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of the Florida/Caribbean AIDS Education and Training Center

May 13-14, 2011
Orlando, FL

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Antiretroviral Drug Interactions

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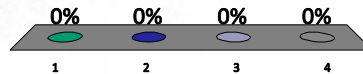
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Which of the following statements most closely reflects your thoughts on drug-drug interactions?

1. They are **all bad** and need to be avoided whenever possible
2. Not all drug interactions are bad and the key is knowing the difference
3. I feel extremely comfortable in identifying and managing drug interactions in my HIV patients
4. I don't have time to think about drug interactions and rely on the pharmacist to detect them and call me



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Drug-Drug Interactions: Why Do We Care?

- Drug-drug interactions are a type of preventable adverse drug event (ADE)
- Estimated 1.5 million injuries each year due to preventable ADEs
- Conservative estimate of \$3.5 billion in extra hospital costs and \$887 million in extra outpatient medical costs due to preventable ADEs

Institute of Medicine (IOM) Committee on Quality of Health Care in America. (2006). *Preventing Medication Errors: Quality Chasm Series*. Washington, DC: National Academy Press.



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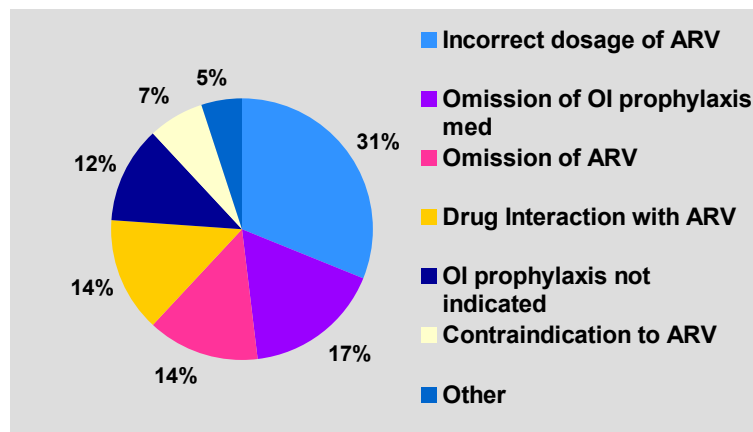
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Why are HIV/AIDS Patients at Risk?

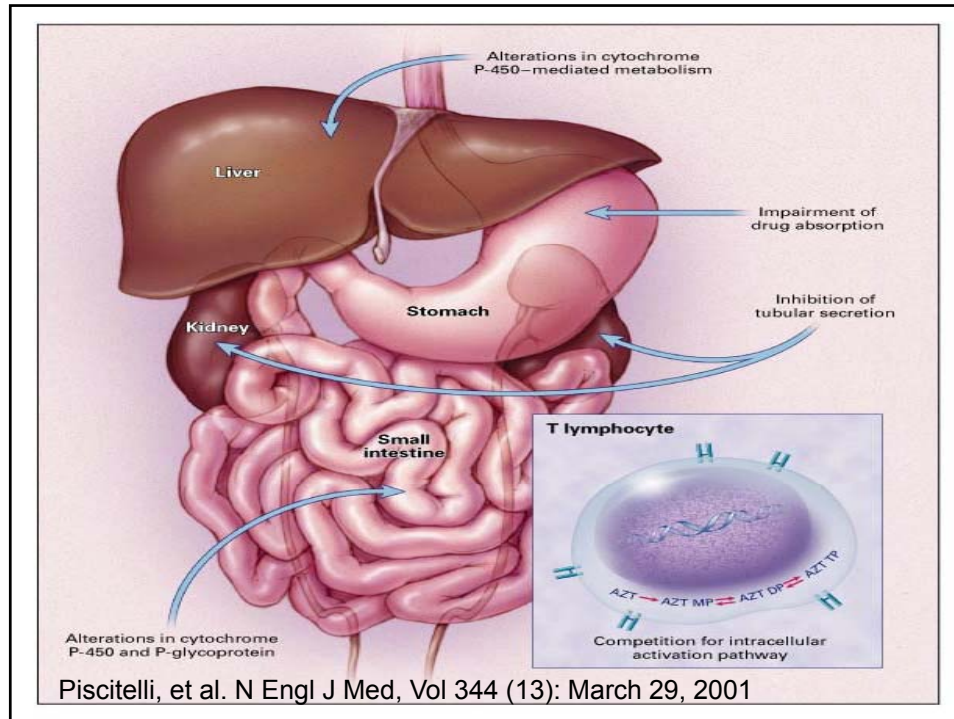
- Use of 3 and 4 drug antiretroviral regimens
- Multiple agents for treatment/prevention of various opportunistic infections
- Patient living longer and being treated for other chronic diseases (e.g. diabetes, CAD)
- Many antiretroviral agents have a profound effect on the cytochrome P450 enzyme system
- **Need for many patients to use multiple pharmacies to get medications complicates identification of drug interactions**



