

# **Understanding and Managing Drug Interactions in HIV Disease**

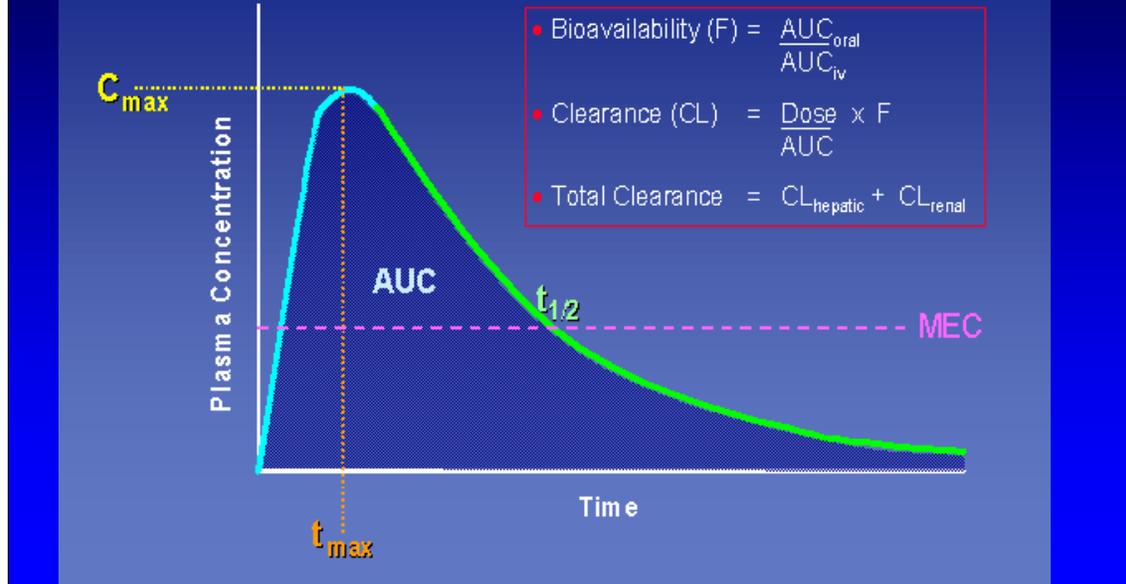
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## Content

- Antiretroviral pharmacodynamics
- Implications of drug interactions in HIV
- Overview of interaction mechanisms
  - drug absorption
  - drug metabolism
- Using pharmacokinetics to enhance HIV drug therapy (boosted regimens)
- Case studies
- Additional resources

## Basic Pharmacokinetic Parameters

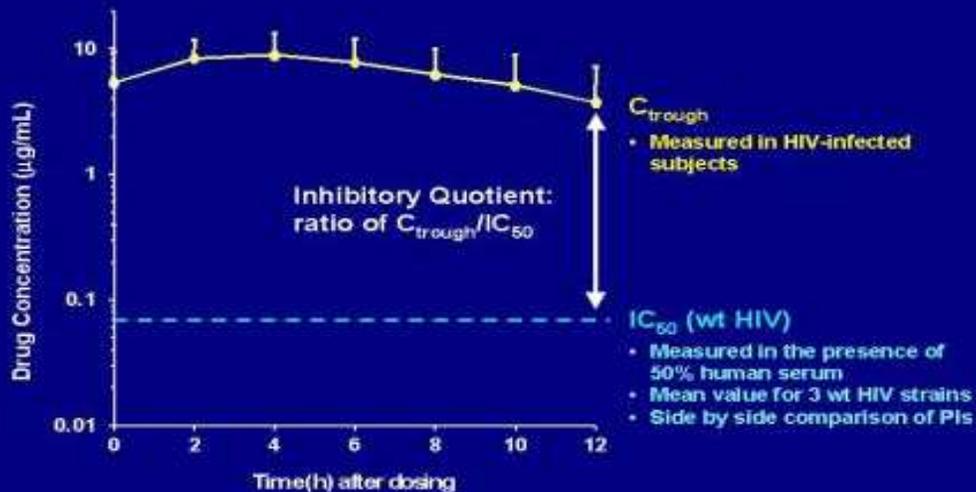


The pharmacokinetics of a drug describe quantitatively how the body deals with a drug after it is administered. When a drug is administered it undergoes absorption, distribution and elimination in the body. After a drug is taken orally, it is quickly absorbed and enters the systemic circulation, and drug concentrations begin to rise. At the same time, the body's organs (eg, liver and/or kidneys) work at a constant rate to break down the drug. When the rate at which a drug is being absorbed is equal to the rate at which it is being removed from the plasma, the maximum plasma concentration of drug is reached (=  $C_{max}$ ). The time it takes to reach this plasma concentration is called  $T_{max}$ . After  $C_{max}$  is reached, the rate of distribution and/or elimination starts to exceed the rate of absorption and so plasma drug levels begin to decline. The time it takes for plasma levels of drug to decrease by half (50%) is called the half-life or  $t_{1/2}$ . When a drug is taken repeatedly over time a series of peaks and troughs occur, where the peak is  $C_{max}$ , and the trough is called  $C_{min}$  ( $C_{min}$  reflects the lowest level of drug in the plasma usually just before the next dose is given). The area under the curve (or AUC) represents the total amount of drug in the plasma during a certain time period. With repeated dosing the AUC is usually expressed as the amount of drug in the plasma over a 24-hour period.

### Reference

Back D. Essential Pharmacokinetic Principles for Understanding ART. Liverpool HIV Pharmacology Website: <<http://www.liv.ac.uk/~hivgroup/learning/learning.html>>.

# Antiretroviral Pharmacodynamics



Protease inhibitors (PIs) demonstrate a wide range of plasma concentrations, with some patients achieving plasma levels ( $C_{\text{min}}$ ) that are below those desired for optimal efficacy. It is important to try to keep PI levels ( $C_{\text{min}}$ ) above a target inhibitory concentration (eg,  $IC_{50}$  or  $IC_{90}$ ). This can be difficult, because even with usual doses of PIs, often the  $C_{\text{min}}$  falls very close to the inhibitory concentration. Therefore, if a patient is late with taking a dose, or has problems with drug absorption or interactions, PI levels may fall below the  $IC_{50}$ , and allow the virus to begin replicating again.

The inhibitory quotient characterizes the relationship between drug exposure and drug susceptibility of the pathogen.

## Potential Consequences of Antiretroviral Interactions

- Factors critical to success of antiretroviral therapy may be adversely affected by:
  - increased risk of toxicity
    - may lead to noncompliance, dose reduction, drug discontinuation
  - decreased antiviral activity
    - subtherapeutic drug levels, inadequate viral suppression, resistance, disease progression

Many antiretroviral agents have narrow therapeutic indices, and maintenance of adequate drug concentrations may be necessary to achieve optimal virological benefit. This is especially problematic, given that cross-class resistance among PIs is common.

In general, patients failing therapy with one PI often do not experience sustained benefit from switching to another PI; (NB: an exception to this is with nelfinavir, where the presence of an isolated D30N mutation may allow for subsequent response to other PIs). Changing a patient's antiretroviral regimen may also be accompanied by possible new side effects, drug interactions, and dosing/adherence considerations.

Thus, achieving adequate drug concentrations may be a very significant factor in determining the success or failure of current, as well as future, highly active combination antiretroviral therapy.

## Hospitalizations Due to ADRs and Drug Interactions

- Chart review of HIV admissions to a Canadian hospital

	<b>Pre-HAART</b>	<b>Post-HAART</b>
	(Apr 1995–Mar 1996)	(Aug 1996–Aug 1997)
ADRs	89/436 (20.4%)	69/323 (21.4%)
Interactions	12/436 (2.5%)	7/323 (2.2%)
	<ul style="list-style-type: none"> <li>– pre-HAART: azole, AZT/ganciclovir interactions</li> <li>– post-HAART: PI interactions (85.7%)</li> </ul>	

Foisy et al. *Can J Infect Dis* 2000;**11**:193-201.

Two large retrospective chart reviews of inpatients receiving a PI showed that approximately 50% were receiving at least 1 other drug that could potentially result in a drug interaction.<sup>2,3</sup> These data highlight the importance of prospective monitoring for drug interactions in patients receiving PIs. The rate was increased in patients with more advanced disease (lower CD4+ cell counts)<sup>2</sup> and approximately half of the drug interactions were deemed to be potentially serious or life-threatening.<sup>3</sup>

### References

1. Foisy MM, Gough K, Quan C, Harris K, Ibanez D, Phillips A. Hospitalization due to adverse drug reactions and drug interactions before and after highly active antiretroviral therapy. *Can J Infect Dis* 2000;**11**:193-201.
2. van Cleef GF, Fisher EJ, Polk RE. Drug interaction potential with inhibitors of HIV protease. *Pharmacotherapy* 1997;**17**:774-778.
3. Preston SL, Postelnick M, Purdy BD, et al. Drug interactions in HIV-positive patients initiated on protease inhibitor therapy. *AIDS* 1998;**12**:228-230.

# Clinical Toxicity Associated with Increased Drug Exposure

- Indinavir (urologic complaints)
  - Dieleman et al. *AIDS* 1999;**13**:473-478.
- Ritonavir (GI, neurologic)
  - Merry et al. *Br J Clin Pharmacol* 1996;**42**:787.
  - Gatti et al. *AIDS* 1999;**13**:2083-2089.
  - Youle et al. ICAAC 1999, abstract 1290.
- Nelfinavir, saquinavir (GI symptoms except diarrhea)
  - Reijers et al. *AIDS* 2000;**14**:59-67.

## Indinavir<sup>1</sup>

Anecdotal data show that high exposure to indinavir is associated with an increased risk for urological complaints (flank pain, hematuria, renal colic).

Hypothesized that  $C_{max}$  of indinavir is correlated with renal toxicity.

Data from the BEST trial suggest that renal toxicity is more often encountered when used in a RTV/IDV 100/800 mg BID regimen as compared to IDV 800 mg TID alone, suggesting that AUC or time > certain concentration rather than  $C_{max}$  might be the main determinant of renal toxicity.

## Ritonavir

High ritonavir exposure has been associated with increased risk for gastrointestinal and neurological complaints. These associations have been reported for AUC,  $C_{max}$  and  $C_{min}$  (all correlated).<sup>2,3,4</sup>

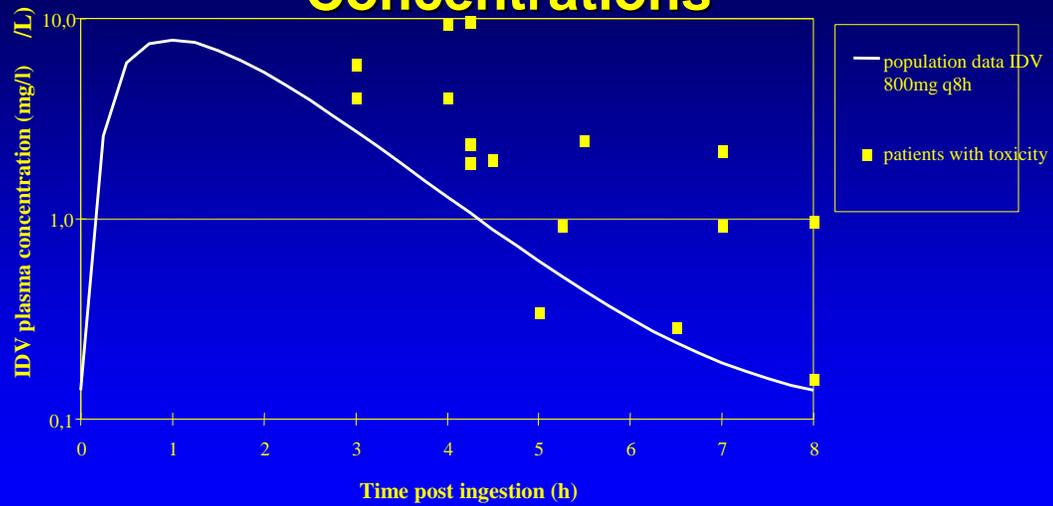
## Nelfinavir and saquinavir

High drug exposure has been associated with increased risk for gastrointestinal complaints such as abdominal pain, distension, and nausea to both nelfinavir and saquinavir. NB: in this study, the incidence/severity of diarrhea was not correlated to drug exposure.<sup>5</sup>

## References

1. Dieleman JP, Gyssens IC, van der Ende ME, de Marie S, Burger DM. Urological complaints in relation to indinavir plasma concentrations in HIV-infected patients. *AIDS* 1999;**13**:473-478.
2. Merry C, Barry M, Gibbons S, Mulcahy F, Back D. Improved tolerability of ritonavir derived from pharmacokinetic principles. *Br J Clin Pharmacol* 1996;**42**:787.
3. Gatti G, Di Biagio A, Casazza R, et al. The relationship between ritonavir plasma levels and side-effects: implications for therapeutic drug monitoring. *AIDS* 1999;**13**:2083-2089.
4. Youle et al. [abstract 1290]. *39th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 26–28 September 1999, San Francisco, CA.
5. Reijers MH, Weigel HM, Hart AA, et al. Toxicity and drug exposure in a quadruple drug regimen in HIV-1 infected patients participating in the ADAM study. *AIDS* 2000;**14**:59-67.

## Nephrotoxicity and IDV Concentrations



Dieleman et al. *AIDS* 1999;**13**:473-478.

### Reference

Dieleman JP, Gyssens IC, van der Ende ME, de Marie S, Burger DM. Urological complaints in relation to indinavir plasma concentrations in HIV-infected patients. *AIDS* 1999;**13**:473-478.

