

KITSO AIDS Training Program

Lecture 8:

Drug-Drug Interactions in ARV Therapy

Drug Interactions

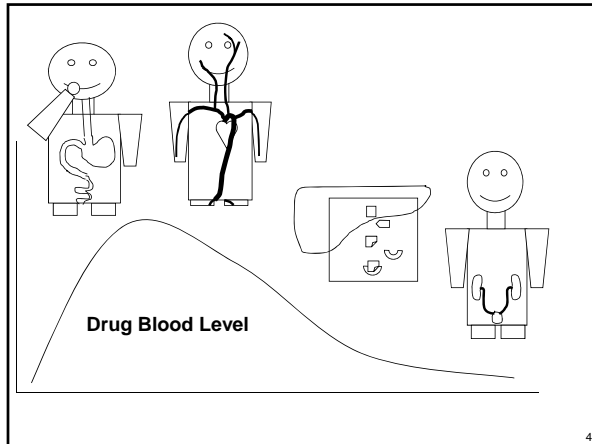
- Potential for drug interactions is significant in the HIV infected patient, *especially the interactions between rifampicin and protease inhibitors.*
- Drug interactions may be an important cause of treatment failure.
- Overlapping toxicities may increase the risk of adverse events.
- Beneficial drug interactions are increasingly being used to enhance efficacy and to reduce toxicity.

2

Drug Therapeutics

- In order for any drug, including ARVs, to exert a therapeutic effect, the blood and tissue level of that drug must be at a certain therapeutic level over a certain period of time.
- If the blood and tissue levels of ARVs are not at therapeutic levels, viral replication will not be suppressed, viral load will increase, and treatment failure will eventually result.

3



NRTI/NtRTI Metabolism

- NRTI/NtRTIs are cleared through the kidneys, *except for ABC*, which undergoes hepatic metabolism.
- Except for **ABC**, dose adjustment of NRTI/NtRTIs is necessary in patients with significant renal failure.
- Consult with pharmacist or HIV Specialist concerning dose adjustment.

5

NRTI Doses with Renal Insufficiency

- As a rule, all NRTIs, excluding ABC, require dose-reduction with renal insufficiency, but there are sparse data on this subject for the African setting. At baseline, many African patients with advanced or severe immunodeficiency have mild to moderate renal insufficiency, *which usually improves significantly over time on HAART prescribed at standard ARV dosages.*
- Although some authorities permit use of reduced TDF doses with baseline $C_{Creat} < 60$ cc/minute, this approach is not recommended, because of the risk of adherence problems with every 48 or 72 hour TDF dosing schedules for renal insufficiency. TDF should not, as a rule, be initiated when baseline C_{Creat} is < 60 cc/minute.
- All patients with baseline $C_{Creat} < 30$ cc/minute, or who are on dialysis, must be discussed with an HIV Specialist before initiating NRTIs, excluding ABC.

6

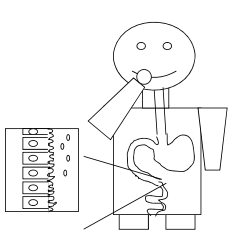
**NRTI Doses
with Renal Insufficiency (2)**

- Patients with baseline C_{Creat} between 30 and 90 cc/minute may be initiated on standard doses of NRTIs, but require follow-up C_{Creat} in three months. If follow-up C_{Creat} has not improved compared to baseline, then an HIV Specialist must be consulted for possible dose reduction of the NRTIs.
 - If any NRTI is prescribed at a lower dose due to renal insufficiency, *it is imperative to monitor C_{Creat} at every three month intervals*, until the clearance has increased to > 50 cc/minute, *at which point the NRTI dose(s) must be increased to standard levels*. Failure to do so risks ARV under-dosing, with subsequent risk of treatment failure.

