

Drug Interactions

Objectives



1. Describe the important drug interactions between different ARVs and discuss the significance of these interactions
2. List the toxicities and common side effects of each drug
3. Discuss monitoring and management of toxicities and side effects
4. Describe class adverse drug reactions, including class-specific and ARV-specific adverse effects of ART

Introduction



- Pharmacokinetic interactions occur when one drug alters the serum or tissue concentration of another by changing its absorption, metabolism, or elimination
- This can lead to significant changes in drug concentration
 - In ARV context, too high of a drug concentration leads to increased toxicity
 - Too low of a drug concentration may lead to resistance or, in the case of antibiotics, decreased clearance of infection

Changes in Drug Absorption



- **Alterations of gastric pH**

- If a drug changes the gastric pH, it can affect the absorption and thus concentration of other drugs that have specific pH requirements for absorption

- * Atazanavir is not absorbed well on empty stomach nor in presence of antacids or H₂ blockers

- Contraindicated with proton pump inhibitors

- **Presence or absence of food**

- Food can enhance or decrease the bioavailability of a drug--often because of gastric acidity

- * Some drugs, such as ddI and IDV, must be administered one hour before or two hours after eating

- **Chelation**

- Binding of two drugs/compounds to form insoluble complexes that cannot be absorbed—this changes absorption of a drug