Medication Errors in Hospitalized HIV-infected Patients



Orrick, J. Medication Errors in Adult Hospitalized Patients Receiving Highly Active Antiretroviral Therapy (HAART): Use of a Clinical Pharmacist to Detect and Correct Errors. Presented at the Summer Meeting of the American Society of Health-System Pharmacists, June 2003.



Classifications of Interactions

Pharmacokinetic

- **Absorption**
 - Acid reducing agents impair atazanavir absorption
- **Distribution**
 - TMP/SMX displaces warfarin from protein binding
- **Metabolism**
 - Rifampin induces metabolism of PIs and NNRTs
 - RTV "boosting"
- **Excretion**

Pharmacodynamic

- **Additive toxicity**
 - Increased bone marrow toxicity of zidovudine (AZT) + ganciclovir
- **Additive/Synergistic**
 - CART effect greater than monotherapy
- **Antagonistic**
 - Zidovudine (AZT) and stavudine (d4T) reduces antiviral effect

Cytochrome P450 (CYP) Enzyme System

- **Substrate:** metabolized by enzyme
- **Inhibitor:** inhibits metabolism of substrate
- **Inducer:** induces metabolism of substrate through increased production of enzyme
- Interactions involving induction may be delayed since new enzyme must be synthesized
- Some drugs may have properties of all 3: efavirenz

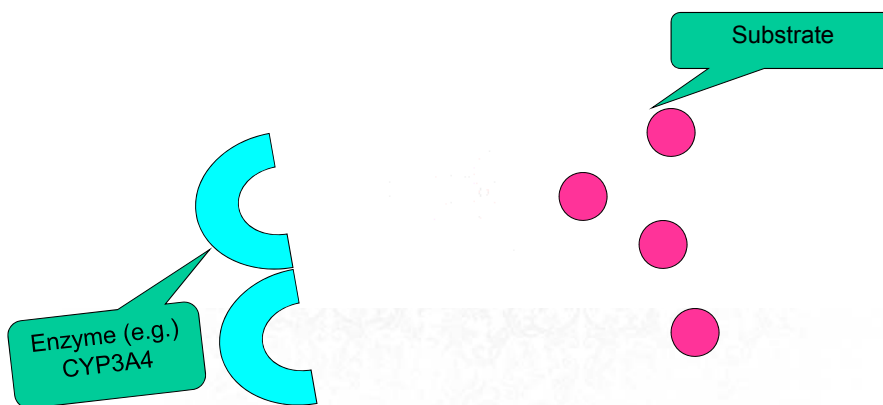


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Enzyme/Substrate Interaction

