

# **Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist**

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Presented as a Midday Symposium and Live Webinar at the  
49<sup>th</sup> ASHP Midyear Clinical Meeting and Exhibition

Tuesday, December 9, 2014  
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# Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist

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## Agenda

- 11:30 a.m. – 11:40 a.m. **Welcome and Introduction**  
Douglas Slain, Pharm.D., BCPS, FCCP, FASHP
- 11:40 a.m. – 12:15 p.m. **Antiretroviral Therapy Overview**  
Douglas Slain, Pharm.D., BCPS, FCCP, FASHP
- 12:15 p.m. – 12:50 p.m. **Primary Care Issues in HIV Patients**  
E. Kelly Hester, Pharm.D., BCPS, AAHIVP
- 12:50 p.m. – 1:00 p.m. **Faculty Discussion and Audience Questions**  
All Faculty

## Faculty

**Douglas Slain, Pharm.D., BCPS, FCCP, FASHP, *Activity Chair***

Associate Professor  
Infectious Diseases Clinical Specialist  
West Virginia University  
Morgantown, West Virginia

**E. Kelly Hester, Pharm.D., BCPS, AAHIVP**

Associate Clinical Professor  
Department of Pharmacy Practice  
Auburn University Harrison School of Pharmacy  
Auburn, Alabama

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- E. Kelly Hester, Pharm.D., BCPS, AAHIVP, is on the ViiV speakers Bureau.
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# Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist

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## Activity Overview

Advancements in antiretroviral therapy have not only reduced mortality but they have extended life expectancy so that HIV has become a chronic disease. New antiretroviral medications continue to be developed that target resistance, improve upon pill burden and increase tolerability.

Since patients are living longer, primary care issues such as hypertension, hyperlipidemia and diabetes are emerging. HIV patients are at increased risk for cardiovascular (CV) disease. The primary care pharmacist has an opportunity to impact outcomes by working collaboratively to optimize therapy and target CV risk reduction. Patient care is enhanced with wellness programs such as smoking cessation and improved immunization rates. Other important efforts are ensuring appropriate opportunistic infection prophylaxis medication adherence to reduce morbidity and hospitalizations.

## Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- Review the current national guidelines for antiretroviral therapy.
- Describe medication therapy management and disease state issues in HIV patients on antiretroviral therapy in the ambulatory care setting.
- Discuss the role of the pharmacist in treating and monitoring patients with HIV in the ambulatory care setting.

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- **Available in 2015**

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- **On-Demand Archive.** Captures the faculty presentations from the live symposium for those unable to attend the Midyear Clinical Meeting (1.5 hours CPE; individuals claiming CPE for the live activity or webinar are ineligible to claim credit for this activity).

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Participants will process CPE credit online at <http://elearning.ashp.org/my-activities>, with the option of printing a CE certificate. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of a live activity or completion of a home study activity.

## Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist

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### **Douglas Slain, Pharm.D., BCPS, FCCP, FASHP, *Activity Chair***

Associate Professor

Infectious Diseases Clinical Specialist

West Virginia University

Morgantown, West Virginia

Douglas Slain, Pharm.D., BCPS, FCCP, FASHP, is currently Associate Professor and Infectious Diseases Specialist at West Virginia University (WVU) in Morgantown, West Virginia. He received his Bachelor of Pharmacy degree and Doctor of Pharmacy degree from Duquesne University in Pittsburgh, Pennsylvania. He completed a residency and fellowship in infectious diseases pharmacotherapy at the Medical College of Virginia in Richmond and is a board certified pharmacotherapy specialist with added qualifications in infectious diseases.

Dr. Slain is an anti-infective clinical specialist on the WVU infectious diseases consult service and in the outpatient infectious diseases clinic. In addition, he teaches in the schools of Pharmacy, Medicine, and Graduate Nursing and is the program director and principal mentor for the infectious diseases pharmacotherapy specialty residency at WVU. He serves as an international consultant to schools of pharmacy and hospitals in other countries and has helped programs in their development of clinical pharmacy education, pharmacy residency training, and antibiotic stewardship. Dr. Slain was a 2013 recipient of a Fulbright Scholars grant, which funded a project in Chennai, India and he serves as the School of Pharmacy's Global Affairs Liaison. He was selected as Clinician of the Year by The Society of Infectious Diseases Pharmacists (SIDP) and has received multiple teaching awards in the School of Pharmacy.

Dr. Slain's research has been published extensively and he speaks frequently at regional, national, and international meetings and conferences.



## Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist

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### **E. Kelly Hester, Pharm.D., BCPS, AAHIVP**

Associate Clinical Professor

Department of Pharmacy Practice

Auburn University Harrison School of Pharmacy

Auburn, Alabama

E. Kelly Hester, Pharm.D., BCPS, AAHIVP, is Associate Clinical Professor in the Department of Pharmacy Practice at Auburn University Harrison School of Pharmacy in Auburn, Alabama. She received her Bachelor of Science and Doctor of Pharmacy from Auburn University. She completed a residency in pharmacy practice at Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina.

Dr. Hester currently has practice affiliations with two adult HIV clinics in Alabama and provides collaborative medication therapy management pharmaceutical care services for the HIV and primary care needs of her patients.

Prior to her current position, she worked for three years at the University of Alabama-Birmingham AIDS outpatient/research clinic serving as a clinical and investigational drug pharmacist.

