

## HIV Drug Interactions

John J. Faragon, PharmD, BCPS, AAHIVE

New York/New Jersey  
AIDS Education & Training Centers  
Regional Pharmacy Director  
Albany Medical Center Department of Pharmacy



The NY/NJ AIDS Education and Training Center is one of a network of 11 regional centers with more than 130 sites representing all 50 states. The mission of the AETC is to improve the quality of life of patients living with HIV/AIDS through the provision of high quality education and training.

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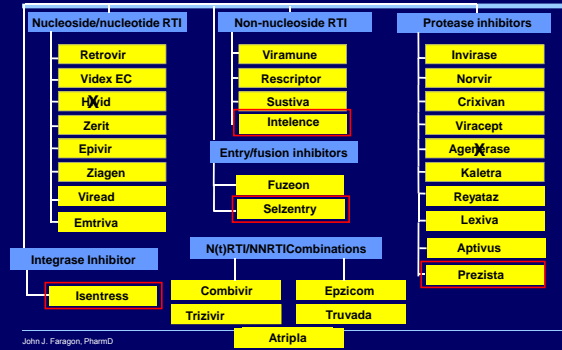
## Objectives

- Review the mechanism of drug interactions in HIV therapy
- Discuss common drug interactions with HIV medications
- Using patient cases, provide examples of interventions to prevent or mitigate drug interactions

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## FDA-Approved Antiretroviral Agents



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## DHHS Guidelines – Recommended Regimens for HIV+ Treatment-naïve Patients: January 2008

	Column A		Column B
	NNRTI	PI	Dual NRTI
Preferred	Efavirenz*	Atazanavir/rtv or Fosamprenavir/rtv (BID) Lopinavir/rtv (BID)	Tenofovir/emtricitabine Abacavir/lamivudine
Alternative	Nevirapine**	Atazanavir Fosamprenavir (BID) Fosamprenavir/rtv (QD) Lopinavir/rtv (QD) Saquinavir/rtv	Zidovudine/lamivudine Didanosine + lamivudine or emtricitabine

**Pick one from Column A and one from Column B**

\*Not recommended for use in 1<sup>st</sup> trimester pregnancy or women with high pregnancy potential. \*\*High incidence (11%) of symptomatic hepatic events was observed in women with pre-NVP CD4 T cell counts >250 cells/mm<sup>3</sup> and men with CD4 T cell counts >400 cells/mm<sup>3</sup> (6.3%). NVP should not be initiated in these patients unless the benefit clearly outweighs the risk.

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Available at: <http://aidsinfo.nih.gov/guidelines>

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### Preferred Regimens – DHHS November 2008

**Preferred NNRTI Regimen**  
Atripla HS or

**Preferred PI Regimen**  
Kaletra BID + Truvada QD  
Prezista/Norvir QD + Truvada QD  
Lexiva/Norvir BID + Truvada QD  
Reyataz/Norvir QD + Truvada QD

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### 3-Drug Combination ART 1996: IDV/AZT/3TC

8AM	4PM	12 MID

Fasting (1 hour before/2 hours after meals) 1.5 liters of hydration/day

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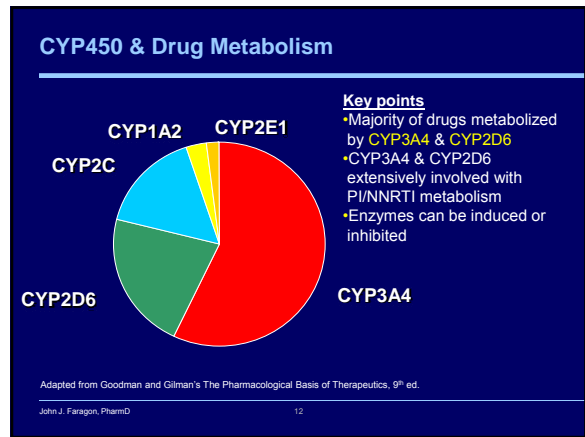
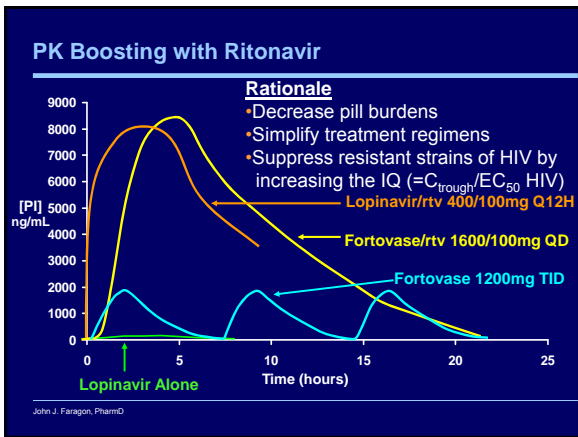
### Select Drug Interactions