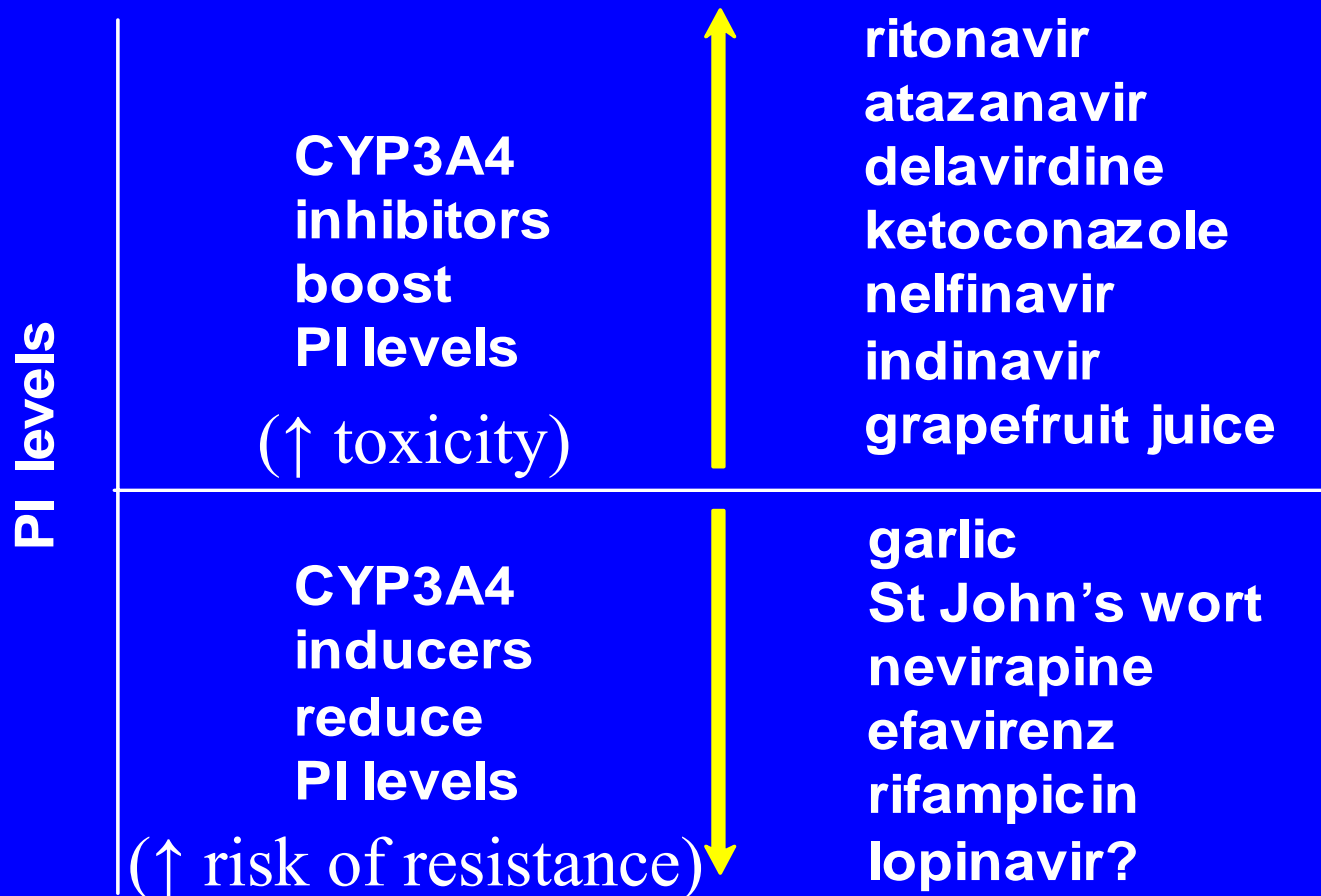
Changes in Metabolism



Metabolism in the liver cytochrome P450 system

- The induction or inhibition of various P450 enzymes by one drug can significantly alter the serum concentration of another drug that is metabolized by the same P450 enzyme
- PIs and NNRTIs, and some drugs to treat OIs are primarily metabolized by the same P450 CYP3A4 isoenzyme and can inhibit or induce this isoenzyme.
- *Inhibitors* of P450: INCREASE drug levels of other drugs that are metabolized by it
- *Inducers* of P450: DECREASE other drug levels
 - (think: INDUCE → REDUCE)

Effect of drugs on PI concentration



Changes in Metabolism, continued



- Each PI and NNRTI has a different drug interaction profile, depending primarily on its potency as an inducer or inhibitor of CYP3A4 and/or other P450 enzymes
 - Ritonavir is the most potent CYP3A4 inhibitor and consequently has the most drug interactions and contraindications
 - * This effect can be desirable in boosting levels of other PIs
 - NVP is a CYP3A4 inducer
 - EFV is both an inducer and inhibitor of CYP3A4
 - Rifampicin is a potent inducer
 - * significantly decreases the concentration of PIs to subtherapeutic levels

Changes in Metabolism, continued



- NFV and the NNRTIs can significantly decrease the estrogen levels in contraceptives.
 - Women taking these drugs cannot rely on oral contraceptives for contraception (use other method like condoms)
- PIs and EFZ
 - raise levels of cisapride and non-sedating antihistamines (astemizole, terfenadine) which can lead to cardiotoxicity.
 - Increase levels of benzodiazepines, and this can result in prolonged sedation. Therefore, PIs and these other drugs should not be administered together.

ARV Interactions



- Do not give Indinavir (Crixivan[®]) and Nelfinavir (Viracept[®]) with:
 - Rifampicin (Rifadine[®])
 - Terfenadine (Triludan[®])
 - Astemizole (Hismanal[®])
 - Cisapride (Cyprid[®], Prepulsid[®])

Interactions with Ritonavir



Do not use ritonavir with:		Possible Alternatives	
Generic name	Brand name	Generic name	Brand name
piroxican	Feldene®	Aspirin	
auriodarone	Cordarone®		
artemizole	Hismanal®	loratidine	Claritin®
terfenadine	Triludan®		
cisapride	Prepulsid®		
alprazolam	Xanax®	temazepam	Euhypnos®
chlorazepate	Tranxene®	lorazepam	Temesta®
DIAZEPAM	Valium®		
MIDAZOLAM	Dormicum®		
triazolam	Halcion®		

Other interactions to remember



- Do not give ketoconazole with NVP
 - Use fluconazole instead
- Avoid use of stavudine (d4T) and AZT simultaneously (antagonistic)
- d4T and ddl
 - Additive toxicities of lactic acidosis, pancreatitis and peripheral neuropathy
 - Use only when no other options available
- When using TDF and ATV, need to boost ATV with RTV

Protease inhibitors and anti-tuberculous treatment



- Rifampicin, an integral part of anti-TB treatment, is a potent inducer of P450
 - Reduces the levels of PIs and NNRTIs
 - * Implications for resistance
 - Major reason why TB should be treated before starting ARVs
 - EFV at 800 mg qhs or SQV/RTV 400/400 mg BD are only approved agents amongst NNRTI and PIs
- Rifabutin has fewer interactions but is MUCH more expensive than rifampicin

ARV Dosage Adjustments due to Elimination Changes



- Adapt ARV dose because of renal dysfunction
- Calculate Glomerular Filtration Rate
- Reduce dosing of ddl, d4T, TDF, 3TC/FTC based on GFR

(all renally excreted drugs)

- No need to reduce dosing of EFV, NVP, ABC, PIs

(all liver metabolized drugs)

- Try not to give ddl and TDF together.

Summary



- Many ARVs interact with other ARVs as well as other medications and nutrients
 - Check for interactions before prescribing new medications, including therapies for intercurrent illness
 - Patients may get medications from other clinicians, some of whom don't know the patients are on ARVs or don't know about interactions
- Check labs from previous visits for changes and abnormalities
 - They may be related to drug interactions
- Drug interactions may lead to increased toxicities or reduced effectiveness of medications
 - Implications for resistance in the ARV context
- If you don't know if a new drug interacts with current medications, **LOOK IT UP!**