CE IN THE MIDDAY

Optimizing Care of the HIV Patient in the Ambulatory Care Setting: Role of the Pharmacist

Douglas Slain, Pharm.D., BCPS, FASHP, Activity Chair

Associate Professor


Infectious Diseases Clinical Specialist

West Virginia University

E. Kelly Hester, Pharm.D., BCPS, AAHIVP

Associate Clinical Professor

Auburn University School of Pharmacy



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Learning Objectives

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- Discuss the role of the pharmacist in treating and monitoring patients with HIV in the ambulatory care setting.

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CE IN THE MIDDAY

Antiretroviral Therapy Overview

Douglas Slain, Pharm.D., BCPS, FCCP, FASHP
Activity Chair
Associate Professor
Infectious Diseases Clinical Specialist
West Virginia University

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Goals of Antiretroviral Therapy (ART)

- Maximal and durable suppression of viral load (HIV RNA < 20-50 copies/mL)
  - Typically achieved within 12-24 weeks after initiating ART
- Restoration and/or preservation of immunologic function
- Reduction of HIV-related morbidity and mortality
- Improvement of quality of life

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. May 2014.

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US Department of Health and Human Services Panel


Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents


Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents - A Working Group of the Office of AIDS Research Advisory Council (OARAC)

- Last updated May 2014
- 285 pages if printed

How to Use the Adult and Adolescent Guidelines

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at: <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>



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### Recommendation & Evidence Grading System

Strength of Recommendation	
A	Strong recommendation
B	Moderate recommendation
C	Optional recommendation

Quality of Evidence	
I	Evidence from at least 1 randomized clinical trial with clinical outcomes and/or validated laboratory endpoints
II	Evidence from at least 1 well-designed clinical trials without randomization, from observational cohort studies with long-term clinical outcomes
III	Expert opinion

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### International Antiviral Society-USA Panel

Gunthard HF et al. *JAMA* 2014; 312 (4):410-25.

- Updated from 2012 version
- Easier to read ☺
- Evidence and recommendation scale are slightly different
- Recommendations are similar

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### When to Start Antiretroviral Therapy (ART)?

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## When To Start Antiretrovirals

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm<sup>3</sup> **(AI)**
  - CD4 count 350 to 500 cells/mm<sup>3</sup> **(AII)**
  - CD4 count >500 cells/mm<sup>3</sup> **(BIII)**
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  - Pregnancy **(AI)**
  - History of an AIDS-defining illness **(AI)**
  - HIV-associated nephropathy (HIVAN) **(AII)**
  - HIV/hepatitis B virus (HBV) coinfection **(AII)**
- Patients starting ART should be willing and able to commit to treatment and should understand the benefits and risks of therapy and the importance of adherence **(AIII)**.

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. May 2014.

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## A Standard Antiretroviral Therapy (ART) Regimen

A combination of  $\geq 3$  antiretroviral drugs that are usually composed of:

A pair of two nucleoside reverse transcriptase inhibitors  
AND  
A non-nucleoside reverse transcriptase inhibitor  
OR  
A “boosted” protease inhibitor  
OR  
An Integrase Inhibitor

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. May 2014.

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## ART Drug Class Reviews

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## Classes of FDA Approved Antiretroviral Agents

- Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Integrase Strand Transfer Inhibitor
- Fusion Inhibitors
- Entry (CCR5) Inhibitors

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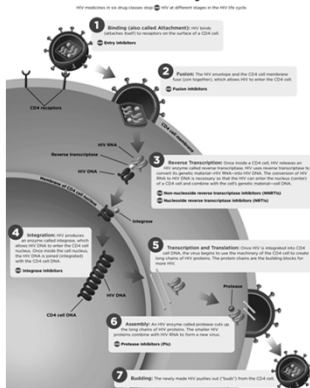
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### The HIV Life Cycle



<http://aidsinfo.nih.gov/education-materials/fact-sheets/19/73/the-hiv-life-cycle>

See page 36 for enlarged view

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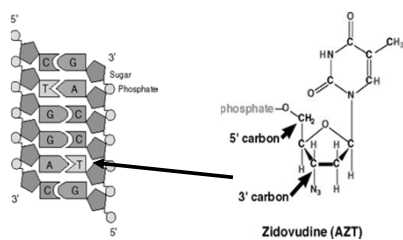
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## Nucleoside Reverse Transcriptase Inhibitors: Mimics of natural deoxynucleosides



Competitive inhibition of RT enzyme & leads to chain termination

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### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine (AZT)
- Stavudine (d4T)
- Zalcitabine (ddC)
- Lamivudine (3TC)
- Emtricitabine (FTC)
- Didanosine (ddI)
- Abacavir (ABC)
- Tenofovir (TDF)\*

\*Nucleotide agent

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### Combination NRTI “Backbone” Tablets

**Once Daily**

- Emtricitabine + Tenofovir (Truvada)
- Lamivudine + Abacavir (Epzicom)

**Twice Daily**

- Lamivudine + Zidovudine (Combivir)

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### One “Pill” Once a Day

- Atripla (efavirenz, tenofovir, emtricitabine)
- Complera (rilpivirine, tenofovir, emtricitabine)
- Stribild (elvitegravir, cobicistat, tenofovir, emtricitabine)

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CJ is a patient with HIV infection who is started on the regimen of emtricitabine + tenofovir + cobicistat + elvitegravir. After two weeks of therapy he appears to have developed some renal insufficiency.



