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Learning Objectives
By the end of this presentation, you will be able to:
1. Identify the HIV cell cycle and how HIV medication classes target certain aspects of this cycle.
2. Apply current HIV guidelines and determine when to begin HIV therapy.
3. Determine appropriate antiretroviral regimens for newly diagnosed, treatment naïve HIV patients.
4. Evaluate the impact of existing literature on HIV agents and their place in therapy.
5. Promote HIV awareness with a focus on health disparities in the Hispanic population and identify a pharmacist’s role in striving for health equity.
I. Background
A. Definitions
1. Human Immunodeficiency Virus (HIV): Any HIV-infected individual
2. Acquired Immunodeficiency Syndrome (AIDS): HIV-infected individuals with CD4 counts <200 cells/µL (or CD4 percentage <14%) or with certain HIV-related conditions/symptoms (Refer to Appendix A)
3. The U.S. Centers for Disease Control and Prevention (CDC) Classification System

<table>
<thead>
<tr>
<th>CD4 Cell Count Categories</th>
<th>Clinical Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) ≥500 cells/µL</td>
<td>A Asymptomatic, Acute HIV, or PGL</td>
</tr>
<tr>
<td>(2) 200-499 cells/µL</td>
<td>B Symptomatic Conditions, not A or C</td>
</tr>
<tr>
<td>(3) &lt;200 cells/µL</td>
<td>C AIDS-indicator Conditions</td>
</tr>
</tbody>
</table>

- PGL= persistent generalized lymphadenopathy; Y Refer to Appendix A; £ Refer to Appendix A

4. The World Health Organization (WHO) Clinical Staging (Refer to Appendix B)

B. Epidemiology
1. Prevalence: Estimated 1,148,200 people (13 years old and older) in 2009 living with HIV in the U.S., including 207,600 (18.1%) undiagnosed cases
2. Incidence: Approximately 50,000 people newly infected with HIV each year in the U.S.
3. In 2011, AIDS was diagnosed in 32,052 people living in the U.S.
4. Texas: Estimated 4,265 HIV diagnoses and 2,541 AIDS diagnoses in 2012 – Texas is the 3rd highest HIV diagnoses state in the U.S. as of 2011 (Refer to Appendix C)
5. El Paso: In 2012, 116 HIV diagnoses and 61 AIDS diagnoses – out of all the counties in Texas, El Paso is the 6th highest county with HIV cases
6. Health Disparity: HIV in Hispanics
   - In 2010, new HIV diagnoses among Hispanics occurred at an annual rate 2.8 times that of Non-Hispanic Whites
   - U.S. Demographics and HIV Cases

- Texas and El Paso Demographics (Refer to Appendix C)
C. **CDC Healthy People 2020 Goals**

1. **Reduce the rate of HIV transmission** among adolescents (10-19 years old) and adults
   - Baseline (2006): 4.6 new HIV infections transmitted per 100 persons living with HIV
   - Goal (2020): 3.5 new infections per 100 persons living with HIV
2. **Reduce new AIDS cases** among adolescents and adults
   - Baseline (2007): 13.8 new AIDS cases diagnosed per 100,000 population, ≥13 years old
   - Goal (2020): 12.4 new cases of AIDS per 100,000 population
3. **Reduce deaths** from HIV infection
   - Baseline (2007): 3.7 deaths due to HIV infection per 100,000 population
   - Goal (2020): 3.3 deaths due to HIV infection per 100,000 population

D. **Risk Factors**

1. Men having sex with men (MSM) – accounted for 61% of all new HIV infections in 2009
2. Multiple sexual partners
3. Anorectal intercourse
4. Sharing of blood-contaminated needles by intravenous injection drug users (IVDUs)
5. Vertical transmission (HIV infected mother to her baby)
6. Healthcare workers in frequent contact with HIV patients

E. **Transmission**

1. **Sexual**
   - Anorectal (receptive: 0.3-3%, insertive: 0.06%)
   - Vaginal (receptive: 0.1-0.2%, insertive: 0.03-0.14%)
   - Oral (male receptive: 0.06%)
   - **Lower risk for insertive versus receptive sexual acts**
2. **Parenteral**
   - Infected blood exposure from needle sticks, receipt of blood products, and organ transplants (0.00000178% transmission risk)
   - **IVDU accounted for 12% of all new HIV infections in 2009**
   - Approximately 0.67% transmission risk for all parenteral transmission
   - Percutaneous needle stick: 0.3% risk, mucocutaneous exposure: 0.09% risk
3. **Vertical/Perinatal**
   - Approximately 25% risk (without antiretroviral therapy)
4. **Breastfeeding**
   - Approximately 4-16% risk

F. **Prevention**

1. No vaccine
2. Abstinence (anal, vaginal, oral)
3. Monogamy: know your HIV status and your partner’s HIV status
   - If >1 partner, CDC recommends HIV testing every 3-6 months
4. Condom use decreases risk by 20-fold
   - Latex condoms are highly effective against HIV – if latex allergy is present, use polyurethane or polyisoprene condoms (lambskin condoms will not protect against HIV)

“It is bad enough that people are dying of AIDS, but no one should die of ignorance.” – *Elizabeth Taylor*

“It is bad enough that people are dying of AIDS, but no one should die of ignorance.” – *Princess Diana*
- A new condom should be used with every sexual act (anal, oral, vaginal)
- Only water-based lubricants should be used, not oil-based products (they can damage condoms and decrease their efficacy)

5. Circumcision decreases risk of male acquisition by 60% in heterosexual vaginal intercourse
6. Decreasing drug abuse or IVDU
- Needle exchange programs: 203 programs in 34 states as of August 2012 (Texas=none)
7. Zidovudine (Retrovir®) use in HIV infected mothers during pregnancy and delivery
8. Avoiding breastfeeding in HIV infected mothers
9. Pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine (Truvada®) for use among sexually active adults at risk for HIV infection – FDA approved in July 2012
10. Under investigation: HIV vaccine, topical vaginal microbicides

G. Etiology
1. HIV is an enveloped single-stranded RNA virus
2. Member of the Lentivirinae subfamily of retroviruses – characterized by lethargic infectious cycle
3. Two types of HIV:
   - HIV-1: Four groups (M, N, O, P), and 9 subtypes of group M (A through D, F through H, J, and K) – Group M, subtype B is common in North America and Western Europe
   - HIV-2: Mostly in western Africa; less virulent – 7 subtypes (A through G)

II. Pathogenesis
A. HIV Virus
1. Retrovirus with RNA as genetic material – replication (about 10 billion viruses/day)
2. Receptors: CD4+, CCR5, CXCR4
3. Enzymes: reverse transcriptase, integrase, protease

B. HIV Life Cycle
1. Entry
2. Fusion
3. Reverse Transcription
4. Reverse Transcription Inhibitors
   - Apricitabine
   - Abacavir
   - Didanosine
   - Emtricitabine
   - Lamivudine
   - Stavudine
   - Tenofovir
   - Zidovudine
   - Efavirenz
   - Delavirdine
   - Nevirapine
   - Rilpivirine
   - Double-stranded unincorporated circularized DNA
5. Integration
6. Assembly
7. Maturation

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III. Screening and Diagnosis

A. Screening

1. Testing for HIV is recommended when infection is suspected due to symptoms and/or high-risk behavior
2. Routine HIV screening in all healthcare settings in patients ages 13 through 64
   - “Opt-out” testing method – consent for medical care will imply consent for HIV testing, but person must be informed of the test and can opt-out

