SPECIALIST HIV PHARMACY · TEACHING SESSION

Induction & Inhibition of Enzymes

Managing the impact on HIV care

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Conflict of Interest

In relation to this presentation, I declare that I have no conflict of interest

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Pharmacokinetics

The transport and metabolism of administered drugs

Absorption

When a drug enters systemic circulation from the site of administration

Distribution

The dispersion of the drug throughout body fluids and tissues

Metabolism

Chemical modification of the drug

Elimination

The removal of the drug and its metabolites from the body

BIOTRANSFORMATION

Metabolism

- Chemical modification of a drug through enzymatic systems
- The liver is the principal site — also kidneys, lungs, intestinal mucosa, synapses & plasma
- **Phase I** – Addition of functional groups – enzymes catalyse conversion of fat-soluble drugs into polar metabolites
- **Phase II –** Conjugation with endogenous molecules to increase water solubility for excretion
- Some medications need to be metabolically converted to their active form (pro-drugs)
- Can lead to loss of drug activity, and drives clearance

AFFECTED BY

Cytochrome P450 Enzymes

- A group of enzymes encoded by P450 genes which are responsible for the metabolism of most drugs
- Play a crucial role in first past metabolism
- Influence drug absorption, bioavailability and clearance
- Converts fat soluble compounds into more water-soluble forms
- Activity is affected by genetic and environmental factors (e.g., other medications)
- Polymorphisms (genetic variants) may contribute to reduced, absent or excessive metabolism of drugs.

THE KEY ISOENZYMES

CYP3A4	**CYP2D6**
CYP2C9	**CYP1A2**
CYP2C19	**CYP2C8**

CYP3A4 metabolises the majority of antiretrovirals.

Substrates, inducers and inhibitors

Category	Effect on CYP450	Examples
Substrates	Drugs or substances that **bind to and are metabolised** by CYP450 enzymes.	Statins, Warfarin, Phenytoin, Codeine, Contraceptives (OCP), Theophylline, SSRIs, Digoxin, Clarithromycin
Inducers	**Increase** CYP450 enzyme levels → faster metabolism → **reduced therapeutic concentrations**.	Carbamazepine, Rifampicin, St John's Wort, Phenytoin, Phenobarbital, Dexamethasone
Inhibitors	**Decrease or block** CYP450 activity → slower metabolism → **increased risk of toxicity**.	Ketoconazole, Fluconazole, Sodium valproate, Grapefruit juice, Omeprazole, Metronidazole, Macrolides, Protease inhibitors

Induction & Inhibition

Levels FALL

Enzyme induction

Metabolism speeds up — the drug is cleared faster, giving sub-therapeutic levels.

Risk: treatment failure & resistance

Levels RISE

Enzyme inhibition

Metabolism slows — the drug accumulates. Used deliberately as pharmaco-enhancement.

Can be reversible/irreversible

“Boosting” — e.g. ritonavir, cobicistat

ANTIRETROVIRALS AT A GLANCE

Inhibition & Induction Potential

Drug	Inhibits	Induces	Metabolism
Bictegravir	OCT2, MATE1	–	CYP3A, UGT1A1
Abacavir	–	–	Alcohol DH, glucuronidation
Cabotegravir IM	–	–	UGT1A1, UGT1A9
Cobicistat	CYP3A, CYP2D6, P-gp, BCRP, MATE1	–	CYP3A, CYP2D6
Darunavir	CYP3A4, CYP2D6, P-gp, BCRP, MATE1	CYP2C9, CYP2C19, CYP2C8	CYP3A4
Dolutegravir	–	–	CYP3A, UGT1A1
Doravirine	–	CYP3A (potential)	CYP3A4, CYP3A5
Efavirenz	CYP2C9, CYP2C19, CYP3A4	CYP3A4	CYP3A4, CYP2B6
Emtricitabine	–	–	Glomerular filtration, tubular secretion
Lamivudine	–	–	Renal excretion
Lenacapavir	CYP3A	–	CYP3A, UGT1A1
Nevirapine	BCRP	CYP3A4, CYP2B6	CYP3A4, CYP2B6
Raltegravir	–	–	UGT1A1
Rilpivirine	P-gp	–	CYP3A, CYP2C19
Ritonavir	CYP3A, CYP2D6, P-gp, BCRP	CYP1A2, CYP2C8, CYP2C9, CYP2C19	CYP3A, CYP2D6
TAF	–	–	CYP3A (minimal)
TDF	–	–	No P450 involvement