What agent is most likely associated with renal problems?

- a. Emtricitabine
- b. Tenofovir
- c. Cobicistat
- d. Elvitegravir

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### NRTI - Associated Toxicity

- Neuromuscular:
  - Polyneuropathy **ddC, d4T, ddl**
  - Myopathy & Cardiomyopathy **AZT, ddl, ddC**
- Cardiac: ↑ risk of MI: **ABC ?**
- Hepatic:
  - Steatosis, lactic acidosis **All agents**
- Gastrointestinal:
  - Nausea / diarrhea **All agents**
  - Pancreatitis **ddl, d4T**
- Hematological:
  - Anemia / neutropenia **AZT**
  - ↑ mean corpuscular volume (MCV)\* **AZT**
- Nephrotoxicity: **Tenofovir**

\* Not an adverse effect

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### Mitochondrial Toxicity

- Toxicities:
  - Hepatic steatosis
  - Lactic acidosis
  - Myopathy
  - Peripheral neuropathy
  - Pancreatitis
- Role of mitochondria may be more important in certain tissues.
- More common with “d” drugs **ddl, ddC, and d4T**
  - NRTIs vary in their ability to inhibit mtDNA polymerase.
  - Different drug levels in different tissues.

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## Abacavir Hypersensitivity Reaction

- Reported in approximately 5% of patients.
- Potentially fatal (hypotension).
- Clinical features (within 6 weeks):
  - Fever
  - Rash
  - Nausea / vomiting / abdominal pain
  - Malaise / fatigue
  - Dyspnea
  - Labs: ↑ CPK & LFTs.
- Don't re-challenge patient.
- Can now genotype patients (HLA-B\* 5701)

Mallal S, et al. *N Engl J Med*. 2008; 358:568-579.

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## Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Delaviridine
  - Nevirapine
  - Efavirenz
  - Etravirine
  - Rilpivirine
- } Newer generation NNRTIs
- Binds to reverse transcriptase enzyme resulting in blockade of RNA/DNA polymerase activity. Not substrates of the enzyme.

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## Newer NNRTIs: Etravirine or Rilpivirine

- Not affected by single K103N mutation
- Activity can be reduced with  $\geq 3$  NNRTI mutations
- Etravirine 200mg PO Twice Daily
- Rilpivirine 25mg PO Once Daily (in Complera)
  - Take with 400 kcal meal

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## NNRTI Adverse Effects

- Rash **All agents**
- Elevated LFTs/hepatitis **All agents**
- CNS side effects\*: **efavirenz**
- Drug interactions (CYP-450). **All agents**
- False-positive cannabinoid test **efavirenz**
- NNRTI cross-resistance common (i.e., K103N)  
– Single mutation
- FDA pregnancy Category “D”: Avoid in 1<sup>st</sup> trimester **efavirenz**
- Dyslipidemia: **efavirenz**

\*dizziness, hallucinations, vivid dreams/nightmares, insomnia, irritability, disorientation, depression, suicidal ideation

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## Protease Inhibitors

- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Fosamprenavir
- Lopinavir/ritonavir (co-formulated tablet)
- Atazanavir
- Darunavir
- Tipranavir

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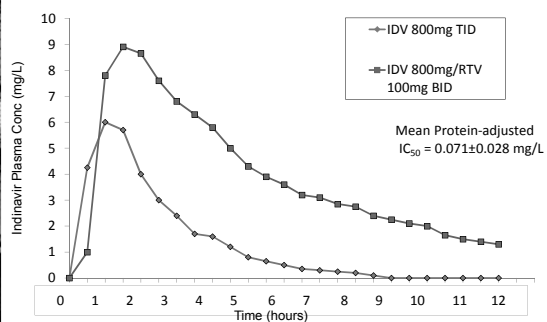
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Steady-State Indinavir (IDV) Concentrations With and Without Ritonavir (RTV) “Boosting”



Kappelhoff BS et al. *Br J Clin Pharmacol*. 2005;60:276-86.

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## Proposed Benefits of “Boosting”

- Administer drugs less often
- Decrease pill burden
- Eliminate food restrictions
- Improve pharmacodynamics
- Less resistance
- Less effect of other drug interactions

Now the standard for protease inhibitor regimens

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## Protease Inhibitor Adverse Effects

- GI intolerance/nausea/diarrhea **All agents**
- Hyperglycemia / insulin resistance **All agents**
- Fat redistribution / dyslipidemia **All agents**
  - ↑ LDL-C and Triglycerides
- Osteopenia, osteoporosis **All agents**
- ↑ indirect bilirubin **Indinavir, Atazanavir**
- Elevated LFTs/hepatitis **All agents**
- Nephrolithiasis / renal disease **Indinavir**
- Drug interactions (CYP-450) **All agents**
- Sulfonamide allergy **Darunavir, Fosamprenavir, Tipranavir**

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. May 2014.