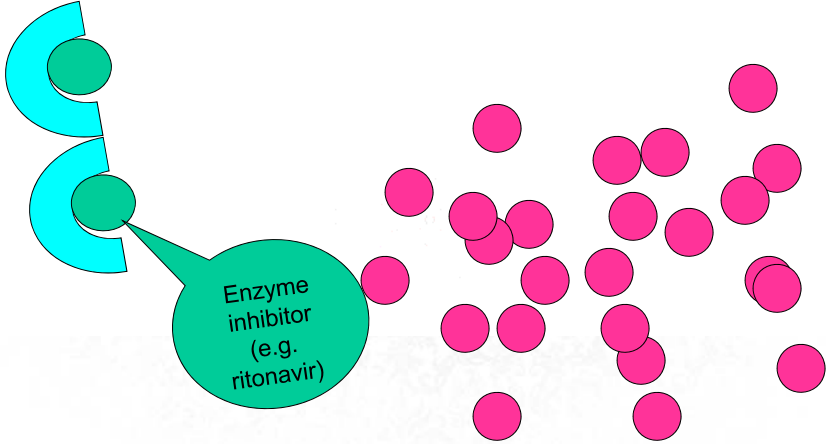


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Enzyme Inhibition



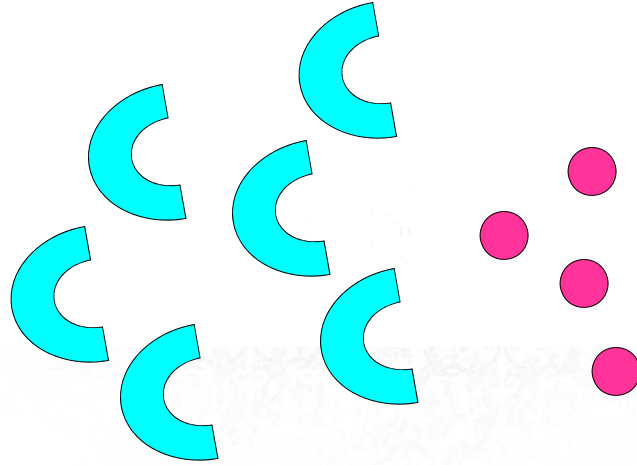
The diagram illustrates enzyme inhibition. On the left, a cyan enzyme is shown with two green substrate molecules bound to its active sites. A green callout bubble points to the enzyme with the text "Enzyme inhibitor (e.g. ritonavir)". To the right, a cluster of pink circles represents substrate molecules that are unable to bind to the enzyme because the active sites are occupied by the inhibitor.

Enzyme inhibitor
(e.g. ritonavir)

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Enzyme Induction



The diagram illustrates enzyme induction. On the left, several cyan enzyme molecules are shown, but none are bound to substrates. On the right, a small cluster of pink circles represents substrate molecules. This indicates that the presence of the substrate has induced the production of the enzyme.

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Outcomes of Drug Interactions: *Beneficial*

- **Additive desirable pharmacodynamic effects**
 - Combination antiretroviral therapy
 - Use of 2NRTIs + PI or NNRTI
 - ↑ potency
 - ↓ resistance
- **PK Boosting**
 - ↑ bioavailability
 - ↓ pill burden
 - Eliminate food restrictions



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Outcomes of Drug Interactions: *Adverse*

- **Toxicity**
 - Rhabdomyolysis: HMG-CoA reductase inhibitors
 - Hypotension: calcium channel blockers, phosphodiesterase inhibitors (e.g. sildenafil, Viagra®)
 - Excessive sedation/respiratory depression: benzodiazepines
- **Drug resistance**
- **Therapeutic failure**



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NRTI Drug Interactions

Drug (s)	Interactions
Abacavir	• Alcohol; metabolized by alcohol dehydrogenase
Didanosine	<ul style="list-style-type: none"> • ↓ absorption of other drugs due to buffer (e.g. quinolones, tetracyclines, ketoconazole) • ↑ levels of ribavirin; do not combine • Allopurinol → ↑ levels of didanosine; do not combine
Didanosine/ stavudine	<ul style="list-style-type: none"> • Agents with additive neurotoxicity (e.g. vincristine, cisplatin, isoniazid) • Agents with additive pancreatoxicity (e.g. alcohol, valproic acid, ritonavir)
Zidovudine	<ul style="list-style-type: none"> • Antagonism with stavudine (compete for intracellular activation) • Additive bone marrow suppression (e.g. ganciclovir, valganciclovir, flucytosine)



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Tenofovir (TDF, Viread®)

- ↓ **atazanavir levels**
 - Boost (ATV 300 mg + RTV 100 mg) daily when given with TDF
- ↑ **didanosine levels (Videx®/Videx EC®)**
 - Dose reduce didanosine when used in regimen with TDF, **BUT**
 - Current Department of Health and Human Services guidelines list TDF + ddl as components **that Should Not Be Offered At Any Time**

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Tables 8 and 15.
<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



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Tenofovir + Didanosine in ARV Regimen

- ↑ ddl levels and potential for toxicity
- Potential for immunologic nonresponse and/or ↓ CD4 cell count
- ↑ rate of early virologic failure and rapid selection of resistance at failure
- **Exceptions: "...consider altering the NRTIs to avoid this combination"**

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Tables 8 and 15. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