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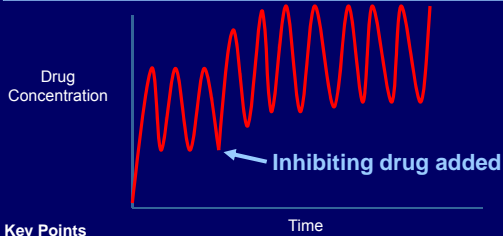
### Outcomes of Drug Interactions: Beneficial

- 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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## CYP450 Inhibition



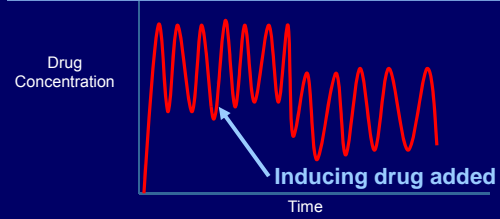
### Key Points

- CYP450 INHIBITION leads to increased levels of drugs metabolized by same enzyme
- Peak effect occurs rapidly, as soon as adequate concentrations of inhibitor are reached

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## CYP450 Induction



### Key Points

- CYP450 INDUCTION leads to decreased levels of drugs metabolized by same enzyme
- Peak effect occurs slowly based upon half-life of drug & time to synthesize new CYP450 enzyme

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## Common Inhibitors of Drug Metabolism

Protease inhibitors	Clarithromycin
Delavirdine	Erythromycin
Fluconazole	Diltiazem
Itraconazole	Verapamil
Ketoconazole	Amiodarone
Voriconazole	Cimetidine
Isoniazid	Omeprazole
Ciprofloxacin	Fluoxetine
	Grapefruit juice

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## Common Inducers of Drug Metabolism

Nevirapine	Phenobarbital
Efavirenz	Carbamazepine
Etravirine	Phenytoin
Rifampin	
Rifabutin	

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## Enzyme Inhibition & Induction

Drug	Enzyme Inhibition	Enzyme Induction
Atazanavir	++	—
Delavirdine	++	—
Efavirenz	+	+++
Fosamprenavir	+	++
Indinavir	++	—
Lopinavir/ritonavir <sup>(1)</sup>	++++	++
Tipranavir/ritonavir <sup>(1)</sup>	++++	+++
Nelfinavir	++	+
Nevirapine	—	++
Ritonavir	++++	++
Saquinavir <sup>(2)</sup>	—	—

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Modified from: Flexner CW. <http://clinicaloptions.com/2004PK>

## Case 1 - JS

48 year old male  
 HIV infected diagnosed in 2002, been on prior ARV therapy  
 Strong family history for CVD, including mother, father & 2 brothers  
 Blood pressure & Lipids well controlled with diet/exercise  
 Medications:  
 Kaletra tabs – 2 BID  
 Trizivir – 1 BID  
 Viread – 1 QD  
 Multivitamins – 1 QD

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## Case 1 - JS

Patient recently admitted to a local hospital for Acute Coronary Syndrome, requiring PCI & stent placement with an uneventful hospital course

### Discharge Medications

Accupril 10mg daily  
 Toprol XL 50mg daily  
 Zocor 40mg daily  
 Aspirin 81 mg daily  
 Plavix 75 mg daily

### Other Meds

Kaletra tabs – 2 BID  
 Trizivir – 1 BID  
 Viread – 1 QD  
 Multivitamins – 1 QD

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## Lipid Lowering Agents & PIs

Contraindicated with ALL protease inhibitors

- Simvastatin (Zocor) and Lovastatin (Mevacor)
- With SQV/RTV, simvastatin levels increased 31 fold!!