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## Integrase Inhibitors

### Raltegravir

- Inhibits the enzyme HIV-1 integrase
- 400 mg orally twice daily dosing
- Can be an initial use agent
- Minimal drug interactions
- GI effects, headache, CPK elevations

### Elvitegravir

- 150 mg orally once Daily
- CYP3A4 substrate
- Only in quad pill (Stribild)

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## Dolutegravir

- Less lipid effects than efavirenz
- Metabolized by UGT1A1 with some CYP3A.
- Substrate of P-glycoprotein and other UGTs
- Separate dosing from cation<sup>+</sup> medications
- Can ↑ SCr

### Dosing

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance*	50 mg twice daily

INSTI = Integrase Strand Transfer Inhibitor  
UGT = Uridine Diphosphate Glycosyltransferases

\*alternative combinations that do not include metabolic inducers should be considered where possible

See page 36 for enlarged view

## The “Quad Pill” (Stribild)

Elvitegravir  
Cobicistat  
Tenofovir  
Emtricitabine

- Dose: 1 Tablet once daily with food
- Drug Interactions!
  - Cobicistat is a CYP3A4, CYP2D6, and P-glycoprotein inhibitor
- Cobicistat can interfere with creatinine tubular secretion (Don't start if CrCL < 70 mL/min, stop if CrCL < 50mL/min)

Arya et al. J Clin Pharmacol. 2014;54: 279-81.

## What to Start with

Preferred regimens for naïve patients (A-I)
<b>NNRTI-Based Regimens</b>
• Efavirenz / Tenofovir / Emtricitabine
<b>Protease Inhibitor-Based Regimen</b>
• Atazanavir/r* + Tenofovir / Emtricitabine
• Darunavir/r* + Tenofovir / Emtricitabine
<b>Integrase Inhibitor-Based Regimens</b>
• Dolutegravir + Abacavir / Lamivudine (Only if HLA-B*5701 negative)
• Dolutegravir + Tenofovir / Emtricitabine
• Elvitegravir / Cobicistat / Tenofovir / Emtricitabine (Only if pre-ART CrCl > 70mL/min)
• Raltegravir + Tenofovir / Emtricitabine

\*ritonavir boosting

U.S. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. May 2014.

## What to Start with

Preferred regimens for naive patients (A-I)
ONLY if pre-ART plasma HIV RNA <100,000 copies/mL
NNRTI-Based Regimens
<ul style="list-style-type: none"> <li>• Efavirenz + Abacavir / Lamivudine (Only if HLA-B*5701 negative)</li> <li>• Rilpivirine / Tenofovir / Emtricitabine (Only if CD4 &gt; 200 cells/mm<sup>3</sup>)</li> </ul>
Protease Inhibitor-Based Regimen
<ul style="list-style-type: none"> <li>• Atazanavir/r* + Abacavir / Lamivudine (Only if HLA-B*5701 negative)</li> </ul>
*ritonavir boosting

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MS is a 34 yr old HIV-positive male patient who is about to begin ART with Atazanavir/r + Tenofovir / Emtricitabine. You review his list of chronic medications and see that he takes: omeprazole, beclomethasone oral inhaler, and a multivitamin.

Which agent can interact with this patients ART regimen?

- Omeprazole
- Beclomethasone inhaler
- Multivitamin
- All of the above




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## Antiretroviral Drug Interactions

- Cytochrome (CYP) P-450 Isoenzymes
  - Primarily CYP3A4
- P-Glycoprotein
- pH alteration

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P-450 CYP3A4 Drug Interactions		
<u>Substrates</u>	<u>Inhibitors</u>	<u>Inducers</u>
<b>PIs</b>	Azole antifungals	Rifampin
Statins	Macrolides	Rifabutin
Macrolides	<b>NNRTIs</b>	<b>NNRTIs</b>
<b>Some NNRTIs</b>	Grapefruit juice	Phenobarbital
<b>Maraviroc</b>	<b>PIs</b>	Carbamazepine
Benzodiazepines	Sertraline	Phenytoin
Azole antifungals	Fluoxetine	
Methadone	<b>Cobicistat</b>	
<b>Elvitegravir</b>	Other P-450 isoenzymes may be involved in interactions	
PI=protease inhibitors inhibitor	NNRTI=non-nucleoside reverse transcriptase	
Developed from: Michalets EL. <i>Pharmacotherapy</i> 1998;18:84-112.		

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Special Interactions to Watch For
ART with acid suppression agents <ul style="list-style-type: none"> <li>• Atazanavir</li> <li>• Rilpivirine</li> </ul>
Interactions between NNRTIs,PIs, and Elvitegravir. <ul style="list-style-type: none"> <li>• Unpredictable</li> </ul>
Methadone and protease inhibitors <ul style="list-style-type: none"> <li>• Lower methadone concentrations</li> </ul>

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Drug Interaction Resources
<ul style="list-style-type: none"> <li>• University of Liverpool <ul style="list-style-type: none"> <li>– <a href="http://www.hiv-druginteractions.org">www.hiv-druginteractions.org</a></li> </ul> </li> <li>• University of California San Francisco <ul style="list-style-type: none"> <li>– <a href="http://arv.ucsf.edu/institute">http://arv.ucsf.edu/institute</a></li> </ul> </li> <li>• U.S. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. May 2014. <ul style="list-style-type: none"> <li>– <a href="http://Aidsinfo.NIH.gov">Aidsinfo.NIH.gov</a></li> </ul> </li> </ul>

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### ART Drugs with Hepatitis B activity

- Tenofovir
- Lamivudine
- Emtricitabine
- Only use these as part of HIV regimen not as monotherapy for Hepatitis B infection

Lok ASF et al. *Hepatology*. 2007;45:507-39.  
Lok ASF et al. *Hepatology*. 2009; 50:661-2.