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NNRTI Drug Interactions

- All NNRTIs are metabolized by the CYP3A4 enzyme (\pm other CYP enzymes)
- Nevirapine can *induce* CYP3A4
- Efavirenz can *inhibit* or *induce* CYP3A4 enzyme
- Etravirine can *induce* CYP3A4 can also *inhibit* 2C9 and 2C19



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PI Drug Interactions

- All PIs are metabolized by the CYP3A4 enzyme system (\pm other CYP enzymes)
- All PIs can inhibit CYP3A4 enzymes
 - Ritonavir most potent inhibitor
- Ritonavir can also *induce* CYP1A2, CYP 2C9, CYP3A4
- Ritonavir can also *inhibit* CYP2D6

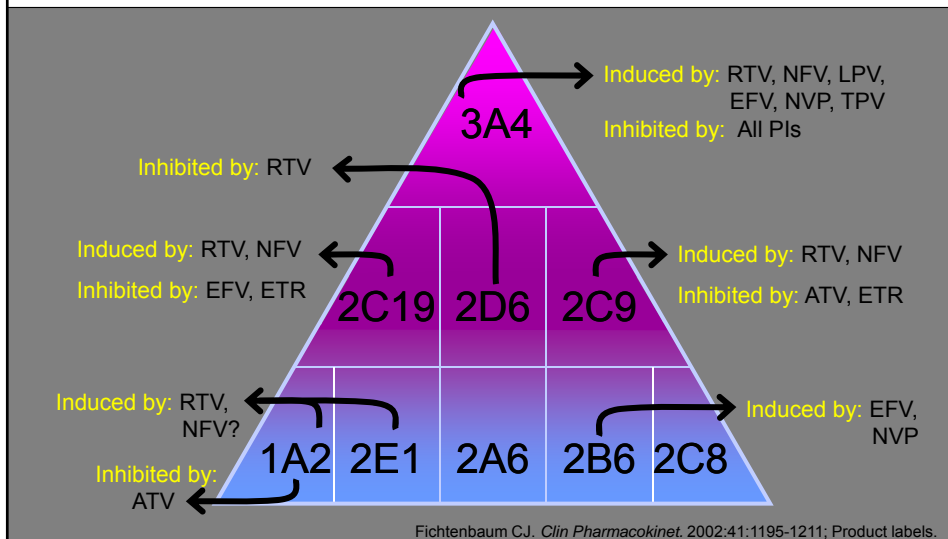


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Effect of ARVs on Drug Metabolism



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Maraviroc (Selzentry®)

Concomitant Medications	Maraviroc Dose
CYP3A inhibitors (with or without a CYP3A inducer) <ul style="list-style-type: none"> ▪ Protease inhibitors (except tipranavir/ritonavir) ▪ Delavirdine ▪ Ketoconazole, itraconazole, clarithromycin ▪ Other strong CYP3A inhibitors (e.g. telithromycin, nefazodone) 	150 mg po bid

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 16b.
<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



Maraviroc (Selzentry®)

Concomitant Medications	Maraviroc Dose
Other meds including tipranavir/ritonavir, nevirapine, all NRTIs, enfuvirtide (T-20)	300 mg po bid
CYP 3A inducers (WITHOUT a strong CYP3A inhibitor) <ul style="list-style-type: none"> ▪ Etravirine ▪ Efavirenz ▪ Rifampin ▪ Carbamazepine, phenobarbital, phenytoin 	600 mg po bid

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 16b.
<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



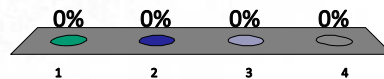
Patient Case JR

- JR is a 45 yo male with HIV, diabetes, hyperlipidemia.
- He has been stable (CD4 > 500 cells/mm³ and VL < 20 copies/mL) on a regimen of emtricitabine/tenofovir, ritonavir-boosted atazanavir (ATV/r) for 5 years.
- He was recently diagnosed with GERD and his physician plans to start therapy with a proton pump inhibitor (PPI, e.g. omeprazole, lansoprazole)



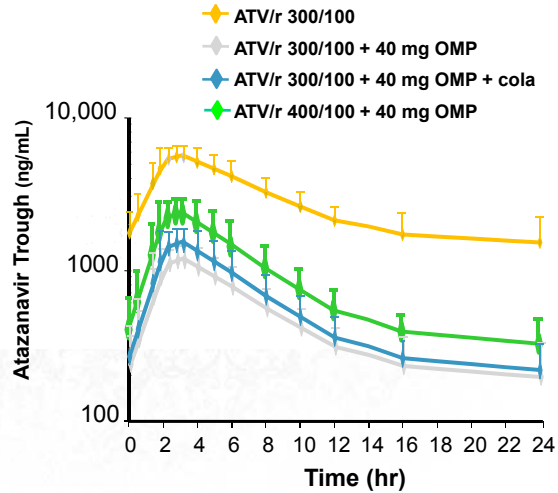
Which of the following statements is true?

