HIV Treatment Update

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Objectives

- Review antiretroviral therapy (ART) medications used for the treatment of HIV, including new combination products
- Outline the “recommended”, “alternative”, and “other” HIV regimens in treatment-naive patients according to the updated 2015 Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents
- Summarize the updates on the treatment and prevention of opportunistic infections in HIV-infected individuals according to the latest 2015 DHHS Guidelines

Epidemiology

- >1.2 million people in the U.S. are living with HIV
- 1 in 8 people are unaware
- 13,712 people with an AIDS diagnosis died in 2012.
Who to treat with ART?

- **Older** recommendations:
  - Based on CD4 count
  - More recently, recommended everyone be treated with ART, but level of evidence depended on CD4 count
  - CD4 350 to 500 cells/mm$^3$ (AII) and >500 cells/mm$^3$ (BIII)

- **New** recommendations:
  - Results from START and TEMPRANO clinical trials published in 2015
  - Large, randomized, controlled trials
  - Provided significant evidence of the benefit of early ART
  - Strength of recommendation for all patients to be started regardless of CD4 count (AII)

Human Immunodeficiency Virus: Treatment

- **Goals of therapy**
  - Prevent disease progression
  - Decrease viral transmission

- **Surrogate markers:**
  - **Viral Load**
    - Surrogate for treatment response
    - Takes 8-24 weeks to achieve viral suppression in most patients
    - Sub-optimal response versus virologic failure
  - **CD4**
    - Immune response
    - Should increase ~150 cells/mm$^3$ after first year of ART therapy, then 50-100 cells/mm$^3$ in subsequent years
    - 15-20% patients with low CD4 count remain low

ART Drug Classes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Entry Inhibitor:</td>
<td>Maraviroc (Selzentry)</td>
<td>CCR5 Tropic HIV-1</td>
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<tr>
<td>2) Entry Inhibitor:</td>
<td>Enfuvirtide (Fuzeon)</td>
<td>Subcutaneous injection</td>
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<tr>
<td>3) Reverse Transcriptase Inhibitors</td>
<td>Nucleoside reverse transcriptase inhibitors (NRTI)</td>
<td>NRTI – &quot;back-bone&quot;</td>
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<tr>
<td></td>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTI)</td>
<td>NNRTI – efavirenz, nevirapine, etravirine</td>
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<tr>
<td>4) Integrase Strand Transfer Inhibitor</td>
<td>INSTI</td>
<td>End in &quot;navir&quot;</td>
</tr>
<tr>
<td>5) Protease Inhibitors</td>
<td>PI</td>
<td>End in &quot;navir&quot;</td>
</tr>
</tbody>
</table>

ART for HIV Infection

- Initial therapy generally consists of:
  - Two NRTIs:
    - Tenofovir/Emtricitabine
    - Or Abacavir/Lamivudine
  - One ARV from either of the following classes:
    - INSTI
    - NNRTI
    - Boosted PI


HIV Cell Entry

1) HIV Cell Entry
2) Cell Membrane Fusion
3) Reverse transcriptase converts viral RNA to DNA
4) Viral DNA integrated into host DNA
5) Immature HIV strands cleaved = infectious virus

Recommended Regimens before April, 2015

NNRTI-Based
- Efavirenz + tenofovir/emtricitabine
- Rilpivirine + tenofovir/emtricitabine (only if CD4 > 200 cells/mm³)

Integrase Inhibitor-Based
- Raltegravir + tenofovir/emtricitabine
- Dolutegravir + tenofovir/emtricitabine
- Elvitegravir/cobicistat/tenofovir/emtricitabine
- Dolutegravir + abacavir/lamivudine

Protease Inhibitor-Based
- Darunavir/ritonavir + tenofovir/emtricitabine
- Atazanavir/ritonavir + tenofovir/emtricitabine
- Atazanavir/ritonavir + abacavir/lamivudine

Only if baseline viral load < 100,000 copies/mL

NNRTI-Based:
- Rilpivirine + tenofovir/emtricitabine (only if CD4 > 200 cells/mm³)
- Efavirenz + abacavir/lamivudine

