The ABCs of ART: Designing Initial Antiretroviral Regimens for Beginners

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Disclosures

- This speaker does not have any financial relationships with commercial entities to disclose.
- The speaker will not discuss any off-label use or investigational product during the program.
- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.
Learning Objectives

- List antiretroviral treatment goals and tools to achieving these goals
- Review the process for selecting antiretroviral regimens
- Identify common mechanisms for drug interactions with antiretrovirals
- Discuss clinically significant drug interactions for patients with HIV
GETTING TO KNOW YOU
Which best describes your profession?

A. Physician
B. Midlevel practitioner
C. Nurse
D. Pharmacist
E. Medical assistant
F. Case manager
G. Student
H. Other
How comfortable are you with constructing ARV regimens and recognizing drug interactions?

A. Extremely comfortable: It’s a slam dunk every time!
B. Somewhat comfortable: I have some experience and great colleagues to consult if I get stuck
C. Uncomfortable: There are so many new medications, it’s hard to keep up!
D. What is Webcast Wednesday and how did I end up here?
Recommended HIV Resources

www.aidsinfo.nih.gov

www.seaetc.com/provider-resources/reference/
Southeast AETC Pocket Cards

ART in Adults & Adolescents

March 2018
Learning Objectives

- List antiretroviral treatment goals and tools to achieving these goals
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HIV Attacks CD4 T Cells

- HIV attacks immune system CD4 T cells
  - T cells are a type of white blood cell
  - HIV uses T cell machinery to replicate

- Depletion of CD4 T cells by HIV impairs immune defenses (leaving host susceptible to opportunistic infection)

- Antiretroviral therapy (ART) suppresses viral load, allowing improvements in immune system functioning
HIV Life Cycle


AETC
AIDS Education & Training Center Program
Southeast
Correlation of Opportunistic Infections with CD4 Count

CD4+ Cell Count (cells/mm$^3$)

- Lymphadenopathy
- Thrombocytopenia
- Bacterial skin infections
- Oral & skin fungal infections
- Herpes simplex & zoster
- Kaposi sarcoma
- Pneumonia
- Thrush
- Hairy leukoplakia
- Tuberculosis
- Cryptococcosis
- Toxoplasmosis
- PCP
- CMV
- MAC

AIDS

Months // Years
Initiation of Antiretroviral Therapy (ART)

- ART is recommended for all individuals with HIV, regardless of CD4 count, to reduce morbidity and mortality associated with HIV infection and to prevent HIV transmission.
- On a case-by-case basis, ART may be deferred because of clinical and/or psychosocial factors, but therapy should be initiated as soon as possible.

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Goals of Antiretroviral Therapy

- Decrease HIV RNA
  - Goal HIV RNA or “viral load” <20-75 copies/mL or “undetectable”
- Increase CD4 count
  - 500-1500 cells/mm$^3$ is normal CD4 for HIV-uninfected
  - AIDS diagnosis is CD4 < 200 or CD4% < 14% (or AIDS defining illness)
- Improve quality of life and reduce HIV-related morbidity & mortality
- Prevent HIV transmission to others
Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence
- Selecting individualized ART regimen
Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence
- Selecting individualized ART regimen
Use of Drug Resistance Testing to Guide Therapy Decisions

- Drug resistance is the reduction of the sensitivity of the virus to a particular drug
- Resistance results from genetic mutation of viral enzymes & proteins leading to changes in the way drugs interact with them
- Mechanisms for ARV drug resistance
  - Transmitted resistance: Infected with a resistant strain of HIV at baseline
  - Spontaneous resistance: HIV develops mutations easily and becomes resistant
- Obtain genotype prior to initiation of therapy to determine if resistant virus transmitted
- Obtain resistance test if virologic failure during ART or suboptimal suppression of viral load after start of therapy to determine if spontaneous resistance occurred
Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence
- Selecting individualized ART regimen
Importance of ART Adherence

- ART adherence correlated with
  - HIV viral suppression
  - Reduced rates of viral resistance
  - Increase in survival
  - Improved quality of life
  - Reduced HIV transmission to others