1. PPIs should never be combined with ATV
2. PPIs can be used with ATV in certain circumstances
3. The interactions between PPIs and ATV are theoretical only and I don't worry about combining
4. Although PPIs/ATV can be combined in certain circumstances, I avoid ATV in patients who require PPI therapy



Atazanavir + Omeprazole

- N = 48 HIV(-) subjects
- ATV exposures substantially reduced by coadministration with OMP 40 mg
- Not corrected by increased ATV dose or 8 oz cola
- OMP exposures not significantly altered



Agarwala S, et al. CROI 2005. Abstract 658.

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Atazanavir and ARAs

ACID-REDUCING AGENTS	TREATMENT-NAÏVE	TREATMENT-EXPERIENCED
Antacids or buffered medications	<ul style="list-style-type: none"> • ATV or ATV/r: Give ≥ 2 hrs before or 1 hr after antacid 	<ul style="list-style-type: none"> • ATV/r: Give ≥ 2 hrs before or 1 hr after antacid
H2 Receptor Antagonists (H2RAs)	<ul style="list-style-type: none"> • ATV: Give ≥ 2 hrs before or 10 hrs after H2RA. Max dose of famotidine 20 mg bid (not to exceed 20 mg in single dose) [or equivalent] • ATV/r: Give simultaneously with or ≥ 10 hrs after H2RA. Max dose of famotidine 40 mg bid [or equivalent] 	<ul style="list-style-type: none"> • ATV/r: Give simultaneously with or ≥ 10 hrs after H2RA. Max dose of famotidine 20 mg bid [or equivalent] • ATV/r (400/100 mg) with TDF: Give simultaneously with or ≥ 10 hrs after H2RA. Max dose of famotidine 20 mg bid [or equivalent]

Beal J, Orrick J, Molnar K, Editors. ARV Therapy in Adults and Adolescents. [pocketcard] Florida/Caribbean AETC. May 2011

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Atazanavir and ARAs

ACID-REDUCING AGENTS	TREATMENT-NAÏVE	TREATMENT-EXPERIENCED
PPIs	<ul style="list-style-type: none"> • ATV: not recommended • ATV/r: Max dose of omeprazole 20 mg once daily [or equivalent] taken \geq 12 hrs prior to ATV/r 	<ul style="list-style-type: none"> • ATV/r: not recommended

Beal J, Orrick J, Molnar K, Editors. ARV Therapy in Adults and Adolescents. [pocketcard] Florida/Caribbean AETC. May 2011



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Patient Case JR (continued)

- JR had been receiving rosuvastatin (Crestor®) 10 mg daily for his hyperlipidemia but was recently switched to simvastatin (Zocor®) 40 mg daily
- Reason for the switch: The pharmacy was able to get a great deal on simvastatin (340b pricing) and suggested that the prescriber switch the patient to simvastatin



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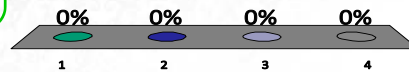
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Which of the following is true regarding the interaction between simvastatin and protease inhibitors (PIs) ?

1. There is no significant interaction or need for dosage adjustment
2. Simvastatin can be used cautiously (low doses with monitoring) with PIs
3. Simvastatin should not be used with PIs due to increased risk of toxicity (e.g. rhabdomyolysis)
4. Simvastatin can ↓ PIs levels and → risk of virologic failure