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### Acute Hepatotoxicity

- Nearly all available antiretroviral drugs have been associated with some risk for hepatotoxic reactions.
- Many patients co-infected with hepatitis B or C.
- Treating HIV can improve viral hepatitis

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### Immune Reconstitution Inflammatory Syndrome (IRIS)

- Inflammatory syndrome triggered by supercharged immune system (post HAART initiation).
- Usually occurs during an acute or subacute infection or disease.
  - *Mycobacterium avium* complex (MAC)
  - Tuberculosis
  - Cytomegalovirus (CMV)
  - Cryptococcal Meningitis
  - *Pneumocystis jiroveci* pneumonia (PJP)-formerly *Pneumocystis carinii* pneumonia
- Paradoxical worsening of their underlying opportunistic infection.
- Role of corticosteroids or delay of HAART initiation ?

HAART=Highly active antiretroviral therapy

Dhasmana DJ et al. *Drugs*. 2008; 68:191-208.

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## When To Change Therapy

- To simplify regimen
- Toxicity or interaction with other drug(s).
- Failure to maintain undetectable HIV RNA.
  - Selection and replication of resistant mutants are more likely to occur as viral load increases.
  - Modifiable reasons for failure (nonadherence, interactions, etc. ) MUST be addressed first.

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## Why Do Regimens Fail?

- Drug resistance
- Insufficient drug exposure
  - Poor adherence
  - Low bioavailability
    - Poor absorption / drug interactions
  - Inability to penetrate viral reservoirs (sanctuary sites)
- Limited antiviral potency
- Progressive immunologic decline

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## Resistance -- Genetic Mutation

- Genetic mutations can result in changes in drug target enzymes (reverse transcriptase, protease, or integrase).
- A mutation of concern is one that does not compromise the enzyme functionality, but resists antiretroviral agents.
- Drug activity can be reduced by single or multiple mutations



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### Points to Remember About Resistance Testing

- Generally recommended for all HIV patients entering care.
- A better test of resistance than susceptibility.
- Minor species not accounted for.
- Testing should be done during a “failed regimen”.
- Generally requires a minimum HIV RNA of 500 copies / mL.

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### Conclusion

- Antiretroviral therapy has dramatically improved the lives of HIV-infected patients and many around them
- These therapies have complex interactions and complications
- Pharmacists must use the best resources when managing pharmacotherapy in HIV infected patients

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### CE IN THE MIDDAY

#### Primary Care Issues in HIV Patients

**E. Kelly Hester, Pharm.D., BCPS, AAHVP**

Associate Clinical Professor  
Auburn University Harrison School of Pharmacy  
Auburn, Alabama

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## Topics

1. Discuss the impact of a pharmacist in the ambulatory care HIV practice setting regarding outcomes with ART and non-ART medications
2. Compare cardiovascular risks between HIV and non-HIV infected patients
3. Provide cardiovascular risk reduction strategies in an HIV patient
4. Describe mechanisms for potential drug-drug interactions in older HIV patients

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## HIV in 2014

- U.S. Epidemiology
  - ~ 50,000 newly diagnosed annually
    - 1 in 4 is female (~65% African American)
  - ~ 20% living with HIV and undiagnosed
- Screening Recommendations  
CDC and American College of Obstetricians and Gynecologists (ACOG):
  - all adults and adolescents aged 13-64 years
  - all pregnant women (opt out screening)

[www.cdc.gov/hiv/basics/statistics.html](http://www.cdc.gov/hiv/basics/statistics.html); Brannon BM et al. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; *Obstet Gynecol*. 2014;123(5): 1137-1139. *Obstet Gynecol*. 2008;112(3):739-42.

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## HIV in 2014

- All HIV-infected patients should be treated
  - To reduce risk of disease progression
  - To prevent HIV transmission
- HIV is a chronic disease
- Adherent, treated HIV-infected patients have increased longevity vs. non-adherent patients

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. May 1, 2014. p. E1-8. Accessed October 28, 2014. Nakagawa F, May M, and Phillips A. *Curr Opin Infect Dis* 2013; 26:17-25.

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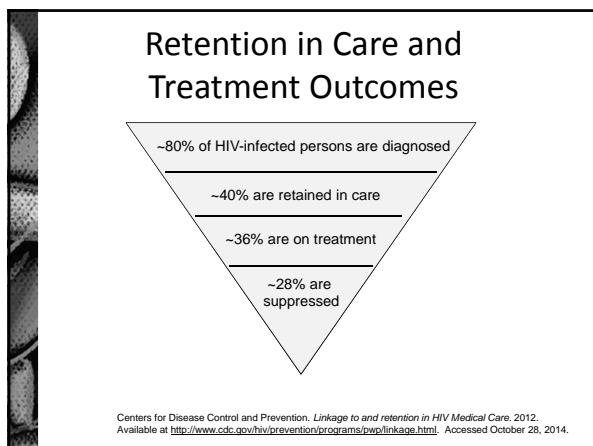
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### Antiretroviral Adherence

- Critical to:
  - Durability of treatment, health improvement, quality of life and survival
  - Emergence of drug resistance
- Predicts:
  - Therapeutic failure
- 90-95% adherence rates are necessary for virologic suppression for most antiretroviral regimens

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. May 1, 2014. p. K1. Accessed October 28, 2014. Paterson DL et al. *Ann Intern Med*. 2000;133(1):21-30. Mannheimer S et al. *Clin Infect Dis* 2002; 34: 1115-21.

