

Cases in HIV Clinical Pharmacology

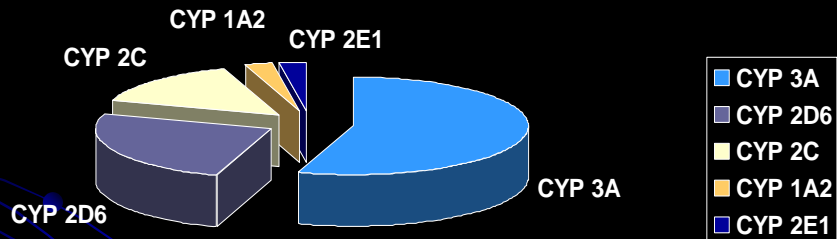
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UC-San Francisco School of Pharmacy

Goals

- Review important drug interactions
- Develop a threshold on identifying if an interaction may exist
- Apply HIV pharmacology knowledge to identifying and solving drug therapy issues

Proportion of Drugs Metabolized by CYP450 Enzymes



Goodman and Gilman's The Pharmacologic Basis of Therapeutics, 9th ed.

Case 1 a

PN, 46 yo CM

PMH:

HIV

cryptococcal meningitis

depression

GERD

MAC

Labs:

CD4 2 (9/12/07)

viral load 71,843

Meds:

AZT/3TC/ABC 1 tab BID

tenofovir 300 mg QD

ethambutol 1200 mg QD

rifabutin 150 mg QOD

All:

TMP/SMX – rash

EFV - nightmares

What is your assessment of the MAC treatment?

MAC Treatment Summary

- 2 agents generally
- Use 3 agents if CD4 count < 50
- If EFV or NVP,
 - Use rifabutin 600 mg QD
- If ANY PI,
 - Use rifabutin 150 mg QD

Association between Acquired Rifamycin Resistance and Pharmacokinetics of Rifabutin among Patients with HIV and Tuberculosis

Table 4. Results of multivariate logistic regression analysis, with adjustment for CD4⁺ cell count, of the association between low rifabutin AUC₀₋₂₄ and the outcome of tuberculosis treatment failure or relapse in association with acquired rifamycin-resistant mycobacteria.

Variable	OR (95% CI)	P _i by the Wald test	P _i by logistic likelihood ratio test
Low rifabutin AUC ₀₋₂₄ ^a	23 (2-279)	.01	.003
CD4 ⁺ cell count	1.04 (1.00-1.08) ^b	.07	.0001

NOTE. R² = 0.46 for the logistic regression model.

^a <4.5 μg·h/mL.

^b Denotes the OR for a decrease in CD4⁺ cell count of 1 cell/mL.

MAC Treatment Summary

- 2 agents generally
- Use 3 agents if CD4 count < 50
- If EFV or NVP,
 - Use rifabutin 600 mg QD
- If ANY PI,
 - Use rifabutin 150 mg QD
- Never use rifampin

Rifampin and Induction of PI Metabolism

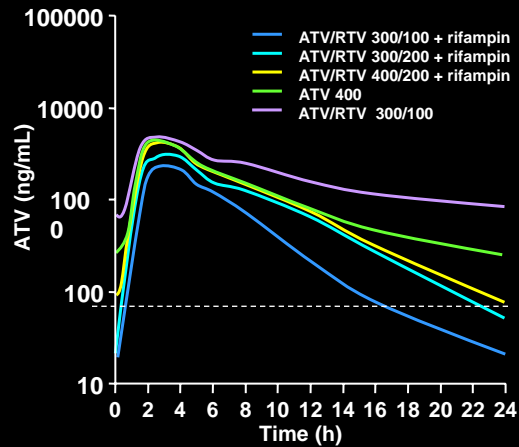
- Rifampin 600 mg in healthy volunteers

- Doses

- ATV 400 mg
- ATV/r 300/100 mg
- ATV/r 300/100 mg + rifampin
- ATV/r 300/200 mg + rifampin
- ATV/r 400/200 mg + rifampin