B. Diagnosis

1. Enzyme-linked immunosorbent assay (ELISA): Gold-standard
   - Detects antibodies (Abs) against HIV-1 (identifies antigen-antibody complexes) – minimum time to develop HIV Abs is 3-4 weeks post-exposure (95% develop Abs after 6 months)
   - Sample: oral mucosal transudate (OraQuick®), whole blood, or plasma
     - Rapid turnaround (10-40 minutes)
     - Sensitivity: 99%, Specificity: 99%
     - False-positive results may occur in multiparous women, patients with recent vaccination (Hep B, HIV, influenza, rabies), blood transfusion, liver disease, renal failure, or hemodialysis
   - If an ELISA test is positive (reactive), then a repeat ELISA is needed – followed by a confirmatory test (usually the Western blot)
   - If an ELISA test is negative, it is safe to rule out HIV (unless acute HIV infection is suspected – obtain HIV RNA)
2. Western blot
   - Detects Abs to specific HIV antigens
   - Sensitivity/Specificity ≥99%
   - If positive: at least 2 of the following bands are present – p24, gp41, gp160/120
   - If negative: No bands present
   - If indeterminate: HIV band is present, but does not meet criteria for positivity
   - If test is indeterminate, retest in 4 weeks
3. p24 Antigen (Ag) Test
   - Detects HIV infection as early as 2 weeks post-infection
   - Approved for diagnosis of acute HIV infection, but has low sensitivity
   - HIV RNA has replaced this test in clinical practice
4. Nucleic Acid Based Tests
   - Donated blood in the U.S. is screened with these tests
   - Detects HIV infection early – 12 days post-infection
   - Can be used for diagnosis of acute HIV infection (especially to confirm ELISA)
5. Combination Tests (i.e., ARCHITECT and Alere Determine Tests)
   - Can provide positive results sooner than ELISA
   - Detect both (HIV-1/2 Ab and p24 Ag)

C. Clinical Presentation

1. Symptoms
   - Acute retroviral syndrome (ARS)
     - As early as 2-4 weeks post-infection, but up to 3 months later
     - Acute illness described as a “severe cold”
- **Symptoms:** fever, chills, rash (morbilliform or maculopapular; usually involves the trunk in 40-80% of patients), night sweats, muscle aches, sore throat, fatigue, swollen lymph nodes, ulcers in mouth – symptoms often last 2 weeks, and 15% of patients require hospitalization.

- **Chronic/latency phase**
  - **Symptoms:** none (most patients) – can last up to 10 years or longer

- **AIDS**
  - **Symptoms:** fatigue, diarrhea, nausea, vomiting, fever, chills, night sweats, wasting syndrome, opportunistic infections

### IV. Pharmacologic Agents

A. **Mechanism of action (MOA)**
   1. Refer to HIV life cycle in Section II-B (p.4)

B. **Antiretroviral (ARV) agent classes** (Refer to Appendix D)
   1. Dolutegravir Monograph (Refer to Appendix E)

### V. Treatment Recommendations

A. **Initiating ARV therapy**

1. Department of Health and Human Services (DHHS) 2013 Guidelines
   - Antiretroviral therapy (ART) is recommended for all HIV-infected individuals

<table>
<thead>
<tr>
<th>Rating</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>ART is recommended for HIV-infected individuals with pretreatment CD4 cell count &lt;350 cells/µL</td>
</tr>
<tr>
<td>AII</td>
<td>ART is recommended for HIV-infected individuals with pretreatment CD4 cell count 350-500 cells/µL</td>
</tr>
<tr>
<td>BIII</td>
<td>ART is recommended for HIV-infected individuals with pretreatment CD4 cell count &gt;500 cells/µL</td>
</tr>
</tbody>
</table>

*Rating of Recommendations: A=Strong, B=Moderate, C=Optional*
*Rating of Evidence: I=Data from randomized controlled trials, II=Data from well-designed non-randomized trials or observational cohort studies with long-term clinical outcomes, III=Expert opinion*

2. **World Health Organization (WHO) 2013 Guidelines** (Refer to Appendix F)

B. **Highly-Active Antiretroviral Therapy (HAART)**

1. HAART consists of at least 3 fully active ARV agents
2. **DHHS 2013 Guidelines**\(^\text{17}\)

### Table 3: Initial Combination Regimens for Antiretroviral-Naïve Patients (DHHS 2013 Guidelines)\(^\text{17}\)

#### Preferred Regimens

<table>
<thead>
<tr>
<th>Rating</th>
<th>Recommendation</th>
<th>Comments</th>
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</table>
| AI | NNRTI-Based Regimen  
- EFV + TDF/FTC | - EFV is teratogenic. Avoid in women who are planning to become pregnant or who are sexually active and not using effective contraception.  
- TDF should be used with caution in patients with renal insufficiency.  
- ATV/r should NOT be used in patients who require >20 mg omeprazole equivalent per day. |
| AI | PI-Based Regimens  
- ATV/r + TDF/FTC  
- DRV/r + TDF/FTC | - Higher rate of virologic failures in patients with pre-ART CD4 count <200 cells/µL who are treated with RPV + 2NRTIs.  
- Use of PPIs with RPV is contraindicated.  
- ABC should NOT be used in patients who test positive for HLA-B*5701.  
- Use ABC with caution in patients with known high risk of CVD or with pre-treatment HIV RNA >100,000 copies/mL. |
| AI | INSTI-Based Regimen  
- RAL + TDF/FTC | - Once-daily LPV/r is NOT recommended for use in pregnant women.  
- EVG/COBI/TDF/FTC should NOT be started if patient’s CrCl <70 mL/min, and should be changed to an alternative regimen if the patient’s CrCl falls <50 mL/min.  
- COBI is a potent CYP3A4 inhibitor. It can increase the concentration of other drugs metabolized by this pathway.  
- EVG/COBI/TDF/FTC should NOT be used with other ART or with nephrotoxic drugs. |

#### Alternative Regimens

<table>
<thead>
<tr>
<th>Rating</th>
<th>Recommendation</th>
<th>Comments</th>
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</table>
| BI | NNRTI-Based Regimen  
- EFV + ABC/3TC  
- RPV + TDF/FTC | - RPV is NOT recommended in patients with pre-treatment HIV RNA >100,000 copies/mL.  
- Higher rate of virologic failures in patients with pre-ART CD4 count <200 cells/µL who are treated with RPV + 2NRTIs.  
- Use of PPIs with RPV is contraindicated.  
- ABC should NOT be used in patients who test positive for HLA-B*5701.  
- Use ABC with caution in patients with known high risk of CVD or with pre-treatment HIV RNA >100,000 copies/mL. |
| BIII | NNRTI-Based Regimen  
- RPV + ABC/3TC | |
| BI | PI-Based Regimens  
- ATV/r + ABC/3TC  
- FPV/r + ABC/3TC or TDF/FTC  
- LPV/r + ABC/3TC or TDF/FTC | |
| BI | INSTI-Based Regimen  
- DRV/r + ABC/3TC | |
| BI | EVG/COBI + TDF/FTC | |
| BIII | INSTI-Based Regimen  
- RAL + ABC/3TC | |

