HIV Medications and Side Effects

Benjamin Young, MD PhD
Rocky Mountain CARES
International Association of Physicians in AIDS Care
Learning Objectives

- Identify classes of HIV medications and mechanism of action
- Appreciate the importance of management of side effects on adherence and doctor-patient relationship
- Discuss commonly prescribed antiretroviral medications and their characteristic side effect profiles
Disclosures

Advisory Board: Bristol-Myers Squibb, Merck & Co, Viiv Healthcare
Research Support: Gilead Sciences, Merck & Co, Viiv Healthcare
Promotional Speakers Bureau: LabCorp, Merck & Co, Viiv Healthcare

Off-Label Disclosure

There will be no off-label/investigational uses discussed in this presentation.
Why antiretroviral medications?

- Availability of potent ART associated with dramatic reductions in HIV-associated morbidity and mortality
- ART can prevent HIV transmission
- Life expectancy among many HIV populations increasing
- Currently recommended ART is effective and well tolerated
HIV LIFE CYCLE

1. Free Virus
2. Binding and Fusion
   - CD4 Receptor
   - CCR5 Coreceptor
   - CXCR4 Coreceptor
3. Infection
4. Reverse Transcription
5. Integration
6. Transcription
7. Assembly
8. Budding
9. Immature virus breaks free and matures

Adapted from a project of the New Mexico AIDS Education and Training Center
Classes of Antiretrovirals

- Fusion inhibitor
- CCR5 antagonist
- Reverse Transcriptase inhibitors
  - Non-nucleosides (NNRTIs)
  - Nucleoside/tide (NRTIs)
- Integrase inhibitor
- Protease inhibitors
Current ARV Medications

**NRTI**
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

**NNRTI**
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

**PI**
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

**Integrase Inhibitor (II)**
- Raltegravir (RAL)

**Fusion Inhibitor**
- Enfuvirtide (ENF, T-20)

**CCR5 Antagonist**
- Maraviroc (MVC)
Initial Treatment: Choosing Regimens

- 3 main categories:
  - 1 NNRTI + 2 NRTIs
  - 1 PI + 2 NRTIs
  - 1 II + 2 NRTIs
- Combination of NNRTI, PI, or II + 2 NRTIs preferred for most patients
- Fusion inhibitor, CCR5 antagonist not recommended in initial ART
- Few clinical end points to guide choices
- Advantages and disadvantages to each type of regimen
- Individualize regimen choice
Initial ART Regimens: DHHS Categories

- **Preferred**
  - Randomized controlled trials show optimal efficacy and durability
  - Favorable tolerability and toxicity profiles

- **Alternative**
  - Effective but have potential disadvantages
  - May be the preferred regimen for individual patients

- **Acceptable**
  - Less virologic efficacy, lack of efficacy data, or greater toxicities
  - May be acceptable but should be used with caution
    - Effective in some studies but have safety, resistance, or efficacy concerns
# Initial Therapy: Dual-NRTI Pairs

| Preferred: TDF/FTC | - Once-daily dosing  
|                   | - High virologic efficacy  
|                   | - Active against HBV  
|                   | - Potential for renal and bone toxicity |

| Alternative: ABC/3TC | - Once-daily dosing  
|                      | - Risk of hypersensitivity reaction if positive for HLA-B*5701  
|                      | - Possible risk of cardiovascular events; caution in patients with CV risk factors  
|                      | - Possible inferior efficacy if baseline HIV RNA >100,000 copies/mL |

| Acceptable: ZDV/3TC | - Twice-daily dosing  
|                     | - Preferred dual NRTI for pregnant women  
|                     | - More toxicities than TDF/FTC or ABC/3TC |
### Initial Regimens: Preferred

<table>
<thead>
<tr>
<th>Category</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI based</td>
<td>- EFV/TDF/FTC&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>PI based</td>
<td>- ATV/r + TDF/FTC&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- DRV/r (QD) + TDF/FTC&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>II based</td>
<td>- RAL + TDF/FTC&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>- LPV/r (BID) + ZDV/3TC&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa. TDF should be used with caution in patients with renal insufficiency.
# Initial Regimens: Alternative

## NNRTI Based

<table>
<thead>
<tr>
<th></th>
<th>EFV¹ + ABC/3TC²,³</th>
<th>RPV + (TDF/FTC or ABC/3TC)²,³</th>
</tr>
</thead>
</table>

1. EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
2. 3TC can be used in place of FTC and vice versa. TDF should be used with caution in patients with renal insufficiency.
3. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
4. RPV: Use with caution if pretreatment HIV RNA >100,000 copies/mL.
## Initial Regimens: Alternative (2)

<table>
<thead>
<tr>
<th>PI based</th>
<th>ATV/r + ABC/3TC(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DRV/r + ABC/3TC(^1,2)</td>
</tr>
<tr>
<td></td>
<td>FPV/r (QD or BID) + (ABC/3TC or TDF/FTC)(^1,2)</td>
</tr>
<tr>
<td></td>
<td>LPV/r (QD or BID)(^3) + (ABC/3TC or TDF/FTC)(^1,2)</td>
</tr>
</tbody>
</table>

| II based                    | RAL + ABC/3TC\(^1,2\) |

1. 3TC can be used in place of FTC and vice versa. TDF should be used with caution in patients with renal insufficiency.
2. ABC should not be used in patients who test positive for HLA-B*5701; caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
3. QD LPV/r is not recommended in pregnant women.
Side Effects and Adherence