### Literature Update

- **ACTG A5257** - A large randomized controlled trial (2014)
  - Atazanavir/ritonavir (n=605) versus darunavir/ritonavir (n=601) or raltegravir (n=603), each with tenofovir/emtricitabine
  - At week 96, all 3 regimens had similar virologic efficacy

### Literature Update

- **2014 Analysis of 4 AIDS Clinical Trial Groups studies of efavirenz containing regimens (n=3241) and efavirenz-free regimens (n=2091)**
  - Conclusion
    - Initial treatment with efavirenz was associated with a 2-fold increased hazard of suicidality compared with an initial regimen without efavirenz

### Literature Update

- **D:A:D (Data collection on Adverse events of Anti-HIV Drugs) study (2014)**
  - Retrospective analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS)
  - Found no association between efavirenz use and suicidality
**Literature Update**

- **Cobicistat (Tybost)**
  - Pharmacokinetic booster that inhibits CYP3A4
  - **Dose:**
    - 150 mg daily with Atazanavir 300 mg (Combination product Evotaz)
    - 150 mg daily with Darunavir 800 mg (Combination product Prezista)
    - 150 mg daily in combination product Elvitegravir/cobicistat/tenofovir DF/emtricitabine (Stribild)
    - 150 mg daily in combination product Elvitegravir/cobicistat/tenofovir DF/emtricitabine (Genvoya)

- **Misconception: Renal dose adjustments**
  - No adjustments necessary
  - If used with tenofovir, CrCl < 70 mL/min, coadministration not recommended

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**Literature Update**

- **Pharmacokinetic enhancer: Cobicistat**
  - The 2013 Gilead Study 114 enrolled 692 treatment-native patients
    - Atazanavir + tenofovir/emtricitabine boosted with ritonavir or cobicistat
  - The two regimens had similar percentages of adverse events, changes in serum creatinine, and changes in bilirubin levels


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**Literature Update**

- **2014 Open-label, single-arm trial of darunavir/cobicistat**
  - N=313
  - Evaluated in combination with NRTIs (99% given tenofovir/emtricitabine)
  - Week 48 → 81% of participants achieved HIV RNA < 50 copies/mL
  - 5% discontinued due to adverse effects

Literature Update

- Tenofovir and renal dysfunction
- Tenofovir disoproxil fumarate
  - Readily converts to tenofovir in plasma after absorption
- Risk factors:
  - Advanced HIV disease
  - Longer treatment history
  - Low body weight, especially in females
  - Pre-existing renal impairment
- Renal impairment
  - Proximal renal tubulopathy
  - Fanconi Syndrome
  - Osteomalacia

New salt form of tenofovir: Tenofovir alafenamide
- Oral prodrug of tenofovir
- Converted to tenofovir and then to tenofovir-diphosphate intracellularly
- Remains stable in plasma resulting in ↓plasma and higher intracellular tenofovir concentration ↑
- Potential for adverse kidney and bone effects: tenofovir alafenamide < tenofovir disoproxil fumarate

Clinical trials
- 2 double-blinded, phase 3, RCTs: Safety and efficacy
  - Elvitegravir/cobicistat/emtricitabine/TDF (Stribild) versus Elvitegravir/cobicistat/emtricitabine/TAF (Genvoya)
  - At 48 weeks, 800 of 866 (92%) in TAF arm and 784 of 867 (90%) in TDF arm:
    - HIV RNA < 50 copies/mL
    - Both regimens well-tolerated
    - TAF arm: smaller decline in eGFR (significant)
    - Less proteinuria, less bone mineral density reduction in spine and hip
**Recommended Regimens after April, 2015**

**NNRTI-Based**
- Efavirenz + tenofovir/emtricitabine

**Integrase Inhibitor-Based**
- Raltegravir + tenofovir/emtricitabine
- Elvitegravir/cobicistat/tenofovir/emtricitabine
- Dolutegravir + tenofovir/emtricitabine
- Dolutegravir + abacavir/lamivudine

**Protease Inhibitor-Based**
- Darunavir/ritonavir + tenofovir/emtricitabine
- Atezcanavir/ritonavir + tenofovir/emtricitabine