## Dose-Response Effect of PIs?

- Antiretroviral concentrations have been shown to be an independent predictor of virological response in both treatment-naïve and -experienced subjects
- Maintaining therapeutic antiretroviral concentrations (via good adherence, management of drug interactions) is critical
- Further research is needed to better define the role and utility of monitoring protease drug levels

### Potential consequences of antiretroviral interactions

#### Decreased antiviral activity

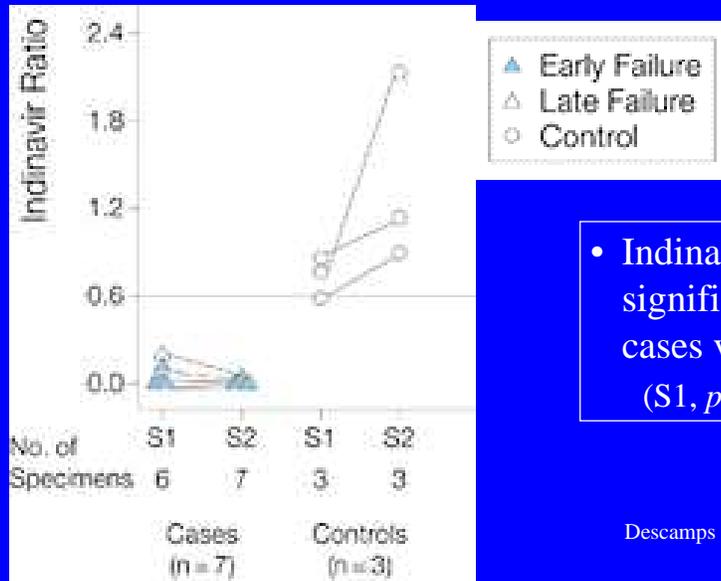
Achieving adequate drug concentrations is a significant factor in determining the success or failure of current, as well as future, highly active combination antiretroviral therapy. Reports of dose-response relationships for PIs and NNRTIs are emerging.

However, the exact nature of these relationships is not yet fully characterized. Observations have often been based on retrospective, uncontrolled studies involving small numbers of patients. Many studies have not controlled for variables such as viral susceptibility, patient heterogeneity, drug doses, and concomitant antiretroviral therapy.

Unanswered questions include:

- Which pharmacokinetic parameter is most predictive of response? Different studies have looked at different pharmacokinetic parameters (eg,  $C_{max}$ ,  $C_{min}$ , AUC). More recently, interest has focused on incorporating pharmacokinetic and virological parameters into a predictive variable, such as the inhibitory quotient (IQ).
- Which patients will benefit from therapeutic drug monitoring?
- Which drugs? Does a dose-response relationship exist for all PIs (and/or NNRTIs)?
- Additional factors such as the role of intracellular vs plasma concentrations, and presence of active metabolites (as in the case of nelfinavir) make this topic even more complex and underscore the need for further research.

## TRILÈGE: Indinavir Levels in Naïve Patients Taking AZT/3TC/Indinavir



- Indinavir levels were significantly lower in cases vs controls (S1,  $p=0.02$ ; S2,  $p<0.01$ )

Descamps et al. *JAMA* 2000; 283:205-211.

**Context:** In the Trilège trial, following induction with a zidovudine, lamivudine, and indinavir regimen, human immunodeficiency virus (HIV) replication was less suppressed by 2-drug maintenance therapy than by triple-drug therapy. **Objective:** To identify mechanisms of virologic failure in the 3 arms of the Trilège trial. **Design:** Case-control study conducted from February to October 1998. **Setting:** Three urban hospitals in Paris, France.

**Patients:** Fifty-eight case patients with virologic failure (HIV RNA rebound to  $>500$  copies/mL in 2 consecutive samples) randomized to 3 therapy groups: triple drug (zidovudine, lamivudine, and indinavir), 8; zidovudine-lamivudine, 29; and zidovudine-indinavir, 21; the case patients were randomly matched with 58 control patients with sustained viral suppression.

**Main outcome measures:** At virologic failure (S1 sample) and 6 weeks later (S2 sample), assessment of protease and reverse transcriptase gene mutations, plasma indinavir level, and degree of viral load rebound; pill count during induction and maintenance periods.

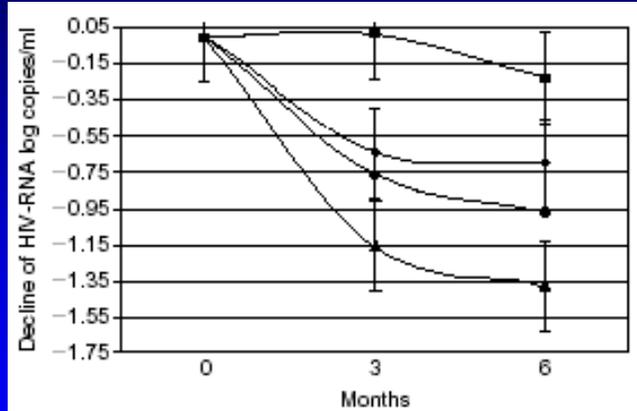
**Results:** Only 1 primary resistance mutation, M184V, was detected in S1 plasma samples from 4 of 6 patients in the triple-drug and in all 22 in the zidovudine-lamivudine therapy groups and in S2 plasma samples from 3 of 6 in the triple-drug and 20 of 21 in the zidovudine-lamivudine groups. Of controls, M184V was detected in 11 of 13 S1 plasma samples and in 10 of 11 S2 plasma samples. Indinavir levels were undetectable in all S1 samples but 2 in 7 triple-drug cases tested, and in the expected range in 11 of 18 S1 and 5 of 12 S2 zidovudine-indinavir case plasma samples tested. Maintenance adherence rates were lower for cases vs controls for zidovudine ( $P=0.05$ ) and indinavir ( $P=0.05$ ). Low indinavir levels, lower adherence rates for zidovudine ( $P=0.04$ ) and lamivudine ( $P=0.03$ ), and rebound to near-baseline values suggested adherence as cause of early failure for 4 of 8 triple-drug cases. In the zidovudine-lamivudine arm, for which case and control adherence rates did not differ significantly ( $P=0.96$ ), most failures occurred late with low rebound, suggesting suboptimal drug potency. In the zidovudine-indinavir arm, virologic failures may be related to both mechanisms.

**Conclusions:** During the maintenance phase early and late virologic failures appeared to be related more to problems of adherence and antiretroviral treatment potency, respectively, than to selection of resistant mutant viruses.

### Reference

Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. *JAMA* 2000;283:205-211.

## VIRADAPT: Efficacy According to Drug Levels and Randomization Arm



**Fig. 3.** Efficacy analysis based on drug levels and randomization arm. —◆— Control optimal concentration; —■— control suboptimal concentration; —▲— genotypic optimal concentration; —●— genotypic suboptimal concentration.

In a prospective randomized study, the impact of plasma PI trough levels on changes in HIV RNA were assessed in patients treated with genotypic-guided therapy. Patients failing combination therapy (HIV-1 RNA > 10,000 copies/mL, and at least 6 months of therapy with nucleoside analogues and 3 months with PI) were randomly assigned into two arms: control group (C) in which the treatment was modified according to the standard of care; genotypic group (G) in which the treatment was modified according to resistance mutation profiles. In this pharmacokinetic substudy, 81 patients had 575 serial PI levels done over the 12-month study period.

Optimal concentration (OC) if  $\geq 2$  samples  $> IC_{50}$ ; Suboptimal concentration (SOC) if  $\geq 2$  samples  $< IC_{50}$

Viral load reductions at 48 weeks:	<i>Genotype</i>	<i>Control</i>
OC	1.33 ( $\pm 0.19$ )	0.92 ( $\pm 0.28$ )
SOC	0.835 ( $\pm 0.41$ )	0.27 ( $\pm 0.29$ )

In a multivariate analysis:	<i>OR (95% CI)</i>	<i>p</i>
PI level $> IC_{50}$	2.48 (1.75-114)	0.013
use of genotyping	2.20 (1.23-31.79)	0.027
presence 1° PI mutations	2.67 (0.012-0.50)	0.008
baseline viral load	1.79 (0.07-1.12)	0.07

### Reference

Durant J, Clevenbergh P, Garraffo R et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradap Study. *AIDS* 2000;**14**:1333-1339.

# Principles of Drug Interactions

- *Pharmacokinetic*
  - change in the amount of drug in body
  - absorption, distribution, metabolism, elimination may be affected
- *Pharmacodynamic*
  - change in the pharmacological effect of a drug
  - additive, synergistic, or antagonistic

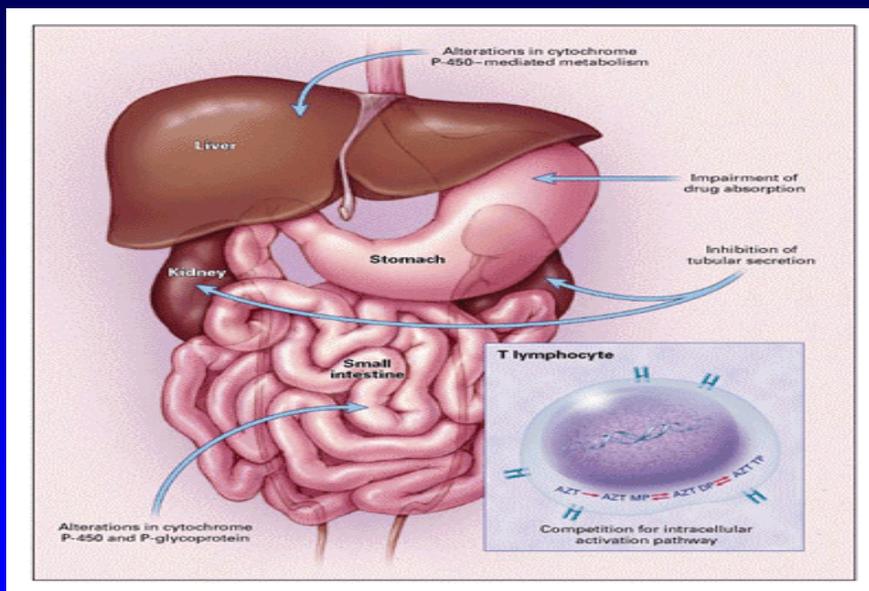
Drug interactions may be classified as being either pharmacokinetic or pharmacodynamic in nature. With *pharmacokinetic* interactions, absorption, distribution, metabolism, or elimination may be affected, resulting in an alteration of the amount and/or concentration of one or both agents in the body. Sometimes this is desirable if the pharmacokinetic profile of a drug is improved. On the other hand, certain interactions may be undesirable when the disposition of an agent with a narrow therapeutic index is affected.

With *pharmacodynamic* interactions, additive, synergistic, or antagonistic drug combinations may affect parameters of pharmacological response, including efficacy and toxicity.

Pharmacodynamic drug–drug interactions may be beneficial, when agents with complementary mechanisms of action (eg, reverse transcriptase inhibitors plus PIs or NNRTIs) are administered to enhance clinical efficacy.

In contrast, certain combinations may be undesirable if antagonism or additive toxicity occurs. For example, lamivudine and zalcitabine have been shown to negatively interact *in vitro*, likely via competition for intracellular phosphorylation, and thus should not be coadministered. Similar concern exists regarding the combination of zidovudine and stavudine.

## Sites in the Body for Drug Interactions



Piscitelli et al. *N Eng J Med* 2001;344:984-996.

### Reference

Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. *N Engl J Med* 2001;344:984-996.

## Absorption Interactions

- Drug absorption can be affected by
  - presence or absence/type of food
  - gastric acid
  - formation of unabsorbable complexes
  - induction of p-glycoprotein

The absence or presence of food or certain beverages may significantly affect the bioavailability of several medications. Drug-food interactions may occur due to a variety of mechanisms, including alteration of gastric pH, formation of unabsorbable cation complexes, increasing solubility, interference with gut metabolism, or decreasing gastric motility.

## Antiretroviral-Food Interactions

*Take with food*  
(to increase absorption)

- **Lopinavir:** ↑ 50–130%
- **Saquinavir:** 7 fold ↑ (fatty meal)
- **Nelfinavir:** 2–3 fold ↑
- **Ritonavir:** 15% ↑, decreased GI toxicity

*Avoid food*

(1 hour before/2 hours after meals)

- **Amprenavir:** ↓ 23% with high fat meal (regular food OK)
- **Indinavir:** 77% ↓ (fatty meal; light snack OK)
- **ddI:** 47% ↓ with meal

### Medications are often recommended to be taken with food for one of two reasons:

1) *To ensure optimal absorption* (eg, nelfinavir is best absorbed if it is taken with a meal or snack.)

In some instances, fat content of a meal may be an important factor affecting drug bioavailability. With lipid-soluble agents, ingestion of dietary fat results in formation of an oil or emulsion phase, with subsequent improvement in solubility. Ingesting a fatty meal also promotes secretion of gastric fluids, which in turn may lower gastric pH, delay stomach emptying, and decrease gastrointestinal transit rates. The absorption of saquinavir is significantly increased when taken within 2 hours of a high-fat meal.

2) *To reduce side effects involving the stomach*

Some agents, such as ritonavir or zidovudine do not necessarily need to be taken with food for adequate absorption. However, the presence of food may often prevent or minimize the risk of stomach upset or nausea. This, in turn, may reduce the chance of non-adherence due to drug side effects.

Certain medications may be sensitive to the conditions in the stomach. For example, indinavir is better absorbed on an empty stomach. High protein and fat-containing foods can significantly lower the amount of indinavir that gets into the body. Therefore indinavir should always be taken on an empty stomach or with a light, low-fat snack such as cereal with skim milk, toast and jam, fresh fruit, yogurt, low-fat pretzels, air-popped popcorn.