- ATV C_{min} ↓ 89–98% relative to 300/100; $t_{1/2}$ ↓ ~50%

Mean ATV AUC



Case 2

YY, 37 yo AF, wt 68 kg, ht 162 cm

PMH

HIV x 6 yrs
GERD
HTN
136/88 mm Hg (on tx)
+ tob 2 ppd

Meds

AZT/3TC 1 tab BID
Darunavir/ritonavir 2 tabs BID
HCTZ 25 mg QD
omeprazole 20 mg QD

Labs

CD4 586 (9/07)
vI 120 (9/07)
FLP
Tchol 290
HDL 40
LDL 190
TG 300

Case 2

How do we manage YY's dyslipidemia?

- a. replace DRV/r with ATV/r 300/100 mg QD
- b. initiate ezetimibe 10 mg QD
- c. initiate atorvastatin 20 mg QD
- d. initiate rosuvastatin 20 mg QD
- e. Initiate pravastatin 20 mg QD

Major Risk Factors That Modify LDL Goals

- Cigarette smoking
- Hypertension
 - BP \geq 140/90 mmHg or on antihypertensive med
- Low HDL cholesterol ($<$ 40 mg/dL)*
- Family history of premature CHD
 - CHD in male first degree relative $<$ 55 years
 - CHD in female first degree relative $<$ 65 years
- Age
 - men \geq 45 years
 - women \geq 55 years

* HDL cholesterol \geq 60 mg/dL counts as a "negative" risk factor removing 1 risk factor from the total count.

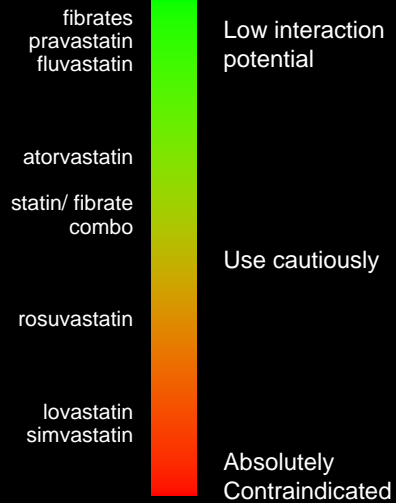
ATP-III Executive Summary 2004 Update. JAMA, 2001;285:2486-2497. www.nhlbi.nih.gov

LDL Goals for Therapeutic Lifestyle Changes and Drug Therapy

Risk Category	LDL Goal (mg/dL)	LDL Level to Initiate Therapeutic Lifestyle Changes (TLC) (mg/dL)	LDL Level to Consider Drug Therapy (mg/dL)
CHD or CHD Risk Equivalents (10-year risk $>$ 20%)	$<$ 100	\geq 100	\geq 130 (100–129: drug optional)
2+ Risk Factors (10-year risk \leq 20%)	$<$ 130	\geq 130	10-year risk 10–20%: \geq 130 10-year risk $<$ 10%: \geq 160
0–1 Risk Factor	$<$ 160	\geq 160	\geq 190 (160–189: LDL-lowering drug optional)

Anti-lipidemics and PIs

- **SQV/RTV**
 - atorvastatin ↑ 347% AUC
 - simvastatin ↑ 3059% AUC
 - pravastatin ↓ 50% AUC
- **NFV**
 - atorvastatin ↑ 74% AUC
 - simvastatin ↑ 505% AUC
- **LPV/r**
 - atorvastatin ↑ 588% AUC
 - pravastatin ↑ 30% AUC



Fichtenbaum CJ, et al. *AIDS* 2002; 16: 569-577. Hsyu PH, et al. *AAC* 2001; 45: 3445-3450. Carr RA, et al. *ICAAC* 2000. abst. 1644. Slide adapted from T. Kakuda.