**Key to Abbreviations:** 3TC=lamivudine, ABC=abacavir, ART=antiretroviral therapy, ARV=antiretroviral, ATV/r=atazanavir/ritonavir, COBI=cobicistat, CrCl=creatinine clearance, CVD=cardiovascular disease, DRV/r=darunavir/ritonavir, EFV=efavirenz, EVG=elvitegravir, FPV/r=fosamprenavir/ritonavir, FTC=emtricitabine, INSTI=integrase strand transfer inhibitor, LPV/r=lopinavir/ritonavir, NNRTI=non-nucleoside reverse transcriptase inhibitor, PPI=proton pump inhibitor, RAL=raltegravir, RPV=rilpivirine, RTV=ritonavir, TDF=tenofovir disoproxil fumarate, ZDV=zidovudine

**Rating of Recommendations:**  A=Strong, B=Moderate, C=Optional

**Rating of Evidence:** I=Data from randomized controlled trials, II=Data from well-designed non-randomized trials or observational cohort studies with long-term clinical outcomes, III=Expert opinion

### 3. WHO 2013 Guidelines (Refer to Appendix F)

#### VI. Goals and Monitoring\(^{8,14,17,19}\)

**A. Goals**

1. Achieve virologic suppression or undetectable viral load (UDVL) = HIV RNA <50 copies/mL
2. Improve immune response = CD4 cells >350 cells/µL
3. Prevent HIV progression and opportunistic infections (OIs)
4. Prevent HIV transmission and resistance

**B. Evaluation of Outcomes**

1. **Virologic failure**
   - Less than 1 log drop in VL, 1-4 weeks after starting ART or not achieving viral load (VL) <200 copies/mL at week 24 or not achieving VL <50 copies/mL by week 48
2. **Virologic rebound**
   - After virologic suppression, repeated detection of VL >200 copies/mL
3. **Immunologic failure**
   - Not increasing CD4 count by 25-50 cells/µL from baseline by week 48
4. **Clinical failure**
   - Disease progression – occurrence of HIV-related events (i.e., OIs) after at least 3 months on ART

**C. Laboratory Monitoring** (Refer to Appendix G)
VII. **Resistance**\(^{14,20}\)

A. *Genotype tests*: describe HIV mutations known to be associated with resistance to specific drugs

B. *Phenotype tests*: measure the ability of individual drugs to inhibit a recombinant virus that is derived from the patient’s isolate

C. Higher barrier to resistance: NNRTI < NRTI/INSTI < PI

D. Integrase Strand Transfer Inhibitors (INSTIs)

**MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS**

<table>
<thead>
<tr>
<th></th>
<th>Dolatgravir™</th>
<th>Elvitegravir™</th>
<th>Raltegravir™</th>
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https://www.iapsa.org/sites/default/files/2013-mutations-chart_0.pdf
### Literature Evaluation

#### A. Treatment-Naive Patients (SPRING-2)\(^2\)

|---|

**Objective**

“*To assess the efficacy and safety of dolutegravir (DTG) versus raltegravir (RAL), in combination with two widely recommended NRTI backbones, as first-line treatment for antiretroviral-naive adults with HIV-1*”

**Study Design**

- Randomized, double-blind, active-controlled, double-placebo, multicenter, parallel-group, non-inferiority study; 96 week phase 3 trial; 100 sites (USA, Canada, Europe, Australia); 822 patients

**Subjects**

- **Inclusion Criteria**
  - Age ≥ 18 yo
  - Plasma HIV-1 RNA ≥ 1000 copies/mL
  - No primary resistance to NRTIs/NNRTIs/PIs
  - *Patients could only receive abacavir after HLA-B*5701 allele was ruled out

- **Exclusion Criteria**
  - Active CDC Category C HIV (AIDS defining illness), except for Kaposi’s sarcoma
  - Pregnancy
  - Moderate/severe hepatic impairment
  - Anticipated need for hepatitis C treatment
  - CrCl < 50 mL/min
  - Recent/ongoing malignancy
  - Treatment with HIV-1 vaccine within 90 days of screening, or with any immunomodulator within 28 days

**Methods**

- Stratified randomization – VL (<100,000 copies/mL or >100,000 copies/mL) and NRTI backbone (TDF/FTC or ABC/3TC); DTG 50 mg daily or RAL 400 mg BID
- **Primary endpoint:** Proportion of patients with HIV-1 RNA <50 copies/mL at week 48
- **Secondary endpoints:** CD4 cell changes from baseline, incidence/severity of ADRs, changes in lab parameters, genotypic/phenotypic evidence of resistance, health outcomes (EQ-5D)

**Statistics**

- **Primary endpoint:** Noninferiority; ITT method; Cochran-Mantel-Haenszel analysis to account for VL/NRTI backbone stratification; **Secondary endpoints:** PP analysis, Kaplan-Meier

**Results**

- **Patients with plasma HIV-1 RNA less than 50 copies per mL at week 48**

<table>
<thead>
<tr>
<th></th>
<th>DTG (n=411)</th>
<th>RAL (n=411)</th>
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<tbody>
<tr>
<td>Virological success(^a)</td>
<td>361 (88%)</td>
<td>351 (85%)</td>
</tr>
<tr>
<td>Virologic non-response(^a) (failure)</td>
<td>20 (5%)</td>
<td>31 (8%)</td>
</tr>
<tr>
<td>No virological data at week 48</td>
<td>30 (7%)</td>
<td>29 (7%)</td>
</tr>
</tbody>
</table>

- **Most common ADRs**
  - Nausea | 59 (14%) | 53 (13%) |
  - Headache (HA) | 51 (12%) | 48 (12%) |
  - Nasopharyngitis | 46 (11%) | 48 (12%) |
  - Diarrhea | 47 (11%) | 47 (11%) |

*Adjusted difference (95% CI) = 3.5% (2.2 to 7.1)

\(^a\)Non-response due to: 1) VL not <50 copies/mL, 2) discontinued for lack of efficacy, 3) discontinued for other reasons while VL not <50 copies/mL

- CD4 cells increased in both groups, by a median of 230 cells/μL
- Majority of ADRs = grade 1 or 2
- Protocol-defined virological failure (PDVF): DTG – 20 (5%), RAL – 28 (7%)
- Resistance mutations to PIs or NRTIs: DTG – 0, RAL – 1 (6%) to PIs and 4 (21%) to NRTIs

**Author’s Conclusions**

- At 48 weeks, **DTG 50 mg daily was non-inferior to RAL 400 mg BID in both efficacy and safety**
- No antiviral resistance to PIs or NRTI backbone with DTG, while both were found in RAL group
- The ↑Scr was not considered clinically significant – DTG inhibits OCT2, which ↓creatine tubular secretion and ↑Scr without affecting glomerular filtration

**Reviewer’s Conclusions**

- **Strengths:** Double-blind, double-dummy study; ITT method was used
- **Weaknesses:** Low number of Non-White and female patients; did not include patients with an AIDS-defining illness (except Kaposi’s sarcoma), with a low CrCl, or with moderate/severe hepatic impairment
- Dolutegravir proved non-inferiority to raltegravir in this study; its once-daily regimen and higher barrier to resistance shows a promising future for this drug’s place in HIV therapy
B. Treatment-Experienced, Integrase Inhibitor-Naïve Patients (SAILING)\(^{22}\)


**Objective**

“To compare the clinical efficacy, safety, and virology outcomes in treatment-experienced, integrase-inhibitor (INSTI)-naïve patients who received dolutegravir (DTG) 50 mg once daily or raltegravir (RAL) 400 mg twice a day, plus investigator-selected background therapy”