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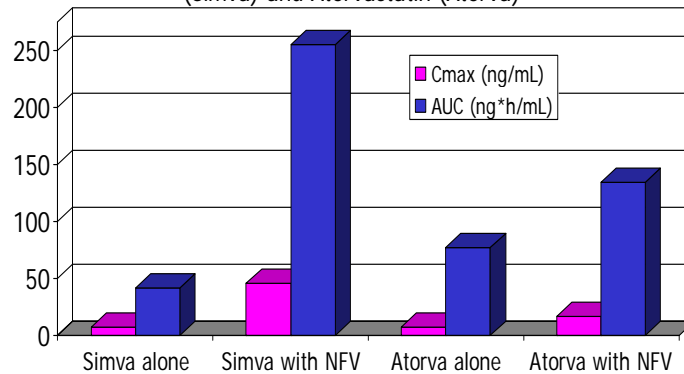
Do Not Use with PIs

- Lovastatin
 - Pitavastatin
 - Simvastatin
 - Cisapride
 - Pimozide
 - Alfuzosin
 - Salmeterol
 - Sildenafil for PAH
 - St. John's Wort
 - Garlic supplements
 - Rifampin
 - Rifapentine
 - Midazolam
 - Triazolam
 - Ergot alkaloids
- Additionally the following should not be given with ritonavir: amiodarone, flecainide, propafenone, quinidine
 - Proton pump inhibitors (some exceptions) and Irinotecan should not be used with atazanavir

Adapted from Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 14. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

PI Interactions with Statins

Effect of Nelfinavir (NFV) on Cmax and AUC of Simvastatin (Simva) and Atorvastatin (Atorva)



Hsyu PH, et al. Antimicrob Agents Chemother 2001;45:3445-50.



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Affect of PIs on Statin Levels

- **Lovastatin, Pitavastatin¹, Simvastatin**
 - **Contraindicated with all PIs (¹Pitavastatin can be used with unboosted ATV)**
- **Pravastatin² and fluvastatin have least potential for interactions**
 - 2. DRV may ↑ pravastatin levels; use lowest dose possible with monitoring

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 15. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



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Affect of PIs on Statin Levels

- **Atorvastatin**
 - Levels of atorvastatin are ↑ with all PIs
 - Use lowest dose possible with monitoring or consider agent that is less likely to interact
- **Rosuvastatin**
 - ATV/r: ↑ rosuvastatin AUC 213%; ↑ C_{max} and 600%
 - LPV/r: ↑ rosuvastatin AUC 108%; ↑ C_{max} and 366%
 - Use lowest dose possible with monitoring or consider agent that is less likely to interact

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 15. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



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Patient Case

- PM is a 48 year old female who was recently diagnosed with active pulmonary tuberculosis and AIDS.
- She has started receiving directly observed therapy with rifampin, isoniazid, pyrazinamide, ethambutol.
- Her CD4 count is 150 cells/mm³ and her viral load is 78,000 copies/mL.



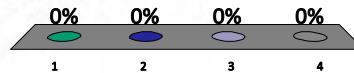
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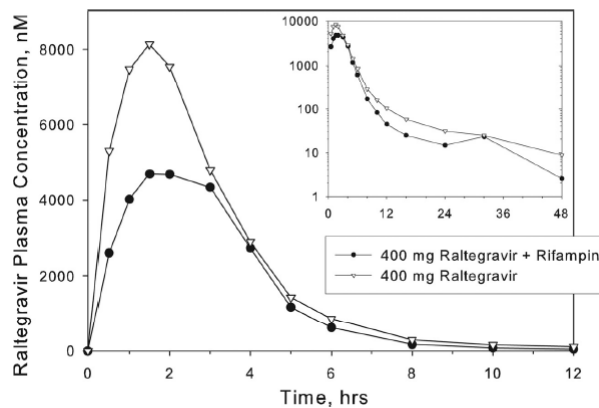
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Which of the following agents can be used with rifampin without the need for a dosage adjustment?

- 1. Raltegravir
- 2. Lopinavir/ritonavir
- 3. Mariviroc
- 4. **Efavirenz**

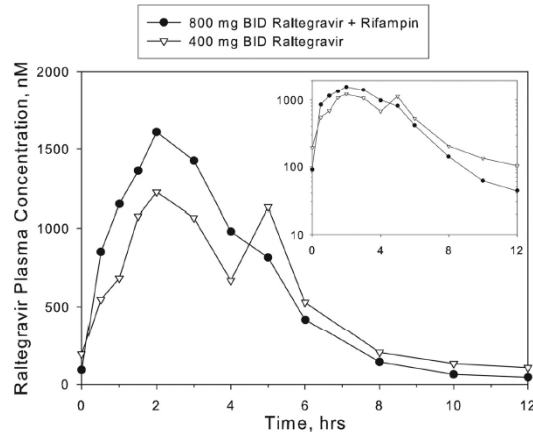


Raltegravir and Rifampin Interaction



Wenning, et al. Antimicrob Agents Chemother. 2009 Jul;53(7):2852-6.