Pharmacokinetic Interactions between LPV and Rosuvastatin

- Rosuvastatin (ROS) not metabolized by CYP450
- HIV-infected patients on LPV/r (400/100 BID, $n=22$) with TC = 239 mg/dL treated with ROS for 12 wks
- Rosuvastatin increase 1.5–1.9-fold, may be used with caution

Dose	Median (IQR) ROS trough levels (ng/mL)		Ratio
	This study	Historic controls*	
10 mg ($n=13$)	0.97 (0.70–1.5)	0.63 (0.27–1.2)	1.5
20 mg ($n=14$)	2.5 (1.3–3.3)	1.6 (0.54–4.1)	1.6
40 mg ($n=10$)	5.5 (3.3–8.8)	2.9 (1.7–3.6)	1.9

*Data on file, Astra-Zeneca

van der Lee M, et al. *13th CROI*, Denver 2006, #588

Rosuvastatin

- **Pharmacology**
 - Metabolized by 2C9 (minor)
 - $t_{1/2} = 19$ hrs
 - AUC \uparrow 2x in Japanese and Chinese pts
- **ADRs**
 - MYOPATHY, myalgia, asthenia, hematuria, proteinuria, abd. pain
- **Precautions**
 - Asians
 - renal insufficiency
 - drug interactions
 - gemfibrozil
 - protease inhibitors

Martin PD, et al. *Clin Ther* 2003;25:2822-35. FDA MedWatch June 9, 2004. Alsheikh-Ali A, et al. *Circulation* 2005; 111: epublished.

Unique Darunavir Drug Interactions

- SQV \downarrow DRV AUC 26%
- LPV/r \downarrow DRV AUC 53%
- DRV \uparrow LPV AUC 37%
- EFV \downarrow DRV
- DRV \uparrow pravastatin AUC 80%
- DRV \downarrow atorvastatin AUC 15%

Hoetelmans R, et al. 44th ICAAC. abst. H-865. Hoetelmans R, et al. XV IAC. abst. TuPeB4634.

Case 3

BM, 54 yo CM

PMH:

HIV

COPD

generalized sz disorder

depression

tobacco abuse

hepatitis C

Meds:

fluoxetine 20 mg QAM

Advair 250/50 1 inh BID

phenytoin 300 mg QHS

Labs:

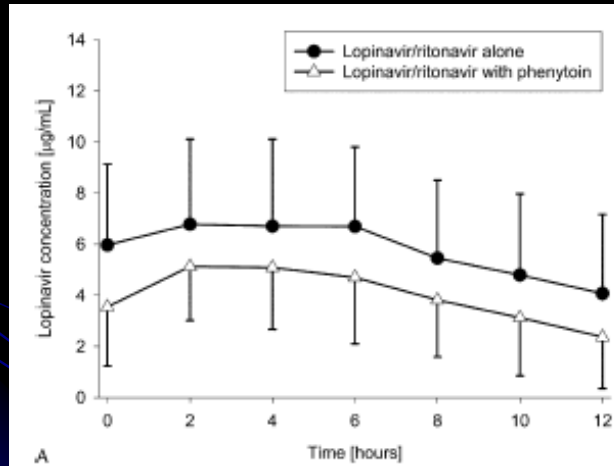
CD4 240 (9/06)

viral load 55,000 (10/06)

Considerations

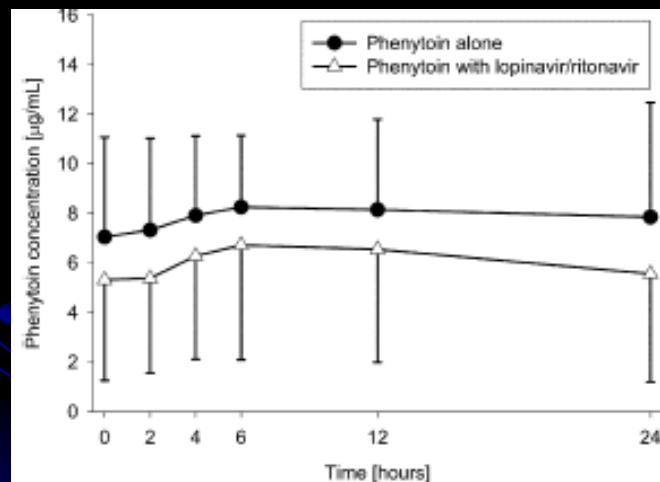
- Are ARVs indicated for this patient?
- What are the concerns with phenytoin?
- How do we initiate ARVs in this patient?
 - other anticonvulsants
 - minimal interactions with PIs
 - titration schedule?