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### Factors Associated with Nonadherence

<ul style="list-style-type: none"> <li>• Dosing schedule</li> <li>• Side effects</li> <li>• Depression, anxiety, mental illness</li> <li>• Neurocognitive impairment</li> <li>• Low health literacy</li> </ul>	<ul style="list-style-type: none"> <li>• Substance abuse (alcohol, illicit drugs)</li> <li>• Poverty (homelessness)</li> <li>• Stigma, nondisclosure of HIV diagnosis</li> <li>• Denial</li> </ul>
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Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at <http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. May 1, 2014. p. K1-6. Accessed October 28, 2014.

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## Counseling Points

- Goals of therapy (“undetectable”)
- ADRs (potential and severe)
- Administer as prescribed
- Alert all HCPs regarding prescription, OTC, and antiretroviral therapy for potential drug-drug interactions
- Rationale for primary and secondary opportunistic infection prophylaxis

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## Impact of HIV Clinical Pharmacists

- HIV treatment outcomes
  - Improved ARV adherence and viral suppression
  - Reduced hospitalizations and ED visits
  - Inappropriate discontinuation of outpatient medications
  - Reduced drug-related problems
    - Ensured accuracy of ARV dosing
    - Addressed drug-drug interactions

Saberi P et al. *Patient Prefer Adherence*. 2012; 6:297-322.  
Molino Cde G et al. *Ther Clin Risk Manag*. 2014; 10:631-9.

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## Cardiovascular Disease and HIV

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The following characteristics increase CVD risk in HIV-infected patients except:



- a. Accelerated aging
- b. Low CD4 cell count
- c. Suppressed viral load
- d. Antiretroviral therapy metabolic changes

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### CVD risks and HIV

- Veterans Aging Cohort Study Virtual Cohort
  - Found an independent association between HIV infection and risk of AMI
  - HIV positive veterans had a 50% increased risk of acute MI after adjustment for standard Framingham risk factors compared with uninfected veterans (hazard ratio 1.48; 95% CI, 1.27-1.72).
  - Risk was maintained with viral loads < 500 copies/ml but highest with CD4 counts < 200 cells/mm<sup>3</sup>.

AMI=Acute myocardial infarction

Freiberg MS et al. *JAMA Intern Med.* 2013; 173(8): 614-22.

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### Veterans Aging Cohort Study Virtual Cohort

	Uninfected	HIV-Infected
Age	Rates of AMI per 1000 person-years (95% CI)	
40-49	1.5 (1.3-1.7)	2.0 (1.6-2.4)
50-59	2.2 (1.9-2.5)	3.9 (3.3-4.5)
60-69	3.3 (2.6-4.2)	5.0 (3.8-6.7)
70-79	6.7 (4.8-9.2)	10.0 (6.7-14.7)

Median age of event (56) and time to event (3.3 years) was similar between groups.

Freiberg MS et al. *JAMA Intern Med.* 2013; 173(8): 614-22.

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## HIV and CVD in Women

- Veterans Aging Cohort Study Virtual Cohort

	HIV-infected women vs. uninfected women
	Hazard Ratio (95% CI)
Risk of CVD after adjusting for Framingham risk factors	2.8 (1.7-4.6)
CVD rates per 1000 person years	
HIV-infected	13.5 (10.1-18.1)
HIV-uninfected	5.3 (3.9-7.3)
Risk of death	2.6 (1.7-3.9)

Median time to event was similar (3.1 vs. 3.7 years,  $p=0.11$ )

Womack JA et al. *J Am Heart Assoc.* 2014;  
available at: <http://jaha.ahajournals.org/content/3/5/e001035>.

## Veterans Aging Cohort Study Virtual Cohort


	VACS	VACS-Female Study
Viral load	HR (95% CI)	
HIV-1 RNA ≥500 copies/mL	1.8 (1.4-2.2)	3.7 (2.1-6.5)
HIV-1 RNA <500 copies/mL	1.4 (1.2-1.7)	1.6 (0.6-4.1)
CD4 count		
≥500 cells/mm <sup>3</sup>	-	2.3 (1.2-4.4)
200-499 cells/mm <sup>3</sup>	1.4 (1.2-1.7)	2.9 (1.5-5.7)
< 200 cells/mm <sup>3</sup>	1.9 (1.5-2.4)	3.8 (1.9-7.6)

Freiberg MS et al. *JAMA Intern Med.* 2013; 173(8): 614-22.  
Womack JA et al. *J Am Heart Assoc.* 2014; available at: <http://jaha.ahajournals.org/content/3/5/e001035>.