7

Absorption

Gastrointestinal pH

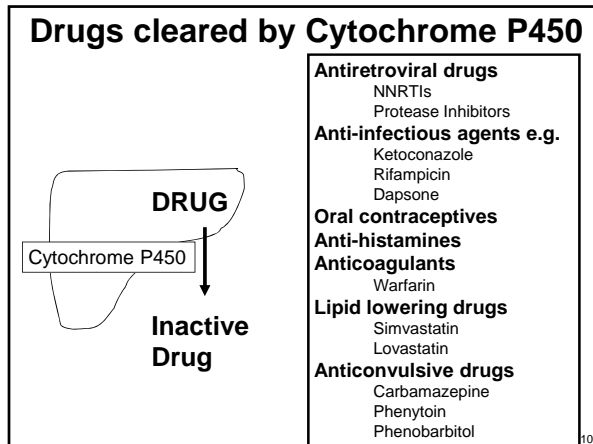


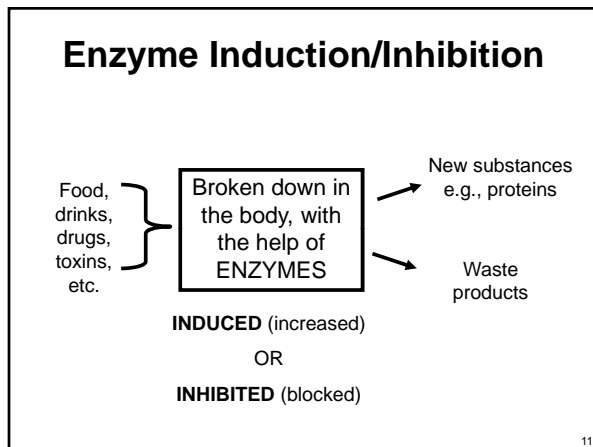
Acid environment:
LPV/r as “Kaletra”
(LPV/r as “Aluvia” tablets
is food-independent.
Pediatric liquid LPV/r
must always be taken
with food.)

Neutral environment:
ddl
(with food, **ddl** absorption
is *decreased by up to
50%*).

8

**Interactions between
ARV Drugs and
other Drugs**





Hepatic Metabolism of Drugs

- The liver's metabolism of drugs is not at a fixed rate, and can vary from drug to drug, from person to person, and *even within the same person*.
- One of the things which can increase or decrease the rate of the liver's metabolism of a given drug is other drugs.
- Many drug-drug interactions involve the way one drug affects the liver's metabolism of another drug.

Enzyme Induction/Inhibition

- Drugs such as *rifampicin* and *nevirapine* **induce** (activate) the P450 enzyme system and therefore **increase** the liver's metabolism of other drugs that are metabolized by the P450 enzyme system, thereby decreasing their plasma level more rapidly over time.
- Drugs such as *protease inhibitors*, especially **RTV**, **inhibit** (suppress) the P450 enzyme and therefore **decrease** the liver's metabolism of drugs that use the P450 enzyme system, thereby keeping their plasma level higher for a longer period of time.

13

NVP Drug Interactions

Drug	NVP Interaction	Comment
Rifampicin	NVP ↓	Dose adjustment of NVP is usually not necessary.
Oral Contraceptives	O/C ↓	Use alternative or additional contraception* *Depo-provera is not affected by this drug interaction, and may be used.
Ketoconazole	NVP ↑, Keto ↓	Not recommended for more than 1-2 weeks use. Try to use alternative antifungal drug
Ergotamine Compounds	Increased ergotamine levels	CONTRAINDICATED

4

EFV Drug Interactions

Drug	EFV Interaction	Comment
Rifampicin	EFV ↓	No dose adjustment of EFV
Ergotamine compounds: ergotamine levels increased, with risk of vascular events		CONTRAINDICATED
Carbamazepine: decreased levels of both drugs		CONTRAINDICATED
Clarithromycin: increased risk of rash and GI side effects		CONTRAINDICATED (use azithromycin instead)

15

Variability of Drug Interactions

- Individual patient variability of drug metabolism is due to unique individual host genetics, and can determine whether or not a particular drug interaction will be clinically significant.
- Thus, although interaction between rifampicin and **NVP** or **EFV** is usually not clinically significant for most patients, there may be an infrequent patient for whom this interaction is clinically significant, such that the NNRTI blood level is lowered to the point that treatment failure may result. Consult an HIV Specialist when such interaction is suspected.
- However, the interaction of rifampicin with all PIs is always clinically significant, as below.

16

Protease Inhibitor Drug Interactions

Drug	Interaction	Comment
Rifampicin	PI ↓	Dose increase of PI is required
Ketoconazole	RTV: Keto ↑	Do not exceed Keto dose of 200 mg OD
Oral Contraceptives	O/C ↓ or ↑	RTV: Use alternative or additional contraception, e.g., depo-provera
Ergotamine compounds St John's Wort lovastatin, simvastatin*		CONTRAINDICATED re: PI-mediated increase of drugs/agents to toxic levels

*Pravastatin and low-dose atorvastatin can be used safely with protease inhibitors.