Didanosine (ddI) is another drug that needs special conditions in the stomach to be absorbed properly. It is destroyed by stomach acid, therefore the didanosine tablets contain an antacid buffer. Didanosine should always be taken on an empty stomach, because the presence of food might interfere with the action of the buffers.

## Gastric pH Interactions

- Drugs that need acidic pH
  - indinavir
  - delavirdine (50% ↓ in alkaline pH)
- Take with acidic beverage if achlorhydric
- Caution with
  - H<sub>2</sub>-blockers, proton pump inhibitors
  - antacids, ddI tablets



Certain medications are sensitive to gastric pH. For instance, optimal absorption of agents, such as indinavir, delavirdine, ketoconazole and itraconazole, occurs in an acidic gastric environment.

However, advanced HIV patients may experience achlorhydria, which may adversely affect drug bioavailability. Thus, if achlorhydria is suspected, administration of an acidic beverage, such as Coca-Cola™ may be recommended.

In addition, patients should avoid taking these drugs at the same time as antacids or didanosine. For instance, although indinavir and didanosine both need to be taken on an empty stomach, they cannot be administered together because they have opposite gastric pH requirements. Doses should be spaced at least 1 hour apart.

## Chelation Interactions

- Cations can form insoluble complexes with certain drugs, and prevent absorption
  - eg, ddI + quinolones
- NB: ddI-EC does not contain buffer, and hence may be coadministered with quinolones
- Separate dosing times (2 hours before/6 hours after ddI/antacid dose)

To avoid chelation interactions, drugs such as quinolones should be administered either 2 hours before or 6 hours after ingestion of antacids or ddI tablets.<sup>1</sup>

However, it is important to make the distinction as to the specific formulation of ddI, since the enteric-coated capsule does not contain a buffer, and hence may be coadministered with ciprofloxacin, as well as indinavir and ketoconazole.<sup>2</sup>

### References

1. Sahai J. Avoiding the ciprofloxacin-didanosine interaction [letter]. *Ann Intern Med* 1995;**123**:394-395.
2. Mummaneni V, Damle B, Kaul S, Knupp CA. Lack of effect of didanosine encapsulated enteric coated beadlet formulation on the pharmacokinetics of indinavir, ketoconazole, and ciprofloxacin in healthy subjects [abstract 1629]. *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 17-20 September 2000, Toronto, Canada.

## Summary of Antiretroviral Absorption Interactions

- *With food*
  - lopinavir, nelfinavir, saquinavir, ritonavir
- *Acidic gastric pH*
  - delavirdine, indinavir, ketoconazole, itraconazole
- *Cation binding*
  - ddI tablets, antacids + quinolones
- *Without food*
  - indinavir, ddI
- *Alkaline gastric pH*
  - ddI (tablets and capsule)

### 1) Medications are often recommended to be taken with food for one of two reasons:

a) *To ensure optimal absorption* (eg, Nelfinavir is best absorbed if it is taken with a meal or snack.)

In some instances, fat content of a meal may be an important factor affecting drug bioavailability. With lipid-soluble agents, ingestion of dietary fat results in formation of an oil or emulsion phase, with subsequent improvement in solubility. Ingesting a fatty meal also promotes secretion of gastric fluids, which in turn may lower gastric pH, delay stomach emptying, and decrease gastrointestinal transit rates. The absorption of saquinavir is significantly increased when taken within 2 hours of a high-fat meal.

b) *To reduce side effects involving the stomach*

Some agents, such as ritonavir or zidovudine do not necessarily need to be taken with food for adequate absorption. However, the presence of food may often prevent or minimize the risk of stomach upset or nausea. This, in turn, may reduce the chance of non-adherence due to drug side effects.

### 2) Empty stomach requirements

Certain medications may be sensitive to the conditions in the stomach. For example, indinavir is better absorbed on an empty stomach. High protein and fat-containing foods can significantly lower the amount of indinavir that gets into the body. Therefore indinavir should always be taken on an empty stomach or with a light, low-fat snack

Didanosine (ddI) is another drug that needs special conditions in the stomach to be absorbed properly. It is destroyed by stomach acid, and therefore the didanosine tablets contain an antacid buffer. Didanosine should always be taken on an empty stomach, since the presence of food might interfere with the action of the buffers.

### 3) Certain medications are sensitive to gastric pH

For instance, optimal absorption of agents, such as indinavir, delavirdine, ketoconazole and itraconazole, occurs in an acidic gastric environment. However, advanced HIV patients may experience achlorhydria, which may adversely affect drug bioavailability. Thus, if achlorhydria is suspected, administration of an acidic beverage, such as Coca-Cola™ may be recommended. In addition, patients should avoid taking these drugs together with antacids or didanosine.

## P-Glycoprotein

- Transmembrane protein first associated with MDR in certain tumor cells
- Acts as transporter pump which prevents drug accumulation in cells (= ↓ activity)
- Physiologic role not fully understood
- Present in GI, renal, hepatic cells, blood-brain barrier, CD4+ subsets, testes

P-glycoprotein (P-gp) is an ATP-dependent, efflux membrane transporter.

Originally detected in numerous tumour cell types, and implicated in the role of multidrug resistance (MDR)

- P-gp expels drug from cells, resulting in decreased intracellular drug concentrations, and consequently decreased antitumour activity.

In addition, P-glycoprotein is present in tissues:

- epithelial cells of the gastrointestinal tract, liver, and kidney
- expressed at level of the blood-brain barrier
- also noted in subsets of CD4+ T lymphocytes.

P-gp has broad substrate specificity, and appears to play a role in the transport of many natural substances and xenobiotics, including chloride ions, hormones, peptides, cardiac glycosides, antitumour drugs, fluorescent dyes.

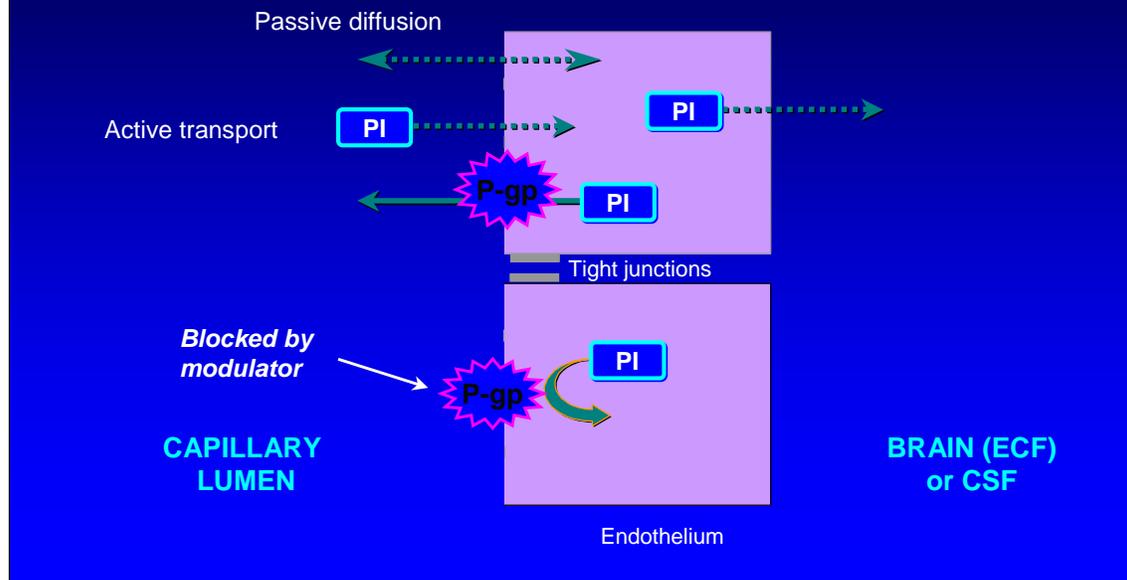
Now being increasingly recognized as having a role in pharmacokinetics of many medications, including PIs.

Also preliminary data to suggest that P-gp expression may be associated with HIV replication. Observations from small studies revealed that patients with good virological control had higher levels of P-gp expression than those who remained viremic. These data require further study and verification, but nonetheless, it is evident that P-gp can impact many aspects of HIV disease.

### Reference

Back DJ, Jones K, Hennessy M, et al. Potential clinical relevance of drug transporters in antiretroviral pharmacology [abstract S3]. *Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections*, 4-8 February 2001, Chicago, Illinois.

## Mechanism of P-gp Transport



P-glycoprotein (P-gp) can actively transport drug from cells, resulting in:

- decreased drug absorption (gastrointestinal tract)
- enhanced elimination into bile (liver) and urine (kidney)
- prevention of drug entry into the central nervous system (blood-brain-barrier).

## P-Glycoprotein Interactions

- Increasing recognition as an important factor in influencing drug pharmacokinetics and efficacy
- Can significantly affect disposition of medications
  - ↓ absorption, ↑ elimination, ↓ entry to CNS, testes
- P-gp inducers
  - phenobarbital, phenytoin, rifampin, St John's wort
- P-gp inhibitors
  - erythromycin, clarithromycin, diltiazem, felodipine, itraconazole, ketoconazole, nicardipine, grapefruit

Now being increasingly recognized as having a role in pharmacokinetics of many medications, including PIs:

- oral absorption: oral bioavailability may be limited by the presence of CYP3A4 in the GI tract and liver (first-pass effect), as well as P-gp, which may transport absorbed drug back into the intestinal lumen.
- CNS exposure: in addition to other factors such as lipophilicity, plasma protein binding, molecular weight, and concentration, P-gp may play a significant role in limiting penetration of PIs into the brain.

Agents which inhibit P-gp may affect disposition of P-gp substrates (eg, ritonavir inhibits P-gp; may partially account for its profound effect on saquinavir metabolism).

### Reference

Metheny CJ, Lamb MW, Brouwer KLR, Pollack GM. Pharmacokinetic and pharmacodynamic implications of P-glycoprotein modulation. *Pharmacotherapy* 2001;**21**:778-796.

## P-Glycoprotein and PIs

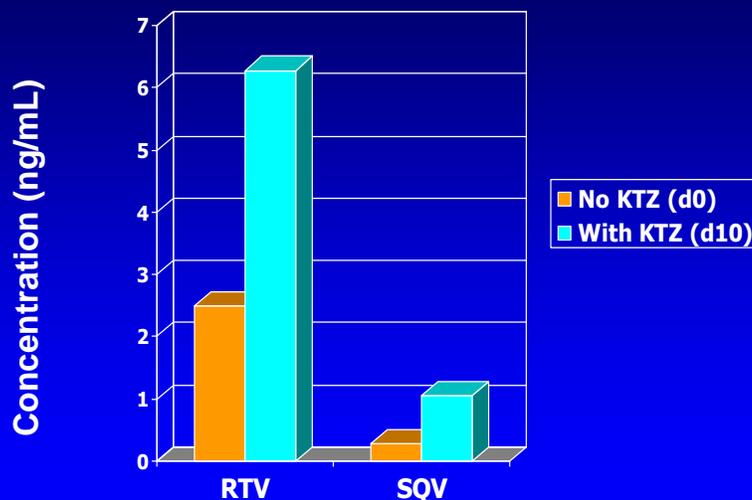
- All PIs are substrates of P-gp
- PIs can also inhibit P-gp to varying degrees
  - ritonavir>nelfinavir, saquinavir
- Interest in using P-gp inhibitors to enhance PI concentrations, particularly in sanctuary sites (eg, CNS)

### References

Kim RB, Fromm MF, Wandel C, et al. The drug transporter P-glycoprotein limits oral absorption and brain entry of HIV-1 PIs. *J Clin Invest* 1998;**101**:289-294.

Lee CGL, Gottesman MM, Cardarelli CO, et al. HIV-1 PIs are substrates for the MDR1 multidrug transporter. *Biochemistry* 1998;**37**:3594-3601.

## Increases in Protease CSF Concentrations with Ketoconazole (P-gp Inhibitor)



Khaliq et al. *Clin Pharmacol Ther* 2000 Dec;68:637-646.

### In this pharmacokinetic study:

12 HIV-positive patients receiving 400 mg of ritonavir and 400 mg of saquinavir BID were given ketoconazole 200–400 mg daily for 10 days. Blood samples were collected over the 12-hour daytime dosing interval of the PIs at baseline and after 10 days of ketoconazole coadministration. One set of paired CSF and blood samples was collected between 4 and 5 hours after the dose on both days.

