HIV Pharmacotherapy: Back to the Basics

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Disclosures

• The speaker has no actual or potential conflict of interest in relation to this presentation
Learning Objectives

1. Distinguish between the different classes of antiretroviral medications
2. Describe the basic principles of forming and initiating an optimal antiretroviral therapy regimen in an HIV infected patient
3. Identify common medication administration errors and adverse events associated with each of the main classes of antiretroviral medications
HIV Nomenclature

- HIV: Human Immunodeficiency Virus
- AIDS: Acquired Immunodeficiency Syndrome
- ART: Antiretroviral Therapy
- HAART: Highly Active Antiretroviral Therapy
- PEP: Post-exposure Prophylaxis
- nPEP: Non-occupational Post-exposure Prophylaxis
- PrEP: Pre-exposure Prophylaxis
- PI: Protease Inhibitor
- INSTI: Integrase Strand Transfer Inhibitor
- NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor
- NRTI: Nucleoside Reverse Transcriptase Inhibitor
When to Start ART
Initiating Therapy

• ART is recommended for all HIV-infected individuals regardless of CD4 T lymphocyte cell count (AI)
  ▫ Traditionally waited for CD4 count to drop
  ▫ Prompt initiation shown to decrease morbidity and mortality of patients

• Recommended to prevent the transmission of HIV (AI)

A Time to First Primary Event

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Immediate initiation</th>
<th>Deferred initiation</th>
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Estimated Percentage

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<tr>
<th></th>
<th>Immediate initiation</th>
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<tr>
<td>Month</td>
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<td>1.5</td>
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<td>2.5</td>
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<tr>
<td></td>
<td>3.1</td>
<td>5.9</td>
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<tr>
<td></td>
<td>3.7</td>
<td>7.4</td>
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</table>
B  Serious AIDS-Related Event

[Graph showing the percentage of patients experiencing AIDS-related events over time, comparing deferred vs. immediate initiation of treatment.]
D Death from Any Cause

Patients (%)

Immediate initiation

Deferred initiation

Month
Early Initiation of ART

Potential Benefits
- Improve laboratory markers
- Decrease severity of disease
- Lower viral set point
- Reduce size of viral reservoir
- Reduce risk of HIV transmission

Potential Risks
- Worldwide costs of HIV treatment
- Drug toxicities
- Possible development of ART resistance
  - Poor adherence with chronic therapy
- Adverse effect on well-being and quality of life

Adapted with Permission from Dr. Michael D. Tiberg, PharmD, BCPS (AQ-ID)
Initiating Therapy

• HIV drug-resistance testing is recommended at initiation of ART (AII)
  ▫ Genotypic drug-resistance testing can test for mutations in medication targets

• Co-Receptor Tropism Assay
  ▫ Performed before initiation of a CCR5 co-receptor antagonist

• HLA-B*5701
  ▫ Genetic test for hypersensitivity when using abacavir

Building a Regimen
Treatment Goals

• Goals of ART:
  ▫ Reduce HIV-related morbidity and mortality
  ▫ Maintain suppression of HIV RNA
  ▫ Restoration and preservation of patient immune function
  ▫ Prevent HIV transmission
Basic Concepts of ART

Baseline testing
- HIV RNA viral level (viral load)
- CD4 cell count
- Viral genotyping

ART regimen
- Utilize at least 3 agents in combination
- Over 25 agents in 6 classes

Regimen backbone
- NRTIs – 2 agents
  - Emtricitabine or lamivudine often combined with either tenofovir or abacavir (HLA-B*5701 testing required prior to initiation)

Backbone combined with
- INSTI, NNRTI, or PI

Adapted with Permission from Dr. Michael D. Tiberg, PharmD, BCPS (AQ-ID)
Building a Regimen

Often either:
- Truvada® (emtricitabine/tenofovir [TDF])
- Epzicom® (abacavir/lamivudine)
Key Points of ART

- Always need a three drug regimen
  - Ideally an NRTI backbone plus additional agent
- Patient compliance is **KEY**
  - Currently, HIV eradication is impossible
  - Incomplete viral suppression can lead to additional mutations that can cause drug-resistance

Considerations When Starting ART

- Patient lifestyle
  - Willingness to participate in care
  - Transmission risk factors
  - Home life
- Co-infection
  - Hepatitis B/C
- Viral Load
- Drug Interactions
HIV Pharmacotherapy
Image available from: http://www.nature.com/nrmicro/journal/v10/n4/fig_tab/nrmicro2747_F1.html
## ART Classes

