Updates on Human Immunodeficiency Virus (HIV)

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Citation
Ojeda, Jose, "Updates on Human Immunodeficiency Virus (HIV)" (2020). All Publications. 3373.
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Updates on Human Immunodeficiency Virus (HIV)

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Baptist Health South Florida
Objectives

- Provide an overview on HIV
- Review the antiretroviral classes available for the management of HIV and their place in therapy
- Evaluate the new HIV treatment options
- Differentiate between pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP)
- Discuss the pharmacist role in the treatment of HIV
HIV Overview

- HIV attacks the body’s immune system, particularly the CD4 cells which are used to fight off infections.
- As the human body is unable to completely eradicate the virus, HIV is considered a life diagnosis and generally uncurable.
- HIV can lead to acquired immunodeficiency syndrome (AIDS) if untreated.
- With proper medical care, HIV can be controlled and patients are expected to have a similar life-expectancy to someone living without HIV.
- Antiretroviral therapy (ART) are medications utilized in the treatment of HIV.
- Patients are usually able to achieve an undetectable viral load by taking their ART as prescribed.

Source: CDC - HIV Basics.
Stages of Untreated HIV

HIV Stages

**Stage 1: Acute Infection**

- The virus invades the body’s CD4 cells and starts to replicate
- In the process of replication, the virus establishes reservoirs
- During the acute phase, the individual’s body tries to fight off the virus
- Many people experience flu-like symptoms during this stage, which occurs around 2-4 weeks after initial exposure
- Seroconversion occurs during this time

HIV Stages

- **Stage 2: Latency Period**
  - Around 6 weeks following HIV infection, a stage with no signs or symptoms begins.
  - This stage is characterized by a slow reduction in CD4 cell count and gradual increase in HIV viral load.
  - Majority of patients remain in this disease stage for around 10 years (in the absence of treatment).

HIV Stages

Stage 3: AIDS

- Usually occurs when CD4 cell count decreases to <200 cells/mm$^3$ or the patient develops an AIDS-defining condition
- Opportunistic infections and cancers start to emerge due to depletion of the immune system
- Viral load once again begins to rapidly increase
- ART prevents patients from reaching this stage
- For patients that have been untreated and reach this stage, ART can still improve CD4 cell count and decrease viral load

AIDS-Defining Conditions

- Cytomegalovirus Retinitis (with loss of vision)
- Pneumocystis Jiroveci Pneumonia
- Chronic Intestinal Cryptosporidiosis
- HIV-Related Encephalopathy
- Mycobacterium Tuberculosis (pulmonary or extrapulmonary)
- Invasive Cervical Cancer

HIV Transmission Myths

Source: Myths About HIV and AIDS. Avert.
HIV Transmission

Source: Myths About HIV and AIDS. Avert.
HIV Transmission Studies

Undetectable = Untransmittable

These four studies included more than a 100,000 sex acts without condom use; yet there were ZERO cases of HIV transmission in partners of undetectable patients.

HIV Transmission

HIV Prevalence

Prevalence increased by 15%

Source: Epidemiology of HIV. National HIV Curriculum.
HIV Incidence

Source: Epidemiology of HIV. National HIV Curriculum.

Incidence decreased by 13%
HIV Rates in the U.S.

## New Diagnosis of HIV in the U.S.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Area</th>
<th>Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Miami – Fort Lauderdale – West Palm Beach, Florida</td>
<td>34.4</td>
</tr>
<tr>
<td>2</td>
<td>Atlanta – Sandy Springs – Roswell, Georgia</td>
<td>28.5</td>
</tr>
<tr>
<td>3</td>
<td>Memphis, Tennessee</td>
<td>27.8</td>
</tr>
<tr>
<td>4</td>
<td>Baton Rouge, Louisiana</td>
<td>27.5</td>
</tr>
<tr>
<td>5</td>
<td>Orlando – Kissimmee – Sanford, Florida</td>
<td>27.3</td>
</tr>
<tr>
<td>6</td>
<td>New Orleans – Metairie, Louisiana</td>
<td>24.6</td>
</tr>
<tr>
<td>7</td>
<td>Jackson, Mississippi</td>
<td>23.6</td>
</tr>
<tr>
<td>8</td>
<td>Augusta – Richmond County, Georgia</td>
<td>23.5</td>
</tr>
<tr>
<td>9</td>
<td>Jacksonville, Florida</td>
<td>21.2</td>
</tr>
<tr>
<td>10</td>
<td>Houston – The Woodlands – Sugar Land, Texas</td>
<td>20.6</td>
</tr>
</tbody>
</table>