**Study Design**

- Randomized, double-blind, active-controlled, double-placebo, multicenter, parallel-group, non-inferiority study; 48 week phase 3 trial; 156 sites (USA, Canada, Europe, Australia, Latin America, Taiwan, South Africa); 715 patients

**Subjects**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- ART-experienced, HIV-1 infected subjects ≥ 18 yo</td>
<td>- Active CDC Category C HIV (AIDS defining illness), except for Kaposi’s sarcoma</td>
</tr>
<tr>
<td>- 2 consecutive plasma HIV-1 RNA ≥ 400 copies/mL (unless &gt;1000 copies/mL at screening)</td>
<td>- Pregnancy, breastfeeding</td>
</tr>
<tr>
<td>- Resistance to ≥2 classes of antiretroviral drugs</td>
<td>- Moderate/severe hepatic impairment; anticipated hepatitis C treatment</td>
</tr>
<tr>
<td>- Patients had 1-2 fully active agent(s) for background therapy</td>
<td>- Recent (≤3 months) history of upper/lower GI bleeding</td>
</tr>
<tr>
<td>- Is integrase-inhibitor naïve</td>
<td>- Recent/ongoing malignancy</td>
</tr>
</tbody>
</table>

**Methods**

- Stratified randomization – VL (<50,000 copies/mL or >50,000 copies/mL), background therapy (DRV/r use without primary PI resistance vs no use or use with primary PI mutations), # of fully active background agents (≥2 agents vs <2 agents); DTG 50 mg daily or RAL 400 mg BID
- **Primary endpoint:** Proportion of patients with HIV-1 RNA <50 copies/mL at week 48
- **Secondary endpoints:** Patients with treatment-emergent integrase inhibitor resistance or background regimen resistance, CD4 cell changes, disease-progression, incidence/severity of ADRs, health outcomes (EQ-5D)

**Statistics**

- **Primary endpoint:** Noninferiority; ITT method; PP was done as a secondary analysis; superiority would be tested if both ITT and PP showed non-inferiority; **Secondary endpoint:** Kaplan-Meier

**Results**

<table>
<thead>
<tr>
<th>Proportion of patients with plasma HIV-1 RNA less than 50 copies per mL at week 24 or week 48, or both</th>
<th>DTG (n=354)</th>
<th>RAL (n=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological success(^c) (p=0.03)</td>
<td>251 (71%)</td>
<td>230 (64%)</td>
</tr>
<tr>
<td>Virologic non-response(^a) (failure)</td>
<td>71 (20%)</td>
<td>100 (28%)</td>
</tr>
<tr>
<td>No virological data at week 48</td>
<td>32 (9%)</td>
<td>31 (9%)</td>
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**Most common ADRs**

<table>
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<tr>
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<th>DTG (n=354)</th>
<th>RAL (n=361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>71 (20%)</td>
<td>64 (18%)</td>
</tr>
<tr>
<td>URTI</td>
<td>38 (11%)</td>
<td>29 (8%)</td>
</tr>
<tr>
<td>Headache (HA)</td>
<td>33 (9%)</td>
<td>31 (9%)</td>
</tr>
</tbody>
</table>

\(^c\)Adjusted difference (95% CI; p value) = 7.4% (0.7 to 14.2; p=0.03)

\(^a\)Non response due to: 1) VL not <50 copies/mL, 2) discontinued for lack of efficacy, 3) discontinued for other reasons while VL not <50 copies/mL, 4) change in ART

- Mean ↑CD4 cells: DTG – 162 cells/μL, RAL – 153 cells/μL
- Majority of ADRs = grade 1 or 2
- Protocol-defined virological failure (PDVF): DTG – 21 (6%), RAL – 45 (12%); also occurred earlier with RAL
- Treatment-emergent genotypic/phenotypic INSTI resistance by week 48: DTG – 4 (1%), RAL – 17 (5%), \(p=0.003\)
- Treatment-emergent resistance to background regimen at week 48: DTG – 4 (1%), RAL – 12 (3%)

**Author’s Conclusions**

- SAILING is the first trial to show superior virological efficacy of an ART over RAL
- Dolutegravir in combination with at least 1 additional ART is more efficacious and has significantly less treatment-emergent INSTI/background therapy resistance at PDVF as compared to raltegravir
- Dolutegravir has a favorable safety profile; the ↑SCR was not considered clinically significant

**Reviewer’s Conclusions**

- **Strengths:** Double-blind, double-dummy study; ITT and PP methods were used for non-inferiority prior to superiority analysis; diverse ethnic backgrounds
- **Weaknesses:** Low number of female patients; did not include patients with an AIDS-defining illness (except Kaposi’s sarcoma) or with moderate/severe hepatic impairment
- Dolutegravir proved superiority in efficacy and resistance as compared to raltegravir; its use in ART-experienced patients (esp. with darunavir resistant), could provide a new opportunity for patients with ↑ART resistance
C. Treatment-Experienced, Integrase Inhibitor-Experienced Patients (VIKING)\textsuperscript{23}


<table>
<thead>
<tr>
<th>Objective</th>
<th>“To assess and demonstrate the activity of dolutegravir (DTG) in HIV-1 infected individuals with raltegravir (RAL)-resistant viral isolates”</th>
</tr>
</thead>
</table>
| Study Design | - Phase Ib, open-label, single-arm, pilot study, 24 weeks, 25 sites (France, Italy, Canada, Spain, U.S.)  
- Two cohorts of HIV-1-infected individuals with current/historic RAL treatment failure and evidence of RAL resistance at screening; 51 patients |
| Subjects | Inclusion Criteria  
- ART-experienced, HIV-1 infected subjects > 18 yo  
- Plasma HIV-1 RNA ≥1000 copies/mL  
- Genotypic integrase inhibitor (INSTI) resistance  
- Documented genotypic and/or phenotypic resistance to ≥1 compound in each of the 2 other ART classes (NRTIs, NNRTIs, PIs, and fusion/entry inhibitors)  

Exclusion Criteria  
- Pre-existing mental, physical, or substance abuse disorders that could interfere with study conduct  
- Pregnancy, breastfeeding  
- ALT≥5xULN  
- Lipase ≥3xULN  
- Receiving/requiring EFV, NVP, FPV/r, or TPV/r  

Methods | - Cohort I: DTG 50 mg daily; Cohort II: DTG 50 mg BID; DAL + failing therapy for 10 days, then optimized therapy  
- Availability of ≥1 fully active ART agent for the optimized background regimen (OBR) was encouraged for cohort I, but mandated for cohort II eligibility  
- Primary endpoint: Patients with HIV-1 RNA <400 copies/mL or ≥0.7 log copies/mL below baseline on day 11  
- Secondary endpoints: Mean change in plasma HIV-1 RNA from baseline, proportion of subjects with plasma HIV-1 RNA loads of <400 and <50 copies/mL, change from baseline in CD4 cells, ADRs |
| Statistics | - Primary endpoint: ITT model; linear regression model to compare both cohorts  
- Secondary endpoints: Baseline characteristics=descriptive statistics; CD4 cells= last observation carried forward |

Results | Efficacy Results (VIKING)  

<table>
<thead>
<tr>
<th>Cohort I, DTG 50 mg daily (n=27)</th>
<th>Cohort II, DTG 50 mg BID (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy at day 11</td>
<td></td>
</tr>
</tbody>
</table>
Primary endpoint 21 (78%)  
23 (96%)  