Pravastatin should be avoided with Darunavir (Prezista)

Safest statin is pravastatin (with exception of Prezista)

Atorvastatin (Lipitor) at low doses safe

Rosuvastatin (Crestor) at low doses safe (avoid with Kaletra)

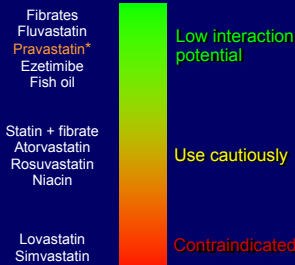
Statin/fibrate combinations generally safe

Fichtenbaum CJ, et al. AIDS. 2002;16:569-577. Hsu PH, et al. Antimicrob Agents Chemother. 2001;45:3445-3450. Carr RA, et al. 40th ICAAC. Toronto, 2000. Abstract #1644. Galza L, et al. AIDS. 2003;17:951-959. Doser N, AIDS. 2002;1:1982-1983. Prezista PI.

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## Lipid-Lowering Agents & PIs: Drug Interactions



Fibrates  
 Fluvastatin  
 Pravastatin\*  
 Ezetimibe  
 Fish oil

Statin + fibrate  
 Atorvastatin  
 Rosuvastatin  
 Niacin

Lovastatin  
 Simvastatin

\*AUC 111 with darunavir.

\* Fichtenbaum et al. AIDS. 2002;16:569-577. • Hsu et al. AAC. 2001;45:3445-3450. • Gerber et al. 2nd IAS. 2002. Abstract #870. • Carr et al. 40th ICAAC. Toronto, 2000. Abstract #1644. • Total Package Insert 2003. • Gerber et al. 11th CROI. 2004. Abstract # 803. • Reyataz Package Insert 2005. • Aptivus Product Label 2005.

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## Sustiva reduces statin concentrations

No effect of statins on non-steady-state pharmacokinetics of efavirenz

Coadministration of efavirenz with statins significantly reduced all area under the curves (AUCs) for statins

Pharmacokinetic Analysis of Statin	AUC, ng·h/mL		Median % Change in AUC	P Value
	Statin Alone	Statin + Efavirenz		
Simvastatin acid	36.48	14.46	-58.0	.003
Active simvastatin (active HMG-CoA reductase inhibitors)	136.94	45.71	-60.2	< .001
Atorvastatin	11.20	6.56	-42.7	< .001
Atorvastatin + active metabolites	28.10	21.42	-34.5	.005
Pravastatin	96.32	42.65	-40.4	.005

Gerber JG et al. J Acquir Immune Defic Syndr 39: 307-312, 2005.

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## Case 2

Reyataz® (atazanavir, ATZ)  
 400mg orally once daily  
 Other dose

Epzicom® (abacavir 600mg/lamivudine 300mg, ABC/3TC)  
 One tablet orally once daily  
 Other dose **TT Q Daily**

Videx EC® (didanosine, ddi)  
 400mg orally once daily  
 250mg orally once daily  
 Other dose

## Case 2 Additional Orders

### General Medications

Heparin 5000 units SQ BID

Ortho Bowel Regimen, APAP for pain management

Nexium 40mg po once daily

### ARV Regimen Recap

Reyataz 400mg once daily

Epzicom 2 tablets once daily

Videx EC 250mg once daily

Any Problems Here?