*Rates are per 100,000 people*

New HIV Diagnosis among MSM

MSM: Men who have sex with men

New HIV Diagnosis among MSM

Incidence of HIV among Latinos and African American MSM ages 25-34 from 2010 to 2016

- **65% Increase** among African American gay & bisexual men ages 25-34
- **68% Increase** among Latino gay & bisexual men ages 25-34

# Types of HIV Tests

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>What does the test detect?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RNA/DNA</td>
</tr>
<tr>
<td>PCR/viral load</td>
<td></td>
</tr>
<tr>
<td>p24 test</td>
<td></td>
</tr>
<tr>
<td>4th generation test</td>
<td></td>
</tr>
<tr>
<td>1st/2nd/3rd generation tests</td>
<td></td>
</tr>
<tr>
<td>Rapid test: finger prick and oral swab</td>
<td></td>
</tr>
<tr>
<td>(ex: OraQuick)</td>
<td></td>
</tr>
<tr>
<td>Western blot tests</td>
<td></td>
</tr>
</tbody>
</table>

Source: HIV i-Base. Different Types of HIV tests.
Time to HIV Antigen and Antibody Detection

Potential Exposure to HIV

- Day 0
  - HIV Viral Load can be detected. HIV RNA Test can be taken.

- Day 16
  - p24 can be detected.

- Day 28
  - 4th Generation Antigen/Antibody Test can detect HIV infection.

- Day 90
  - Antibody Test Can Detect HIV infection.

Source: HIV RNA Test. HIV RNA Test for HIV Early Detection.
Rapid ART Initiation

- ART should be initiated as soon as possible
- Immediate ART treatment has been shown to reduce both AIDS and non-AIDS related events
- There is no increase in adverse events with immediate versus delayed ART

HIV Life Cycle

1. **Binding (also called Attachment):** HIV binds to receptors on the surface of a CD4 cell.
   - CCR5 Antagonist
   - Post-attachment inhibitors

2. **Fusion:** The HIV envelope and the CD4 cell membrane fuse, allowing HIV to enter the CD4 cell.
   - Fusion inhibitors

3. **Reverse Transcription:** Inside the CD4 cell nucleus, HIV releases and uses reverse transcriptase (an HIV enzyme) to convert its genetic material—HIV RNA—into HIV DNA. The conversion of HIV RNA to HIV DNA allows HIV to enter the CD4 cell nucleus and combine with the cell’s genetic material—cell DNA.
   - Nucleoside reverse transcriptase inhibitors (NRTIs)
   - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

4. **Integration:** Inside the CD4 cell nucleus, HIV releases integrase (an HIV enzyme). HIV uses integrase to insert (integrate) its viral DNA into the DNA of the CD4 cell.
   - Integrase inhibitors

5. **Replication:** Once integrated into the CD4 cell DNA, HIV begins to use the machinery of the CD4 cell to make long chains of HIV proteins. The protein chains are the building blocks for more HIV.

6. **Assembly:** Newly formed immature (noninfectious) HIV moves to the surface of the cell and assembles into immature (noninfectious) HIV.

7. **Budding:** Newly formed immature (noninfectious) HIV pushes itself out of the host CD4 cell. The new HIV releases protease (an HIV enzyme). Protease breaks up the long protein chains in the immature virus, creating the mature (infectious) virus.
   - Protease inhibitors (PIs)

HIV Treatment

- An ART regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a 3rd active drug from one of the following classes:
  - Integrase strand transfer inhibitors (INSTI)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTI)
  - Protease inhibitors (PI)

- Currently, the Department of Health and Human Services (DHHS) guidelines recommend INSTI-based regimens for most ART-naive patients.

Source: US DHHS. Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2019.
# First-Line Treatment

<table>
<thead>
<tr>
<th>Brand</th>
<th>Recommended Initial Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biktarvy®</td>
<td>Bictegravir/tenofovir alafenamide/emtricitabine</td>
</tr>
<tr>
<td>Dovato®</td>
<td>Dolutegravir/lamivudine (Except for patients with HIV RNA &gt;500,000 copies/mL or with hepatitis B co-infection)</td>
</tr>
<tr>
<td>Triumeq®</td>
<td>Dolutegravir/abacavir/lamivudine (Except for patients who are HLA-B*5701 positive or with hepatitis B co-infection)</td>
</tr>
<tr>
<td>Tivicay® and Truvada® or Descovy®</td>
<td>Dolutegravir plus tenofovir*/emtricitabine</td>
</tr>
<tr>
<td>Isentress® and Truvada® or Descovy®</td>
<td>Raltegravir plus tenofovir*/emtricitabine</td>
</tr>
</tbody>
</table>