- ART works by reducing viral replication to below level of detection
  - Adherence rates near 100% needed for optimal viral suppression

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Consequences of Non-adherence

- HIV progression
- Increase AIDS-related morbidity and mortality
- Increased hospitalization rates
- Immunologic failure
- Development of resistant virus
Factors Associated with Poor Adherence

- Neurocognitive impairment
- Untreated major psychiatric disorders
- Active substance abuse
- Unstable housing
- Medication side effects
- Non-adherence to clinic appointments
- Low health literacy
- Low levels of social support
- Stressful life events
- Busy or unstructured daily routines
- Nondisclosure of HIV serostatus
- Denial; stigma
- Cost and insurance coverage issues

DHHS panel on antiretroviral guidelines for adults and adolescents. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
Adherence Interventions

- Positive interface with clinic
- Encourage regular care
- Patient education
- Social support network
- Counsel and manage side effects
- Medication scheduling reminders
- Simplified regimens
## Single Tablet Regimens (STRs)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Year of FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz/tenofovir DF/emtricitabine</td>
<td>NNRTI + dual NRTI</td>
<td>2006</td>
</tr>
<tr>
<td>Rilpivirine/tenofovir DF/emtricitabine</td>
<td>NNRTI + dual NRTI</td>
<td>2011</td>
</tr>
<tr>
<td>Rilpivirine/tenofovir AF/emtricitabine</td>
<td>NNRTI + dual NRTI</td>
<td>2016</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/tenofovir DF/emtricitabine</td>
<td>INSTI + booster + dual NRTI</td>
<td>2012</td>
</tr>
<tr>
<td>Elvitegravir/cobicistat/tenofovir AF/emtricitabine</td>
<td>INSTI + booster + dual NRTI</td>
<td>2015</td>
</tr>
<tr>
<td>Dolutegravir/abacavir/lamivudine</td>
<td>INSTI + dual NRTI</td>
<td>2014</td>
</tr>
<tr>
<td>Dolutegravir/rilpivirine</td>
<td>INSTI + NNRTI</td>
<td>2017</td>
</tr>
<tr>
<td>Bictegravir/tenofovir AF/emtricitabine</td>
<td>INSTI + dual NRTI</td>
<td>2018</td>
</tr>
</tbody>
</table>

Key: DF = disoproxil fumarate; AF = alafenamide; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleos(t)ide reverse transcriptase inhibitor; INSTI = integrase strand transfer inhibitor

Slide credit: clinicaloptions.com
Advantages and Disadvantages of Single Tablet Regimens (STRs)

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>§ Simplicity</td>
<td>§ Inability to adjust dosages of components if needed due to drug–drug interactions or renal insufficiency</td>
</tr>
<tr>
<td>§ Convenience</td>
<td>§ Not available for all ART regimens and combinations</td>
</tr>
<tr>
<td>§ Fewer copays</td>
<td></td>
</tr>
<tr>
<td>§ Reduces selective non-adherence to components of regimen</td>
<td></td>
</tr>
</tbody>
</table>
Observational Studies of STRs vs Multicomponent Regimens

<table>
<thead>
<tr>
<th>Study</th>
<th>Main Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>LifeLink Database[1] (N = 7073)</td>
<td>STRs associated with higher rate of adherence and lower risk of hospitalization</td>
</tr>
<tr>
<td>Commercially insured US HIV pts[2] (N = 6938)</td>
<td>Non STRs associated with 1.5 x risk of incomplete dosing; partial adherence associated with increased rate of hospitalization</td>
</tr>
<tr>
<td>Quebec Cohort[3] (N = 4996)</td>
<td>Higher proportion of STR pts adherent to therapy; STRs also associated with lower rate of hospitalization and healthcare utilization</td>
</tr>
<tr>
<td>VA Cohort[4] (N = 15,602)</td>
<td>STRs associated with significantly better adherence, lower hospitalization rate</td>
</tr>
</tbody>
</table>

References:

Slide credit: clinicaloptions.com
Tools to Achieve Treatment Goals

- Performing pretreatment resistance testing
- Maximizing adherence
- Selecting individualized ART regimen
Learning Objectives