WHICH ENZYMES MATTER MOST

Relative Importance of CYP450s in HIV

CYP2D6

Inhibited by **RTV**

CYP3A4

Induced by **NVP/EFV/RTV** · Inhibited by **RTV/EFV**

CYP2C19

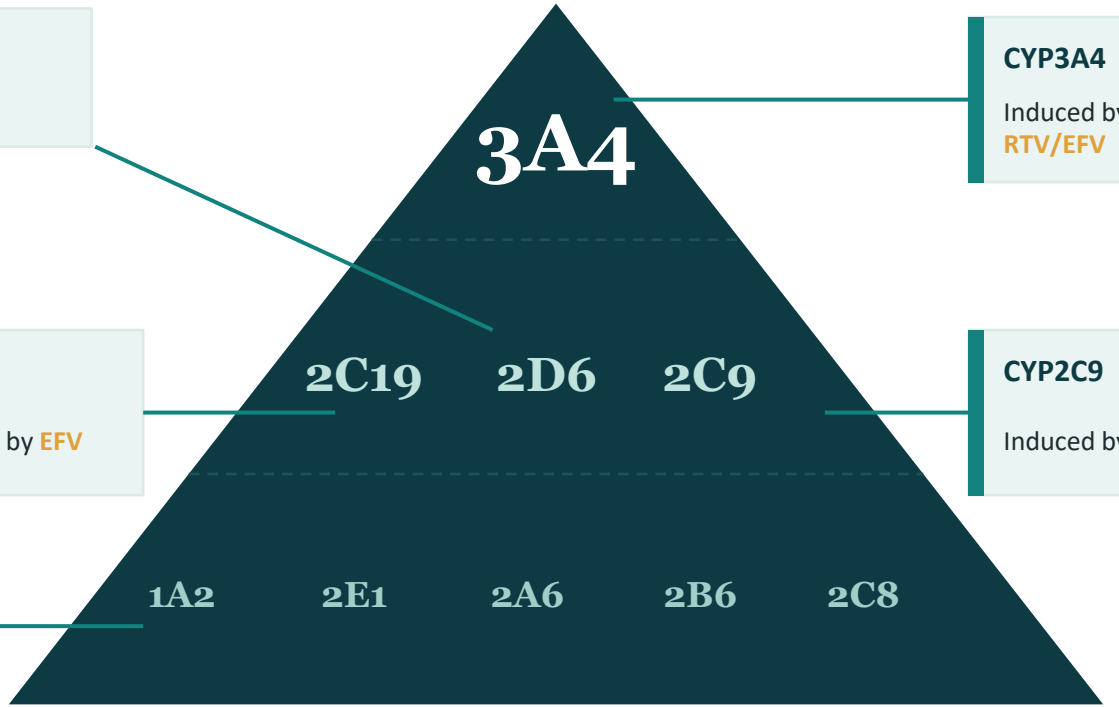
Induced by **RTV** · inhibited by **EFV**

CYP2C9

Induced by **RTV** · inhibited by **EFV**

CYP1a2/2E1

Induced by **RTV**



Transporters- P-glycoprotein (P-gp)

Drugs and other substances are sometimes carried across membranes via transporters

Where is P-gp found?

P-gp is present in various tissues and organs including the gut wall, liver, kidneys, and blood-brain barrier — acting as a defence mechanism.

How does P-gp work?

P-gp pushes drug molecules that have been absorbed back into the gut lumen, reducing the amount of drug that reaches systemic circulation.

P-gp inhibition

Inhibition of P-gp increases gut absorption — more drug passes through the gut wall and enters the bloodstream, raising drug levels.

P-gp induction

Induction of P-gp reduces gut absorption — P-gp activity is increased, pushing more drug back into the gut lumen and lowering drug levels.

P-gp = P-glycoprotein | Efflux transporter affecting drug bioavailability

Other transporters: OAT, OCT, MRP, MATE, BCRP

IN COMORBID PATIENTS

Impact of Drug–Drug Interactions

A DDI can lead to over- or under-exposure of the antiviral or co-administered medication

Reduced clinical effectiveness

Need higher doses, risk of resistance

OR

Increased risk of adverse events

Toxicity or harm to the patient

https://hiv-druginteractions.org/checker

RITONAVIR & COBICISTAT

Pharmaco-enhancement “Boosting” drugs

Why they exist

Ritonavir and cobicistat are added deliberately to **boost** the levels of other antiretrovirals.

Both are potent **CYP3A4 inhibitors** — the very effect that helps the ARV also pushes up the levels of many co-prescribed drugs.

Levels can climb dangerously

- Some statins
- Corticosteroids
- Sedatives
- DOACs

Always screen any new medicine against a boosted regimen before it starts.