Raltegravir and Rifampin Interaction



Wenning, et al. Antimicrob Agents Chemother. 2009 Jul;53(7):2852-6.



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Rifamycins with ARVs

- Rifamycins can induce CYP3A4 enzyme → potential to ↓ PI, NNRTI, integrase inhibitor, maraviroc levels
 - Rifampin (RIF) > rifapentine* > rifabutin (RBT)
- **Rifampin: Due to significant interactions and/or need for ↑ doses of ritonavir to overcome interactions, it is impractical to use RIF with a PI-containing regimen (boosted or unboosted) and it is not recommended**
- **Rifabutin is also a substrate for CYP3A4 and its levels can be affected by PIs and NNRTIs → need for adjustment of doses of RBT and/or ARVs**

*Rifapentine is a long-acting rifamycin that is not recommended for use in HIV-infected patients due to acquired rifamycin resistance



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Treatment of Tuberculosis (TB) in HIV/AIDS


May 2011

<p>Editors: Jeffrey Beal, MD, AAHIVS Joanne J. Orrick, PharmD, AAHIVE Jerry Jean Stambaugh, PharmD</p>	<p>Managing Editor: Kim Molnar, MAcc</p> <p>Layout: Maximo Lora, BA</p>
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Beal J, Orrick J, Stambaugh JJ, Molnar K, Editors. ARV Therapy in Adults and Adolescents. [pocketcard] Florida/Caribbean AETC and Southeastern National Tuberculosis Center. May 2011

Rifampin (RIF)³-based Regimen with ARVs
NNRTIs
Efavirenz 600 mg qhs (standard) or consider ↑ to 800 mg qhs (patients > 60 kg)
Do not use RIF with etravirine or nevirapine
Protease Inhibitors
Due to significant interactions and/or need for high doses of ritonavir to overcome the interactions, it is impractical to use RIF with a PI-containing regimen (boosted or unboosted) and it is not recommended
Integrase Inhibitor
Increase raltegravir (RAL) to 800 mg bid
CCR5 inhibitor
Not recommended, but if used: maraviroc (MVC) 300 mg bid (with potent CYP3A inhibitor); MVC 600 mg bid (without potent CYP3A inhibitor)

3. All are with RIF standard dose



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Rifabutin (RBT)-based Regimen with ARVs	
NNRTIs	
NNRTI	RBT
Efavirenz (standard dose)	450 mg-600 mg daily or 600 mg 3x/week if no PI in the regimen ⁴
Etravirine standard dose (do not combine with RBT if used with RTV-boosted PI)	300 mg daily or 3x/week (standard dose)
Nevirapine (standard dose)	300 mg daily or 3x/week (standard dose)

4. Some experts recommend 450 mg 3x/week
 Hollender E, Stambaugh JJ, Ashkin D, et al. 10th Conference on Retroviruses and Opportunistic Infections, Boston, February 2003, abstract 785.

Rifabutin (RBT)-based Regimen with ARVs	
Protease Inhibitors	
Ritonavir-boosted PIs	
ATV/r	RBT 150 mg every other day or 3x/week. Some recommend RBT 150 mg daily or 300 mg 3x/week. TDM recommended since LPV/r with RBT 150 mg 3x/week has been shown to result in sub-therapeutic RBT levels in some patients.
DRV/r	
FPV/r	
LPV/r	
SQV/r	
TPV/r	
Unboosted PIs	
ATV	RBT 150 mg every other day or 3x/week
FPV	RBT 150 mg daily or 300 mg 3x/week

Rifabutin (RBT)-based Regimen with ARVs
Integrase Inhibitor
No dosage adjustments recommended for RAL or RBT
CCR5 inhibitor
MVC 150 mg bid (with potent CYP3A inhibitor); MVC 300 mg bid (without potent CYP3A inhibitor or inducer); Dose RBT based on other drugs in regimen (consider TDM)


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Patient Case TE

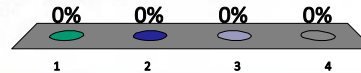
- TE is 48 yo male who presents to the hospital with fever and mental status changes
- A friend brought him in and stated that he witnessed the patient having what he thought was a seizure
- He is diagnosed with presumptive toxoplasmic encephalitis based on MRI showing a single ring-enhancing lesion and lab tests showing a positive Toxo IgG
- In addition to initiating therapy for Toxoplasmosis, the team wants to initiate anti-seizure therapy to prevent further seizures


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Which of the following anti-seizure medications is least likely to interact with ARVs?