## CVD Risks and HIV

- Framingham risk score and 2013 ASCVD risk calculator may underestimate AMI risk:
  - Other risk factors: hepatitis C, anemia, renal disease, HIV-1 RNA, CD4 cell count
- Possible mechanisms for increased CVD risk
  - HIV infection: Inflammation, endothelial dysfunction, impaired arterial elasticity, altered coagulation, dyslipidemia, CD4 cell count deficiency.
  - Accelerated aging

Freiberg MS et al. *JAMA Intern Med.* 2013; 173(8): 614-22. Tsiert VA et al. *J Acquir Immune Defic Syndr.* 2009; 51(3): 268-73. Lichtenstein KA et al. *Clin Infect Dis.* 2010; 51(4): 435-47. Kuller LH et al. *PLoS Med.* 2008; 5(10):e203. Ridder SA et al. *JAMA.* 2003; 289(22): 2979-82. Baker JV et al. *J Acquir Immune Defic Syndr.* 2009; 52(1): 25-31. Torriani FJ et al. *J Am Coll Cardiol.* 2008; 52(7): 969-76. Deeks SG. *Top HIV Med.* 2009;17(4):118-23. Law MG et al. *HIV Med.* 2006; 7(4):218-30. Zeevi MV et al. *AIDS.* 2014; 28(14):2381-70.



### CVD Risks and HIV

- Possible mechanisms for increased CVD risk
  - ART: metabolic changes, fat redistribution, insulin resistance
- Strategies for Management of Antiretroviral Therapy (SMART) study:
  - HIV viral suppression with ART lowered CVD risk compared to interrupting therapy to minimize ART exposure
  - Suggests greater association with HIV viral load compared to ART

El-Sadr WM et al. *N Engl J Med*. 2006; 355(22): 2283-96. Hadigan C et al. *Clin Infect Dis*. 2001; 32(1): 130-9. Jacobson DL et al. *Clin Infect Dis*. 2005; 40(12): 1837-45. Grunfield C et al. *AIDS*. 2010; 24(11): 1717-26. Wohl D et al. *J Acquir Delic. Syndr*. 2008; 48(1):44-52.

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### Role of the Pharmacist

- CV Risk Reduction Services
  - ART adherence
  - Smoking cessation counseling
  - Dyslipidemia management
  - HTN management
  - Diabetes management

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### Tobacco abuse and HIV

- High cigarette smoking rates in HIV-infected patients (> 50%)
- Risk of MI is more than two-fold higher in HIV-infected smokers compared to uninfected smokers.
- Tobacco abuse is an important modifiable risk factor
- Pharmacist managed smoking cessation programs can reduce cardiovascular risk.

Saves M et al. *Clin Infect Dis*. 2003; 37(2):292-8.

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## Dyslipidemia and HIV

- HIV-infected patients more likely have low total cholesterol, HDL, LDL and elevated triglycerides (TG) than uninfected patients
- ART can potentially increase HDL and worsen TG
- Potential for drug-drug interactions between statin therapy and ART (CYP450 and organic anion transporters)
- Pharmacists can address ASCVD risk and underutilization of statin therapy for CV risk reduction

Grunfeld C et al. *J Clin Endocrinol Metab* 1992; 74: 1045-52  
Periard D et al. *Circulation* 1999; 100: 700-5.  
Hauwrich RH et al. *AIDS* 2009; 23: 1109-18.

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## Hypertension and HIV

- Cohort studies indicate greater incidence of HTN compared with uninfected patients.
- An important modifiable risk factor
- Pharmacist-managed collaborative drug therapy programs can reduce cardiovascular risk.
- Pharmacists can address underutilization and optimization of therapy for compelling indications (diabetes, CKD, CHF, stroke).

Hadigan C et al. *Clin Infect Dis* 2001; 32:130-9.  
Triant VA et al. *J Clin Endocrinol Metab*. 2007; 92(7):2506-12.

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## Diabetes and HIV

- Rates of new onset diabetes in HIV patients receiving ART are 4-fold higher than in uninfected patients.
- Insulin resistance with protease inhibitor-based ART is estimated >60%.
- Pharmacist-managed collaborative drug therapy programs can improve glycemic outcomes and safety with therapy (insulin, incretin therapy).
- Pharmacists can address underutilization of metformin therapy and provide education on lifestyle modifications (diet, weight loss).

Tsiolodras S et al. *Arch Intern Med*. 2000; 160(13): 2050-6.  
Brown TT et al. *Arch Intern Med* 2005; 165:1179-84.

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## The Older HIV Patient

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Which of the following medications would be contraindicated in an older HIV patient on protease inhibitor therapy?



- a. Warfarin
- b. Rivaroxaban
- c. Pantoprazole
- d. Alprazolam

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## Aging and HIV

- In the US, >50% of the HIV-infected population will be over the age of 50 by 2015
- Increased number of comorbid conditions
  - Shah et al: 89%  $\geq 1$  comorbidity
  - 2.4 conditions per person (mean)
- Cost of HIV health care is increasing with aging HIV population

Elfrors RB et al. Clin Infect Dis 2008; 47(4): 542-53. Shah SS et al. Clin Infect Dis. 2002; 35(10): 1238-43.  
Krentz HB et al. HIV Med. 2014 Aug 8. doi: 10.1111/hiv.12176.