- List antiretroviral treatment goals and tools to achieving these goals
- Review the process for selecting antiretroviral regimens
- Identify common mechanisms for drug interactions with antiretrovirals
- Discuss clinically significant drug interactions for patients with HIV
Process for Selecting an Initial ART Regimen

- Regimen efficacy
  - Standard therapy for HIV typically consists of 3+ drugs from 2+ classes (no monotherapy)
- Comorbidities
  - Potential adverse effects or drug-drug interactions
- Drug resistance
  - Presence of transmitted drug resistance or development of drug resistance on failure
- Adherence potential
  - Pill burden, dosing frequency, food restrictions
Overview of ART Drug Classes

- Classification based on where in the viral life cycle each drug acts

- 5 Antiretroviral Classes
  - Nucleos(t)ide reverse transcriptase inhibitors (NRTI)
  - Integrase strand transfer inhibitors (INSTI)
  - Protease inhibitors (PI)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTI)
  - Entry inhibitors

†Recommended in certain clinical situations
‡‡Not recommended for initial therapy
HIV Life Cycle & ART Drug Classes

**Antiretroviral Medications**

**Nucleoside Reverse Transcriptase Inhibitors**
- Abacavir (ABC) (Ziagen®)
- Didanosine (ddl) (Videx®)
- Emtricitabine (FTC) (Emtriva®)
- Lamivudine (3TC) (Epivir®)
- Stavudine (d4T) (Zerit®) - to be withdrawn by 2020
- Tenofovir (TDF) (Viread®)
- Zalcitabine (ddC) (Hivid®) - withdrawn 2005
- Zidovudine (ZDV, AZT) (Retrovir®)
- 3TC/ABC (Epzicom®)
- 3TC/ABC/ZDV (Trizivir®)
- 3TC/ZDV (Combivir®)
- FTC/TDF (Truvada®)
- FTC/TAF (Descovy®)

**Non-nucleoside Reverse Transcriptase Inhibitors**
- Delavirdine (DLV) (Rescriptor®)
- Efavirenz (EFV) (Sustiva®)
- Etravirine (ETR) (Intellence®)
- Nevirapine (NVP) (Viramune®)
- Rilpivirine (RPV) (Edurant®)

**Integrase Inhibitors**
- Bictegravir (BIC)
- Dolutegravir (DTG) (Tivicay®)
- Elvitegravir (EVG)
- Raltegravir (RAL) (Isentress®)

**Protease Inhibitors**
- Amprenavir (APV) (Agenerase®) - discontinued 2004
- Atazanavir (ATV) (Reyataz®)
- Atazanavir/cobicistat (ATV/c) (Evotaz®)
- Darunavir (DRV) (Prezista®)
- Darunavir/cobicistat (DRV/c) (Prezcobix®)
- Fosamprenavir (FPV) (Lexiva®)
- Indinavir (IDV) (Crixivan®)
- Lopinavir/ritonavir (LPV/r) (Kaletra®)
- Nelfinavir (NFV) (Viracept®)
- Ritonavir (RTV) (Norvir®)
- Saquinavir (SQV) (Invirase®)
- Tipranavir (TPV) (Aptivus®)

**Entry Inhibitors**
- Enfuvirtide (ENF, T20) (Fuzeon®)
- Maraviroc (MVC) (Selzentry®)

**Single Tablet Regimens**
- EFV/FTC/TDF (Atripla®)
- RPV/FTC/TDF (Complera®)
- RPV/FTC/TAF (Odefsey®)
- EVG/cobi/FTC/TDF (Stribild®)
- EVG/cobi/FTC/TAF (Genvoya®)
- DTG/3TC/ABC (Triumeq®)
- DTG/RPV (Juluca®)
- BIC/FTC/TAF (Biktarvy®)

**Pharmacokinetic Enhancers “Boosters”**
- Cobicistat (COBI) (Tybost®)
- Ritonavir (RTV) (Norvir®)
HIV Management Principles