Plasma HIV-1 RNA level, log copies/mL  
Baseline, mean (SD) 4.40 (0.79)  
4.38 (0.74)  
Day 11, mean (SD) 2.94 (1.01)  
2.62 (0.78)  
Change from baseline, mean (SD)\textsuperscript{c} -1.45 (0.77)  
-1.76 (0.54)  

Efficacy at week 24 |  
HIV-1 RNA load, copies/mL  
<50 11 (41%)  
18 (75%)  
<400 14 (52%)  
20 (83%)  
HIV-1 RNA, mean change from baseline, log copies/mL (SD) -1.3 (1.29)  
-2.3 (1.05)  

Most common ADRs  
Diarrhea 1 (4%)  
2 (8%)  
Insomnia 3 (11%)  
0  
Bronchitis 1 (4%)  
2 (8%)  
Cough 1 (4%)  
2 (8%)  

Key to Abbreviations: DTG=dolutegravir, BID=twice daily, SD=standard deviation; \textsuperscript{c}p=0.017 |

- Median ↑CD4 cells: cohort I – 54, cohort II – 60 cells/μL  
- ADRs (grade ≥2): cohort I – 13 (48%), cohort II – 16 (67%)  
- Serious ADRs were not considered to be related to DTG; no grade 3 or 4 ↑Scr  
- Protocol-defined virologic failure (PDVF), week 24: cohort I – 12 (44%), cohort II – 5 (21%) |

Author’s Conclusions  
- VIKING is the first trial to explore DTG treatment of HIV-1-infected patients with RAL virologic failure and genotypic evidence of resistance to RAL; rapid antiviral response was seen, especially with DTG 50 mg BID  
- Dolutegravir has a favorable safety profile; the ↑Scr was not considered clinically significant |

Reviewer’s Conclusions  
- Strengths: ITT method was used; diverse ethnic backgrounds; patients with an AIDS-defining illness, low renal function, or moderate/severe hepatic impairment were not excluded  
- Weaknesses: Low number of female patients; patients with mental disorders were excluded; open-label, single-arm study with a small patient sample; cohort I did not have a mandated fully active ART agent for OBR  
- Dolutegravir 50 mg BID could be a viable option for patients who have failed RAL – creating a niche for this ART
D. **VIKING-3**
   1. **Phase 3**, multicenter, open-label, single-arm trial; 183 HIV-1 infected, treatment-experienced adults with virological failure and current/historical evidence of RAL and/or EVG resistance
   2. Patients received DTG 50 mg BID with current failure background regimen for 7 days without RAL or EVG; then with optimized background regimen (OBR) from Day 8 to Week 24.
   3. INSTI-resistance at screening= 124 patients; historical resistance= 59 patients
   4. **Primary endpoints**: 1) Change from baseline in plasma HIV-1 RNA at Day 8, and 2) Percentage of patients with HIV-1 RNA <50 copies/mL at Week 24
   5. **Results**: Mean ↓HIV-1RNA was 1.43 log copies/mL at Day 8 (p<0.001). At week 24, 126 (69%) of patients had HIV-1 RNA <50 copies/mL. In patients with the Q148 plus ≥2 secondary mutations, the response was less – ↓1.0 log copies/mL in HIV-1 RNA at Day 8, and 44 (24%) of patients had HIV-1 RNA <50 copies/mL at Week 24. A total of 50 (27%) patients were virologic non-responders.
   6. **ADRs**: diarrhea (5%), nausea (6%), HA (5%)
   7. Note: In a multivariate analysis, the presence of the Q148 plus ≥2 mutations correlated with fewer patients achieving HIV-RNA<50 copies/mL at week 24 (p<0.001)

E. **Summary**

<table>
<thead>
<tr>
<th>Objective</th>
<th>SPRING-2</th>
<th>SAILING</th>
<th>VIKING</th>
<th>VIKING-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>DTG in ARV-naive patients</td>
<td>DTG in ARV-experienced, INSTI-naive patients</td>
<td>DTG activity in RAL-resistant isolates</td>
<td>DTG in ARV-experienced, INSTI-resistant patients</td>
</tr>
<tr>
<td>Phase III</td>
<td>DTG 50 mg daily vs RAL 400 mg BID</td>
<td>DTG 50 mg daily vs RAL 400 mg BID</td>
<td>Cohort I: DTG 50 mg daily</td>
<td>DTG 50 mg BID</td>
</tr>
<tr>
<td>Phase IIB</td>
<td>Proportion of patients with VL &lt;50 copies/mL at week 48: DTG: 88%, RAL: 85%</td>
<td>Proportion of patients with VL &lt;50 copies/mL at week 48: DTG: 71%, RAL: 64% (p=0.03)</td>
<td>Patients with VL &lt;400 copies/mL or ≥0.7 log copies/mL below baseline on day 11: Cohort I: 78%, Cohort II: 96%</td>
<td>Change in VL at day 8: ↓1.43 log copies/mL (p&lt;0.001)</td>
</tr>
<tr>
<td>CD4 cell changes from baseline: ↑both groups (median of 230 cells/µL)</td>
<td>Treatment-emergent INSTI resistance: DTG: 1%, RAL: 5% (p=0.003)</td>
<td>Mean change in HIV-1 RNA from baseline: Cohort I: -1.45, Cohort II: -1.76 (p=0.017)</td>
<td>Patients with VL &lt;50 copies/mL at week 48: 126 (69%)</td>
<td></td>
</tr>
<tr>
<td>DTG non-inferior to RAL (efficacy and safety)</td>
<td>DTG superior to RAL, and creates less resistance</td>
<td>Rapid antiviral activity with DTG, especially in Cohort II</td>
<td>DTG can be used in RAL/EVG resistant patients, but not ideal if Q148 plus ≥2 mutations</td>
<td></td>
</tr>
</tbody>
</table>

IX. **Role of a Pharmacist in HIV**

A. **Care**
   1. ART selection
   2. Managing ADRs and patient counseling
   3. Access to care – Expanded Access Programs (EAPs), Named Patient Programs (NPPs), Patient Assistance Programs (PAPs)

B. **Prevention**
   1. Education on decreasing high-risk sexual behavior and contraception

X. **Conclusions**

A. **Clinical Question**
   1. Question
      - Is dolutegravir just another “me too” drug, or does it have a specific place in HIV therapy?
   2. Response
      - Dolutegravir does have a niche in HIV therapy – can be used in RAL/EVG HIV-resistant patients
      - Further evaluation of VIKING trials is needed after they are published, as well as post-marketing surveillance studies

12 | Gomez 2013
Appendix A

I. CDC Category B Symptomatic Conditions

A. Symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least one of the following criteria:
   1. They are attributed to HIV infection or indicate a defect in cell-mediated immunity, or 2) They are considered to have a clinical course or management that is complicated by HIV infection
   2. Examples:
      - Bacillary angiomatosis
      - Oropharyngeal candidiasis (thrush)
      - Vulvovaginal candidiasis, persistent or resistant
      - Pelvic inflammatory disease (PID)
      - Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
      - Hairy leukoplakia, oral
      - Herpes zoster (shingles), involving two or more episodes or at least one dermatome
      - Idiopathic thrombocytopenic purpura
      - Constitutional symptoms, such as fever (>38.5˚C) or diarrhea lasting >1 month
      - Peripheral neuropathy