*Tenofovir formulation can be either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)

Source: US DHHS. Guidelines for Use of Antiretroviral Agents in Adults and Adolescents with HIV. 2019.
## TAF versus TDF

<table>
<thead>
<tr>
<th></th>
<th>TAF</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>Comparable</td>
<td>Comparable</td>
</tr>
<tr>
<td><strong>Renal toxicity</strong></td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td><strong>risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bone density</strong></td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td><strong>decrease risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight gain</strong></td>
<td>↑</td>
<td>⇄</td>
</tr>
</tbody>
</table>

## INSTI-Based Regimen Selection

Factors that influence the choice of INSTI regimen in treatment-naive patients:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Dolutegravir | • Few drug interactions  
• Single-tablet formulation  
• Higher barrier to resistance  
• Preferred ARV in pregnancy  
• Can be used for rapid ART start | • Co-formulated with abacavir and lamivudine                                   |
| Bictegravir | • Few drug interactions  
• Single-tablet formulation  
• Higher barrier to resistance  
• Can be used for rapid ART start | • Lack of data in pregnancy                                                  |
| Raltegravir  | • Few drug interactions  
• Available as daily dosing  
• Preferred ARV in pregnancy | • Not available as a single-tablet formulation  
• Lower barrier to resistance  
• Twice daily option           |
| Elvitegravir | • Single-tablet formulation  
• Can be used for rapid ART start | • Lower barrier to resistance  
• Avoid in pregnancy due to inadequate drug concentrations in the 2\textsuperscript{nd}/3\textsuperscript{rd} trimesters |

Abacavir Hypersensitivity Reaction

- **Black box warning:** 2-9% incidence of hypersensitivity reaction
  - Caucasian > African American > Latino > Asian

- HLA-B*5701 testing should precede the use of abacavir
  - Record positive result as a true allergy

- Patients should be counseled on signs and symptoms of abacavir hypersensitivity, which include:
  - Fever, rash, nausea/vomiting, flu-like symptoms
  - Onset is 4-6 weeks with a median of 9 days

True/False Question

- The initial antiretroviral regimen recommended for most treatment-naive patients consists of two NRTIs and a boosted PI.
True/False Question

Answer

- The initial antiretroviral regimen recommended for most treatment-naive patients consists of two NRTIs and a boosted PI —False!
  - The initial antiretroviral regimen for a treatment-naive patient usually consists of two NRTIs plus an INSTI
Complete Two-Drug ART

- Dovato® is now recommended for treatment-naive patients first-line
- There are considerations as to whom should be taking this medication
  - Still not recommended for certain patient populations
  - Adherence is extremely important
  - Good for patients that cannot use abacavir, TDF, or TAF

Juluca® (dolutegravir/rilpivirine) is FDA-approved for HIV treatment in select patients.

Considerations for this medication include:

- Not recommended for treatment-naive patients
- Approved for use in patients that are virologically suppressed ≥ 6 months on a stable regimen with no treatment failure and no resistance mutations
- Adherence is very important
- Rilpivirine requires food for optimal absorption
- Patients should not use proton pump inhibitors

True/False Question

- Dovato® is the first FDA-approved complete two-drug regimen for treatment-naive HIV-infected patients
Dovato® is the first FDA-approved complete two-drug regimen for treatment-naive HIV-infected patients—True!

- Dovato® components include dolutegravir and lamivudine
HIV Comorbidities

- Evaluate the patient as a whole when initiating ART treatment
- Most common comorbidities in people living with HIV include:
  - Hypertension: 25-65%
  - Hyperlipidemia: 22-48%
  - Diabetes: 9-31%
  - Renal impairment: 5-20%
  - Cardiovascular (CV) events: 3-16%

### HIV Treatment

**ART to avoid in patients with select comorbidities:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Consider Avoiding</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| Chronic Kidney Disease (CrCl ≤ 59 mL/min) | TDF  
  Exception: ESRD                                   | Risk of nephrotoxicity                             |
| Osteoporosis                          | TDF                                                    | Risk of decreasing bone mineral density            |
| Severe Liver Disease                  | Abacavir, nevirapine, atazanavir, darunavir, elvitegravir | Risk of increasing liver enzymes                   |
| Psychiatric Disorders                 | Efavirenz, rilpivirine                                 | Risk of exacerbating psychiatric behaviors and/or increasing suicide risk |
| Cardiovascular Risk                   | Abacavir, lopinavir/ritonavir                          | Increased CV risk observed in studies              |
| Dyslipidemia                          | Boosted protease inhibitors, efavirenz, elvitegravir/cobicistat, TDF | Risk of hyperlipidemia                            |

