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Antiretrovirals: Drug Interactions

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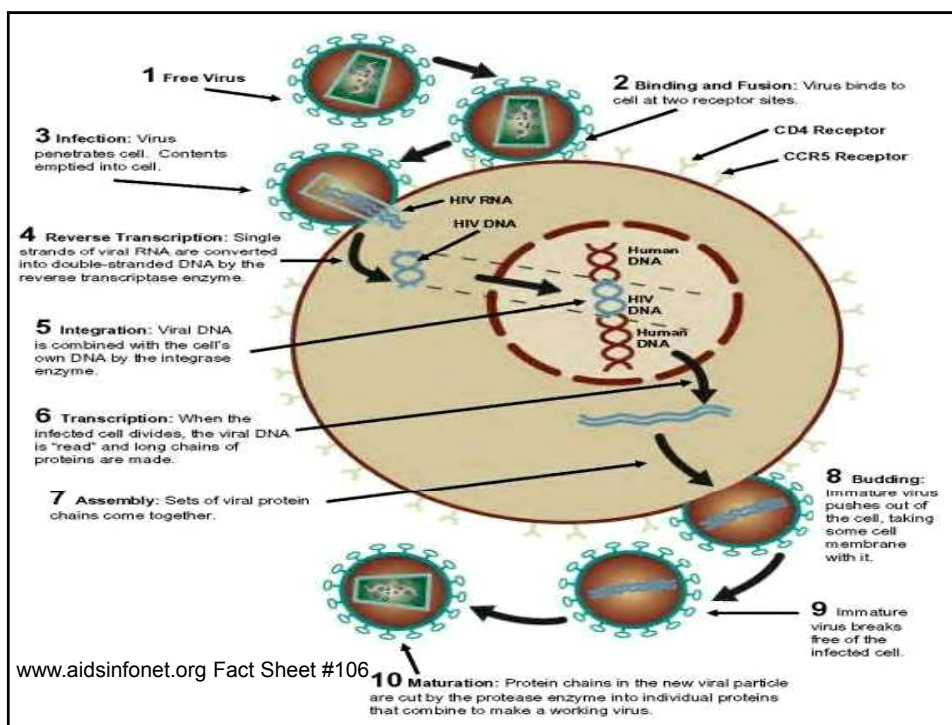
Objectives

- To review mechanisms of action of commonly used antiretroviral agents
- To discuss drug-drug interactions associated with antiretroviral use
- Highlight the role of the clinician in prevention, detection and monitoring of drug-drug interactions when providing care for HIV-infected patients



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Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)

Agent	Approved
• Zidovudine (AZT, ZDV, Retrovir®)	3/87
• Didanosine (ddI, Videx®, Videx EC®)	10/91
• Zalcitabine (ddC, Hivid®)	6/92
• Stavudine (d4T, Zerit®)	6/94
• Lamivudine (3TC, Epivir®)	11/95
• Abacavir (ABC, Ziagen®)	12/98
• Combivir® (AZT/3TC)	9/97
• Trizivir® (AZT/3TC/ABC)	11/00
• Tenofovir (TDF, Viread®)*	10/01
• Emtricitabine (FTC, Emtriva®)	7/03
• Epzicom® (ABC/3TC)	8/04
• Truvada® (FTC/TDF)	8/04



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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Agent	Approved
• Nevirapine (NVP, Viramune®)	6/96
• Delavirdine (DLV, Rescriptor®)	4/97
• Efavirenz (EFV, Sustiva®)	9/98
• Etravirine (Intelence®)	1/08




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Protease Inhibitors (PIs)

Agent	Approved
<ul style="list-style-type: none"> • Saquinavir-HGC (SQV-HGC, Invirase®) • Ritonavir (RTV, Norvir®) • Indinavir (IDV, Crixivan®) • Nelfinavir (NFV, Viracept®) • Saquinavir-SGC (SQV-SGC, Fortovase®) • Amprenavir (APV, Agenerase®) • Lopinavir/ritonavir (KAL, Kaletra®) • Atazanavir (ATV, Reyataz®) • Fosamprenavir (fos-APV, Lexiva®) • Tipranavir (TPV, Aptivus®) • Darunavir (DRV, Prezista®) 	<p>12/95 3/96 3/96 3/97 11/97 4/99 9/00 6/03 10/03 6/05 6/06</p>

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Entry Inhibitors

Agent	Approved
<p>Fusion Inhibitor</p> <ul style="list-style-type: none"> • Enfuvirtide (T-20, Fuzeon®) 	<p>3/03</p>
<p>CCR5 Inhibitor</p> <ul style="list-style-type: none"> • Maraviroc (Selzentry®) 	<p>8/07</p>

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Integrase Inhibitor

- **Raltegravir (Isentress®)**
 - Introduced October 2007
 - New class used in naïve and treatment experienced patients
 - Used in patients with multiple-resistant strains of HIV
 - Inhibition of integrase prevents insertion of HIV DNA into the human DNA genome, thus blocking the ability of HIV to replicate



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What Would You Do?