II. CDC Category C AIDS-Indicator Conditions

1. Bacterial pneumonia, recurrent (two or more episodes in 12 months)
2. Candidiasis of the bronchi, trachea, or lungs
3. Candidiasis, esophageal
4. Cervical carcinoma, invasive, confirmed by biopsy
5. Coccidioidomycosis, disseminated or extrapulmonary
6. Cryptococcosis, extrapulmonary
7. Cryptosporidiosis, chronic intestinal (>1 month in duration)
8. Cytomegalovirus disease (other than liver, spleen, or nodes)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcers (>1 month in duration), or bronchitis, pneumonitis, or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (>1 month in duration)
13. Kaposi sarcoma
14. Lymphoma, Burkitt, immunoblastic, or primary central nervous system
15. Mycobacterium avium complex (MAC) or Mycobacterium kansasii, disseminated or extrapulmonary
16. Mycobacterium tuberculosis, pulmonary or extrapulmonary
17. Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
18. Pneumocystis jiroveci (formerly carinii) pneumonia (PJP or PCP)
19. Progressive multifocal leukoencephalopathy (PML)
20. Salmonella septicemia, recurrent (nontyphoid)
21. Toxoplasmosis of brain
22. Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (two or more loose stools per day for >1 month) or chronic weakness and documented fever for >1 month
### Table 1: WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| **Primary HIV Infection** | - Asymptomatic  
- Acute retroviral syndrome |
| **Clinical Stage 1** | - Asymptomatic  
- Persistent generalized lymphadenopathy |
| **Clinical Stage 2** | - Moderate unexplained weight loss (<10% of presumed or measured body weight)  
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)  
- Herpes zoster  
- Angular cheilitis  
- Recurrent oral ulceration  
- Papular pruritic eruptions  
- Seborrheic dermatitis  
- Fungal nail infections |
| **Clinical Stage 3** | - Unexplained severe weight loss (>10% of presumed or measured body weight)  
- Unexplained chronic diarrhea for >1 month  
- Unexplained persistent fever for >1 month (>37.6˚C, intermittent or constant)  
- Persistent oral candidiasis (thrush); oral hairy leukoplakia  
- Pulmonary tuberculosis (current)  
- Severe presumed bacterial infections (i.e., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)  
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis  
- Unexplained anemia (Hg <8 g/dL)  
- Neutropenia (neutrophils <500 cells/µL)  
- Chronic thrombocytopenia (platelets <50,000 cells/µL) |
| **Clinical Stage 4** | - HIV wasting syndrome, as defined by the CDC (Refer to Appendix A)  
- *Pneumocystis* pneumonia or recurrent severe bacterial pneumonia  
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)  
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)  
- Extrapulmonary tuberculosis or disseminated nontuberculosis mycobacteria infection  
- Kaposi sarcoma  
- Cytomegalovirus infection (retinitis or infection of other organs)  
- Central nervous system toxoplasmosis  
- HIV encephalopathy  
- Cryptococcosis, extrapulmonary (including meningitis)  
- Progressive multifocal leukoencephalopathy  
- Candida of the trachea, bronchi, or lungs  
- Chronic cryptosporidiosis (with diarrhea)  
- Chronic isosporiasis  
- Disseminated mycosis (i.e., histoplasmosis, coccidioidomycosis, penicilliosis)  
- Recurrent nontyphoidal *Salmonella* bacteremia  
- Lymphoma (cerebral or B-cell non-Hodgkin)  
- Invasive cervical carcinoma  
- Atypical disseminated leishmaniasis  
- Symptomatic HIV-associated nephropathy or cardiomyopathy  
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis) |
### Table 2: CDC Top 10 States with Highest HIV Diagnoses in 2011

<table>
<thead>
<tr>
<th>State/Dependent Area</th>
<th>Number of HIV Diagnoses (% of state population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. California</td>
<td>5,973 (0.016%)</td>
</tr>
<tr>
<td>2. Florida</td>
<td>5,403 (0.028%)</td>
</tr>
<tr>
<td>3. Texas</td>
<td>5,065 (0.019%)</td>
</tr>
<tr>
<td>4. New York</td>
<td>4,960 (0.025%)</td>
</tr>
<tr>
<td>5. Georgia</td>
<td>2,522 (0.025%)</td>
</tr>
<tr>
<td>6. Illinois</td>
<td>2,142 (0.017%)</td>
</tr>
<tr>
<td>7. Maryland</td>
<td>1,783 (0.030%)</td>
</tr>
<tr>
<td>8. North Carolina</td>
<td>1,672 (0.017%)</td>
</tr>
<tr>
<td>9. New Jersey</td>
<td>1,567 (0.018%)</td>
</tr>
<tr>
<td>10. Pennsylvania</td>
<td>1,545 (0.012%)</td>
</tr>
</tbody>
</table>

---

**Texas Demographics, 2012**
- White: 44.30%
- Hispanic/Latino: 12.30%
- Black/African American: 3.40%
- Asian: 0.10%
- Multiple Races: 0.10%

**El Paso, TX Demographics, 2012**
- White: 80.50%
- Hispanic/Latino: 14.00%
- Black/African American: 0.70%
- American Indian/Alaska Native: 0.10%
- Native Hawaiian/Other Pacific Islander: 0.10%
- Multiple Races: 0.10%
### Table 3: Antiretroviral Agents\(^{9,26}\)

#### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir DF*</td>
<td>Viread®</td>
<td>TDF</td>
<td>300 mg daily</td>
<td>---</td>
<td>Nephrotoxicity, ↓BMD, pigmentation on soles/palms</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Emtriva®</td>
<td>FTC</td>
<td>200 mg daily</td>
<td>---</td>
<td>Minimal (HA, N/V)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Epivir®</td>
<td>3TC</td>
<td>150 mg BID or 300 mg daily</td>
<td>---</td>
<td>HA, pancreatitis, N/V</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Retrovir®</td>
<td>ZDV or AZT</td>
<td>300 mg BID</td>
<td>---</td>
<td>Marrow suppression (anemia, neutropenia), N/V, HA, myopathy</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Zerit®</td>
<td>d4T</td>
<td>40 mg BID</td>
<td>---</td>
<td>Lipatrophy, PN, lactic acidosis, pancreatitis</td>
</tr>
<tr>
<td>Abacavir</td>
<td>Ziagen®</td>
<td>ABC</td>
<td>300 mg BID</td>
<td>---</td>
<td>Hypersensitivity (HLA-B5701), rash</td>
</tr>
<tr>
<td>Didanosine EC</td>
<td>Videx®</td>
<td>ddI</td>
<td>400 mg daily</td>
<td>S</td>
<td>Lipatrophy, PN, lactic acidosis, pancreatitis</td>
</tr>
</tbody>
</table>

#### NRTI Combos

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir/Emtricitabine</td>
<td>Truvada®</td>
<td>TDF/FTC</td>
<td>1 tab daily</td>
<td>---</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>Lamivudine/Zidovudine</td>
<td>Combivir®</td>
<td>3TC/ZDV</td>
<td>1 cap BID</td>
<td>---</td>
<td>Marrow suppression</td>
</tr>
<tr>
<td>Lamivudine/Abacavir</td>
<td>Epivir®</td>
<td>3TC/ABC</td>
<td>1 tab daily</td>
<td>---</td>
<td>Hypersensitivity, rash</td>
</tr>
<tr>
<td>Lamivudine/Zidovudine/Abacavir</td>
<td>Trizivir®</td>
<td>3TC/ZDV/ABC</td>
<td>1 cap BID</td>
<td>---</td>
<td>Marrow suppression, hypersensitivity, rash</td>
</tr>
</tbody>
</table>

#### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Viramune®</td>
<td>NVP</td>
<td>IR: 200 mg daily x 2 wks, then 200 mg BID XR: 400 mg daily (only after 14-day IR 200 mg lead-in)</td>
<td>---</td>
<td>Hepatotoxicity (hepatitis), potentially serious rash</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Rescriptor®</td>
<td>DLV</td>
<td>400 mg TID</td>
<td>TID (1h apart from antacids)</td>
<td>Rash, ↑LFTs</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva®</td>
<td>EFV</td>
<td>600 mg at hs</td>
<td>S</td>
<td>CNS disturbances, teratogenicity, rash</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Inteleone®</td>
<td>ETV</td>
<td>200 mg BID</td>
<td>C</td>
<td>Rash, N/V</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Edurant®</td>
<td>RVP</td>
<td>25 mg daily</td>
<td>C</td>
<td>GI (minimal), depression, rash, HA</td>
</tr>
</tbody>
</table>

#### Protease Inhibitors (PIs)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saquinavir</td>
<td>Invirase®</td>
<td>SQV</td>
<td>Hard gel (boosted): 500 mg BID</td>
<td>C fatty meal</td>
<td>GI (mild N/V, bloating, diarrhea)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crinon®</td>
<td>IDV</td>
<td>800 mg QDH</td>
<td>S (drink ≥48 oz water/day)</td>
<td>Nephrolithiasis, ↑bilirubin</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir®</td>
<td>RTV</td>
<td>300-200 mg daily</td>
<td>C</td>
<td>GI intolerance, circumoral parathesias</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Lexiva®</td>
<td>FPV</td>
<td>700 mg BID</td>
<td>---</td>
<td>Rash, N/V, diarrhea</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Reyataz®</td>
<td>ATV</td>
<td>400 mg daily</td>
<td>C</td>
<td>↑bilirubin, nephrolithiasis</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Aptivus®</td>
<td>TPV</td>
<td>500 mg BID (boosted)</td>
<td>C</td>
<td>Hepatotoxicity, ICH, GI upset</td>
</tr>
<tr>
<td>Lopinavir/RTV</td>
<td>Kaletra®</td>
<td>LPV/RTV</td>
<td>2 tabs BID or 4 tabs daily</td>
<td>C</td>
<td>Hypertriglyceridemia, GI upset</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept®</td>
<td>NFV</td>
<td>1250 mg BID</td>
<td>C meal/ snack</td>
<td>Diarrhea, N/V</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Prezista®</td>
<td>DRV</td>
<td>600 mg BID (boosted or 800 mg boosted)</td>
<td>C</td>
<td>Rash, DLD, GI upset</td>
</tr>
</tbody>
</table>

#### Entry Inhibitor

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>Selzentry®</td>
<td>MVC</td>
<td>150 mg BID</td>
<td>---</td>
<td>Hepatotoxicity; should only be used in pts w/ documented CCR5-tropic only virus, CV</td>
</tr>
</tbody>
</table>

#### Fusion Inhibitor

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide</td>
<td>Fuzeon®</td>
<td>T-20</td>
<td>90 mg subcut BID</td>
<td>---</td>
<td>Injection site rxn, respiratory infxns</td>
</tr>
</tbody>
</table>

#### Integrase Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltegravir</td>
<td>Isentress®</td>
<td>RAL</td>
<td>400 mg BID</td>
<td>---</td>
<td>Renal, minimal GI (N/V, diarrhea)</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>---</td>
<td>EVG</td>
<td>150 mg daily</td>
<td>C</td>
<td>Minimal GI (N/V)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Tivicay®</td>
<td>DTG</td>
<td>50 mg daily or 50 mg BID</td>
<td>---</td>
<td>Insomnia, ↑lipase, GI upset (N/V), HA</td>
</tr>
</tbody>
</table>

#### Combination Therapy

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Abbrev.</th>
<th>Dose</th>
<th>Food</th>
<th>Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir/Emtricitabine/ Rilpivirine</td>
<td>Complera®</td>
<td>TDF/FTC/RVP</td>
<td>1 tab daily</td>
<td>C (Can NOT take w/ PPIs)</td>
<td>Nephrotoxicity, rash</td>
</tr>
<tr>
<td>Tenofovir/Emtricitabine/ Efavirenz</td>
<td>Atripla®</td>
<td>TDF/FTC/EFV</td>
<td>1 tab at hs</td>
<td>Avoid fatty meal</td>
<td>CNS disturbances, nephrotoxicity</td>
</tr>
<tr>
<td>Tenofovir/Emtricitabine/ Rilpivirine/Cobicistat</td>
<td>Stridal®</td>
<td>TDF/FTC/ EVG/COBI</td>
<td>1 tab daily</td>
<td>C</td>
<td>Minimal GI (diarrhea), nephrotoxicity</td>
</tr>
</tbody>
</table>

---

Key to Abbreviations: Abbreviations, ADR=adverse drug effects, Tenofovir DF=tenofovir disoproxil fumarate, TDF=tenofovir DF, BMD=bone mass density, FTC=emtricitabine, IDV=indinavir, NVP=nevirapine, RTV=ritonavir, P=protease inhibitor, MVC=maraviroc, d4T=stavudine, ZDV=zidovudine, 3TC=lamivudine, BID=twice daily, XR=extended release, DLV=delavirdine, ZDVV=azidothymidine, ZDV=AZT, RTV=ritonavir, ddI=didanosine, S=without food, C=with food, EFV=efavirenz, DRV=darunavir, IDV=indinavir, SQV=saquinavir, FPV=fosamprenavir, RTV=ritonavir, EVG/COBI=elvitegravir, r=ritonavir, LPV=lopinavir, NFV=nelfinavir, DRV=darunavir, DDV=didanosine, MVC=maraviroc, w/meal, C=fatty meal/ snack, S=on empty stomach, C meal/ snack=on full meal/ snack, NVP=nevirapine, IR=immediate release, TID (1h apart)=three times daily, h-hour, LT=low titer, BV=bone density, CV=cardiovascular, CNS=central nervous system, C=myopathy, N=nausea/vomiting, GI=gastrointestinal, T6=triglycerides, LFT= lactic acidosis, pancreatitis, HA=headache, N/V=nausea/vomiting, 3TC=lamivudine, BID=twice daily, EFV=efavirenz, ZDV=zidovudine, d4T=stavudine, PPIs=proton pump inhibitors, COBI=cobicistat

* Tenofovir DF is a nucleoside reverse transcriptase inhibitor; C Elvitegravir not available as a single agent, only available as a co-formulation in Stridal®

---

Appendix D\(^{9,26}\)
### Dolutegravir (Tivicay®) Monograph\textsuperscript{26,27}

<table>
<thead>
<tr>
<th>Class/Abbrev.</th>
<th>Integrase strand transfer inhibitor (INSTI) / DTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOA</td>
<td>Binds to integrase active site and inhibits the strand transfer step of HIV-1 DNA integration necessary for the HIV replication cycle</td>
</tr>
</tbody>
</table>

**Indications**
- Treatment naïve or treatment-experienced INSTI-naïve: \textbf{50 mg po daily}
- Treatment naïve or treatment-experienced INSTI-naïve when co-administered with efavirenz, fosamprenavir/r, tipranavir/r, or rifampin: \textbf{50 mg po BID}
- INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance: \textbf{50 mg po BID}