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## PPIs and Reyataz – Guidelines

Do not use if unboosted – ie on Reyataz 400mg daily without RTV

If ARV experienced, PPIs not recommended to be taken at all with Reyataz

If naïve, can use up to the equivalent of omeprazole 20mg daily, IF boosting with RTV

If on Reyataz/Norvir with omeprazole & tenofovir (Viread) increase to 400mg with 100mg RTV daily

H2 blockers separated by 12 hours probably OK, ie Pepcid 40mg QHS, ARVs in the AM

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## Norvir & Erectile Dysfunction Agents

Drug	Usual Dose	Fold Change in AUC with RTV	Modified Dose
Sildenafil	50 mg qd	11	25 mg q 48h
Vardenafil	10 mg qd	49 (T1/2 = 26h)	2.5 mg q 72h
Tadalafil	10 mg qd	2.2	10 mg q 72h

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## Methadone and NNRTIs

	Effect	Comment
Efavirenz (Sustiva)	Methadone AUC ↓ 57%	Monitor for symptoms of opiate withdrawal
Nevirapine (Viramune)	Methadone AUC ↓ 51%	Monitor for symptoms of opiate withdrawal
Delavirdine (Rescriptor)	Effect on methadone not studied	Monitor for symptoms of opiate toxicity

• **Opiate withdrawal:** lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection

• **Opiate toxicity:** miosis, drowsiness, ↓ rate & depth of respiration, nausea, vomiting, constipation, bradycardia, hypotension

Br J Clin Pharmacol 2001;51:213-7, AIDS 2000;14:1291-2, Clin Infect Dis 2001;33:1595-7, Ann Pharmacother 2000;34:405-7, AIDS 1999;28:957-62, Pharmacotherapy 1999;19:471-2.

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## Methadone & Protease Inhibitors

HIV Medication	Effect on Methadone
Amprenavir, FPV	r-methadone decreased 13%
Darunavir	Methadone AUC decreased 16-36%
Indinavir	No change
Lopinavir/ritonavir	Methadone AUC decreased 53%
Nelfinavir	May decrease methadone
Ritonavir	Methadone AUC decrease 37%
Saquinavir	Methadone AUC decreased 20%
Tipranavir	No data, likely decrease in methadone

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## Antidepressants

### • CONTRAINDICATED

- Fluvoxamine (Luvox®)
- Nefazodone (Serzone®)

### • SSRIs

- Fluoxetine (Prozac®) & paroxetine (Paxil®, Pexeva®):
  - some interactions, but not generally clinically significant
- Citalopram (Celexa®), escitalopram (Lexapro®), & sertraline (Zoloft®):
  - have fewest interactions

### • Tricyclic antidepressants

- Most are metabolized all or in part by 2D6
- Ritonavir can inhibit 2D6 metabolism and increase levels of TCAs
- TCA levels may be helpful if using high doses, ACH side effects

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DHHS Guidelines, 2008

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## Antidepressants

### • Dual-action agents:

- Venlafaxine (Effexor®) & duloxetine (Cymbalta®)
- Well tolerated without adjusting dose

### • Bupropion (Wellbutrin®, Zyban®)

- 57% reduction in bupropion with lopinavir/ritonavir
- 30% reduction in hydroxybupropion

### • Mirtazapine (Remeron®)

- Well tolerated, although some 3A4 metabolism

### • Trazodone (Deseryl®)

- Levels can be increased by RTV boosted PIs, start with low dose and titrate slowly

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Kaletra Product Information, Hogeland GW, et al. Clin Pharmacol Ther. 2007;81:69-75.

## Anxiolytics

- **CONTRAINDICATED**
  - Triazolam (Halcion®)
  - Midazolam (Versed®) – Single dose for sedation acceptable...
- Safest to use glucuronidated benzodiazepines (LOT):
  - Lorazepam (Ativan®)
  - Oxazepam (Serax®)
  - Temazepam (Restoril®)
- Caution with buspirone (Buspar®), and dosing of other benzodiazepines with ART (3A4)
- Use at lower doses & titrate
  - Alprazolam
  - Clonazepam

## Antipsychotics

- **CONTRAINDICATED**
  - Pimozide (Orap®)
- Avoid chlorpromazine (Thorazine®), thioridazine (Mellaril®)
- When used with ritonavir, start with lowest dose
  - Haloperidol (Haldol®) – risk of EPS & TD
  - Olanzapine (Zyprexa®), clozapine (Clozaril®), risperidone (Risperdal®)
- Metabolized by CYP3A4
  - Aripiprazole (Abilify®), ziprasidone (Geodon®), quetiapine (Seroquel®) clozapine (Clozaril®)
  - Likely to be increased by protease inhibitors