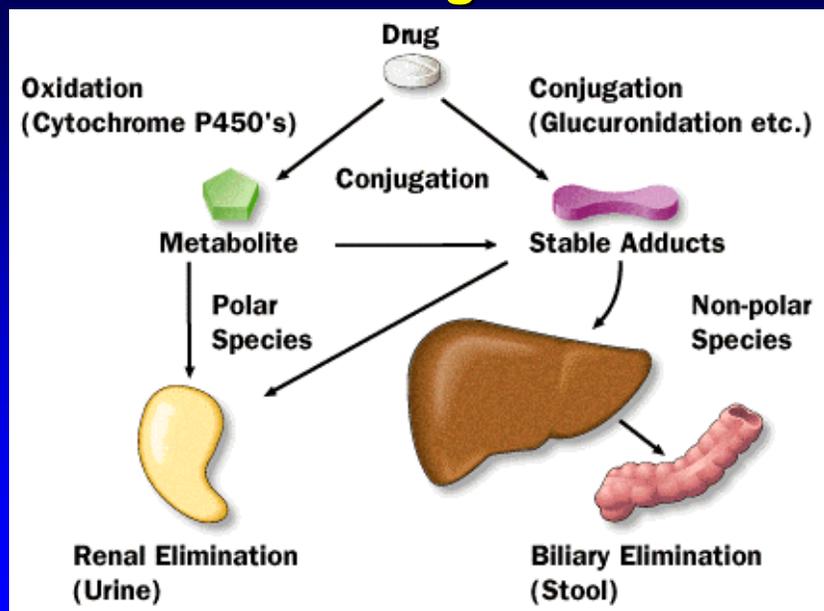
**Results:** Ketoconazole significantly increased area under the plasma concentration-time curve, plasma concentration at 12 hours after the dose, and half-life of ritonavir by 29% (95% confidence interval (CI), 13–46%), 62% (95% CI, 37–92%), and 31% (95% CI, 13–51%), respectively. Similar increases of 37% (95% CI, 4–81%), 94% (95% CI, 41–167%), and 38% (95% CI, 15–66%), respectively, were observed for these parameters for saquinavir. Ketoconazole significantly elevated ritonavir CSF concentration by 178% (95% CI, 59–385%), from 2.4 to 6.6 ng/mL, with no change in paired unbound plasma level (26 ng/mL); this led to a commensurate 181% increase (95% CI, 47–437%) in CSF/plasma unbound ratio. All pharmacokinetic changes were unrelated to ketoconazole dose or plasma exposures. Corresponding changes for saquinavir CSF pharmacokinetics were insignificant ( $p > 0.06$ ); saquinavir CSF levels were unmeasurable in 7 patients ( $< 0.2$  ng/mL).

**The authors concluded** that the disproportionate increase in CSF compared with plasma concentrations of ritonavir is consistent with ketoconazole inhibiting both drug efflux from CSF and systemic clearance. Clinical implications of these data are still unclear.

### Reference

Khaliq Y, Gallicano K, Venance S, Kravcik S, Cameron DW. Effect of ketoconazole on ritonavir and saquinavir concentrations in plasma and cerebrospinal fluid from patients infected with human immunodeficiency virus. *Clin Pharmacol Ther* 2000;68:637-646.

## Routes of Drug Metabolism



Flexner, Piscitelli. *Medscape*. 8 March, 2000.

After oral administration, drugs pass from the intestinal tract into the liver via the portal circulation, and then enter the systemic circulation. Metabolized drugs are mainly eliminated from the body through chemical modification in the liver. The goal of metabolism is to detoxify drugs, and make them either more water soluble (for excretion in the urine) or more fat soluble (for excretion in the bile, and then into the feces). Drug metabolism can occur in two ways:

1) Phase I Reactions. *Cytochrome P450 enzymes* chemically oxidize or reduce drugs.

2) Phase II Reactions. *Conjugation enzymes* link one chemical to another. For example, glucuronyl transferases link a glucuronide group to zidovudine, which makes it more water soluble and allows elimination in the urine.

Reference

Flexner C, Piscitelli SC. Managing Drug-Drug Interactions in HIV Disease. *Medscape*, 8 March, 2000. <http://hiv.medscape.com/Medscape/HIV/ClinicalMgmt/CM.drug/public/toc-CM.drug.html>

## Metabolic Interactions

- Majority of drugs transformed to inactive forms prior to elimination
- Phase I (oxidation) or phase II (conjugation) reactions
- Phase I primarily involves cytochrome P450 system (most common)

Many drugs that are administered orally are fat-soluble.

This is a desirable characteristic for oral absorption because lipophilic agents can passively diffuse through membranes of the gut, whereas drugs that are not lipophilic pass unaltered through body in the stool.

However, once lipophilic drugs are absorbed, they circulate in blood bound to plasma proteins, or are sequestered in fat; thus, they are not readily excreted by the kidney into the urine.

Therefore, to eliminate these agents, they are converted in the body to more water-soluble metabolites which can then be excreted by the kidney.

The majority of these conversions occur in the liver, via phase I and phase II reactions.

Phase I reactions are the most common, and involve the cytochrome P450 system

## Cytochrome P450 Enzymes

- Superfamily of microsomal enzymes
- Primarily located in liver, small bowel; also kidney, lung, brain
- Regulate rate and extent of drug breakdown in the body
- Classified into families and subfamilies
- Three main cytochrome (CYP) families: 1, 2, 3

The cytochrome P450 system is a superfamily of microsomal heme-containing enzymes which chemically oxidize or reduce drugs and endogenous substances such as steroid hormones, fatty acids, and prostaglandins. The P450 term is derived from:

- Initial beliefs that these enzymes were thought to be similar to mitochondrial *cytochromes*
  - they are red in colour (*p*igment)
  - they maximally absorb light at **450** nm wavelength under certain conditions.
- Classified into families, subfamilies, and individual enzymes
  - families: all members have >40% identity in amino acid sequences (indicated by a number)
  - subfamilies: amino acid sequences are >55% identical (indicated by letter)
  - individual enzymes within a subfamily (indicated by number).

Approximately 30 P450 families have been identified in human beings.

Of these, only 3 families (CYP1, CYP2, CYP3) are currently thought to be responsible for the majority of hepatic drug metabolism.

CYP450 enzymes are present in high concentrations in the liver; they are also present in lower concentrations in other areas of the body, including the gastrointestinal tract, kidneys, lungs, and brain.

The presence and amount of certain CYP isozymes may also vary between individuals (ie, genetic polymorphism), and may also be affected by HIV status.<sup>1</sup>

### Reference

1. Gotzkowsky SK, Kim J, Tonkin J, Morlan M, Gaedigk A, Van der Horst C, Kashuba ADM. Altered drug metabolizing enzyme activity (DMEA) and genotype-phenotype discordance in HIV infected subjects [abstract 1169]. *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 17-20 September, 2000, Toronto, Canada.

## Substrate

- Agent which is primarily cleared via CYP450 enzymes
- Rate of drug breakdown affected by:
  - enzyme inhibitors
  - enzyme inducers
- *All PIs, NNRTIs* are substrates of CYP3A4

A substrate is any drug that is metabolized by one or more of the P450 enzymes.

Most drugs are primarily metabolized by a single P450 enzyme.

Over 50% of metabolized drugs are substrates for the CYP3A4 enzyme.

All PIs and NNRTIs are substrates of the cytochrome P450 system.

More specifically, these agents are substrates of CYP3A4; therefore, their disposition may be affected by the presence of enzyme inducers, particularly those that affect CYP3A4.

In addition, all PIs and NNRTIs possess enzyme inhibiting and/or inducing properties, and may thus affect the metabolism of other CYP450 substrates.

## Enzyme Inhibitor

- Agent which competes with another drug for binding at enzymatic site
- Rate of substrate metabolism is decreased, resulting in increased drug concentrations
- Inhibitors vary in selectivity and potency
- *PIs are CYP3A inhibitors*

A P450 enzyme inhibitor is any drug that inhibits the metabolism of a P450 substrate.

This inhibition process is generally competitive in nature (ie, the inhibitor competes with a substrate for binding at the enzyme's binding site), and is reversible.

This competitive mechanism results in accumulation of the target drug (substrate). However, once the inhibitor is gone, metabolism is back to normal.

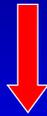
NB: a drug does not necessarily need to be a P450 substrate to be an enzyme inhibitor (eg, fluconazole is primarily excreted renally, but is a moderate to weak P450 inhibitor).

Enzyme inhibitors vary in both selectivity and potency, in terms of their effects on CYP enzymes.

## Selectivity — Which CYP Isozymes?

Indinavir inhibits

CYP3A4

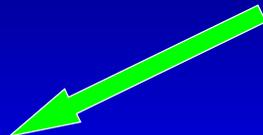


CYP3A4

PIs, NNRTIs  
Benzodiazepines  
Macrolides  
Antifungals  
Anticonvulsants

Ritonavir inhibits

CYP3A4, 2D6, 2C9, etc.



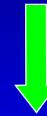
CYP2D6

Antidepressants  
Codeine



CYP1A2

Theophylline



CYP2C9

Diclofenac  
Flurbiprofen  
Ibuprofen

Most PIs and NNRTIs primarily affect CYP3A4.

On the other hand, ritonavir inhibits many cytochrome P450 isoenzymes including CYP3A, CYP2D6, CYP2C9, CYP2C19 and others.

Therefore, ritonavir has the potential to interact with many more classes of agents which are metabolized via similar routes.

## Potency

- *Inhibitors of CYP3A4*

**Ritonavir >> Indinavir > Lopinavir**  
**Nelfinavir Saquinavir**  
**Delavirdine**  
**Amprenavir**

- More potent inhibitors will have greater effect on drug concentrations

Ritonavir has extremely potent inhibitory effects on the cytochrome P450 system. Agents such as indinavir, nelfinavir, amprenavir and delavirdine have moderate inhibitory effects, while saquinavir is a weak inhibiting agent.

Therefore, of the currently available PIs and NNRTIs, ritonavir would be expected to have the most pronounced effect on the metabolism of cytochrome P450 substrates, and consequently may be associated with more potentially significant interactions.

For example, different PIs have different effects on saquinavir (SQV) metabolism

- *SQV + indinavir (IDV)*: 620% increase in SQV-soft gel capsule AUC (area under the concentration-time curve); no apparent clinically relevant changes to IDV
- *SQV + nelfinavir (NFV)*: 392% increase in SQV-soft gel capsule AUC (similar effect observed with SQV-hgc plus NFV); may use lower dose of SQV-SGC (ie, 800 mg vs 1200 mg TID)
- *SQV + ritonavir (RTV)*: 50- to 100-fold increase in SQV AUC (Regimen of SQV 400 mg BID and RTV 400 mg BID well tolerated).

## Enzyme Inhibition Interactions

- Effect varies according to
  - dose (amount)
  - potency (strength)
- Quick onset, resolution of interaction

Inhibition interactions occur when two agents compete for the same enzymatic binding site.

Competitive inhibition depends upon:

- the affinity of the substrate for the enzyme being inhibited
- the concentration of substrate required for inhibition
- the half-life of the inhibitor drug.

These types of interactions usually occur rapidly, ie, within a few doses, once sufficient concentrations of the inhibiting agent are present in the liver.

These interactions also tend to resolve quickly once the offending agent (inhibitor) is removed.

Another, less common mechanism of inhibition is noncompetitive; this can occur as a result of inactivation of the enzyme. The duration of this type of inhibition may be longer if new enzymes need to be synthesized after removal of the inhibitor drug.

## Enzyme Inducer

- Drug that stimulates the production of additional metabolic enzymes  $\Rightarrow$   $\uparrow$  clearance,  $\downarrow$  substrate concentrations
- Also varies in potency and specificity of effect
  - potency: rifampin > rifabutin
  - isozymes: ritonavir induces 1A2, glucuronyl transferase
- *Nevirapine, efavirenz are CYP3A4 inducers*

An enzyme inducer stimulates the production of more P450 enzymes. It does this by binding directly to promoter elements in the DNA region, resulting in an increase in P450 transcription (ie, increasing messenger RNA), and subsequently increasing the amount of enzymes present. The presence of these additional enzymes results in a net increase in metabolic activity; the body is able to eliminate substrates more quickly, which results in a net reduction in substrate concentrations. Unlike inhibition, induction persists for several days, even after the inducing drug is gone. This is because the enzymes persist for several days following induction.

Enzyme induction is also influenced by age and liver disease. For instance, elderly patients, or those with cirrhosis or hepatitis may be less susceptible to enzyme induction.

• Inducers may also vary by specificity and potency:

- Some inducers are able to influence several types of enzymes. For instance, ritonavir induces the amount of CYP1A2 and glucuronyl transferase.
- Inducers also affect enzyme activity to varying degrees. For example, rifampin is a more potent inducer than rifabutin and, as such, substrate levels are more likely to be reduced to a greater extent in the presence of rifampin vs rifabutin. For instance, nelfinavir concentrations are reduced by 32% with rifabutin, and by 82% with rifampin. Similarly, saquinavir concentrations are reduced by 40% with rifabutin, and by 80% with rifampin.
- Common classes of inducers include anticonvulsants and rifamycins.

Among antiretrovirals, nevirapine and efavirenz are potent enzyme inducers.

## Enzyme Induction Interactions

- Slower onset, resolution of effect
- Depends upon half-life of inducer, as well as enzymes
- Usually see maximum induction effect in ~2 weeks; similar time to resolution when drug inducer is discontinued

Enzyme induction interactions do not usually become apparent for a week or more, since the enzyme inducer must first reach steady state, and new drug metabolizing enzymes need to be synthesized.

Similarly, once the inducing agent is removed, the interaction may take a few weeks to resolve (time for the inhibitor to be cleared, and for enzymes to degrade).

## Some Antiretrovirals May Induce and Inhibit CYP450

	<u>Induction</u>	<u>Inhibition</u>
Nelfinavir	glucuronyl transferase	CYP3A, 2B6
Ritonavir	CYP1A2, glucuronyl transferase	CYP3A, 2D6, 2C9, 2C19, 2B6
Efavirenz	CYP3A4	CYP3A, 2B6

NB: Some agents may possess both enzyme inhibiting *and* enzyme inducing properties.

### *Ritonavir*

- inhibits CYP3A4, 2D6, 2C9, 2C19
- induces CYP1A2, glucuronosyl transferase.

### *Nelfinavir*

- inhibits CYP3A4
- induces glucuronosyl transferase.

### *Efavirenz*

- can inhibit or induce CYP3A4.

Therefore, it may be much more difficult to predict metabolic interactions with these agents.