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Emtricitabine</td>
<td>- Efavirenz</td>
<td>- Darunavir</td>
</tr>
<tr>
<td>- Lamivudine</td>
<td>- Rilpivirine</td>
<td>- Lopinavir</td>
</tr>
<tr>
<td>- Tenofovir</td>
<td>- Etravirine</td>
<td>- Atazanavir</td>
</tr>
<tr>
<td>- Abacavir</td>
<td>- Nevirapine</td>
<td>- Ritonavir</td>
</tr>
<tr>
<td>- Zidovudine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ART Classes

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Entry/Fusion Inhibitors</th>
<th>PK Enhancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>Maraviroc</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Enfuvirtide</td>
<td>Cobicistat</td>
</tr>
<tr>
<td>Raltegravir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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# Current Antiretroviral Medications

## NRTI
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir disoproxil fumarate (TDF)
- Tenofovir alafenamide (TAF)
- Zidovudine (AZT, ZDV)

## INSTI
- Dolutegravir (DTG)
- Elvitegravir (EVG)
- Raltegravir (RA)

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

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

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

## CCR5 Antagonist
- Maraviroc (MVC)

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Adapted with Permission from Dr. Michael D. Tiberg, PharmD, BCPS (AQ-ID)
Nucleoside Reverse Transcriptase Inhibitors

• Form backbone of most antiretroviral regimens

• Most common:
  ▫ Tenofovir/emtricitabine
  ▫ Abacavir/lamivudine
  ▫ Zidovudine
Nucleoside Reverse Transcriptase Inhibitors

- **Truvada® (Tenofovir/emtricitabine)**
  - Taken with or without food
  - Not recommended CrCl < 50 mL/min
  - **Tenofovir**
    - Nephrotoxic
    - Decreases bone mineral density (BMD)
  - **Emtricitabine**
    - Can cause skin pigmentation
    - Structurally similar to lamivudine
      - Resistance often comes concomitantly
Nucleoside Reverse Transcriptase Inhibitors

- Epzicom® (Abacavir/lamivudine)
  - Taken with or without food
  - Abacavir
    - MUST test for HLA-B*5701 status
      - Potential for deadly hypersensitivity reaction
  - Lamivudine
    - Structurally similar to emtricitabine
      - Resistance often comes concomitantly
Nucleoside Reverse Transcriptase Inhibitors

- **Retrovir® (Zidovudine)**
  - The first antiretroviral medication available
  - Causes bone marrow suppression
  - Limited use today except for prevention of maternal-fetal HIV transmission
NRTI Adverse Reactions

- Lactic acidosis
- Pancreatitis
- Peripheral neuropathies
- Lipoatrophy
Non-Nucleoside Reverse Transcriptase Inhibitors

- **Most common:**
  - Nevirapine
  - Efavirenz
  - Etravirine
  - Rilpivirine

Non-Nucleoside Reverse Transcriptase Inhibitors

Nevirapine

• **Brand Name:** Viramune®
  - With or without food
  - Common skin rash
  - Black box (BB) warning for hepatotoxicity

Efavirenz

• **Brand Name:** Sustiva®
  - On an empty stomach at night
    - Food increases absorption ~ 80%
  - Causes CNS toxicity
    - Dizziness
    - Fogginess
    - Vivid dreams
    - BB warning for suicidal ideations

Lexicomp Online. Hudson, Ohio: Lexi-Comp, Inc.; 2015
## Non-Nucleoside Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Etravirine</th>
<th>Rilpivirine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Name:</strong> Intelence®</td>
<td><strong>Brand Name:</strong> Edurant®</td>
</tr>
<tr>
<td>▫ Taken with food</td>
<td>▫ Taken with a meal containing at minimum 400 calories</td>
</tr>
<tr>
<td>▫ Causes elevations in hepatic enzymes</td>
<td>▪ Used to enhance absorption</td>
</tr>
</tbody>
</table>
NNRTIs ADRs

- Hepatotoxicity
- Skin rash
  - Usually resolves with continued therapy
Protease Inhibitors

- High genetic barrier to resistance when compared to other classes
- Metabolized by CYP P450 = MANY drug interactions!
- Boosted to enhance drug levels and length between dosing intervals
- Most common:
  - Ritonavir
  - Lopinavir
  - Atazanavir
  - Darunavir
# Protease Inhibitors