- Initiate ART with 1 of 3 types of regimens
- Most regimens should include at least 2 NRTIs plus at least 1 drug from a separate class:
  - 2 NRTIs + 1 INSTI
  - 2 NRTIs + 1 PI (boosted PI)
  - 2 NRTIs + NNRTI†

†Recommended in certain clinical situations

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Boosting a Protease Inhibitor (PI) With Ritonavir (RTV) or Cobicistat (COBI)

<table>
<thead>
<tr>
<th>Dosing Interval</th>
<th>Area of Potential HIV Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Time</td>
</tr>
</tbody>
</table>

- **Unboosted PI**
  - $C_{\text{max}1}$
  - $C_{\text{min}1}$

- **Boosted PI**
  - $C_{\text{max}2}$
  - $C_{\text{min}2}$

- Increased AUC
- Decreased variability in trough concentrations
Recommended Initial Regimens for Most People with HIV

2 NRTIs
- Tenofovir + Emtricitabine
- Abacavir + Lamivudine
  *only w/ Dolutegravir

INTEGRASE INHIBITOR
- Raltegravir
- Elvitegravir + COBI
- Dolutegravir*

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Recommended Initial Regimens in Certain Clinical Situations

**PROTEASE INHIBITOR**
- (boosted with ritonavir or cobicistat)
  - Darunavir + RTV or Darunavir + COBI
  - Atazanavir + RTV or Atazanavir + COBI

**NNRTI**
- Efavirenz
- Rilpivirine

**INTEGRASE INHIBITOR**
- Raltegravir

### 2 NRTIs

- Tenofovir + Emtricitabine
  - OR
- Abacavir + Lamivudine

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
“What Are The Certain Clinical Situations?”

**PROTEASE INHIBITOR**
(boosted with ritonavir or cobicistat)

- Darunavir + RTV or Darunavir + COBI
- Atazanavir + RTV or Atazanavir + COBI

**OR**

**NNRTI**

- Efavirenz
- Rilpivirine

**OR**

**INTEGRASE INHIBITOR**

- Raltegravir

**2 NRTIs**

- Tenofovir + Emtricitabine
- Abacavir + Lamivudine

**PI:** Patients with uncertain adherence or no resistance testing

**EFV:** Minimal drug interactions with rifamycins

**RPV:** Small pill size

**ABC:** No renal dose adjustment
Selecting an Initial HIV Regimen: The “Chinese Food Rule”*

*Tip of the hat to Royce Lin, MD, Associate Clinical Professor of Medicine, UCSF
Recommended Initial Regimens in Certain Clinical Situations

PROTEASE INHIBITOR (boosted with ritonavir or cobicistat)

- Darunavir + RTV or Darunavir + COBI
- Atazanavir + RTV or Atazanavir + COBI

OR

NNRTI

- Efavirenz
- Rilpivirine

OR

INTEGRASE INHIBITOR

- Raltegravir

2 NRTIs

- Tenofovir + Emtricitabine
- Abacavir + Lamivudine

OR

- Tenofovir + Emtricitabine

OR

- Abacavir + Lamivudine

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Recommended CHINESE FOOD in Certain Clinical Situations

- **PROTEASE INHIBITOR**
  - (boosted with ritonavir or cobicistat)
  - Darunavir + RTV or Darunavir + COBI
  - Atazanavir + RTV or Atazanavir + COBI

- **OR**

- **NNRTI**
  - Efavirenz
  - Rilpivirine

- **OR**

- **INTEGRASE INHIBITOR**
  - Raltegravir

---

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Recommended CHINESE FOOD in Certain Clinical Situations

- **PROTEASE INHIBITOR** (boosted with ritonavir or cobicistat)
  - Darunavir + RTV or Darunavir + COBI
  - Atazanavir + RTV or Atazanavir + COBI

- **NNRTI**
  - Efavirenz
  - Rilpivirine

- **INTEGRASE INHIBITOR**
  - Raltegravir

**2 NRTIs**
- Tenofovir + Emtricitabine
- Abacavir + Lamivudine

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Recommended CHINESE FOOD in Certain Clinical Situations