## Effect on CYP450 — Summary

### Inducers

- NNRTIs
- tipranavir
- rifamycins
- anticonvulsants
- St John's wort

### Inhibitors

- PIs
- delavirdine
- azoles
- macrolides

Usually a class effect (NB: NNRTIs are an exception)

Effects on CYP450 are often consistent within a drug class. However, there are certain exceptions:

- Macrolides: clarithromycin and erythromycin are potent CYP inhibitors, but azithromycin does not inhibit or induce CYP450.
- Anticonvulsants: carbamazepine, phenobarbital and phenytoin are potent enzyme inducers; however, valproic acid and gabapentin do not affect CYP450.
- NNRTIs: delavirdine is a potent enzyme inhibitor, while nevirapine and efavirenz primarily act as enzyme inducers.

Also, as previously mentioned, some agents may possess both enzyme inhibiting *and* enzyme inducing properties.

## Pharmacokinetically Enhanced PI Combinations

- Can exploit drug interactions to enhance/improve therapy
  - double protease combinations
  - ritonavir boosted regimens
  - delavirdine boosted regimens
- Possible outcomes of improving PI kinetics
  - increase antiviral activity
  - less frequent/lower dosing, remove food restrictions
  - overcome low-level viral resistance

Combining agents from different classes, or even using various agents from similar classes may be desirable, for a number of different reasons:

- *To improve antiretroviral pharmacokinetics.* Often, the efficacy of an antiretroviral is limited or affected by its disposition in human beings. One may sometimes take advantage of enzyme inhibiting properties to improve the bioavailability and/or pharmacokinetic profile of one or more drugs.
- *To improve adherence.* When certain drugs are combined, dosing regimens may be simplified, and often pill burden and/or food restrictions may be minimized. For instance, when indinavir and ritonavir are combined, the dosage of indinavir may be reduced to 400 mg BID. In addition, in the presence of ritonavir, indinavir absorption is no longer significantly affected by the presence of food.
- *To minimize side effects.* The standard dosage of ritonavir is 600 mg BID. At this dosage, many patients may experience significant toxicity. When ritonavir is combined with saquinavir, a lower dosage may be used, with better tolerance. Another example may be seen when indinavir is coadministered with ritonavir: indinavir peak levels are lower, which may potentially be associated with a reduced risk of nephrolithiasis.
- *To enhance antiviral activity.* Additive or synergistic antiviral effects may be observed when various antiretrovirals are administered together.

## Dual Protease Combinations

- *Combining 2 PIs at therapeutic doses*
  - Saquinavir 400 mg + ritonavir 400 mg BID: 50-fold ↑ saquinavir
  - Saquinavir 1200 mg + nelfinavir 1250 mg BID: 392% ↑ saquinavir
  - Indinavir 400 mg + ritonavir 400 mg BID: 3-fold ↑  $C_{\min}$ , 62% ↓  $C_{\max}$  indinavir
  - other examples

Dual protease combinations are often a desirable therapeutic option. Besides additive or synergistic antiviral activity, the pharmacokinetic profile of one or both agents may be enhanced.

### a) Increased drug concentrations

- For instance, the hard-gel capsule formulation of saquinavir has a low oral bioavailability of approximately 4%. Since a dose-related antiviral effect has been observed with saquinavir, saquinavir may be combined with other PIs such as ritonavir or nelfinavir, to enhance saquinavir exposure.

### b) Improved pharmacokinetic profile

- The pharmacokinetics of indinavir may vary by up to 2-fold among individuals. When indinavir is combined with ritonavir, the interpatient variability of indinavir is minimized, and more consistent drug concentrations may be expected.

### c) Simplified dosing regimen

- Also, when PIs are coadministered, the resulting interaction may allow for few dosing times (eg, BID vs TID), or fewer pills to take.

## Dual Protease Combinations (con't)

- Advantages
  - therapeutic doses/effect of two antiretrovirals
  - enhanced concentrations of both PIs
- Disadvantages
  - often high pill burden
  - additive/synergistic side effects of both drugs

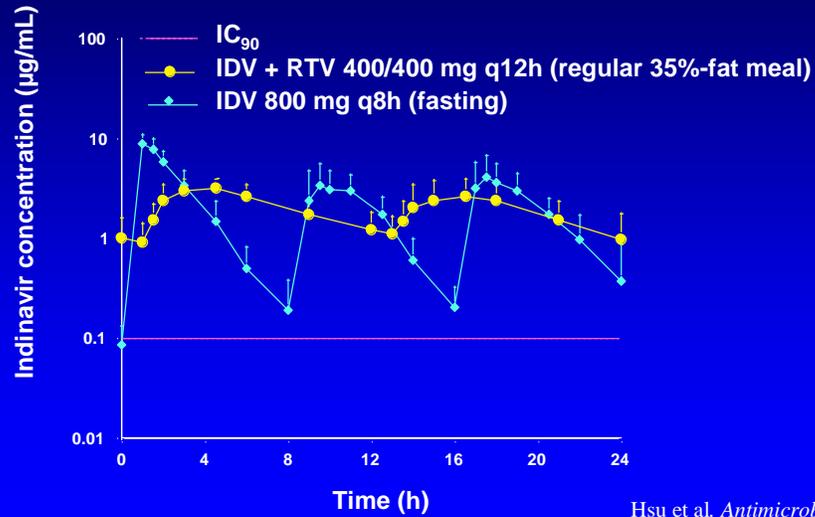
Combining PIs may be desirable, for a number of different reasons:

– *To improve adherence.* The logistics of taking multiple antiretroviral agents can be very burdensome, and may adversely affect medication adherence. When certain drugs are combined, dosing regimens may be simplified, and often pill burden and/or food restrictions may be minimized. For instance, when indinavir and ritonavir are both used for therapeutic effect, lower dosages of both (ie, indinavir 400 mg BID and ritonavir 400 mg BID) may be used. In addition, in the presence of ritonavir, indinavir absorption is no longer significantly affected by the presence of food.

– *To minimize side effects.* The standard dosage of ritonavir is 600 mg BID. At this dosage, many patients may experience significant toxicity, such as gastrointestinal upset, nausea, diarrhea, flushing, and perioral tingling. When ritonavir is combined with saquinavir, a lower dosage may be used, with better tolerance. Another example may be seen when indinavir is coadministered with ritonavir at doses of 400 mg BID each: indinavir peak levels are lower, which may potentially be associated with a reduced risk of nephrolithiasis. NB: with other indinavir–ritonavir dosage regimens, eg, 800/200 mg BID, 800/100 mg BID, indinavir peaks may be similar or even higher compared to peaks associated with indinavir 800 mg q8h.)

– *To enhance antiviral activity.* Additive or synergistic antiviral effects may be observed when various antiretrovirals are administered together. For instance, ritonavir and saquinavir have demonstrated in vitro synergy against HIV, and long-term viral suppression in PI-naïve patients has been demonstrated with this combination.

## Steady-State IDV Plasma Profile After IDV + RTV 400 mg Q12H with Food



Hsu et al. *Antimicrob Agents Chemother* 1998;**42**:2784-2791.

### Reference

Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrob Agents Chemother* 1998;**42**:2784-2791.

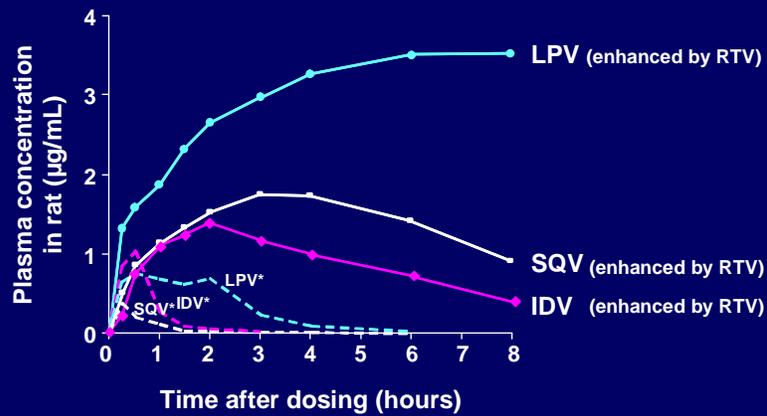
## Ritonavir Boosted PI Regimens

- *Using low dose ritonavir in combination with another PI*
  - atazanavir 300 mg/ritonavir 100 mg QD
  - darunavir 800 mg/ritonavir 100 mg QD or 600 mg/100 mg BID
  - fosamprenavir 700 mg/ritonavir 100 mg BID
  - lopinavir 400 mg/ritonavir 100 mg BID (coformulated)
  - saquinavir 1000 mg/ritonavir 100 mg BID

PI boosting can be achieved by adding ritonavir in a dose much lower than that used to treat HIV (ie, ritonavir 100–400 mg BID to boost vs 1200 mg daily to treat). In other words, in this situation, ritonavir is used at small doses for the main purpose of inhibiting CYP450 activity; ritonavir is not being used for its own antiviral activity, and hence this approach is different compared to the *dual PI* strategy, where therapeutic levels of both PIs are achieved.

In general the effect of ritonavir on other PIs has been to increase  $C_{\min}$  and  $t_{1/2}$ , with a variable effect on  $C_{\max}$ . Ritonavir itself has many side effects (hepatotoxicity, dyslipidemia, GI intolerance and multiple drug–drug interactions), so using lower doses may result in fewer hepatic and lipid abnormalities.

## Ritonavir Enhances Kinetics of Other PIs



\*Without RTV enhancement

Ritonavir is a potent enzyme inhibitor and it can significantly enhance the kinetics of other PIs.

## Impact of Ritonavir on Protease Concentrations

- Ritonavir can ↑ PI exposure by one or more of the following mechanisms:
  - P-glycoprotein inhibition
    - ↑ absorption
  - CYP3A4 inhibition (GI, liver)
    - ↓ first-pass effect
    - ↓ drug clearance
- Different effects on PK profile, depending upon the PI

It appears that ritonavir can have differential effects on the kinetic profile of different PIs.

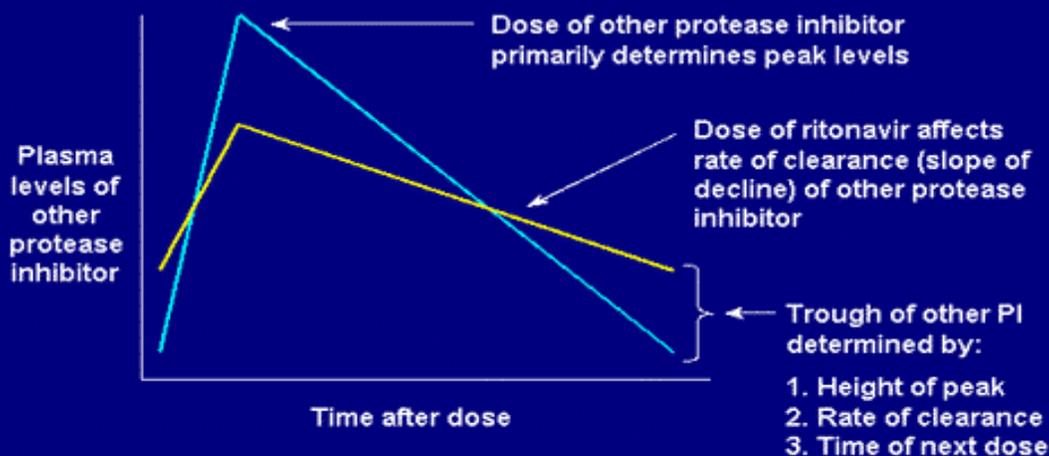
- a)  $C_{\max}$  boosting: Saquinavir, nelfinavir and lopinavir are highly susceptible to P-gp degradation in the intestinal tract and/or first pass metabolism; thus the primary effect of ritonavir coadministration will be to enhance bioavailability. This allows for use of lower protease dosages.
- b) Half-life boosting: On the other hand, with amprenavir and indinavir, the primary effect of ritonavir is to decrease drug clearance and prolong half-life. This may allow for decreased dosing frequency.

It should be noted that the overall effect on PI disposition is often a combination of these two mechanisms.

### Reference

Hoetelmans RMV, Piscitelli SC, Hill AM. *A Guide to Protease Inhibitor Boosting*, 2nd ed. London, UK: FSP International, 2001[copyright F.Hoffmann-LaRoche].

## Effect of drug dose on the pharmacokinetics of dual protease inhibitor regimens



Hsu et al. *2nd HIV Pharmacol* 2001 [abstract 3.3].

Hsu et al analyzed steady-state PK of PIs in combination with RTV from 9 studies. In each study, at least 2 doses of RTV were investigated for a given PI dose. Results suggest that for a given PI dose, increasing the ritonavir dose will increase PI  $C_{min}$ , while the PI  $C_{max}$  remains relatively unchanged. In other words, for dual PI combinations involving ritonavir:

- to increase PI  $C_{min}$ , one should increase the ritonavir dose
- to increase PI  $C_{max}$ , AUC, one should increase the PI dose.

This additional data provides clinicians with further guidance on how to manipulate dosages of PI combinations to maximize the pharmacokinetic profile.

PK parameter	Primary determinant of parameter	Effect of ritonavir on parameter
$C_{min}$	ritonavir dose	median 90% ↑
$C_{max}$	PI dose	median 10% ↑
AUC	PI dose	median 20% ↑

• A good illustration of these principles is demonstrated with the combination of indinavir and ritonavir. These two drugs are often combined in various dosages, including indinavir/ritonavir 400/400 mg BID, 800/100 mg BID, and 800/200 mg BID. It is interesting to note that indinavir  $C_{max}$  is lower with the 400/400 mg combination, compared to the 800/100 or 800/200 mg dosages, which supports the principle that PI peaks are more closely associated with the PI dose as compared to the ritonavir dose.