- Only if baseline viral load < 100,000 copies/mL

**NNRTI-Based**
- Rilpivirine/tenofovir/emtricitabine (only if CD4 > 200 cells/mm³)
- Efavirenz + abacavir/lamivudine

**Protease Inhibitor-Based**
- Atazanavir/ritonavir + abacavir/lamivudine

**Alternative regimens**

**NNRTI-Based**
- Efavirenz/tenofovir/emtricitabine
- Rilpivirine/tenofovir/emtricitabine
  - (Only with pre-treatment HIV RNA < 100,000 copies/mL & CD4 < 200 cells/mm³)

**Protease Inhibitor-Based**
- Atazanavir/cobicistat + tenofovir/emtricitabine
- Darunavir/ritonavir + tenofovir/emtricitabine
- Darunavir/cobicistat or Darunavir/ritonavir + abacavir/lamivudine
- Darunavir/ritonavir + tenofovir/emtricitabine
Other regimens

**NNRTI-Based**
- Efavirenz plus abacavir/lamivudine
  - (Only with pre-treatment HIV RNA < 100,000 copies/mL)

**Protease Inhibitor-Based**
- Atazanavir/cobicistat or Atazanavirritonavir + abacavir/lamivudine
  - (Only with pre-treatment HIV RNA < 100,000 copies/mL)
- Lopinavir/ritonavir + abacavir/lamivudine
- Lopinavir/ritonavir + tenofovir/emtricitabine

**When Tenofovir or Abacavir cannot be used**
- Darunavir/ritonavir + raltegravir (HIV RNA <100,000 copies/mL and CD4 >200 cells/mm³)
- Lopinavir/ritonavir + lamivudine

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**Once Daily Combination Pills**

<table>
<thead>
<tr>
<th>Drug Name Brand Name</th>
<th>FDA Approval date</th>
<th>Guidelines</th>
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</thead>
<tbody>
<tr>
<td><strong>NNRTI-Based</strong></td>
<td></td>
<td></td>
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<tr>
<td>Efavirenz, tenofovir, and lamivudine</td>
<td>Atripla July 13, 2006</td>
<td>Alternative</td>
</tr>
<tr>
<td>Rilpivirine, tenofovir disoproxil fumarate, and emtricitabine</td>
<td>Complera August 10, 2011</td>
<td>Alternative</td>
</tr>
<tr>
<td><strong>INSTI-Based</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir, cobicistat, tenofovir disoproxil fumarate</td>
<td>Stribild August 27, 2012</td>
<td>Recommended</td>
</tr>
<tr>
<td>Elvitegravir, cobicistat, tenofovir alafenamide fumarate</td>
<td>Genvoya November 5, 2015</td>
<td>Recommended</td>
</tr>
<tr>
<td>Elvitegravir, abacavir, and ritonavir</td>
<td>Triumeq August 22, 2014</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

**More Combination Pills**

<table>
<thead>
<tr>
<th>Drug Name Brand Name</th>
<th>FDA Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine and tenofovir</td>
<td>Combivir September 27, 1997</td>
</tr>
<tr>
<td>Lopinavir and ritonavir</td>
<td>Kaletra September 15, 2000</td>
</tr>
<tr>
<td>Abacavir, lamivudine, and zidovudine</td>
<td>Trizivir November 14, 2000</td>
</tr>
<tr>
<td>Emtricitabine and tenofovir</td>
<td>Truvada August 2, 2000</td>
</tr>
<tr>
<td>Abacavir and lamivudine</td>
<td>Epivir August 2, 2000</td>
</tr>
<tr>
<td>Atazanavir and cobicistat</td>
<td>Evotaz January 28, 2015</td>
</tr>
<tr>
<td>Dolutegravir and cobicistat</td>
<td>Prezista January 29, 2015</td>
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</tbody>
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Updates to the Treatment and Prevention of Opportunistic Infections in HIV-Infected Adults and Adolescents