<table>
<thead>
<tr>
<th><strong>Ritonavir</strong></th>
<th><strong>Lopinavir/ritonavir</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Brand Name:</strong> Norvir®</td>
<td><strong>Brand Name:</strong> Kaletra®</td>
</tr>
<tr>
<td>▫ Taken with food</td>
<td>▫ Taken with or without food</td>
</tr>
<tr>
<td>▫ No longer used as a PI but now as a pharmacokinetic (PK) enhancer due to its potent inhibition of CYP P450 enzymes</td>
<td>▫ Only PI offered in co-formulation with ritonavir</td>
</tr>
<tr>
<td>▫ High incidence of diarrhea</td>
<td>▫ May cause significant diarrhea</td>
</tr>
</tbody>
</table>

Lexicomp Online. Hudson, Ohio: Lexi-Comp, Inc.; 2015
## Protease Inhibitors

<table>
<thead>
<tr>
<th>Atazanavir</th>
<th>Darunavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Brand Name: Reyataz® or Evotaz®</td>
<td></td>
</tr>
<tr>
<td>▫ Taken with food</td>
<td></td>
</tr>
<tr>
<td>▫ Evotaz formulated with cobicistat</td>
<td></td>
</tr>
<tr>
<td>▫ Can cause jaundice due to increases in total bilirubin</td>
<td></td>
</tr>
<tr>
<td>• Brand Name: Prezista® or Prezcobix®</td>
<td></td>
</tr>
<tr>
<td>▫ Taken with food</td>
<td></td>
</tr>
<tr>
<td>▫ Prezcobix formulated with cobicistat</td>
<td></td>
</tr>
<tr>
<td>▫ May have an even higher barrier for resistance when compared to other PIs</td>
<td></td>
</tr>
</tbody>
</table>
PI Adverse Reactions

- Diarrhea
- Dyslipidemia
- Hyperglycemia
- Insulin resistance
- Lipodystrophy
INSTIs

- Drugs of choice for treatment naïve patients
- Well tolerated
- Most common:
  - Raltegravir
  - Dolutegravir
  - Elvitegravir

## Integrase Strand Transfer Inhibitors

<table>
<thead>
<tr>
<th>Raltegravir</th>
<th>Elvitegravir</th>
<th>Dolutegravir</th>
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</thead>
<tbody>
<tr>
<td><strong>Brand name:</strong></td>
<td><strong>Brand Name:</strong></td>
<td><strong>Brand name:</strong></td>
</tr>
<tr>
<td>Isentress®</td>
<td>Vitekta®</td>
<td>Tivicay®</td>
</tr>
<tr>
<td><strong>Only twice daily</strong></td>
<td><strong>Taken with or</strong></td>
<td><strong>Taken with or</strong></td>
</tr>
<tr>
<td>INSTI</td>
<td>without food**</td>
<td>without food**</td>
</tr>
<tr>
<td><strong>Taken with or</strong></td>
<td><strong>Seldom used as</strong></td>
<td><strong>May have a</strong></td>
</tr>
<tr>
<td>without food**</td>
<td>stand-alone drug**</td>
<td>higher genetic**</td>
</tr>
<tr>
<td><strong>May elevate CPK</strong></td>
<td><strong>Used in</strong></td>
<td><strong>barrier than other</strong></td>
</tr>
<tr>
<td>levels and cause</td>
<td>combination with</td>
<td>INSTIs**</td>
</tr>
<tr>
<td>myopathies**</td>
<td>cobicistat**</td>
<td></td>
</tr>
</tbody>
</table>

- INSTIs not associated with any class adverse reactions

Lexicomp Online. Hudson, Ohio: Lexi-Comp, Inc.; 2015
Entry Inhibitor

• Used in cases where resistance has developed
• Be sure to perform co-receptor tropism assay!
• Only agent:  
  ▫ Maraviroc
Fusion Inhibitor

- Not commonly used anymore
- Given as a SQ injection
  - Injection site reactions common
- Only agent:
  - Enfuvirtide
PK Enhancers

- Used to improve drug levels of other antiretroviral medications and extend dosing frequencies
  - A controlled drug interaction!
- Two agents:
  - Ritonavir
  - Cobicistat
PK Enhancers

**Ritonavir**
- Brand Name: Norvir®
  - Co-formulated with other antiretrovirals and as stand alone product
  - Take with food
  - MANY drug interactions
  - Has limited antiretroviral activity

**Cobicistat**
- Brand Name: Tybost®
  - Co-formulated with other antiretrovirals and as stand alone product
  - Take with or without food
  - MANY drug interactions
  - Has no antiretroviral activity
  - Can falsely elevate SCr ~ 0.1mg/dL
# ART Combination Formulations