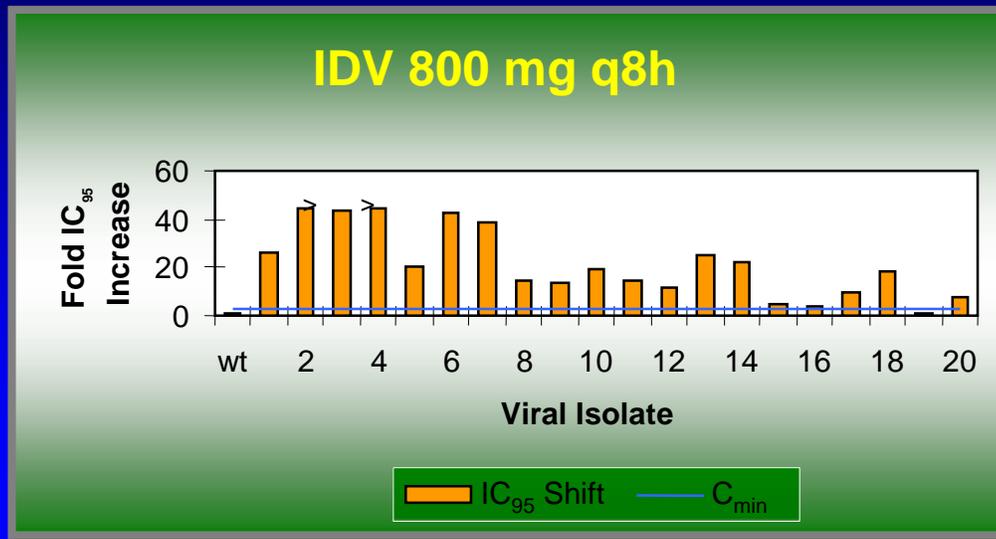
### Reference

Hsu A, Bertz R, Granneman GR. Assessing ritonavir dose effect on the pharmacokinetic parameters of protease inhibitors [abstract 3.3]. *2nd International Workshop on Clinical Pharmacology of HIV Therapy*, 2–4 April, 2001, Noordwijk, Netherlands.

## Advantages of Ritonavir-Boosted Regimens

- Adherence
  - simplify pill burden, food restrictions
- Toxicity
  - lower dose of ritonavir better tolerated
- Enhanced kinetics of boosted PI
  - allow for more convenient dosing schedule
  - boosting of  $C_{\min}$  above inhibitory concentration of HIV virus may allow one to overcome low-level resistance

## Boosting Protease Levels May Expand Antiviral Activity



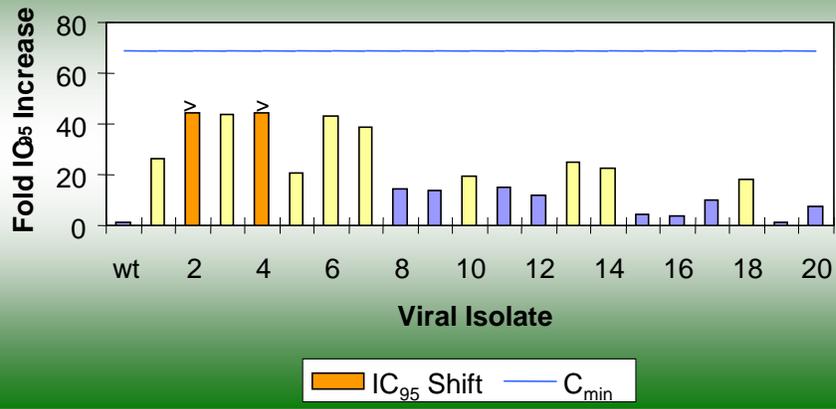
### Abstract

*The extent to which human immunodeficiency virus (HIV) type 1 drug resistance compromises therapeutic efficacy is intimately tied to drug potency and exposure. Most HIV-1 protease inhibitors maintain in vivo trough levels above their human serum protein binding-corrected IC(95) values for wild-type HIV-1. However, these troughs are well below corrected IC(95) values for protease inhibitor-resistant viruses from patients experiencing virologic failure of indinavir and/or nelfinavir. This suggests that none of the single protease inhibitors would be effective after many cases of protease inhibitor failure. However, saquinavir, amprenavir, and indinavir blood levels are increased substantially when each is coadministered with ritonavir, with 12-h troughs exceeding corrected wild-type IC(95) by 2-, 7-, and 28-79-fold, respectively. These indinavir and amprenavir troughs exceed IC(95) for most protease inhibitor-resistant viruses tested. This suggests that twice-daily indinavir-ritonavir and, to a lesser extent, amprenavir-ritonavir may be effective for many patients with viruses resistant to protease inhibitors.*

### Reference

Condra et al. Drug resistance and predicted virologic responses to human immunodeficiency virus type 1 protease inhibitor therapy. *J Infect Dis* 2000;**182**:758-765.

### IDV 800 mg with RTV 200 mg q12h



## Saquinavir Intensification

Intensification with boosted saquinavir sgc for 18 patients failing saquinavir hgc regimen

- FTV 1600 mg daily + RTV 200 mg daily
- Baseline VL 957-8750 copies/mL
- Mean hgc exposure was 31 mo (24–48)
- Baseline trough concentration < IC<sub>90</sub> for wild-type in all

At 3 months

- 12 responders (VL < 200 copies/mL)
- Mean trough concentration ~ 0.4 ug/mL

Blanco et al. *Int Clin Pharmacol of HIV*, Noordwijk, April 2001.

Eighteen patients who were on saquinavir-hgc 600 mg TID with NRTI backbone were switched to saquinavir-sgc 1600mg/ritonavir 200 mg daily and continued on their backbone NRTIs for at least 3 weeks. Mean viral load at baseline was 3869 copies/mL, and mean time on saquinavir-hgc was 31 months (range 24–48 months). In all patients, trough levels of saquinavir were less than the published IC<sub>90</sub> for WT virus at baseline.

There were 12/13 responders at 3 months. Trough was 0.4157 ug/mL for those who were boosted.

These data suggest that in some cases, adding low-dose ritonavir may increase saquinavir concentrations sufficiently to allow for regained viral suppression.

### Reference

Blanco JL, Mallolas J, Sarasa M, et al. Intensification therapy with saquinavir soft gel/ritonavir QD in patients failing on a saquinavir hard gel containing HAART [abstract 5.8]. *2nd International Workshop on Clinical Pharmacology of HIV Therapy*, 2–4 April, 2001, Noordwijk, Netherlands.

## **Disadvantages of Ritonavir Boosted Regimens**

- May be higher risk of dose-related toxicities (eg, nephrolithiasis with indinavir) of target drug
- Risk of additive PI toxicities (especially GI, lipids, liver)
- Wide-ranging interactions with other classes of drugs (eg, antidepressants, psychotropics, lipid-lowering)
- PI levels can still be decreased by inducers if ritonavir dosage is not high enough

## Boosted PI Regimens plus NNRTIs

	+ <u>Efavirenz</u>	+ <u>Nevirapine</u>
<i>Indinavir 800 mg/ritonavir 100 mg BID:</i>		
IDV C <sub>min</sub>	48% ↓	75% ↓
C <sub>max</sub>	13% ↓	25% ↓
AUC	19% ↓	
<i>Lopinavir 400 mg/ritonavir 100 mg BID:</i>		
LPV C <sub>min</sub>	44% ↓	55% ↓
C <sub>max</sub>	19% ↓	14% ↓
AUC	25% ↓	22% ↓

Aarnoutse et al, [abstract 423]. Bertz et al, [abstract 424]. *40th ICAAC*, September 2000, Toronto, Ontario.  
 Burger et al, [abstract 824]. *7th ECCAT*, October 1999, Lisbon, Portugal.  
 Kaletra Monograph, 2000.

*Indinavir/ritonavir + efavirenz.* When efavirenz was added to indinavir 800 mg/ritonavir 100 mg BID regimen, indinavir exposure was significantly reduced (19% ↓ AUC, 48% ↓ C<sub>min</sub>). C<sub>min</sub> were still >0.1 mg/L but caution should still be used with this combination, especially in advanced patients. May wish to consider increasing to indinavir 800 mg/ritonavir 200 mg BID with efavirenz.

With indinavir/ritonavir QD regimens, coadministration of efavirenz significantly lowers indinavir and ritonavir concentrations. Avoid using efavirenz with once-daily indinavir/ritonavir regimens until further data available.

*Indinavir/ritonavir + nevirapine.* In observational series, nevirapine 400 mg/day combined with indinavir 800 mg/ritonavir 100 mg BID resulted in 75% ↓ indinavir C<sub>min</sub>, 75% ↓ ritonavir C<sub>min</sub>; in all cases, indinavir C<sub>min</sub> remained >0.1 mg/L, but caution is still warranted with combination, especially in advanced patients.

*Lopinavir/ritonavir + efavirenz.* Efavirenz 600 mg daily + lopinavir 400 mg/ritonavir 100 mg BID resulted in 25% ↓ AUC and 44% ↓ C<sub>min</sub> of lopinavir. Using lopinavir 533 mg/ritonavir 133 mg BID plus EFV resulted in similar lopinavir concentrations to those achieved in the absence of EFV.

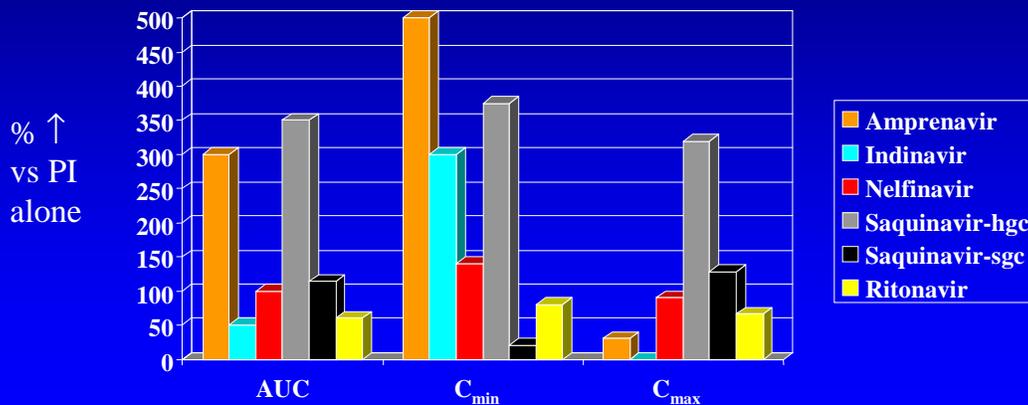
*Lopinavir/ritonavir + nevirapine.* Potential for reduced lopinavir concentrations; suggest using increased dose (lopinavir 533 mg/ritonavir 133 mg BID) with concomitant nevirapine.

### References

1. Aarnoutse R E, Burger DM, Hugen PWH, et al. A pharmacokinetic study to investigate the influence of efavirenz on a BID indinavir 800 mg/ritonavir 100 mg in healthy volunteers [abstract 423]. *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 17-20 September, 2000 Toronto, Canada.
2. Bertz R, Lam W, Hsu A, et al. Assessment of the pharmacokinetic interaction between ABT-378/ritonavir and efavirenz in healthy volunteers and in HIV+ subjects [abstract 424]. *40th Interscience Conference on Antimicrobial Agents and Chemotherapy*, 17-20 September, 2000 Toronto, Canada.
3. Burger D, Hugen P, Aarnoutse R, Reiss P, Lange J. Indinavir + ritonavir BID regimens: pharmacokinetics, safety and efficacy [abstract 824]. *7th European Conference on Clinical Aspects and Treatment of HIV Infection*, 23-27 October, 1999, Lisbon, Portugal.
4. Kaletra monograph, 2000.
5. Saah A, Winchell G, Rhodes R, Nessly M, Deutsch P. Multiple-dose pharmacokinetics and tolerability of indinavir with ritonavir and efavirenz combinations in a once-daily regimen in healthy volunteers (Merck 093) [P284]. *5th International Congress on Drug Therapy in HIV Infection*, 22-26 October, 2000, Glasgow, Scotland.

## Effect of Delavirdine on PI Concentrations

- In contrast to other NNRTI agents, delavirdine is a CYP3A4 inhibitor, and will enhance PI levels



Tran et al. *Clin Pharmacokinet* 2001;40:207-226.

Besides using dual PI combinations, other agents with enzyme inhibiting properties may also increase PI concentrations.

One such agent is delavirdine, which is a potent inhibitor of CYP3A4.

- Advantages of combining delavirdine with a PI include

- improved PI bioavailability
- possibility of simplified dosing regimens
- ability to use lower PI doses
- pharmacodynamic/virological advantage of using two agents with different mechanisms of action.

*DLV + indinavir.* With IDV 600 mg q8h + DLV, IDV AUC and C<sub>min</sub> vs values obtained with IDV 800 mg q8h alone. Thus, use IDV 600 mg q8h with delavirdine.

*DLV + nelfinavir.* DLV 600 mg TID + standard NFV results in approximately 2-fold increase in NFV AUC, and DLV C<sub>min</sub> similar to that with DLV 400 mg TID alone. Recommendations on dosage adjustments not available. Use together with caution and monitor for drug toxicities, including neutropenia. Regimens currently being studied: NFV 750 mg TID + DLV 600 mg TID, and NFV 1250 mg BID + DLV 600 mg BID.

*DLV + ritonavir.* 70% increase in RTV concentrations; kinetics of delavirdine and its metabolite unchanged. Recommendations on dosage adjustments not available.