CrCl: Creatinine clearance

# Opportunistic Infection Prophylaxis

## Pneumocystis jiroveci Pneumonia (PJP)

<table>
<thead>
<tr>
<th>Indication for initiation</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. CD4 count &lt; 200 cells/mm³ or 2. CD4 percentage &lt; 14% or 3. CD4 count 200-250 cells/mm³ with delayed initiation of ART and frequent CD4 count monitoring not possible</td>
<td></td>
</tr>
</tbody>
</table>

### Prophylaxis

**Preferred therapy:**
- TMP/SMX DS or SS daily

**Alternative therapy:**
- TMP/SMX DS three times per week
- Dapsone 100 mg daily or dapsone 50 mg twice daily
- Atovaquone 1,500 mg daily
- Aerosolized pentamidine 300 mg (nebulizer) every month

### Indication for discontinuation
- CD4 count ≥ 200 cells/mm³ for ≥ 3 months in response to ART
- CD4 count between 100-200 cells/mm³ and HIV RNA undetectable for ≥ 3 months

---

**Abbreviations:**
- TMP/SMX: Sulfamethoxazole/Trimethoprim
- DS: Double strength; SS: Single strength

### Opportunistic Infection Prophylaxis

**Toxoplasma gondii Encephalitis**

<table>
<thead>
<tr>
<th>Indication for initiation</th>
<th>1. CD4 count $&lt; 100$ cells/mm$^3$ and Toxoplasma IgG positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prophylaxis</strong></td>
<td><strong>Preferred therapy:</strong></td>
</tr>
<tr>
<td></td>
<td>• TMP/SMX DS daily</td>
</tr>
<tr>
<td></td>
<td><strong>Alternative therapy:</strong></td>
</tr>
<tr>
<td></td>
<td>• TMP/SMX DS three times per week</td>
</tr>
<tr>
<td></td>
<td>• TMP/SMX SS daily</td>
</tr>
<tr>
<td></td>
<td>• Atovaquone 1,500 mg daily</td>
</tr>
<tr>
<td><strong>Indication for discontinuation</strong></td>
<td>• CD4 count $\geq 200$ cells/mm$^3$ for $\geq 3$ months in response to ART</td>
</tr>
<tr>
<td></td>
<td>• CD4 count between 100-200 cells/mm$^3$ and HIV RNA undetectable for $\geq 3$ months</td>
</tr>
</tbody>
</table>

### Opportunistic Infection Prophylaxis

| Indication for initiation | Primary prophylaxis is not recommended for adults and adolescents who immediately initiate ART  
| | 1. CD4 count < 50 cells/mm³ not on fully suppressive ART |
| Prophylaxis | Preferred therapy:  
| | • Azithromycin 1,200 mg once weekly  
| | • Azithromycin 600 mg twice weekly  
| | • Clarithromycin 500 mg twice daily  
| | Alternative therapy:  
| | • Rifabutin 300 mg daily |
| Indication for discontinuation | • Initiation on effective ART |

PrEP versus PEP

- PrEP and PEP are methods for preventing HIV infection that involve taking HIV medications.
- PrEP and PEP are for people who do not have HIV but are at risk of acquiring it.

<table>
<thead>
<tr>
<th></th>
<th>PrEP</th>
<th>PEP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When is it taken?</strong></td>
<td>Before HIV exposure</td>
<td>After HIV exposure, should be taken within 72 hours after possible exposure</td>
</tr>
<tr>
<td><strong>Who is it for?</strong></td>
<td>For people that are HIV-negative and:</td>
<td>For people that are HIV-negative but may have been exposed through:</td>
</tr>
<tr>
<td></td>
<td>• Have sex with an HIV-positive partner</td>
<td>• Sexual intercourse</td>
</tr>
<tr>
<td></td>
<td>• Have multiple partners or partner(s) with unknown HIV status</td>
<td>• Needle-stick injury</td>
</tr>
<tr>
<td></td>
<td>• Share injection drug equipment</td>
<td>• Sharing injection drug equipment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sexual assault</td>
</tr>
<tr>
<td><strong>How effective is it?</strong></td>
<td>If used as directed, can reduce HIV risk from:</td>
<td>PEP effectiveness decreases as time passes after exposure, but if started soon after exposure, it can reduce HIV risk by more than 80%</td>
</tr>
<tr>
<td></td>
<td>• Sexual intercourse by 99%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Injection drug use by at least 74%</td>
<td></td>
</tr>
</tbody>
</table>