RAL · EVG · DTG · BIC

Key Characteristics of Integrase Inhibitors

	RALTEGRAVIR	ELVITEGRAVIR	DOLUTEGRAVIR	BICTEGRAVIR
Dose	400 mg BD* 1200 mg OD	150 mg OD with cobicistat	50 mg OD 50 mg BD (INI-R)	50 mg OD with F/TAF
Metabolism	UGT1A1	CYP3A (major) UGT1A1/3 (minor)	UGT1A1 (major) CYP3A (minor)	UGT1A1 & CYP3A (equal)
DDI potential	**Least**	**Highest**	**Slightly > RAL**	**Slightly > DTG**

***RAL 400 mg BD licensed dose.** *UGT1A1, uridine glucuronyl transferase 1A1.*

THE HIDDEN HISTORY

Recreational, Herbal & OTC

Recreational drugs	MDMA, cocaine, mephedrone, and GHB can reach toxic levels with boosters
Steroid nasal sprays	Boosted by CYP 3A4 inhibitors
Herbal & supplements	Widely used, rarely reported unless you ask

Ask routinely and without judgement — frame it around safety, not policing behaviour.

Case Study 1

57-year-old, male

- Diagnosed 2020
- Well controlled HIV
- Baseline VL – 22,000cp/ml, Current VL<20
- Wildtype on baseline resistance test

- PMH: New hypertension

- Current ARVs:

Tenofovir 245mg/emtricitabine 200mg OD
Darunavir 800mg OD and Ritonavir 100mg OD

Newly started on:

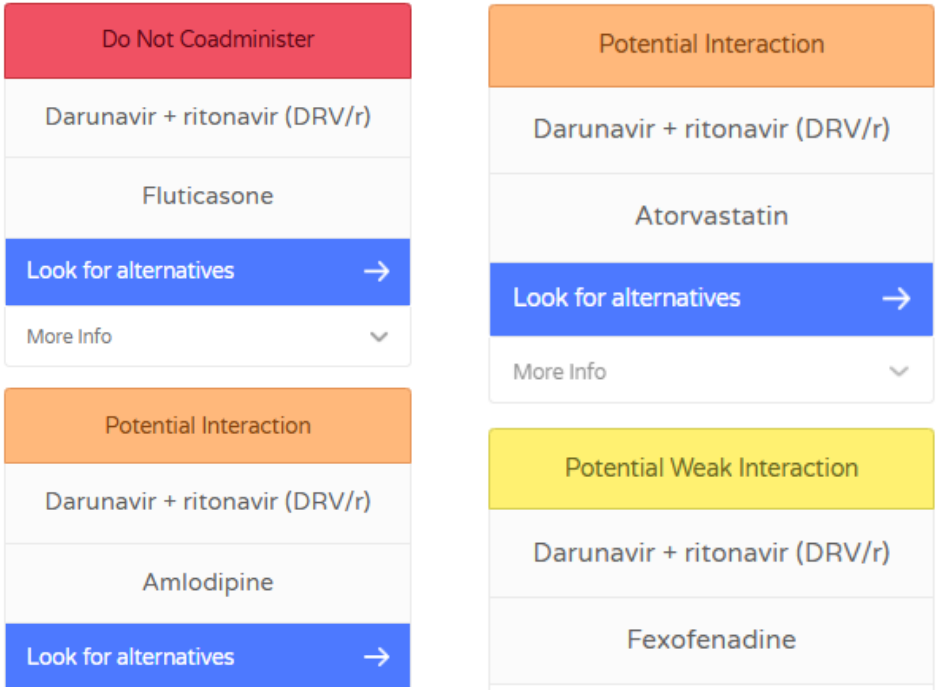
- Amlodipine 10mg OD
- Atorvastatin 20mg OD (As per REPRIEVE)

OTC:

- Fexofenadine 180mg PRN
- Fluticasone nasal spray 50mcg PRN

Liverpool HIV Drug Interaction Checker
https://hiv-druginteractions.org/

HIV Drug Interactions



Case Study 2

25 year old female

Vertical transmission
Diagnosed at the age of 4
VL<20 cp/ml
CD4 count 390 cells/uL
On Dovato since 2023

PMH: Nil

Acute: Carbamazepine 100mg OD

Issues?

Options?

- Add additional dose of DTG 12 hours apart*
- Change ARV regime
- Advise GP on alternative medication for trigeminal neuralgia
- TDM
- Food boosts dolutegravir

*Double dose for 2 weeks after discontinuation of carbamazepine

PUTTING IT INTO PRACTICE

Your Role & Practical Tools

Take a full medicines history	Every contact: OTC, herbal, supplements & recreational drugs
Use the Liverpool checker	hiv-druginteractions.org — the gold-standard resource
Counselling & monitoring	Ensuring the patients are aware of monitoring needed
Refer when unsure	Know the local pathway to the specialist pharmacist
Document & communicate	Record any new or changed medicine promptly

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