Phenytoin Effects on Protease Inhibitors



Lim ML, et al. J Acquir Immune Defic Syndr 2004; 36: 1034-40.

Protease Inhibitor Effects on Phenytoin



Lim ML, et al. J Acquir Immune Defic Syndr 2004; 36: 1034-40.

Anticonvulsant Comparison

<u>Generic</u>	<u>Brand</u>	<u>P450 Effects?</u>
Carbamazepine	Tegretol	Y
Gabapentin	Neurontin	N
Lamotrigine	Lamictal	N
Levetiracetam	Keppra	N
Oxcarbazine	Trileptal	Y
Phenytoin	Dilantin	Y
Pregabalin	Lyrica	N
Tiagabine	Gabitril	Y
Topiramate	Topamax	Y
Valproate	Depakote	Y
Zonisamide	Zonegran	Y

Adapted from ACCP. PSAP-V. Seizure Disorders.

Case 4

- You have a marginally housed patient on a QD ARV regimen with a history of asthma.
- You assess the frequency AND severity of symptoms both at daytime and nighttime.
- You stage the asthma as stage 2 mild persistent, where a corticosteroid is indicated.
- What are your treatment options?

Asthma Step Therapy

	Long-Term Control	Quick Relief	Education
STEP 4 Severe Persistent	<p>Daily medications:</p> <ul style="list-style-type: none"> Anti-inflammatory: inhaled corticosteroid (high dose) <p>AND</p> <ul style="list-style-type: none"> Long-acting bronchodilator: either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets <p>AND</p> <ul style="list-style-type: none"> Corticosteroid tablets or syrup long term (make repeat attempts to reduce systemic steroids and maintain control with high dose inhaled steroids) 	<ul style="list-style-type: none"> Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy. 	<p>Steps 2 and 3 actions plus:</p> <ul style="list-style-type: none"> Refer to individual education/counseling
STEP 3 Moderate Persistent	<p>Daily medication:</p> <ul style="list-style-type: none"> Either <ul style="list-style-type: none"> Anti-inflammatory: inhaled corticosteroid (medium dose) <p>OR</p> <ul style="list-style-type: none"> Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets. <ul style="list-style-type: none"> If needed <ul style="list-style-type: none"> Anti-inflammatory: inhaled corticosteroids (medium-high dose) <p>AND</p> <ul style="list-style-type: none"> Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta₂-agonists, sustained-release theophylline, or long-acting beta₂-agonist tablets. 	<ul style="list-style-type: none"> Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy. 	<p>Step 1 actions plus:</p> <ul style="list-style-type: none"> Teach self-monitoring Refer to group education if available Review and update self-management plan

NHLBI. Asthma guidelines Expert Panel 2. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed 12/1/06.

Asthma Step Therapy

	Long-Term Control	Quick Relief	Education
STEP 2 Mild Persistent	<p>One daily medication:</p> <ul style="list-style-type: none"> Anti-inflammatory: either inhaled corticosteroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil). Sustained-release theophylline to serum concentration of 5-15 mcg/mL is an alternative, but not preferred, therapy. Zafirlukast or zileuton may also be considered for patients ≥12 years of age, although their position in therapy is not fully established. 	<ul style="list-style-type: none"> Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicates the need for additional long-term-control therapy. 	<p>Step 1 actions plus:</p> <ul style="list-style-type: none"> Teach self-monitoring Refer to group education if available Review and update self-management plan
STEP 1 Mild Intermittent	<ul style="list-style-type: none"> No daily medication needed. 	<ul style="list-style-type: none"> Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. Use of short-acting inhaled beta₂-agonists more than 2 times a week may indicate the need to initiate long-term-control therapy. 	<ul style="list-style-type: none"> Teach basic facts about asthma Teach inhaler/spacer/holding chamber technique Discuss roles of medications Develop self-management plan Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants

NHLBI. Asthma guidelines Expert Panel 2. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed 12/1/06.