**Dosing Considerations**
- \textbf{No} renal adjustment required
- \textbf{No} hepatic adjustment required
- \textbf{May be taken} without regards to meals
- \textbf{Take 2 hours} before or \textbf{6 hours} after multivitamins, antacids, or \textbf{Mg}\textsuperscript{2+}/\textbf{Al}\textsuperscript{3+}/\textbf{Fe}\textsuperscript{2+}/\textbf{Ca}\textsuperscript{2+} products

**Medication Guide**
REQUIRED

**PK/PD**
- Absorption: High fat meals increased dolutegravir AUC by 66% and increased Cmax by 67% - but may be taken without regards to meals
- Distribution: \(V_d=17.4\) L
- Protein binding: 98.9%
- Metabolism: Primarily via UGT1A1; some with CYP3A4
- Half-life: 14 hours
- Time to peak: 2-3 hours
- Excretion: feces (53% as unchanged drug); urine (31% as metabolites, <1% as unchanged drug)

**Warnings/Precautions**
- \textbf{Fat redistribution}: Buffalo hump, peripheral wasting with ↑abdominal girth, and cushingoid appearance
- \textbf{Hypersensitivity reactions}: Rash, constitutional findings, and organ dysfunction (i.e., liver injury)
- \textbf{IRIS}: Patients may develop immune reconstitution inflammatory syndrome
- \textbf{Increased LFTs}: Patients with underlying hepatic disease (i.e., hepatitis B or C co-infection) may be at increased risk of development or worsening ↑LFTs

**Drug Interactions**
- Leads to ↓DTG: NNRTIs (etravirine, efavirenz, nevirapine), PIs (fosamprenavir/r, tipranavir/r), antiepileptics (oxcarbazepine, phenytoin, phenobarbital, carbamazepine), antidepressants (St. John’s wort), antacids (containing Mg\textsuperscript{2+}, Al\textsuperscript{3+}, Fe\textsuperscript{2+}, or Ca\textsuperscript{2+}), antibiotics (rifampin)
- Leads to ↑metformin: metformin co-administered with DTG

**Adverse Reactions (1-10%)**
- **CNS**: insomnia (7%), HA (2%), fatigue (2%)
- **Dermatologic**: pruritus (2%), hypersensitivity reaction (1%)
- **Endocrine/metabolic**: hyperglycemia (5-7%), hyperbilirubinemia (2%)
- **GI**: ↑serum lipase (8%), abdominal distress (2%), flatulence (2%), vomiting (2%), diarrhea (1%), nausea (1%)
- **Hematologic/oncologic**: leukopenia (2-3%), neutropenia (1%)
- **Hepatic**: hepatitis (2%), ↑ALT (8%), ↑AST (6%)
- **Neuromuscular/skeletal**: Myositis (2%), ↑CPK (1-4%)
- **Renal**: renal insufficiency (2%)
- **Immune**: IRIS (1%)

**Pregnancy**
Category B

**Lactation**
Excretion in breast milk unknown/CI

**Additional Information**
### Appendix F

**Table 4: When to start ART in adults and adolescents (WHO 2013 Guidelines)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, moderate-quality evidence</td>
<td>ART should be initiated in all individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count &lt;350 cells/µL</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence</td>
<td>ART should be initiated in all individuals with HIV with a CD4 count between 350 – 500 cells/µL regardless of WHO clinical stage</td>
</tr>
<tr>
<td>Strong recommendation, high-quality evidence</td>
<td>ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in partners with HIV in serodiscordant couples</td>
</tr>
<tr>
<td>Strong recommendation, low-quality evidence</td>
<td>ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in individuals with HIV and active TB disease</td>
</tr>
<tr>
<td>Strong recommendation, low-quality evidence</td>
<td>ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in individuals co-infected with HIV and HBV with evidence of severe chronic liver disease</td>
</tr>
<tr>
<td>Strong recommendation, moderate-quality evidence</td>
<td>ART should be initiated in all individuals with HIV regardless of WHO clinical stage or CD4 cell count in pregnant and breastfeeding women with HIV</td>
</tr>
</tbody>
</table>

---

**Table 5: What ART regimens to start with for adults and adolescents (WHO 2013 Guidelines)**

#### First Line

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Strong recommendation, moderate-quality evidence | **2 NRTIs + 1 NNRTI**  
- *Preferred:* TDF + 3TC (or FTC) + EFV  
  If *preferred* option is contraindicated or not available, one of the following is recommended:  
  - AZT + 3TC + EFV  
  - AZT + 3TC + NVP  
  - TDF + 3TC (or FTC) + NVP |

**Comments:** Countries should discontinue d4T use in first-line regimens because of its well-recognized metabolic toxicities

#### Second Line

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Strong recommendation, moderate-quality evidence | **2 NRTIs + 1 PI (boosted with ritonavir)**  
- *Preferred:* AZT + 3TC as NRTI backbone + ATV/r (or LPV/r)  
  If *preferred* option has resulted in treatment failure:  
  - TDF + 3TC (or FTC) as NRTI backbone + ATV/r (or LPV/r) |

#### Third Line

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Conditional recommendation, low-quality evidence | - National programs should develop policies for 3rd line ART  
- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and 2nd generation NNRTIs and PIs |
| Conditional recommendation, very low-quality evidence | - Patients on failing 2nd line regimen with no new ARV options should continue with a tolerated regimen |

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Key to Abbreviations: ART=antiretroviral therapy, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, TDF=tenofovir disoproxil fumarate, 3TC=lamivudine, FTC=emtricitabine, EFV=efavirenz, AZT=zidovudine, NVP=nevirapine, PI=protease inhibitor, RTV=ritonavir, d4T=stavudine, ATV=atazanavir/ritonavir, LPV=lopinavir/ritonavir
Table 6: Laboratory Monitoring Schedule for Patients Before and After Initiation of Antiretroviral Therapy (ART)\textsuperscript{17}

<table>
<thead>
<tr>
<th>Test</th>
<th>Entry into care</th>
<th>F/u prior to ART</th>
<th>ART initiation or change</th>
<th>F/u 2-8 weeks post-ART initiation or change</th>
<th>Every 3-6 months</th>
<th>Every 6 months</th>
<th>Every 12 months</th>
<th>Treatment failure</th>
<th>Clinically indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV serology</td>
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<td>CD4 count</td>
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<td>HIV VL</td>
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<td>Resistance testing</td>
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<td>HLA-B*5701 testing</td>
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<tr>
<td>Tropism testing – If considering CCR5 antagonist or CCR5 antagonist failure</td>
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<tr>
<td>Hepatitis B serology</td>
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<tr>
<td>Hepatitis C serology, with confirmation of positive results</td>
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<tr>
<td>Basic chemistry</td>
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<tr>
<td>ALT, AST, bilirubin</td>
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<td>CBC with differential</td>
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<tr>
<td>Fasting lipid panel</td>
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<tr>
<td>Fasting glucose or HgA1C</td>
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<tr>
<td>Urinalysis</td>
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<tr>
<td>Pregnancy test</td>
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</tbody>
</table>

Key to Abbreviations: F/u=follow-up; VL=viral load; dx=diagnosis; pts=patients; UDVL=undetectable viral load; ABC=abacavir; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; EFV=efavirenz; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; TDF=tenofovir; ZDV=zidovudine
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References