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<tr>
<th>Trade-name</th>
<th>Agents</th>
<th>Year FDA Approved</th>
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<tbody>
<tr>
<td>Combivir®</td>
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<td>Trizivir®</td>
<td>ABC, 3TC, AZT</td>
<td>2000</td>
</tr>
<tr>
<td>Epzicom®</td>
<td>ABC, 3TC</td>
<td>2004</td>
</tr>
<tr>
<td>Truvada®</td>
<td>TDF, FTC</td>
<td>2004</td>
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<tr>
<td>Atripla®</td>
<td>EFZ, TDF, FTC</td>
<td>2006</td>
</tr>
<tr>
<td>Complera®</td>
<td>RPV, TDF, FTC</td>
<td>2011</td>
</tr>
<tr>
<td>Stribild®</td>
<td>EVG, TDF, FTC, Cobi</td>
<td>2012</td>
</tr>
<tr>
<td>Triumeq®</td>
<td>ABC, DTG, 3TC</td>
<td>2014</td>
</tr>
<tr>
<td>Evotaz®</td>
<td>ATV, Cobi</td>
<td>2015</td>
</tr>
<tr>
<td>Prezcobix®</td>
<td>DRV, Cobi</td>
<td>2015</td>
</tr>
<tr>
<td>Genvoya®</td>
<td>EVG, Cobi, FTC, TAF</td>
<td>2015</td>
</tr>
<tr>
<td>Descovy®</td>
<td>TAF, FTC</td>
<td>2016</td>
</tr>
<tr>
<td>Odefsey®</td>
<td>RPV, FTC, TAF</td>
<td>2016</td>
</tr>
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</table>
Single-Tablet Regimens

- **Atripla®**
  - Efavirenz/Emtricitabine/Tenofovir (TDF)
- **Complера®**
  - Rilpivirine/Emtricitabine/Tenofovir (TDF)
- **Stribild®**
  - Elviregravir/Cobicistat/Emtricitabine/Tenofovir (TDF)
- **Triumeq®**
  - Doutegravir/Abacavir/Lamivudine
“New” Single-Tablet Regimens

- Genvoya®
  - Elvitegravir/Cobicistat/Emtricitabine/Tenofovir (TAF)
- Odefsey®
  - Rilpivirine/Emtricitabine/Tenofovir (TAF)
TDF vs TAF?

- 91% lower plasma TFV levels minimize renal and bone effects while maintaining high potency for suppressing HIV

*T1/2 based on in vitro plasma data.

Drug Interactions

- Drug-drug interactions can put patients at risk
  - Increased toxicity
  - Decreased viral suppression
    - Increased antiretroviral resistance!
  - Decreased immune function
Drug Interactions

• Major methods of drug-drug interactions
  ▫ Absorption
    • Acid reducing agents can impair drug absorption
    • Polyvalent cations can “bind up” drug
  ▫ Metabolism
    • CYP P450 Inhibitors
      • Increase drug concentrations
    • CYP P450 Inducers
      • Decrease drug concentrations
Drug Interactions

- Major Classes to Watch:
  - Antiarrhythmic medication
  - Antifungal medication
  - Antiepileptic medication
  - Anticoagulant medication
- When in doubt, always ask your pharmacist!
- Pharmacists, use your resources!
  - Drug interaction databases
  - HIV treatment guidelines!
Initial Therapy Selection

- Recommended regimens for treatment-naïve patients
  - Tivicay® + Truvada®
    - Dolutegravir + tenofovir/emtricitabine (AI)
  - Triumeq®
    - Dolutegravir/abacavir/lamivudine (AI)
  - Genvoya®
    - Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine (AI)
  - Stribild®
    - Elvitegravir/cobicistat/tenofovir/emtricitabine (AI)
  - Isentress® + Truvada®
    - Raltegravir + tenofovir/emtricitabine (AI)
Initial Therapy Selection

- **Protease Inhibitor - Based Regimen**
  - Prezista® + Truvada®
    - Darunavir/ritonavir + tenofovir/emtricitabine (AI)
- **INSTI-based regimens becoming treatment of choice in treatment-naïve patients**

Factors to Consider...

- Patient characteristics
  - Comorbidities
  - Chronic kidney disease
  - Compliance potential

- Regimen characteristics
  - High genetic barrier
  - Drug interactions
  - Food interactions
  - Tolerability

- CD4 count & HIV viral load
  - Rilpiverine-based regimens

- Genetic characteristics
  - HLA-B*5701 status
  - HIV genotypes

Questions

- Email: dvanderhorst@mhc.net