- Fear of adverse effects of medications can affect patient willingness to initiate or to continue treatment
- Adverse effects of medications can negatively affect adherence
  - Some persons will self-discontinue medications
  - Some will selectively discontinue some medications
  - Some will drop out of care
- Side effects can negatively impact doctor-patient relationship
- Suboptimal adherence is associated with treatment failure, emergence of drug resistance, and disease progression
Side Effects: Interventions

- Counsel patients about treatment options and appreciate aversion to side effects.
- Review possible side effects prior to selecting treatment.
- Anticipate and treat side effects; develop a strategy to address the side effect (using non-judgmental communication) before starting a new regimen.
- Assess adherence and side effects at every visit.
Adverse Effects: NRTIs

- All NRTIs:
  - Lactic acidosis and hepatic steatosis (highest incidence with d4T, then ddI and ZDV, lower with TDF, ABC, 3TC, and FTC)
  - Lipodystrophy (higher incidence with d4T)
Adverse Effects: NRTIs (2)

- ABC
  - HSR*
  - Rash
  - Possible increased risk of MI
- ddI
  - GI intolerance
  - Peripheral neuropathy
  - Possible increased risk of MI
  - Pancreatitis
  - Possible noncirrhotic portal hypertension

* Screen for HLA-B*5701 before treatment with ABC; ABC should not be given to patients who test positive for HLA-B*5701.
Adverse Effects: NRTIs (3)

- **d4T**
  - Peripheral neuropathy
  - Lipoatrophy
  - Pancreatitis

- **TDF**
  - Renal impairment
  - Decrease in bone mineral density
  - Headache
  - GI intolerance

- **ZDV**
  - Headache
  - GI intolerance
  - Lipoatrophy
  - Bone marrow suppression
Adverse Effects: NNRTIs

- All NNRTIs:
  - Rash, including Stevens-Johnson syndrome
  - Hepatotoxicity (especially NVP)
  - Drug-drug interactions
Adverse Effects: NNRTIs (2)

- EFV
  - Neuropsychiatric
  - Teratogenic in nonhuman primates + cases of neural tube defects in human infants after first-trimester exposure
  - Dyslipidemia

- NVP
  - Higher rate of rash
  - Hepatotoxicity (may be severe and life-threatening; risk higher in patients with higher CD4 counts at the time they start NVP, and in women)

- RPV
  - Depression
Adverse Effects: PIs

- All PIs:
  - Hyperlipidemia
  - Lipodystrophy
  - Hepatotoxicity
  - GI intolerance
  - Possibility of increased bleeding risk for hemophiliacs
  - Drug-drug interactions
Adverse Effects: PIs (2)

- **ATV**
  - Hyperbilirubinemia
  - PR prolongation
  - Nephrolithiasis

- **DRV**
  - Rash
  - Liver toxicity

- **FPV**
  - GI intolerance
  - Rash
  - Possible increased risk of MI
Adverse Effects: PIs (3)

- IDV
  - Nephrolithiasis
  - GI intolerance
  - Diabetes/insulin resistance
- LPV/r
  - GI intolerance
  - Diabetes/insulin resistance
  - Possible increased risk of MI
  - PR and QT prolongation
- NFV
  - Diarrhea
Adverse Effects: PIs (4)

- RTV
  - GI intolerance
  - Hepatitis

- SQV
  - GI intolerance
  - PR and QT prolongation

- TPV
  - GI intolerance
  - Rash
  - Hyperlipidemia
  - Liver toxicity
  - Contraindicated if moderate-to-severe hepatic insufficiency
  - Cases of intracranial hemorrhage

Contraindicated if moderate-to-severe hepatic insufficiency

Cases of intracranial hemorrhage
Adverse Effects: II

- RAL
  - Nausea
  - Headache
  - Diarrhea
  - CPK elevation, myopathy, rhabdomyolysis
  - Rash
Regimen Simplification

- Changing a suppressive ARV regimen to:
  - Reduce pill burden
  - Reduce dosing frequency
  - Enhance tolerability
  - Decrease food and fluid requirements

- Goals: improve patient’s quality of life, improve ART adherence, avoid long-term toxicities, reduce risk of virologic failure
Regimen Simplification (2)

- Types of substitution
  - Within class: substitution of a new agent or coformulation, or of the same ARV at a lower dosing frequency
  - Out-of-class: eg, change from PI to NNRTI or agent from another class

- Reducing number of active drugs in ARV regimen: simplification to boosted-PI monotherapy is not recommended

- After simplification, monitor in 2-6 weeks (laboratory and clinical)
Summary

• Six classes of HIV medications and mechanism of action
• Management of side effects has important impacts on medication adherence and doctor-patient relationship
• Antiretroviral medications are generally effective and well tolerated, but have characteristic side effect profiles
• Anticipate and counsel about side effects
• Regimen simplification/modification can be a useful tool to improve side effects and quality of life
HIV Medications and Side Effects

Benjamin Young, MD PhD
Rocky Mountain CARES
International Association of Physicians in AIDS Care