Cases: drug interactions/toxicity

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Case 1

August 2015, Soho, London

- 37 y.o. MSM diagnosed with HIV infection 2 wks ago
- VL 5,660,523 copies/mL
- CD4 924 (34%) cells/mm^3
- Comeds
  - Lamotrigine 100 mg BD
  - Carbamazepine depot 600 mg OD
  - Valproate 1 g BD
- Epilepsy only partially controlled

“I want to start cART as TasP today”

Case 1

What did I do?

• van Luin et al. 2009: no interaction between **lamotrigine** and RAL

• Not studied: low interaction potential between **valproate** and RAL

• **http://www.hiv-druginteractions.org** Not studied but could decrease RAL concentrations as it is mainly glucuronidated by UGT1A1 and *in vitro* data suggest that **carbamazepine** induces UGT1A1

TDF/FTC plus RAL 800 mg BD

Effect of RAL on the PK of other drugs

- No effect on the PK of etravirine, maraviroc, tenofovir, hormonal contraceptives, methadone, midazolam or boceprevir …
- DRV/r?

Effect of other drugs on the PK of RAL

Pharmacokinetics of Raltegravir in HIV-Infected Patients on Rifampicin-Based Antitubercular Therapy

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What about DTG?

Impact of moderate/strong UGT1A1 and/or CYP3A4 inducers on DTG

Co-administered drug	n	DTG dose studied	DTG C_τ or C_{24} GLS mean ratio (90% CI) Ratio of 1 = no impact	Recommendation
FPV/r 700/100 mg BID	12	50 mg QD	**0.51 (0.41–0.63)**	DTG 50 mg BID should be given*
TPV/r 500/200 mg BID	16	50 mg QD	**0.24 (0.21–0.27)**	DTG 50 mg BID should be given*
DRV/r 600/100 mg BID	15	30 mg QD	**0.62 (0.56–0.69)**	No DTG dose adjustment required
EFV 600 mg QD	**12**	**50 mg QD**	**0.25 (0.18–0.34)**	**DTG 50 mg BID should be given***
ETR 200 mg BID	**15**	**50 mg QD**	**0.12 (0.09–0.16)**	**DTG 50 mg BID should be given***
Rifampin 600 mg QD	**11**	**50 mg BID**	**0.28 (0.23–0.34)**	**DTG 50 mg BID should be given***
Rifabutin 300 mg QD	9	50 mg QD	**0.70 (0.57–0.87)**	No DTG dose adjustment required
CBZ 100 mg BID	**14**	**50 mg QD**	**0.274 (0.24–0.31)**	**DTG 50 mg BID should be given**

The GLS ratio values in red signify that in these cases, C_τ for DTG is reduced significantly below 75% (the lower boundary of a clinically significant alteration in DTG exposure)

Tivicay SPC; Song et al 2011; Song et al 2011; Dooley et al 2013

Any other DDI with unboosted InSTI?

InSTI and Cation Containing Antacids: Recommendations

Integrase Inhibtor	Recommendation
Raltegravir	Aluminium and magnesium containing antacids reduce RAL plasma levels. Co- or staggered administration of RAL with these antacids is ***not recommended***. However with Ca^{++} no dose adjustment.
Dolutegravir	Magnesium/ aluminium-containing antacid should be taken ***well separated*** in time from the administration of DTG (minimum 2 hours after or 6 hours before). Applies also to Ca^{++} and Fe^{++} supplements.
Elvitegravir/cobicistat	It is recommended to ***separate*** Stribild and antacid administration by at least 4 hours. No specific recommendation for Ca^{++} and Fe^{++}.

Tivicay SPC; Isentress SPC; Stribild SPC

Case 2

- 57 years old man, diagnosed with HIV 3 years ago
- Current CD4 418 cells/mm^3
- VL undetectable (<50 copies/mL)
- On cART

- Hx of depression

- High cholesterol at HIV diagnosis
  - Now partially controlled by treatment

- At early consultations, complained of:
  - Incomplete emptying of the bladder
  - Difficulties in passing urine
  - Erectile dysfunction
  - Heartburn (not on treatment, currently under investigation)

- At current consultation:
  - Fasting glucose = 8.1 mmol/L (being investigated for diabetes)
  - Blood pressure = 160/105 mmHg (not on treatment)
  - Complains of erectile dysfunction (not on treatment)

On polypharmacy

- **cART**
- Tenofovir (TDF, NRTI
- Emtricitabine (FTC, NRTI)
- Atazanavir/ritonavir (ATV/r, boosted PI)

- **COMEDICATION**
- Paroxetine 40 mg OD
- Atorvastatin 10 mg OD
- Tamsulosin 0.4 mg OD

Case 2

Also needs treatment for…

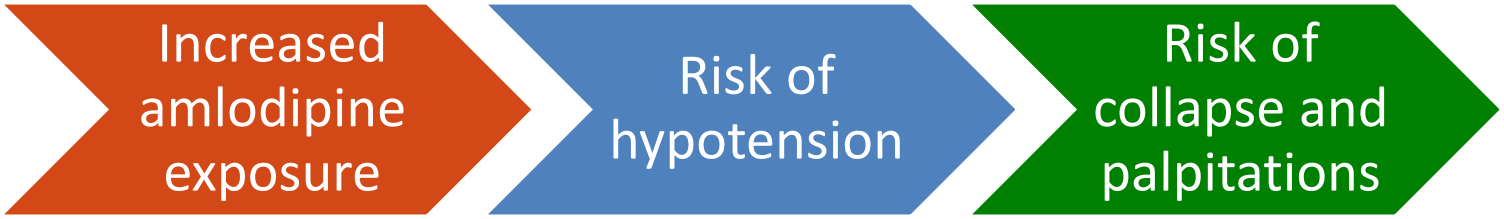
- Hypertension
- Erectile dysfunction

Treatment for hypertension?