## BPH & HIV Meds

- **Avodart (dutasteride)**
  - Metabolized by CYP3A4, avoid in patients on PIs, especially ritonavir boosted PIs
  - Ketoconazole, etc can also increase levels of dutasteride
- **Uroxatral (alfuzosin)**
  - Metabolized by CYP3A4, contraindicated with 3A4 inhibitors such as ritonavir, ketoconazole, & other PIs so avoid this
- **Cardura (doxazosin)**
  - Metabolized by 3A4, drug levels can be increased PIs (esp ritonavir)
  - Can be titrated
- **Flomax (tamsulosin)**
  - Not metabolized by 3A4, safest option from a drug interaction standpoint
- **Detrol LA (tolteridone)**
  - Metabolized by CYP3A4 and CYP2D6, drug levels can be increased by PIs (esp ritonavir and in poor metabolizers)
  - Can be titrated

## Case 3 – New Patient

62 year old HIV infected Hispanic male moving to Albany area after living in Miami, Florida area  
Speaks minimal English, daughter present at visit to translate  
HIV infected for past 15 years, previous IVDU  
PMH – Asthma, DM, HTN, HIV (currently <50 copies/ml, CD4 in 500's)  
Medications on transfer to us  
Kaletra 2 tabs PO twice daily  
Truvada – 1 PO daily  
Advair 250/50 – 1 puff twice daily  
Glyburide – 10mg po twice daily  
Metformin – 1000mg po twice daily with meals  
Enalapril – 10mg po twice daily  
Multivitamin – 1 po once daily  
Aspirin – 81 mg po daily

## Fluticasone & Boosted PIs

Cushing's syndrome reported after treatment with RTV-boosted PIs & inhaled fluticasone:

- Case reports in children (2 LPV/r, 1 FPV/RTV)<sup>1</sup> & 6 cases (3 LPV/r, 1 ATV/LPV/r, 1 ATV/RTV, 1 SQV/RTV) in adults<sup>2</sup>

RTV inhibits metabolism of fluticasone through CYP3A4

3 patients switched to beclomethasone had resolution of symptoms

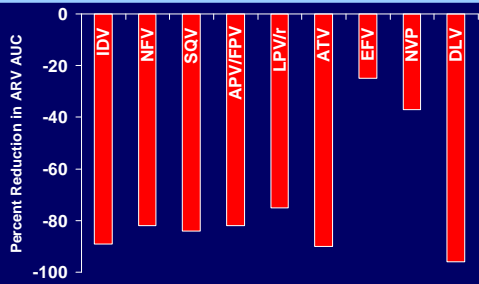
- Beclomethasone is mainly metabolized by tissue esterases and this may explain the difference in outcome
- Other case reports available

1. Dollfus C, et al. 10<sup>th</sup> EACS, Dublin 2005, #PE 15.4/1;  
2. Samaras K, et al. J Clin End Met 2005;90:4394-6

Index	Age (years)	Sex	Antiretroviral and/or other drugs	Method of corticoid release	Action course
1	41	M	EFV/3TC/ABC	Compression, vapor, nebulizer	Fluticasone tapered
2	51	M	EFV/3TC/ABC	Compression	Fluticasone and ketoconazole discontinued
3	51	M	EFV/3TC/ABC	Altered release	Fluticasone discontinued
4	45	M	EFV/3TC/ABC	Altered release	RTV replaced by EFV
5	45	M	EFV/3TC/ABC	Altered release	Fluticasone discontinued
6	51	M	EFV/3TC/ABC	Altered release	Fluticasone discontinued
7	51	M	EFV/3TC/ABC	Altered release	Fluticasone replaced by budesonide. Improved within 6 months
8	41	M	ABC/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
9	30	M	EFV/3TC/ABC	Coding's nebulizer	Fluticasone replaced by BNP. Improved within 3 weeks
10	36	M	EFV/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
11	36	M	EFV/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
12	45	M	EFV/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
13	46	M	EFV/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
14	50	M	ABC/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
15	44	F	ABC/3TC/ABC	Coding's nebulizer	Fluticasone discontinued
16	15	F	EFV/3TC/ABC	Altered release	Fluticasone discontinued
17	12	F	EFV/3TC/ABC	Altered release	Fluticasone discontinued
18	54	F	EFV/3TC/ABC	Coding's nebulizer	Fluticasone discontinued