1. **Levetiracetam (Keppra®)**
2. **Oxcarbazepine (Trileptal®)**
3. **Phenobarbital**
4. **Phenytoin (Dilantin®)**



Anticonvulsant Interactions

- Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin can ↓ levels of PIs or NNRTIs
- Consider alternative anticonvulsant or monitor levels
- See resource below for detailed information regarding anticonvulsant interactions with ARVs

http://www.hivclinic.ca/main/drugs_interact_files/anticonvulsant-int.pdf

Interactions with Azole Antifungals

- **Fluconazole** can generally be used without the need for dosage adjustments (except with tipranavir/ritonavir, consider max dose of fluconazole 200 mg daily)
- **Itraconazole**
 - > 200 mg daily not recommended with boosted PIs
 - Itra levels may be ↓ with NNRTIs

Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 15. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



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Interactions with Azole Antifungals (continued)

- **Posaconazole**
 - Limited data; posa levels ↓ 50% with efavirenz; ATV levels ↑ by posa
- **Voriconazole**
 - Boosted PIs, EFV, and NVP → ↓ vori levels
 - Etravirine → ↑ vori levels
- **Interactions with azole antifungals can be bi-directional and complex, consider TDM**

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Erectile Dysfunction Drugs

- Metabolized by CYP3A4
- Sildenafil, vardenafil, tadalafil
- Concentrations ↑ by four-fold with PIs
- Low BP, dizziness, fainting, headaches, vision disturbances, and priapism
 - Sildenafil (Viagra®): starting dose 25 mg in 48 hours
 - Vardenafil (Levitra®): starting dose 2.5 mg in 24 hours
 - Tadalafil (Cialis®): starting dose 5 mg in 72 hours



Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Table 15. <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>.



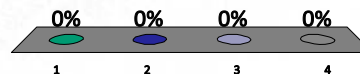
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Which of the following medications is considered safest to use with protease inhibitors?

1. Fluticasone (Flonase®)
2. Colchicine (Colcrys®)
3. Salmeterol (Serevent®)
4. Pravastatin (Pravachol®)



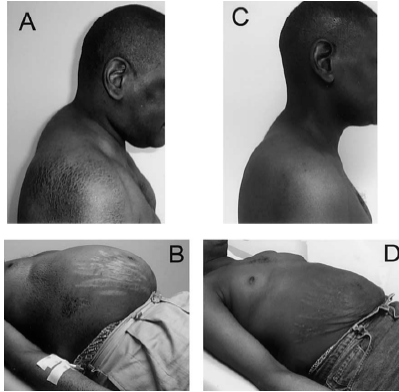
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Fluticasone and Ritonavir

(Flovent[®] and Flonase[®])



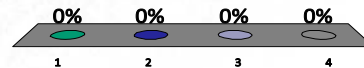
- Fluticasone induced Cushing's Syndrome
- Fluticasone is a 3A4 substrate and RTV a 3A4 inhibitor

Gupta SK. CID 2002:35:e69-e71

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Due to its effects on CYP2C19 and CYP3A, which of the following ARVs should not be used in patients taking clopidogrel (Plavix[®])?

1. Ritonavir
2. Saquinavir
3. Efavirenz
4. Etravirine



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Managing Drug Interactions

- Review medication list (including herbals and OTCs) with patient at each visit
- Whenever new medications are prescribed, check for drug-drug interactions
- Look for drugs that should not be used or are contraindicated→ use alternatives
- When other potentially significant drug interactions identified, use alternatives that avoid the interaction when available



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Drug Interaction Resources

- Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; Tables 14 and 15.
<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>
- www.hiv-druginteractions.org
- www.fcaetc.org/Consultation



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Questions?

Disclosure of Financial Relationships

This speaker has no significant financial relationships with commercial entities to disclose.

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

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