**PROTEASE INHIBITOR** (boosted with ritonavir or cobicistat)
- Darunavir + RTV or Darunavir + COBI
- Atazanavir + RTV or Atazanavir + COBI

**OR**

**NNRTI**
- Efavirenz
- Rilpivirine

**OR**

**INTEGRASE INHIBITOR**
- Raltegravir

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Recommended CHINESE FOOD in Certain Clinical Situations

- **2 SCOOPS OF RICE**
  - Tenofovir + Emtricitabine
  - OR
  - Abacavir + Lamivudine

- **PROTEASE INHIBITOR**
  - (boosted with ritonavir or cobicistat)
  - Darunavir + RTV or Darunavir + COBI
  - Atazanavir + RTV or Atazanavir + COBI

  - **OR**

- **NNRTI**
  - Efavirenz
  - Rilpivirine

  - **OR**

- **INTEGRASE INHIBITOR**
  - Raltegravir

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Recommended CHINESE FOOD in Certain Clinical Situations

2 SCOOPS OF RICE
- Tenofovir + Emtricitabine
- OR
- Abacavir + Lamivudine

BEEF (enhanced with MSG)
- Darunavir + RTV or Darunavir + COBI
- Atazanavir + RTV or Atazanavir + COBI

OR

CHICKEN
- Efavirenz
- Rilpivirine

OR

FISH
- Raltegravir

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
HIV Regimen / Chinese Food Selection: A Stepwise Approach

1. Get 2 scoops of rice
   - Choose 2 NRTIs, Co-formulated when possible
     - Example: Tenofovir + emtricitabine
     - Example: Abacavir + lamivudine

2. Beef, fish, or chicken?
   - Decide which class to use (PI, INSTI, NNRTI)
   - Choose specific agent based on comorbidities, pill burden, drug interactions, resistance testing, etc.
<table>
<thead>
<tr>
<th>PI + RTV or COBI (Beef + MSG)</th>
<th>INSTI (Fish)</th>
<th>NNRTI (Chicken)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRO</strong></td>
<td><strong>PRO</strong></td>
<td><strong>PRO</strong></td>
</tr>
<tr>
<td>• Very strong, potency well established</td>
<td>• Highly effective for most patients</td>
<td>• Low pill burden (1 pill daily)</td>
</tr>
<tr>
<td>• Harder to get resistance</td>
<td>• Very few side effects</td>
<td>• Efavirenz: minimal drug interactions w/ rifamycins</td>
</tr>
<tr>
<td>• Best for pts w/ uncertain adherence or if resistance tests not available</td>
<td>• Less drug interactions</td>
<td>• Rilpivirine is in smallest single tablet regimen</td>
</tr>
<tr>
<td><strong>CON</strong></td>
<td><strong>CON</strong></td>
<td><strong>CON</strong></td>
</tr>
<tr>
<td>• No single tablet regimen</td>
<td>• Some delicate, prone to resistance (except dolutegravir)</td>
<td>• Prone to resistance</td>
</tr>
<tr>
<td>• Many drug interactions (P450 metabolism)</td>
<td></td>
<td>• Efavirenz has CNS side effects; cases of neural tube defects after first trimester exposure</td>
</tr>
<tr>
<td>• Metabolic effects (↑ cholesterol, glucose)</td>
<td></td>
<td>• Rilpivirine has lower efficacy in some patients</td>
</tr>
<tr>
<td>• GI side effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Boosting required</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Learning Objectives

- List antiretroviral treatment goals and tools to achieving these goals
- Review the process for selecting antiretroviral regimens
- Identify common mechanisms for drug interactions with antiretrovirals
- Discuss clinically significant drug interactions for patients with HIV
ART Undergoes Pharmacokinetic Transformation

1. Absorption
   • Setting for most ARV drug interactions

2. Distribution
   • Cytochrome P450 drug metabolizing enzyme influences/influenced by, many ARVs and many other drugs

3. Metabolism
   • PIs, NNRTIs, maraviroc, INSTIs & cobicistat can be P450 substrates, inducers, or inhibitors

4. Elimination
Normal Metabolism of a Drug That is a P450 Substrate

Drug alone
Metabolism of a Drug That Inhibits P450 With a Drug That is a P450 Substrate