17

NRTI Drug Interactions

AZT	Do not combine with d4T (Intracellular competition negates anti-HIV effects).
ddl	Differing absorption requirements with PIs
3TC	No significant drug interactions
D4T	Do not combine with AZT .

18

**Interactions Between
 ARVs and Seizure Medications**

- Carbamazepine and **EFV** lower each other's blood levels, and their concomitant use is not advised.
- Phenytoin and phenobarbital:
 - Potent inducers of hepatic metabolism
 - Their effects on ARV levels are largely unknown.
 - ARVs may increase (with PIs) or decrease (with NNRTIs) the levels of these seizure medications.
 - No specific dosing recommendations for ARVs used along with these medications, but monitor viral load more closely and more frequently. If failure occurs, discuss with an HIV Specialist.
 - Closely monitor phenytoin or phenobarbital levels, if possible, or consider empiric increase in dose if breakthrough seizures occur. Consider switch to valproic acid.

19

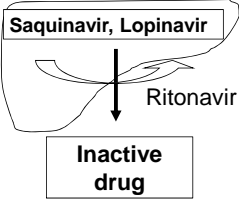
**Interactions between
 ARV Drugs**

Interactions between ARV drugs

Drug Combinations	Comments
NRTI combinations	Do not combine AZT and d4T, as above
NRTI + NNRTI	No significant interactions
NRTI + PI	ddl + "Kaletra" : different optimal absorption environments (potential problem re: pediatric adherence)
PI combinations	Possible pharmacological enhancement

21

PI Boosting



A diagram showing a box labeled "Saquinavir, Lopinavir" with an arrow pointing down to a box labeled "Inactive drug". A hand labeled "Ritonavir" is shown holding the arrow, indicating inhibition of the conversion process.

Among PIs, RTV is the most potent inhibitor of the P450 enzyme system.

A low, non-therapeutic dose of **RTV** ("r") will increase **SQV** and **LPV** from ineffective, sub-therapeutic levels to highly potent levels.

22

PI boosting (2)

- The combination **SQV/r** or **LPV/r** has multiple benefits:
 - Reducing pill burden and dosing frequency
 - Improving medication adherence
 - Improving PI potency, overcoming PI resistance
 - Reducing risk of toxicity
 - Reducing cost

23

Interactions of Anti-TB Treatment and ARV Therapy

Anti-Tuberculosis Agents and ARVs

Rifampicin

- Rifampicin is a highly potent P450 inducer, and lowers plasma levels of both NNRTIs and PIs.
- **NNRTI** levels are lowered by 30-37%; this reduction is usually not clinically significant. However, there may be occasional patients in whom rifampicin lowers the blood level of **NVP** or **EFV** to a much greater extent, such that treatment failure could result (consult an HIV Specialist).
- Rifampicin lowers PI levels 75-90%, an interaction which is highly significant, and can cause treatment failure.

25

Anti-Tuberculosis Agents and ARVs (2)

Favorable clinical experience:

- 2 NRTIs + **EFV** (600 mg OD) or **NVP** (200 mg BD)
+ Rifampicin-containing ATT

(2008 Guidelines no longer recommend 800 mg **EFV** dose for patients > 60kg: use the standard 600mg dosing)

- **RTV/SQV** + Rifampicin-containing ATT*

*This combination requires close monitoring of LFTs re: increased risk of hepatotoxicity. Consult with HIV Specialist before using.

26

Anti-Tuberculosis Agents and ARVs (3)

Because of serious drug-drug interactions between rifampicin and protease inhibitors, patients who develop TB while on second-line regimen should be managed by experienced HIV clinicians.

27

Anti-Tuberculosis Agents and ARVs (4)

- Rifampicin lowers **LPV/r** levels by 75%. Options to overcome this adverse interaction in adults:
 - Extra **RTV** boosting: extra **RTV** 300mg BD with regular dose of **LPV/r** (i.e., **LPV/r** 400mg/**RTV** 100mg BD + **RTV** 300mg BD)
 - Doubling of standard **LPV/r** dose:
 - LPV/r** 800mg/**RTV** 400mg BD
 - Switch to **RTV/SQV** (400mg/400mg BD)
 - For pediatric patients: double the **LPV/r** dose.
 - All of the above options carry the risk of increased hepatotoxicity: monitor closely and educate patient/care-giver re: symptoms of hepatitis.