*DLV + Saquinavir.* 5-fold increase in SQV C<sub>min</sub>; monitor LFTs during initial weeks of combination therapy. Dosage adjustments not necessary.

### Reference

Tran JQ, Gerber JG, Kerr BM. Delavirdine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2001;40:207-226.

## Delavirdine Boosted Regimens (cont'd)

- Advantages
  - using 2 different antiviral classes at therapeutic dosages
  - pharmacokinetic enhancement of PI
  - simplified dosing frequency of both drugs
  - less potential for overlapping toxicities (ie, metabolic disorders)
- Disadvantages
  - often high pill burden

## **Boosted Regimens — Summary**

- Variety of strategies and agents available
- Can manipulate dose as well as choice of boosting agent to achieve optimal balance between
  - enhanced kinetics/efficacy
  - improved convenience and adherence
  - minimized toxicity

## Undesirable Antiretroviral Interactions

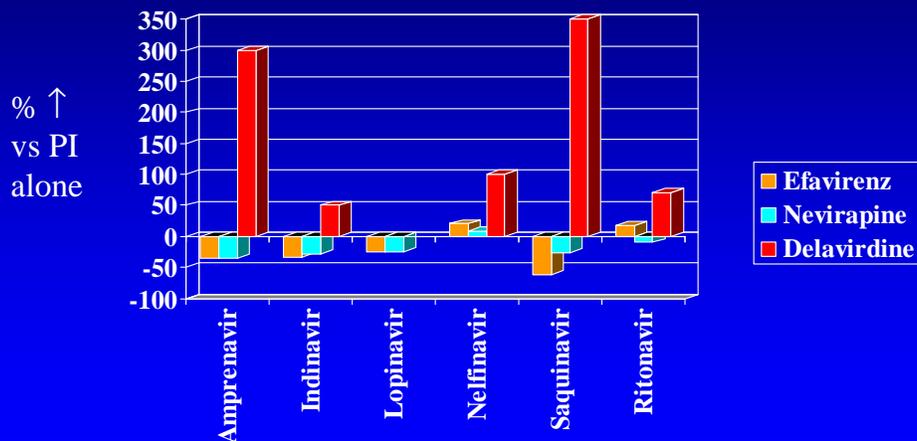
- Decreases drug concentrations via metabolic induction
  - may lead to decreased antiviral activity, development of resistance
- Increases drug concentrations
  - may lead to increased risk of drug toxicity

Achieving adequate drug concentrations is a very significant factor in determining the success or failure of highly active combination antiretroviral therapy.

In a case series of high-dose saquinavir monotherapy, increases in viral load were apparent when drug therapy was interrupted for as few as 3 days.

Preliminary reports also suggest that adequate PI exposure may be an independent factor in long-term virological response.

## PI-NNRTI Combinations: Effect on PI AUC



In contrast to delavirdine, nevirapine and efavirenz are both potent CYP inducers, and may adversely affect PI concentrations. In such cases, options include:

- increasing the PI dosage (NB: extra cost and inconvenience of additional pills)
- switching from one PI to another (eg, switching from saquinavir to a PI whose levels are not as adversely affected)
- switching from one NNRTI to another (eg, substituting delavirdine for nevirapine or efavirenz).

## Antiretrovirals + MAC/TB Agents

- *Rifampin*
  - 35–99% ↓ in antiretroviral concentration
  - DLV > SQV, NFV, IDV, AMP, LPV/r > RTV, NVP
  - AVOID combination
- *Rifabutin*
  - AVOID with SQV, DLV (40–60% ↓)
  - dose adjustment: NFV, IDV, LPV/r
  - caution: RTV

Rifamycins are potent hepatic enzyme inducers (rifampin more potent than rifabutin).

PI	Rifabutin	Rifampin
Amprenavir, 141W94	14% ↓ amprenavir, 3–6 fold ↑ rifabutin C <sub>min</sub> . Decrease dose of rifabutin to avoid toxicity.	81% ↓ AUC and 91% ↓ C <sub>min</sub> of amprenavir. <b>Avoid combination.</b>
Indinavir (Crixivan®)	150 mg rifabutin + indinavir: 155% ↑ rifabutin AUC, 33% ↓ indinavir AUC. <b>Thus, ↑ indinavir to 1000 mg q8h and ↓ rifabutin to 150 mg daily.</b>	May reduce indinavir concentrations. <b>Avoid combination.</b>
Nelfinavir (Viracept®)	32% ↓ nelfinavir AUC, 3-fold ↑ rifabutin AUC. Reduce rifabutin dose by 50%.	82% ↓ nelfinavir AUC. <b>Avoid combination.</b>
Ritonavir (Norvir®)	400% ↑ rifabutin AUC, risk of toxicity. <b>Avoid combination.</b>	35% ↓ ritonavir AUC. May need to ↑ ritonavir dose.
Saquinavir (Invirase®, Fortovase®)	40% ↓ saquinavir AUC. <b>Avoid combination</b> if possible, or ↑ saquinavir dose.	80% ↓ saquinavir AUC. <b>Avoid combination.</b>
NNRTI		
Delavirdine (Rescriptor®)	50–60% ↓ delavirdine concentrations (not adequately compensated with 600 mg TID dose); also >200% ↑ rifabutin AUC. <b>Therefore, avoid concomitant use.</b>	Virtually undetectable delavirdine concentrations; <b>combination contraindicated.</b>
Efavirenz (Sustiva®)	Potential for ↓ efavirenz concentrations and ↑/↓ rifabutin concentrations.	26% ↓ efavirenz concentrations; clinical significance unknown. Rifampin dosage adjustment not required.
Nevirapine (Viramune®)	16% ↓ nevirapine concentrations.	37% ↓ nevirapine concentrations.

## Anticonvulsant Interactions: PI–Carbamazepine (CBZ)

- *Therapeutic failure with indinavir*
  - 48-year-old male on AZT, 3TC, indinavir, VL<50, received CBZ 200 mg/d for post-herpetic neuralgia
  - IDV levels ↓ to 4–25% of mean population values, viral breakthrough occurred
- *Toxicity with ritonavir*
  - 70–85% increase in CBZ levels when RTV added to a pediatric patient stabilized on CBZ
  - separate case report of CBZ-related ataxia with combination

Report of antiretroviral failure with concomitant CBZ–indinavir therapy. ↓ IDV levels to 4–25% of mean population values. Patient later experienced viral breakthrough.<sup>1</sup>

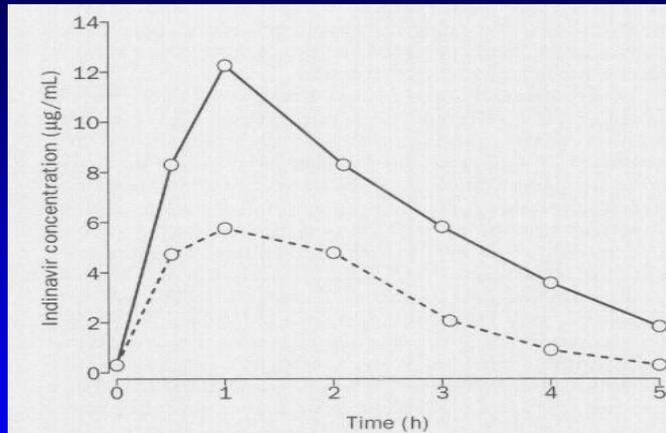
Addition of ritonavir (200–600 mg per day) to a pediatric patient stabilized on CBZ resulted in 70–85% ↑ serum CBZ levels. Ritonavir concentrations were not measured.<sup>2</sup>

Combination resulted in CBZ-related ataxia. Avoid combination if possible.<sup>3</sup>

### References

1. Hugen PWH, Burger DM, Brinkman K., et al. Carbamazepine-indinavir interaction causes antiretroviral therapy failure. *Ann Pharmacother* 2000;**34**:465-70.
2. Kato Y, Fujii T, Mizoguchi N, et al. Potential interaction between ritonavir and carbamazepine. *Pharmacotherapy* 2000;**20**:851-854.
3. Berbel GA, Latorre IA, Porta EJ, et al. Protease inhibitor-induced carbamazepine toxicity. *Clin Neuropharmacol* 2000;**23**:216-218.

## St John's Wort + Indinavir



- Indinavir AUC ↓ 57%
- Indinavir trough ( $C_{8h}$ ) ↓ by 81% (range 49–99%)
  - ie, ↓ by factor of 10 (0.49 ug/mL --> 0.048 ug/mL)

Piscitelli et al. *Lancet* 2000;355:547-548.

**Abstract:** *St John's wort* reduced the area under the curve of the HIV-1 protease inhibitor indinavir by a mean of 57% (SD 19) and decreased the extrapolated 8-h indinavir trough by 81% (16) in healthy volunteers. A reduction in indinavir exposure of this magnitude could lead to the development of drug resistance and treatment failure.<sup>1</sup>

- Case report of an HIV-infected patient receiving nevirapine as part of a combination regimen. Addition of *St John's Wort* caused a 20% ↓ in nevirapine  $C_{ss}$  vs historical data; Investigators suggest possible interaction due to CYP450 induction.<sup>2</sup>
- These findings, along with other interaction reports led to the issuing of an FDA Advisory:<sup>3</sup> *St John's Wort* should be *avoided* in patients taking indinavir as sole PI. It is also reasonable to avoid its use with other PIs and NNRTIs.
- The use of low-dose ritonavir may prevent interaction, but the optimal dosage has not yet been defined.

### References

1. Piscitelli SC, Burstein AH, Chait D, Alfaro RM, Falloon J. Indinavir concentrations and *St John's wort*. *Lancet* 2000;355:547-548.
2. de Maat MMR, Hoetelmans RMW, Van Gorp ECM, de Boer A, Beijnen JH. A potential drug interaction between *St. John's wort* and nevirapine? [abstract 2.8]. *1st International Workshop on Clinical Pharmacology of HIV Therapy*, 30-31 March, 2000, Noordwijk, Netherlands.
3. Food and Drug Administration. Risk of drug interactions with *St. John's wort*. *JAMA* 2000;283:1679.

## Drugs to Avoid or Use with Caution with PIs

- Non-sedating antihistamines
- Long-acting opiate analgesics
- Long-acting benzodiazepines
- Proton pump inhibitors
- Promotility agents
- Antiarrhythmics
- Calcium channel blockers
- Anticonvulsants
- Ergotamines and dihydroergotamine
- Illicit drugs
- Coumarin anticoagulants
- Oral contraceptives
- Lipid lowering agents (statins)

The non-sedating antihistamines **astemizole** (Hismanal) and **terfenadine** (Seldane) are substrates of CYP3A4. In the presence of CYP3A4 inhibitors, concentrations of these agents are significantly increased, and the risk of dose-related adverse events (including cardiotoxicity) is increased. Similar concern exists for **cisapride**. Therefore, use of these agents should be avoided in people currently taking medications that inhibit CYP450.

The metabolism of many **benzodiazepines** may be significantly reduced by the presence of CYP450 inhibitors. To minimize the risk of excessive sedation, practitioners may wish to consider reducing the benzodiazepine dose, or using an agent with a different metabolic pathway (eg, lorazepam, oxazepam, or temazepam).

**Calcium channel blockers** are primarily metabolized by CYP3A. Therefore, these agents should be used cautiously with inhibiting agents, to avoid excessive drops in blood pressure.

Many **antidepressants** are substrates of CYP2D6. They are at risk of interacting with agents that inhibit this isoenzyme; greatest precaution with ritonavir.

**Oral contraceptives** are glucuronidated. Significant reductions in ethinyl estradiol concentrations are seen in the presence of ritonavir or nelfinavir. Patients taking these agents should be counselled about using an alternative method of birth control, such as barrier contraception.

## Systematic Approach to Managing Drug Interactions

- *Obtain complete medication history*
  - include Rx, OTC, herbals, vitamins, recreational
  - categorize drugs by pharmacokinetic/dynamic properties
- *Identify potential conflicting combinations*
  - different absorption requirements
  - opposing/overlapping metabolic characteristics
    - CYP450 substrate, induction/inhibition

With new therapeutic agents continually being developed, keeping abreast of potential interactions is extremely challenging. Many antiretroviral agents may be administered via clinical trials or compassionate access programs before comprehensive interaction studies are conducted. Consequently, patients may receive combinations of drugs for which pharmacokinetic interaction data are not available.

In such situations, familiarity with the basic pharmacokinetic and pharmacodynamic characteristics of the involved agents may help practitioners predict the likelihood of interactions.

All PIs and NNRTIs are substrates of the cytochrome P450 system, and also possess enzyme inhibiting and/or inducing properties. Careful consideration of such information is crucial to anticipate possible interactions, and to optimize therapeutic efficacy and minimize drug toxicity.

## Systematic Approach to Managing Drug Interactions (cont'd)

- *Assess data in literature*
  - type of report, population studied, applicability to clinical practice
- *Assess clinical significance*
  - depends on magnitude of interaction, therapeutic indices of drugs, potential consequences (eg, impact on efficacy/toxicity)

Once the potential for a significant interaction has been identified, the clinical significance must be determined.

The clinical significance of an interaction will depend upon several factors, including:

- the magnitude of change in pharmacokinetic parameters
- the efficacy and toxicity of the affected agent(s).

As already discussed, achieving and maintaining adequate antiretroviral concentrations may play an important part in successful and durable viral suppression. Because the risk of cross-resistance is high with PIs and NNRTIs, subtherapeutic drug levels should be avoided, to minimize the risk of resistance developing.