Drug + Inhibitor

Inhibitor blocks P450 enzyme

Too much drug!
Metabolism of a Drug That Induces P450 With a Drug That is a P450 Substrate

Drug + Inducer

Inducer increases P450 enzyme production

Not enough drug!
## ARV Metabolism and Drug Interaction Potential

<table>
<thead>
<tr>
<th>ARV Drug Class</th>
<th>Route of Metabolism</th>
<th>Drug Intxn Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Mostly renal</td>
<td>Medium</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Liver metabolism: P450 substrates, some are P450 inducers/inhibitors</td>
<td>High</td>
</tr>
<tr>
<td>PI</td>
<td>Liver metabolism: P450 substrates, most are P450 inhibitors (sometimes act as inducers)</td>
<td>High</td>
</tr>
<tr>
<td>Integrase Inhibitors</td>
<td>Liver metabolism&lt;br&gt;• Raltegravir: UGT1A1 enzyme (not P450)&lt;br&gt;• Elvitegravir: P450 substrate/inducer (Cobicistat: P450 inhibitor)&lt;br&gt;• Dolutegravir: P450 substrate &amp; UGT1A1&lt;br&gt;• Bictegravir: P450 substrate &amp; UGT1A1</td>
<td>Medium-High</td>
</tr>
<tr>
<td>Entry Inhibitor: CCR5</td>
<td>Liver metabolism: P450 substrate</td>
<td>Medium</td>
</tr>
<tr>
<td>Entry Inhibitor: Fusion</td>
<td>Peptide undergoes catabolism to amino acids: No known drug interactions</td>
<td>Low</td>
</tr>
</tbody>
</table>
Learning Objectives

- List antiretroviral treatment goals and tools to achieving these goals
- Review the process for selecting antiretroviral regimens
- Identify common mechanisms for drug interactions with antiretrovirals
- Discuss clinically significant drug interactions for patients with HIV
Antiretrovirals Have Drug Interactions With Multiple Medications

- Cholesterol medications
- Anti-acid therapy
- TB and MAC medications
- Hormonal contraceptives
- Asthma medications and corticosteroids
- Seizure medications
- Hepatitis C medications
- Other antiretrovirals

- Antifungals
- Benzodiazepines
- Antiplatelets & anticoagulants
- Erectile dysfunction medications
- Antiarrhythmics, calcium channel blockers
- Antipsychotics and antidepressants
- Herbal and dietary supplements
ARV Interactions with Cholesterol Medications

- Statins (HMG Co-A reductase inhibitors)
  - P450 substrates
    - Degree of 3A4 metabolism varies: simva, lova >> rosuva > atorva > pravastatin
  - May be affected by NNRTIs, PIs, & cobicistat
- PIs and COBI ↑ statin levels
  - Avoid simvastatin, lovastatin (2000% ↑)
- NNRTIs can ↓ statin levels
  - Monitor statin efficacy, ↑ dose as necessary
### Managing ARV Interactions with Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Interacting Antiretroviral(s)</th>
<th>Prescribing Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>• Atazanavir ± ritonavir</td>
<td>Titrate atorvastatin dose carefully and use lowest dose necessary while monitoring for toxicities</td>
</tr>
<tr>
<td></td>
<td>• Darunavir/cobicistat • Darunavir + ritonavir • Elvitegravir/cobicistat • Lopinavir/ritonavir</td>
<td>Do not exceed 20 mg atorvastatin daily</td>
</tr>
<tr>
<td></td>
<td>• Atazanavir/cobicistat • Tipranavir + ritonavir</td>
<td>Do not co-administer</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>• HIV protease inhibitors • Elvitegravir/cobicistat</td>
<td>CONTRAINDIATED</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>• HIV protease inhibitors • Elvitegravir/cobicistat</td>
<td>No dose adjustment necessary</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>• Atazanavir + ritonavir; Atazanavir/cobicistat • Darunavir + ritonavir; Darunavir/cobicistat</td>
<td>Titrate pravastatin dose carefully while monitoring for toxicities</td>
</tr>
<tr>
<td></td>
<td>• Lopinavir + ritonavir</td>
<td>No dose limitations</td>
</tr>
<tr>
<td></td>
<td>• Elvitegravir/cobicistat</td>
<td>No data; no dosage recommendation</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>• Darunavir + ritonavir • Elvitegravir/cobicistat</td>
<td>Titrate rosuvastatin dose carefully and use lowest necessary dose while monitoring for toxicities</td>
</tr>
<tr>
<td></td>
<td>• Darunavir/cobicistat</td>
<td>Do not exceed 20 mg rosuvastatin daily</td>
</tr>
<tr>
<td></td>
<td>• Atazanavir/cobicistat • Atazanavir + ritonavir • Lopinavir/ritonavir</td>
<td>Do not exceed 10 mg rosuvastatin daily</td>
</tr>
<tr>
<td></td>
<td>• Tipranavir + ritonavir</td>
<td>No dose limitations</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>• HIV protease inhibitors • Elvitegravir/cobicistat</td>
<td>CONTRAINDIATED</td>
</tr>
</tbody>
</table>