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## Aging and HIV

- Tseng et al: Older HIV patients ( $\geq 50$  years) and drug interactions
  - On more medications than younger patients (9 vs. 7,  $p < .0001$ )
  - 75% of interactions were between ARV and non-ARV medications
- More likely to be on anti-infectives, anticoagulation/antiplatelet agents, cardiovascular medications, antidepressants, psychotropics, musculoskeletal agents, narcotics/analgesics
- Interactions more likely with use of protease-inhibitor regimens

Tseng A et al. *Ann Pharmacother*. 2013; 47(11): 1429-39.  
Marzolini C et al. *J Antimicrob Chemother*. 2011; 31:480-9.

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## Polypharmacy and ART

- Risk of drug interactions
  - Many ARV medications are CYP450 substrates and either inducers or inhibitors
  - ART failure possible with enzyme inducers, acid reducers, and cation-binding concomitant medications
  - Older patients more likely to have  $\geq 1$  potential drug-drug interaction compared to younger patients (71% vs 55%,  $p < .0001$ )<sup>1</sup>
    - Median of 2 interactions per patient (IQR=1-4)
    - Each 10-yr increase in age increased the likelihood of a drug-drug interaction (OR=1.72,  $p < .0001$ )
    - More likely prescribed a contraindicated medication (OR=1.44, CI 1.14-1.82)<sup>2</sup>

<sup>1</sup>Tseng A et al. *Ann Pharmacother*. 2013; 47(11): 1429-39.  
<sup>2</sup>Holtzman C et al. *J Gen Intern Med* 2013; 28(10): 1302-10.

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## Primary Care Guidelines: Immunizations

Pharmacists can improve vaccination rates through education on vaccine preventable disease

- |                                    |                           |
|------------------------------------|---------------------------|
| • Hepatitis A                      | CD4 > 200 cells/ $\mu$ L: |
| • Hepatitis B (40 $\mu$ g/mL dose) | • Pneumococcal            |
| • HPV                              | • Varicella               |
| • Influenza                        | • Zoster                  |
| • Tetanus toxoid                   |                           |

Aberg JA et al. *Clin Infect Dis*. 2014; 58(1):e1-34.

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### Role of the Pharmacist

- Older HIV patients
  - Drug-drug interaction review and tolerability with ART and concomitant therapy
  - Medication review for untreated indications
  - Appropriate ART dosing with declining renal function
- Health and Wellness for all patients
  - Ensuring optimization of indicated vaccinations

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### Role of the Pharmacist

- Emphasis on medication adherence and retention in care is key
- Prioritize optimal management of primary care comorbidities
- Address modifiable lifestyle risk factors for cardiovascular risk reduction
- Address vaccine-preventable diseases
- Review and address drug-drug interactions with polypharmacy and older patients

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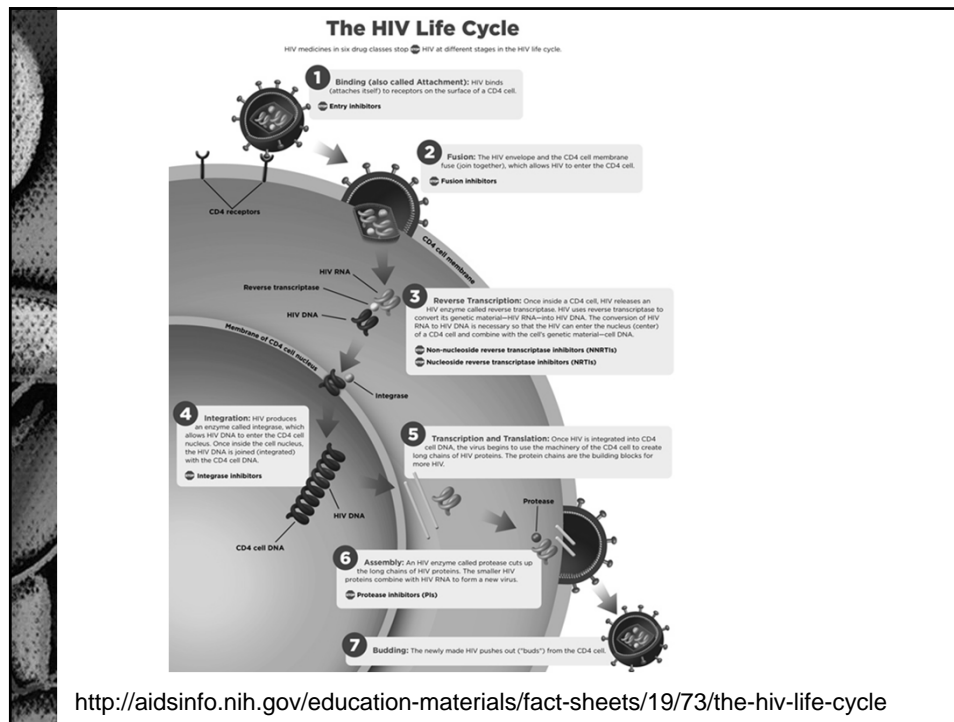
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## Dolutegravir

- Less lipid effects than efavirenz
- Metabolized by UGT1A1 with some CYP3A.
- Substrate of P-glycoprotein and other UGTs
- Separate dosing from cation<sup>+</sup> medications
- Can ↑ SCr

### Dosing

Adult Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with the following potent UGT1A/CYP3A inducers: efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance*	50 mg twice daily

\*alternative combinations that do not include metabolic inducers should be considered where possible

INSTI = Integrase Strand Transfer Inhibitor

UGT = Uridine Diphosphate Glycosyltransferases