28

Overlapping Toxicities

Overlapping Toxicities

Bone Marrow Toxicity	Pancreatitis	Nephrotoxicity	Hepatotoxicity
AZT Hydroxyurea Anticancer drugs (e.g., KS) Sulfonamides Pyrimethamine Primaquine Ganciclovir	ddl 3TC d4T RTV Sulfonamides Alcohol	Aminoglycosides Amphotericin TDF Sulfonamides	EFV NVP Protease Inhibitors Fluconazole Ketoconazole INH Rifampicin Alcohol Sulfonamides

30

Overlapping Toxicities (2)			
Neuropathy	Rash	Diarrhea	Eye Toxicity
ddl d4T INH Alcohol	NVP EFV Sulfonamides Dapsone	ddl RTV LPV/r Clindamycin	Ethambutol ddl

31

Case 1

A patient has recovered well from severe immune deficiency (baseline CD4 56, weight 41 kg) since starting (**AZT+3TC**) + **NVP**.

Her weight is now 59 kg. She is now menstruating regularly and has a partner.

What contraception do you recommend?

32

Case 2

A patient with a CD4 of 63 is started on TDF + FTC + **NVP**. She reports difficulty eating because of severe oral thrush.

What treatment would you recommend for her thrush?

33

Case 3

A patient with chronic migraine and on treatment with dihydroergotamine will be starting ART with TDF + FTC + **EFV**.

34

Case 4

A 7 year-old patient is started on ART with AZT + 3TC + **NVP**. He also receives cotrimoxazole, plus chemotherapy for his KS. Six weeks after ART initiation, the patient presents with pallor and a HgB of 3.9 g%.

35

Case 5

- A patient has been on (**AZT+3TC**) + **NVP** for the past 2 years. She now develops symptoms of TB, and the sputum AFB returns positive.

36

Case 6

- A 32 year old HIV-infected woman is beginning her 3rd month of ATT. Her baseline CD4 count is 155 cells/uL, and baseline FBC, chemistry, and AST/ALT are within normal or acceptable range. She has reproductive potential, is not pregnant, and has had no sd-NVP in the past. She is believed ready to start HAART.

What regimen do you recommend?

37

Case 7

A patient presents with a CD4 of 36, wasting syndrome and oral candidiasis. You want to initiate ART.

On questioning about other medications he is taking, he reports that he also takes a tea from a traditional doctor every morning.

38

Traditional Medicine

- None of the medications (teas, herbs, tablets, concoctions, etc.) given for traditional/spiritual healing in Botswana has been studied with regard to their content and/or potential effect on ARV medications and their toxicities. Although most *muti* probably does not interact with ARVs, patients should be advised not to mix *muti* with their ARVs. This advice must be given non-judgmentally. However, do not discourage patients from going to those spiritual healers who do not practice invasive procedures (e.g., piercing, enemas) or give ingested *muti*, since spiritual healers often fill important cultural needs for many patients.
- So-called immune boosters are of unproven benefit and often drain patient finances, and should not be recommended.

39

Summary

ARV Food Requirements		
Take on empty stomach: – ddl* *Cannot be taken with Kaletra	Take with food – LPV/r (as Kaletra or as pediatric liquid preparation)** **Not applicable to LPV/r as Aluvia for adults	Food independent – AZT – 3TC/FTC – d4T – NVP – EFV – TDF – ABC

- ### Review Drug Interactions When Prescribing:
- ATT, especially with PIs: adjust dose of PIs
 - Oral contraceptives: use alternative contraception
 - Ketoconazole: use for no more than 1-2 weeks
 - Ergotamines: CONTRAINDICATED
 - Seizure medications: monitor viral load and drug levels/clinical symptoms closely

Management of Drug Interactions

- Potentially harmful interactions occur in a small proportion of patients. However, a thorough drug history, including non-prescription drugs and alternative or traditional therapies, must be taken at each patient visit.
 - Because of fragmentation of medical care, with multiple caregivers, many patients may not report non-HIV medications which they are receiving at other clinics, *including ATT*. Careful questioning is necessary to determine *all* medications a patient is taking.
 - Always consider potential interactions between HIV medications and non-HIV medications, e.g., warfarin and other medications metabolized by the liver

43

Management of Drug Interactions (2)

- **Drug-drug interactions are one of the causes of treatment failure, which, if left unaddressed, may lead to ARV resistance.**
- **Be aware of the serious drug interaction between rifampicin and all protease inhibitors!**

44

Resources for Drug-Drug Interactions

- Knowledge of drug-drug interactions continues to evolve. Consult guidelines i.e., www.hiv-druginteractions.org or www.HIVinsite.org

45