**PrEP**

**ESTIMATED NUMBER OF ADULTS WHO COULD POTENTIALLY BENEFIT FROM PREP, UNITED STATES, 2015**

<table>
<thead>
<tr>
<th></th>
<th>Gay, bisexual, or other men who have sex with men</th>
<th>Heterosexually active adults</th>
<th>Persons who inject drugs</th>
<th>Total by race/ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black/African American, non-Hispanic</td>
<td>309,190</td>
<td>164,660</td>
<td>26,490</td>
<td>500,340</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>220,760</td>
<td>46,580</td>
<td>14,920</td>
<td>282,260</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>238,670</td>
<td>36,540</td>
<td>28,020</td>
<td>303,230</td>
</tr>
<tr>
<td>Total who could potentially benefit from PrEP</td>
<td><strong>813,970</strong></td>
<td><strong>258,080</strong></td>
<td><strong>72,510</strong></td>
<td><strong>1,144,550</strong></td>
</tr>
</tbody>
</table>

Notes: PrEP = pre-exposure prophylaxis; data for "other race/ethnicity" are not shown

Only 90,000 PrEP prescriptions were filled in 2015

PrEP

44% of people who could potentially benefit from PrEP are African American – approximately 500,000 people…

…but only 1% of those – 7,000 African Americans – were prescribed PrEP*

25% of people who could potentially benefit from PrEP are Latino – nearly 300,000 people…

…but only 3% of those – 7,600 Latinos – were prescribed PrEP*

Source: CDC – 2018 Conference on Retroviruses and Opportunistic Infections.
PrEP

- As of December 2019, there are two FDA-approved medications that can be utilized for PrEP
  - Truvada® (TDF plus emtricitabine)
  - Descovy® (TAF plus emtricitabine)
- There are other options currently being tested for PrEP
  - Long acting injectable (late phase development)
  - Long acting implantable (early phase development)
  - Topical/local approach (early phase development)

Why is PrEP important?

PrEP is 99% effective in reducing the risk of acquiring HIV through sexual contact.
PrEP is 99% effective in reducing the risk of acquiring HIV through sexual contact — True!
## PEP

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Preferred/Alternative</th>
<th>Medication</th>
</tr>
</thead>
</table>
| Adults, adolescents ≥ 13 years of age, or pregnant women with normal renal function (CrCl ≥ 60 mL/min) | Preferred | Emtricitabine/tenofovir once daily *with either:*  
  - Raltegravir 400 mg twice daily *or* dolutegravir 50 mg once daily |
| | Alternative | Emtricitabine/tenofovir once daily *with both:*  
  - Darunavir 800 mg once daily *and* ritonavir 100 mg once daily |
| Adults, adolescents ≥ 13 years of age, or pregnant women with renal dysfunction (CrCl ≤ 59 mL/min) | Preferred | Lamivudine/zidovudine once daily (renally adjusted) *with either:*  
  - Raltegravir 400 mg twice daily *or* dolutegravir 50 mg once daily |
| | Alternative | Lamivudine/zidovudine once daily (renally adjusted) *with both:*  
  - Darunavir 800 mg once daily *and* ritonavir 100 mg once daily |

Duration: Taken for 28 days

Source: Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV. 2016.
Pharmacist Role

- **Counseling**
  - Adherence
  - Common and severe side effects
  - Time to undetectable viral load

- **Supportive treatment**
  - Serve as a liaison to provide the most appropriate treatment to patients

- **Therapy recommendation**
  - Support the patients and encourage them to advocate for themselves
  - Contact prescribers and inform them about possible side effects

Tools to Assist with Adherence

- Pharmacy refill reminders or auto-refill
- Device reminders (alarms/smartphone apps)
- Medication diaries
- Reminder packaging (pill boxes)
- Involve patient’s support system

Conclusion

- New and groundbreaking ART options keep emerging
- Populations such as MSM are still at risk
- Novel and simpler therapies are being integrated into the guidelines
- Pharmacists can have a significant impact on HIV treatment
  - Linkage to care
  - Counseling
  - Selection and optimization of ART
  - Management of concurrent disease states

Questions?
References

- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. 2019.