Pyrimethamine (Daraprim)
- Antiparasitic agent:
  - Inhibits parasitic dihydrofolate reductase, inhibiting vital tetrahydrofolic acid synthesis
- Recommended for:
  - Treatment and prophylaxis of Toxoplasma encephalitis and Isospora infection
  - Prophylaxis of Pneumocystis pneumonia
- June 2015, no longer available in retail pharmacies
  - Sold only through special pharmacy program
  - Can no longer order from general wholesaler
- Be familiar with alternative agents for specific pathogens
  - Use until pyrimethamine available

Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Toxoplasmosis Encephalitis
- Toxoplasmic encephalitis (TE) is caused by the protozoan Toxoplasma gondii.
- Prevalence is 11% in the US
- Patients with CD4 counts < 50 cells/µL are at greatest risk
- Primary prophylaxis indications:
  - Toxoplasma IgG (+) patients with CD4 count <100 cells/mm3 (AII)
  - Toxoplasma seronegative patients receiving a PCP prophylaxis regimen not active against toxoplasmosis should have toxoplasma serology retested if CD4 count declines to <100 cells/mm3 (CIII)
  - Prophylaxis against toxoplasmosis should be initiated if seroconversion occurred (AII)
Toxoplasmosis Encephalitis

Treatment:
- Preferred Regimen (AI):
  - Pyrimethamine 200 mg PO once, then dose based on body weight:
    - Body Weight ≤60 kg:
      - Pyrimethamine 50 mg PO daily plus sulfadiazine 1000 mg PO q6h plus leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)
    - Body Weight >60 kg:
      - Pyrimethamine 75 mg PO daily plus sulfadiazine 1500 mg PO q6h plus leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

Alternative Regimens:
- Pyrimethamine (leucovorin) plus clindamycin 600 mg IV or PO q6h (AI)
- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO BID (BI))
- Atovaquoneb 1500 mg PO BID plus pyrimethamine (leucovorin) (BII)
- Atovaquoneb 1500 mg PO BID plus sulfadiazine (BII)
- Atovaquoneb 1500 mg PO BID (BII)
- Pyrimethamine (leucovorin) plus azithromycin 900–1200 mg PO daily (CII)

Note:
- If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine/sulfadiazine (BI).
- History of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI).
- Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).
Toxoplasmosis Encephalitis

**Treatment:**
- **TMP-SMX** (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID
  - Small, Randomized trial (n=77) comparing trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine
  - 40 patients treated with TMP-SMX and 37 were treated with pyrimethamine-sulfadiazine
  - There was no statistically significant difference in clinical efficacy during acute therapy

<table>
<thead>
<tr>
<th>Table 1. Radiologic response at the end of acute therapy for TE</th>
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<tbody>
<tr>
<td>Treatment response</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Cure</td>
</tr>
<tr>
<td>Death</td>
</tr>
<tr>
<td>No change or progression</td>
</tr>
<tr>
<td>*P = n.s.</td>
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</tbody>
</table>


Toxoplasmosis Encephalitis

- **Sulfa Desensitization Protocol**
  - example:
    - After each dose, patients drank 6 oz. of water
    - No pre-medication given
    - Mild toxic effects: macular rash, fever, nausea—symptomatic treatment
    - Anaphylactoid reactions: urticaria, dyspnea, severe vomiting, hypotension= stopped


Assessment Questions

**True/False:**
- Efavirenz/tenofovir/emtricitabine (Atripla) remains a preferred regimen for treatment-naive HIV-infected individuals
  - **False**
- The two protease inhibitors darunavir and atazanavir that may require boosting with ritonavir can now be boosted with cobicistat and are included as Alternative regimens
  - **True**
- Patients who are in need of a pyrimethamine-containing regimen for the treatment of an indicated opportunistic infection should have treatment withheld until pyrimethamine is available
  - **False**
Conclusion

- New, emerging information from clinical trials are continually coming out.
- It is important to keep up with the DHHS Guidelines on the treatment of HIV and opportunistic infections.
- Pharmacists can serve as pivotal team members in both outpatient and inpatient settings by having the latest information accessible.
- The Aids Info website (https://aidsinfo.nih.gov/) provides the guidelines from DHHS and the CDC and has pop-up announcements for updated information.

Questions?

References

References