## Rifampin Effects on PIs & NNRTIs



Finch, et al. Arch Intern Med. 2002;162:985-92, Product Information Reyataz® 2003, Product Information Lexiva® 2003

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## Rifabutin (RFB) Use with PI/NNRTIs

ARV	RFB?	RFB Dosing Comments
NVP	Yes	RFB 300mg/d or 2-3x/wk
DLV	No	Contraindicated
EFV	Probably	RFB 450-600mg/d, 600mg 2-3x/wk
SQV	Probably	Boost w/RTV, RFB??
RTV	Probably	RFB 150mg 2-3x/wk
IDV	Yes	RFB 150mg/d or 300mg 2-3x/wk
NFV	Yes	RFB 150mg/d or 300mg 2-3x/wk
APV	Yes	RFB 150mg/d or 300mg 2-3x/wk
LPV/r	Yes	RFB 150mg/d or 300mg 2-3x/wk
ATV	Yes	RFB 150mg QOD or 3x/wk
FPV	Yes	RFB 150mg/d or 300mg 2-3x/wk
FPV/r	Yes	RFB 150mg QOD or 3x/wk

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MMWR 2000;49:185-9, Product Information Reyataz® 2003, Product Information Lexiva® 2003, Product Information Kaletra © 2003, MMWR 2004;53:37.

## Newer HIV Medications

## Dosing of Maraviroc

Concomitant Medication	MRV Dose
Strong CYP3A4 inhibitors including: • protease inhibitors (except tipranavir/ritonavir) • delavirdine • ketoconazole, itraconazole, clarithromycin, nefazadone,	150mg PO BID
CYP3A4 inducers (without a CYP3A4 inhibitor) including: • efavirenz, etravirine • rifampin/rifabutin, phenobarbital, phenytoin, carbamazepine	600mg PO BID
Other meds, including all other antiretrovirals including: • tipranavir/ritonavir, nevirapine	300mg BID

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## Raltegravir

- Eliminated by UGT1A1-mediated glucuronidation
- High variability in raltegravir  $C_{12hr}$  after oral dosing that spans a 5-log range (10 to 10,000)
- Rifampin – strong UGT1A1 inducer, reduced raltegravir levels
- TPV/RTV – also reduces raltegravir levels, comparable efficacy in this subgroup – No dosage adjustment needed
- ATV/RTV – inhibits UGT1A1, increases raltegravir levels, no safety concerns – No dosage adjustment needed
- Other UGT1A1 drugs – Use with caution – ie: irinotecan
- Etravirine (TMC-125) – reduces raltegravir by about 1/3

JPhrod:ral:lgfr:PharmD: Isentress, 2007, FDA Advisory Panel for Isentress.

## New Drugs – Etravirine (Intencele)

- Etravirine (Intencele)
- Do not use with Reyataz/Norvir, Lexiva/Norvir, or Aptivus/Norvir or any unboosted PI – ie Nelfinavir, unboosted Reyataz or Lexiva

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## Objectives

Review the mechanism of drug interactions in HIV therapy  
Discuss common drug interactions with HIV medications  
Using patient cases, provide examples of interventions to prevent or mitigate drug interactions

## Web Resources of Interest for Drug Interactions

- AIDS Meds  
– <http://www.aidsmeds.com/>
- DHHS Guideline Tables  
– <http://www.aidsinfo.nih.gov/guidelines/>
- Toronto HIV Clinic  
– <http://www.tthivclinic.com/>
- Clinical Options Drug Interaction Tool  
– <http://www.clinicaloptions.com/>