- **You have a visit today from a 56 yo HIV positive, treatment experienced male on the following medications:**
 - Verapamil 180mg po daily
 - Atazanavir 300mg po daily
 - Ritonavir 100mg po daily
 - Emtricitabine/Tenofovir 1 tab po daily
 - Ibuprofen 600mg po daily
 - Mylanta® (aluminum/magnesium hydroxide, simethicone) prn GI irritation

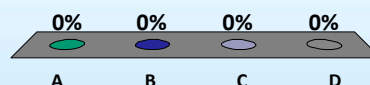


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Drug Interactions in this case may result in:

- A. Potential increase in viral load
- B. Increase in verapamil levels
- C. Decrease in atazanavir levels
- D. All of the above are possible



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Mechanisms Associated with Case

- Absorption issues with Mylanta[®]
- Effects of enzyme inhibition with ritonavir and other PIs



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Understanding Drug Interactions with Antiretrovirals

- **Mechanisms of Drug Interactions**
 - Pharmacokinetic Interactions
 - These interactions affect:
 - Absorption of drugs
 - Distribution of drugs
 - Metabolism
 - Elimination of drugs
 - Pharmacodynamic Interactions



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Interactions Affecting Drug Metabolism Most Common

- **Cytochrome P450 is an enzyme system containing many enzyme families**
- **The majority of interactions reported involve CYP3A4**
 - Medications can induce OR inhibit the action of enzymes responsible for their own metabolism or the metabolism of other drugs
 - Inducing enzymes result in lower drug levels; Inhibiting enzymes result in increased levels



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Drug Interactions: HAART

- Nucleoside and Nucleotide drugs are not eliminated via cytochrome P450 therefore these interactions are minimal
- Drug interactions here may occur via other mechanisms (eg GI absorption, renal elimination)



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Non-nucleoside Interactions

- **Drugs involved:**
 - Efavirenz: can induce or inhibit CYP3A4 (most often acts as an inducer and can also induce others)
 - Nevirapine acts as an inducer to CYP3A4
 - Etravirine serves as substrate and inducer of CYP3A4. Can also inhibit 2C9 and 2C19



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Protease Inhibitor Interactions

- All PIs inhibit CYP3A4
- Ritonavir is the most potent inhibitor while Saquinavir is the least potent
- Ritonavir can inhibit other cytochrome P450 inhibitors and can induce CYP1A2
- Fusion inhibitors and integrase inhibitors are not metabolized by these systems

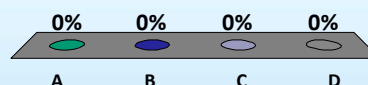


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The dosage of which of the following should be reduced if given with ritonavir?

- A. Lamivudine**
- B. Sildenafil**
- C. Emtricitabine**
- D. Azithromycin**



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Drug Interactions: Maraviroc (Selzentry®)

Maraviroc plus CYP3A inhibitors (with or without a CYP3A inducer)

These include:

- protease inhibitors (except tipranavir/ritonavir)
- delavirdine
- ketoconazole, itraconazole, clarithromycin
- other strong CYP3A inhibitors (e.g., nefazadone, telithromycin)
- **The recommended dose is 150 mg twice daily.**



Dosage considerations

Maraviroc plus other concomitant medications

- **These include:**
 - tipranavir/ritonavir
 - nevirapine
 - all NRTIs
 - raltegravir
 - enfuvirtide
- **The recommended dose is 300 mg twice daily.**



Dosage considerations

Maraviroc plus CYP3A inducers (without a strong CYP3A inhibitor)

- **These include:**
 - efavirenz
 - etravirine
 - rifampin
 - carbamazepine, phenobarbital, and phenytoin
- **The recommended dose is 600 mg twice daily.**