Fluticasone and Protease Inhibitors

- Cushing's syndrome reported after treatment with RTV-boosted PIs and inhaled fluticasone:
 - 3 cases in children (2 LPV/r, 1 FPV/RTV) and 6 cases (3 LPV/r, 1 ATV/LPV/r, 1 ATV/RTV, 1 SQV/RTV) in adults
- Clinical features
 - adrenal suppression
 - facial plethora, moon facies, abdominal obesity
 - low bone mineral density and fractures in some pts
- Observed with RTV 100-1200 mg/d
- PK study fluticasone 200 µg QD and RTV 100 mg BID x 7 d
 - fluticasone AUC_{0-24h} ↑ 350-fold
 - plasma cortisol AUC ↓ 86%

Samares K, et al. J Clin Endocrin Metab 2005; 90: 4394-8. Rouanet L, et al. HIV Med 2003; 4: 149-150. Woolley I, et al. Intern Med J 2005; 35: 67-72. Gupta SK, et al. Clin Infect Dis 2002; 35: e69-71. GSK. Flonase prescribing information. 2004. Dollfus C, et al. 10th EACS, Dublin 2005, #PE 15.4/1; 2.

Corticosteroid Comparison

<u>Generic</u>	<u>Brand</u>	<u>Metabolism</u>
Beclomethasone	QVAR <i>Beconase AQ</i>	CYP450 3A4
Budesonide	Pulmicort Turbuhaler <i>Rhinocort Aqua</i>	CYP450 3A4
Fluticasone	Flovent , Advair <i>Flonase</i>	CYP450 3A4
Flunisolide	Aerobid-M <i>Nasarel</i>	CYP450 3A4
Mometasone	Asmanex Twisthaler <i>Nasonex</i>	CYP450 3A4
Triamcinolone	Azmacort <i>Nasocort</i>	poss. CYP450 3A4

Asthma Management for HIV-Positive Patients

- Quantify asthma/COPD symptoms
- Use modern, patient friendly steroid inhaler
- Avoid older generation inhalers due to:
 - more frequent dosing
 - difficult to use
 - not as potent
- Reassess symptoms 1 month post-
- Initiate low and titrate steroid inhaler to effect
 - all CS metabolized by CYP450
 - no way to avoid interaction

Case 5

DR, 45 yo CM, wt 64 kg, ht 185 cm

PMH:

HIV
HTN
amphetamine use
chronic hepatitis B
esophageal candidiasis x 4

Meds:

FPV/r 1400/100 mg QD
FTC/TDF 1 tab QD
HCTZ 25 mg QD

Labs:

CD4 143 (5/06)
vI 120
Scr 0.9

Case 5

How would you treat this patient for his current episode?

- a. Clotrimazole
- b. Caspofungin
- c. Posaconazole
- d. Fluconazole
- e. Voriconazole

Antifungals

- **Drug Interactions**

- **Voriconazole and RTV**

- vori AUC ↓ 82% with RTV 400 mg Q12H - contraindicated
- vori AUC ↓ 39% with RTV 100 mg BID
- vori AUC ↓ 100 mg QD - ?

- **Posaconazole and RTV**

- No P450 interactions

Integrating Interaction Knowledge into Patient Care

- May be able to substitute rifabutin
- Use lower dose
 - Rifabutin 150 mg QD
- Induction
 - 5-7 days to induce P450
 - After discontinuation, 2 week washout period before starting ARVs
- Inhibition
 - 1 day to inhibit
- Multidisciplinary, collaborative patient care
- Where to Look
 - <http://hivinsite.ucsf.edu>
 - www.aidsinfo.nih.gov