DHHS. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Available at [http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf](http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf)
ARV Interactions with Anti-acid Medications

- Indicated for GERD/peptic ulcer disease to decrease gastric acidity
  - Antacids: aluminum, magnesium hydroxide, or calcium carbonate
  - H2 receptor antagonists: cimetidine, famotidine, ranitidine
  - Proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, pantoprazole
- Medications decreasing stomach acidity can interfere with ARVs requiring an acidic environment for absorption (e.g., atazanavir, rilpivirine)
- INSTI absorption is decreased by binding with di/trivalent cations
# Managing ARV Interactions with Anti-acid Medications

<table>
<thead>
<tr>
<th>Antacid</th>
<th>Atazanavir (ATV) Intxns</th>
<th>Rilpivirine (RPV) Intxns</th>
<th>INSTI Intxns</th>
</tr>
</thead>
</table>
| Aluminum, Magnesium, Calcium (Al, Mg, Ca) Antacids | ATV 2 hrs before or 1-2 hours after antacids | Antacids 2 hours before or 4 hours after RPV | • Separate EVG by ≥ 2 hours  
• RAL not recommended with Al or Mg; RAL HD not recommended with Ca; if RAL then no dose adjustment with Ca  
• DTG 2 hours before or 6 hours after antacid  
• Take BIC without food 2 hours before antacid |
| H2 Receptor Antagonists (H2RA) | • Atazanavir with ritonavir or cobicistat: ATV with or 10 hours after H2RA (max famotidine 40mg BID for treatment naïve; 20mg BID for treatment experienced)  
• Atazanavir alone: ATV 2 hours before or 10 hours after H2RA (max famotidine 20mg dose for treatment naïve; CONTRAINDICATED for treatment experienced) | H2RA 12 hours before or 4 hours after RPV | No dose adjustment |
| Proton Pump Inhibitors (PPI) | Atazanavir must be boosted with ritonavir or cobicistat: PPI 12 hours prior to ATV (max omeprazole 20mg for treatment naïve; CONTRAINDICATED for treatment experienced) | CONTRAINDICATED | No dose adjustment |
## Managing ARV Interactions with Anti-acid Medications

<table>
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<tr>
<th>Anti-acid</th>
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<th>Rilpivirine (RPV) Intxns</th>
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</tr>
</tbody>
</table>
ARV Drug Interaction Resources

- Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. [www.aidsinfo.nih.gov]
  - Tables 17-20

- University of Liverpool HIV iChart app for iPhone and Android [www.hiv-druginteractions.org]
Summary

- ART recommended for all HIV+
  - Treatment goals achievable by selecting individualized ART regimen and maximizing adherence
- Initial ART = 2 NRTIs + INSTI or PI or NNRTI
  (2 scoops of rice + 1 main entrée)
- ART presents high potential for drug interactions due to the way the medications are absorbed and metabolized
The ABCs of ART: Designing Initial Antiretroviral Regimens for Beginners

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