Raltegravir (Isentress®)

- **Coadministration of drugs that are strong inducers of UGT1A1 (uridine diphosphate glucouronosyltransferase) may result in reduced plasma concentrations of raltegravir**
- **Examples:**
 - Usual dosage: 400 mg po bid,
 - With rifampin the dose is 800 mg po bid



Effects of Food on Absorption of Antiretrovirals

- **Didanosine (Videx[®], Videx EC[®])**
 - Levels decrease by 55%
 - Take ½ hour before or 2 hours after meals
- **Efavirenz (Sustiva[®], Atripla[®])**
 - Empty stomach, food increases levels as high as 39%-79%
- **Nelfinavir (Viracept[®])**
 - Levels increase 2-3 fold with food; Take with food



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Food Effects continued...

- **Saquinavir (Invirase[®])**
 - Levels increase 6-fold if taken with food
 - Take with or up to 2 hours after a meal as sole PI or with RTV
- **Lopinavir/Ritonavir (Kaletra[®])**
 - Take tabs with or without food
 - Take solution with food
- **Consult AETC Pocket Cards for food effects!**



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Effect of Buffering Agents on PI Concentrations

- **Mechanism**

- PI absorption is related to its solubility properties
- For weak bases-solubility increases in gastric acid
- When pH is less acidic, PIs become less soluble to varying degrees



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Effect of Buffering Agents on Gastric pH

Buffering agents

- Proton-pump inhibitors (PPIs)
- Histamine-2 (H2) blockers
- Antacids
 - Aluminum/magnesium hydroxide in didanosine oral solution (Videx[®])

Duration of action

- Decrease in gastric acidity varies by drug class

<u>PPI</u>	>	<u>H2 blockers</u>	>	<u>antacids</u>
24 - 72h		10 - 12h		a few hours

References: Product Monographs



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Effect of Acid Suppression on Atazanavir Dosage

- **Antacids or buffered medications**
 - Tx naïve: Give ATV or ATV/r >2hrs before or 1hr after antacid
 - Tx experienced: ATV/r: Give > 2hrs before or 1hr after antacid
- **PPIs**
 - Tx naïve: ATV/r max dose omeprazole 20mg once daily (or equivalent) taken >12hrs prior
 - Tx experienced: ATV/r: not recommended



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Atazanavir continued

- **H2 Receptor Antagonists (H2RA)**
 - Tx naïve: ATV only: Give >2hrs before or 10 hrs after. Max dose of famotidine 20 mg po bid – do not exceed single dose of 20 mg-or equivalent
 - Tx naïve: ATV/r:
 - Give with or >10hrs after H2RA. Max dose 40 famotidine 40 mg bid or equivalent



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Atazanavir continued

- **H2 Antagonists continued:**
 - Tx experienced: ATV/r:
 - Give with or >10hrs after H2RA, max dose of famotidine 20 mg bid or equivalent
 - ATV/r (400mg/100mg) with TDF:
 - Give with or >10hrs after H2RA, max dose of famotidine 20mg po bid or equivalent



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pH Influences With Other Meds

- **Didanosine (ddl)-Buffered Oral Solution**
 - Contains buffering agents that can affect absorption of:
 - Atazanavir
 - Tetracyclines
 - Quinolones
 - Itraconazole
 - Not a problem with oral capsules



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Examples of Noted Interactions Between Antiretrovirals

- **Efavirenz, Etravirine, and Nevirapine**
 - Decrease atazanavir levels
 - Interactions with other PIs as well (see AETC pocketcard)
- **Tenofovir and ddl**
 - ddl levels are elevated (exact mechanism not known fully)
 - Recommend 250mg ddl-EC (>60 kg)
 - Some reports to suggest decreased virologic control and blunted immunologic response when this combination used as NRTI backbone with EFV or NVP



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Antiretroviral Interactions continued

- **Tenofovir and atazanavir**
 - Atazanavir levels are decreased
 - Tenofovir concentrations increased
 - Atazanavir should be boosted with RTV when combined
- **Tenofovir may compete for tubular secretion for wide variety of drugs as well (salicylates, acyclovir etc)**



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Drug Interactions with Drugs Used in Treating Addiction

- **Methadone**
 - Efavirenz and nevirapine decrease methadone levels (usually seen after 7 days of coadministration)
 - Delavirdine can inhibit metabolism and incr levels
 - Abacavir decreases methadone clearance
 - Methadone decreases stavudine levels but increases zidovudine
 - PIs decrease levels and patients can have symptoms of withdrawal