In addition, the risk of drug toxicity may be higher with increased drug concentrations (eg, ritonavir, indinavir).

## Evaluate Therapeutic Alternatives

- Consider the following
  - mechanism, clinical consequences of interaction
  - availability, efficacy of therapeutic alternatives
  - patient convenience, cost
- Options may include
  - altering dose or dosing regimen
  - changing one or both drugs
  - increased monitoring

Management options may vary depending upon a number of factors, including the mechanism and clinical consequences of the interaction, availability of therapeutic alternatives, patient convenience, and cost.

*Space dosing times* (eg, separate delavirdine and ddI by 1 hour). Can this be done in a practical and/or convenient way for the patient?

*Change drug dose.* The potential impact of dosage manipulation on patient adherence should be carefully considered. This in turn may depend upon the drug formulations available, existing pill burden and dosing schedule, and cost. For instance, to adequately adjust for the interaction between indinavir and rifabutin, indinavir should be increased to 1 g every 8 hours and rifabutin should be decreased to 150 mg daily. This can be done with no additional dosing times and minimal increase in pill burden. On the other hand, the interaction between delavirdine and rifabutin is not as straightforward to manage. With standard doses of both agents, delavirdine concentrations are decreased by 50–60%. Even with a median delavirdine dose of 600 mg three times daily, trough concentrations are often still not adequate, and rifabutin concentrations are significantly elevated. In such situations, therapeutic alternatives to either delavirdine or rifabutin need to be considered.

*Change agent* (eg, change rifabutin to azithromycin for MAC prophylaxis). What are the comparative efficacy, side effects, cost, availability, compliance issues, and drug interactions associated with the new agent?

*Take no action.* In certain situations (eg, low likelihood of an interaction occurring, minor or insignificant clinical impact of a potential interaction) the practitioner may wish to maintain the patient's current regimen and monitor the patient's condition.

## Summary

- High potential for drug interactions with antiretroviral agents
- Consequences may include therapeutic failure and increased toxicity
- Use systematic approach to identify and manage individual drug regimens

# Case Study Review

## Case 1 – Ms MC

- MC is a 28-year-old female, newly Dx with HIV+
  - antiretroviral naïve, CD 408, VL 50,000 copies/mL
  - also has preexisting seizure Hx (Rx carbamazepine)
- Started on AZT, 3TC, nelfinavir
  - good initial response, but then viral load ↑ (interaction with anticonvulsant?)
  - genotype shows presence of D30N mutation
- Wishes to switch to boosted regimen
  - d4T, ddI, indinavir 800 mg/ritonavir 100 mg BID

MC likely is experiencing viral breakthrough because of subtherapeutic nelfinavir levels secondary to an interaction with her anticonvulsant.

- Carbamazepine is a potent CYP3A inducer, likely decreased nelfinavir.
- Emergence of D30N mutation supports likelihood of viral replication in presence of low nelfinavir concentrations.

MC's physician would like to change her regimen to one containing a boosted PI combination. This regimen has many advantages, including

- high likelihood of antiviral success (given that the D30N mutation has been associated with retained susceptibility to other PIs)
- greatly increased indinavir concentrations secondary to ritonavir inhibition
- potent antiviral activity
- BID dosing, fewer pills to take
- no empty stomach requirements for indinavir
- lower dose of ritonavir, better tolerated.

## Potential Interactions

- ddI–indinavir
  - absorption (pH) interaction
  - space doses apart by at least 1 hour
- Indinavir–carbamazepine
  - switch CBZ to another anticonvulsant
  - increase ritonavir to 200 mg BID
  - f/u with TDM?

### *Carbamazepine interaction*

There is still a potential for carbamazepine to interact with the new PI combination.

As mentioned previously in this presentation, carbamazepine has been shown to decrease indinavir concentrations, while ritonavir has been shown to increase carbamazepine levels.

There are a variety of potential outcomes associated with combining carbamazepine with indinavir 800 mg/ritonavir 100 mg BID. In other words:

- carbamazepine could decrease indinavir and/or ritonavir levels
- ritonavir could increase carbamazepine concentrations.

When this combination of indinavir/ritonavir has been administered with other enzyme inhibitors, such as efavirenz or nevirapine, the net effect observed was a decrease in indinavir concentrations. This suggests that ritonavir doses of 100 mg BID may not be sufficient to counteract the effects of concomitant enzyme inducers.

Therefore, one might anticipate that carbamazepine could exert a similar effect on indinavir concentrations.

To avoid this potential outcome, clinicians may consider one or more of the following options:

- switch carbamazepine to an anticonvulsant without CYP450 inducing properties
- increase ritonavir dosage to 200 mg BID (keep indinavir 800 mg BID)
- monitor carbamazepine levels for possible toxicity
- monitor PI concentrations.

## Case 2 – Mr JS

- JS is a 38-year-old male, former IDU, HIV+ for 3 years
  - CD4 300, viral RNA 30,000 copies/mL
- Has been stable on methadone DOT x 1 year
- Decided he was ready to initiate antiretrovirals, and started on Combivir, nelfinavir 1 week ago

This patient is a former injection drug user (IDU) who tested HIV-positive approximately 3 years ago. He initially declined antiretroviral therapy, but has now been stable on methadone maintenance for the past year, and feels ready to initiate HAART.

JS's physician decided to start him on a combination of zidovudine, lamivudine (as Combivir) and nelfinavir.

What potential interactions might one anticipate with this regimen?

## Potential Methadone Interaction?

- In one case series (n=14), nelfinavir shown to decrease methadone levels by 29–47%
  - however, no Sx withdrawal noted in any of subjects
- Clinical significance
  - expect ↓ levels within 1–2 weeks after starting ARVs
  - patient already on ARVs for 3 weeks; no signs of methadone withdrawal
  - therefore, methadone dose may not need adjusted

Methadone is partly metabolized by CYP3A and glucuronyl transferase. While nelfinavir is a CYP3A inhibitor, it also induces the activity of glucuronyl transferase. In clinical practice, 29–47% ↓ methadone concentrations have been noted when nelfinavir was given to patients on stable methadone dosages. However, no symptoms of methadone withdrawal were observed in these subjects.

Monitor for symptoms of methadone withdrawal; adjustment of methadone dosage may be necessary.

### References

1. Hsyu PH, Lillibridge JH, Maroldo L, Weiss WR, Kerr BM. Pharmacokinetic and pharmacodynamic interactions between nelfinavir and methadone [abstract 87]. *7th Conference on Retroviruses and Opportunistic Infections*, 30 January–2 February, 2000, San Francisco, California.
2. Beauverie P, Taburet AM, Dessalles MC, Furlan V, Touzeau D. Therapeutic drug monitoring of methadone in HIV-infected patients receiving protease inhibitors. *AIDS* 1998;**12**:2510-2511.

## Case 3 – Mr GM

- Mr GM is a 53-year-old male, HIV+ for 9 years
  - CD4 <10, viral RNA 100,000 copies/mL
- Extensive antiretroviral treatment including AZT, ddC, ddI, 3TC, indinavir, nelfinavir
- GM's physician has prescribed a regimen of d4T, abacavir, 3TC, amprenavir 750 mg BID, lopinavir/ritonavir 400/100 mg BID, efavirenz
  - also on fenofibrate, pravastatin, TMP/SMX, acyclovir, fluconazole

## Three Weeks Later ...

- TDM reveals low amprenavir and lopinavir levels
- Viral load started to ↓ fall, but lipid levels ↑↑
- Management options
  - ↑ amprenavir, lopinavir/r dosages
  - add extra ritonavir
    - both options may further exacerbate lipids, other toxicities
  - replace efavirenz with delavirdine
    - still including full-dose NNRTI in regimen
    - because delavirdine is an enzyme inhibitor, will boost PI levels without risk of significantly increasing lipids

## Case 4: Problem Solving

- Patient started on zidovudine, 3TC, lopinavir/ritonavir 400 mg/100 mg BID
- What if the patient ...
  - requires an antidepressant?
  - requires a sleeping pill?
  - requires MAC prophylaxis?
  - wants to use Viagra?

Patient started on following regimen:

- zidovudine 300 mg BID
- 3TC 150 mg BID
- lopinavir 400 mg/ritonavir 100 mg BID.

At initial counselling session, no issues identified; patient motivated to be on regimen.

Over the course of the next few months, different therapeutic issues develop.

Need to constantly reassess for potential drug interactions!

## What If ... Patient Wants To Take Zyban (bupropion)?

- *Bupropion is a substrate of CYP2B6*
  - in vitro data show that ritonavir, efavirenz, and nelfinavir can inhibit CYP2B6
- Although the amount of ritonavir contained in Kaletra formulation is relatively low, still potential for interaction
- Use combination with caution, monitor for bupropion toxicity, may need to ↓ dose

Many antidepressants have narrow therapeutic windows, so careful attention to dosing is required.

Many agents in this class are primarily substrates of CYP2D6, for example,

- TCAs: amitriptyline, nortriptyline, desipramine, imipramine
- SSRIs: fluoxetine, fluvoxamine, paroxetine.

However, bupropion is a substrate of CYP2B6. In vitro experiments have shown that ritonavir, efavirenz and nelfinavir can inhibit CYP2B6; therefore, the potential exists for interactions with bupropion. **Indinavir, saquinavir and amprenavir** were only weakly inhibitory of bupropion; hence no or only minor increase in bupropion levels anticipated.<sup>1</sup>

Similar caution should be used when giving bupropion with lopinavir/ritonavir.

### Reference

1. Hesse LM, von Moltke LL, Shader RI, Greenblatt DJ. Ritonavir, efavirenz, and nelfinavir inhibit CYP2B6 activity in vitro: potential drug interactions with bupropion. *Drug Metab Dispos* 2001;**29**:100-102.

## What If ... Patient Requires a Sedative?

- *Benzodiazepines*
  - majority are substrates of CYP3A4
  - thus, a patient is at risk for prolonged/excessive sedation
- Reduce BZD dose and monitor
- Use BZD that are glucuronidated (lorazepam, oxazepam, temazepam)

The majority of benzodiazepines are substrates of CYP3A4, and hence are susceptible to interactions with CYP3A4 inhibitors.

Significantly elevated benzodiazepine concentrations may result in prolonged or excessive sedative effects.

Therefore, a reduced benzodiazepine dose should be used, with further dosage adjustments depending upon efficacy or toxicity.

An alternative is to use a benzodiazepine which undergoes a different route of metabolism; oxazepam, lorazepam, and temazepam undergo glucuronidation, and may be less susceptible to inhibition interactions.

## What If ... Patient Requires MAC Prophylaxis?

- *Rifabutin*
  - is a substrate and inducer of CYP3A4
  - lopinavir/r significantly ↑ concentrations of rifabutin and its metabolite: risk of toxicity
  - need to ↓ rifabutin dose by 75% (ie 150 mg 2–3 times/week)
- Consider using *azithromycin* which does not induce CYP3A4 enzymes

With concomitant administration of rifabutin and lopinavir/ritonavir:

5–6-fold ↑ rifabutin + metabolite AUC; rifabutin 150 mg daily had no significant effect on lopinavir/r concentrations. Reduce rifabutin dosage by at least 75% (ie, max. 150 mg q2d or 3 times/week); monitor for adverse events and further decrease rifabutin dose if necessary.

Azithromycin 1250 mg once weekly is a suitable alternative to rifabutin for the indication of MAC prophylaxis. Azithromycin does not affect the cytochrome P450 system, and therefore should not affect lopinavir concentrations.

## What If ...Patient Wants To Use Viagra?

- Sildenafil
  - substrate of CYP3A4
  - potential for lopinavir/r to ↑ sildenafil concentrations
  - dose-related side effects (H/A, vasodilation, etc)
- Start with lower sildenafil dose (ie, 25 mg every 48 hours, titrate accordingly)

Sildenafil is the first oral phosphodiesterase inhibitor approved for the treatment of erectile dysfunction. Kinetics:

- substrate of CYP3A4; minor route of metabolism: CYP2C9
- weak inhibitor of CYP1A2, 2C9, 2C19, 2D6, 2E1, 3A4; unlikely to alter clearance of other drugs metabolized via these pathways
- usual dose 25–100 mg/day (for most patients, recommended dose is 50 mg, taken 1 hour (range 0.5–4 hours) before sexual activity; side effects (dose-related): headaches, vasodilation, dyspepsia, visual disturbances.

Drug interactions studied with the following PIs:

- *Indinavir* — 4.4 fold ↑ sildenafil concentrations (ie, plasma levels greater than that achieved with 100 mg sildenafil dosed alone); effects of sildenafil persisted up to 72 hours post-ingestion in some subjects
- *saquinavir* — 140% increase in  $C_{max}$  and a 210% increase in sildenafil AUC; no effect on saquinavir pharmacokinetics
- *ritonavir* — 300% (4-fold) increase in sildenafil  $C_{max}$  and a 1,000% (11-fold) increase in sildenafil plasma AUC. At 24 hours the plasma levels of sildenafil were still ~200 ng/mL, compared to approximately 5 ng/mL when sildenafil was dosed alone.

Also potential for interactions with other PIs. Therefore, may wish to suggest lower dose (ie, 25 mg every 24–48 hours) and adjust according to efficacy/toxicity.

## Summary

- Important to individualize therapy
- Adequate drug concentrations and combinations maximize treatment
- Weigh drug effects on cytochrome P450 system
- Consider absorption effects
- Monitor combined effects of non-antiretroviral drugs

## Additional Resources

- **General**
  - Bertz et al. *Clin Pharmacokinet* 1997;**32**:210-258.
  - Hansten PD. *Science Med* 1998:16-25.
- **Interactions in HIV**
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