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Interactions Between HAART and Recreational/Other Drugs

- **Alcohol**
- **Marijuana**
- **Ecstasy**
- **Heroin**
- **Benzodiazepines**
- **Barbiturates**
- **Amphetamines**



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Drug Interactions with Antiretrovirals

- **Antifungal agents**
 - Specific Agents to consider
 - Fluconazole (Diflucan®)
 - Itraconazole (Sporanox®)
 - Posaconazole (Noxafil®)
 - Voriconazole (Vfend®)
 - Potential effects to consider
- **Antihyperlipidemic agents**
 - Avoid simvastatin and lovastatin. Toxic levels can accumulate



Drug Interactions continued

Anticonvulsants

- First generation agents (e.g. phenobarbital, phenytoin and carbamazepine) are substrates and inducers of CYP450 pathways
- NNRTIs, PIs, maraviroc and raltegravir may potentially interact with these agents.
 - Ex: Accumulation of carbamazepine when combined with PIs especially ritonavir
 - NNRTIs have been shown to reduce reduce carbamazepine levels



Anticonvulsant Interactions

- Ritonavir can not only inhibit metabolism, but its ability to induce glucuronidation has been reported to be the cause of reduced valproic acid levels
- Carbamazepine, phenytoin and phenobarbital can induce metabolism of some ARVs (PIs, NNRTIs, maraviroc, raltegravir) thereby reducing levels!!!



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Anticonvulsant Interactions

- **Less interaction when second generation anticonvulsants are used because they are minimally metabolized by CYP450 and include:**
 - Gabapentin
 - Levetiracetam
 - Lamotrigine
- **These agents can be considered to avoid drug interactions with first generation anticonvulsants**



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Anticonvulsant Interactions

- **Other second generation anticonvulsants should be used with caution because they have induction/inhibition properties and include:**
 - Topiramate
 - Felbamate
 - Tiagabine
- **Because these interactions are difficult to predict—important to obtain blood levels of anticonvulsants**
 - Go to the DHHS guidelines and http://www.hivclinic.ca/main/drugs_interact_files/anti_convulsant-int.pdf for more information on anticonvulsant interactions



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Cardiac Meds

- **Calcium Channel Blockers**
 - Nifedipine and Diltiazem
 - Stimulation by NNRTIs will decrease levels
 - Inhibition by PIs may increase diltiazem levels
 - Caution in patients with hypertension



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Other Medications to Consider

- **Antidepressants**
 - For example: NNRTIs may decrease levels of sertraline and bupropion
- **Erectile Dysfunction Agents**
 - Metabolism inhibited by PIs
 - Relative contraindication---must adjust dose of ED med



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Recent Drug Interactions Updates

With ALL PIs:

- Sildenafil (Revatio®) is contraindicated when prescribed for the treatment of pulmonary arterial hypertension
- New dosing recommendation for bosentan (Tracleer®) and tadalafil (Adcirca®) when prescribed for the treatment of pulmonary arterial hypertension

<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSactivities/ucm209920.htm>



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Recent Drug Interactions Updates

With ALL PIs:

- Due to ↑ risk of CV events (e.g. QT prolongation, palpitations, sinus tachycardia), salmeterol (Serevent[®], Advair[®]) should not be coadministered with PIs
- Alfuzosin (Uroxatral[®]) is contraindicated
- Colchicine
 - New dosage recommendations when prescribed for gout (treatment or prophylaxis) or familial Mediterranean fever
 - Recommendation to not use with PIs in pts with renal or hepatic impairment



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Herbal Interactions

- **Herbal Products**
 - St John's Wort
 - Kava Kava
 - Garlic Supplements
 - Other herbals that cause hepatotoxicity
 - Other herbal products to consider



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Role of the Clinician in Drug Interaction Detection and Prevention

- **Question patients concerning**
 - Nonprescription Drug Usage
 - Herbal and Natural Product Usage
- **Use appropriate literature sources to obtain reliable and consistent information**
 - www.aidsinfo.nih.gov
 - www.hivinsite.com
 - www.hiv-druginteractions.org
 - Prescribing information on web
- **Communication among providers is key**



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Summary



- **Talk with patients to stress adherence to therapy**
- **Review all medications with patients**
- **Function in an interdisciplinary environment**



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