- Over 55
  - So start with CCB e.g. amlodipine

Any DDI risk?

- Amlodipine metabolised by CYP3A4
- Co-administration with ritonavir…



CCB = calcium channel blocker

Drug-drug interaction resources
HIV

DDIs with calcium channel blockers

Calcium channel blockers	PIs			NNRTIs				ENTRY AND INTEGRASE INHIBITORS			
	ATV	DRV	RTV	EFV	ETV	NVP	RPV	DTG	EVG/ COBI	MVC	RAL
Amlodipine	■	■	■	■	■	■	◆	◆	■	◆	◆
Diltiazem	■	■	■	■	■	■	■	◆	■	■	◆
Felodipine	■	■	■	■	■	■	◆	◆	■	◆	◆
Nicardipine	■	■	■	■	■	■	■	◆	■	■	◇
Nifedipine	■	■	■	■	■	■	◇	◆	■	◇	◇
Nisoldipine	■	■	■	■	■	■	◇	◆	■	◇	◇
Verapamil	■	■	■	■	■	■	■	◆	■	■	◇

⬢ / ⬡ These drugs should not be coadministered

■ / □ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration

◆ / ◇ No clinically significant interaction expected

✦ / ✧ No clear data, actual or theoretical to indicate whether an interaction will occur

Empty symbols indicate the combination has not been studied; an interaction has been predicted based on the metabolic profiles of the drugs

Adapted from http://www.hiv-druginteractions.org/Interactions.aspx. Accessed April 2015

DDIs with antyhypertensives

Hypertension/heart failure agents	PIs			NNRTIs				ENTRY AND INTEGRASE INHIBITORS			
	ATV	DRV	RTV	EFV	ETV	NVP	RPV	DTG	EVG/ COBI	MVC	RAL
Enalapril	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Furosemide	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Indapamide	□	□	□	□	□	□	◆	◆	□	◆	◆
Lisinopril	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Losartan	□	□	□	□	□	◆	◇	◆	□	◆	◇
Perindopril	◇	◇	◇	◇	◇	◇	◇	◆	◆	◇	◇
Ramipril	◇	◇	◇	◇	◇	◇	◇	◆	◆	◇	◇

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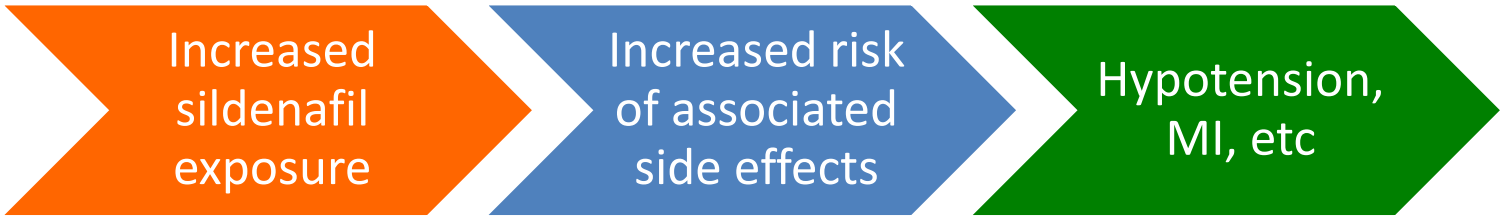
Need for dose adjustment

1. Decrease amlodipine dose
2. Change to non-CYP3A4 metabolised CCB/antyhypertensive

CCB = calcium channel blocker

Sildenafil

- Viagra™
- Common treatment for erectile dysfunction
- Metabolised by CYP3A4
- Co-administration with ritonavir…



Guidelines recommend to use no more than 25 mg every 48 hours

Case 3

- 63 years old
- British white male
- MSM
- Specialist Nurse

PMH:

1985 - Acute Hep B infection

2002 - HIV Diagnosis: CD4+ 324, VL 43282 cp/mL
Resistance test: wild type virus

2007 – Criptosporidiosis

2013 – Dx of hiatus hernia w/ acid reflux

Case 3

Apr 2008: Atripla

HIV VL < 40 c/mL since July 2008

Since starting ARVs: vivid dreams + not restful sleep

Jul/Aug 2014: symptoms exacerbated with

- Nightmares / disturbed sleep
- Tiredness
- Difficulty concentrating at work / forgetfulness

Case 3

March 2015: switched to Truvada + DTG within a clinical trial (SSAT056) - VL < 40 c/mL (CD4 711, 33.9%)

- Discloses recent (3-4 months) use of *Chems* (GHB, crystal meth, mephedrone) - injecting
- No previous history of recreational drugs use

Case 3

May 2015 (1 month after switch)- on TDF/FTC+DTG:

- No more vivid dreams/nightmares
- Better mood
- Still tired

August 2015 - End of Study

Switched from TDF/FTC+DTG to Triumeq (ABC/3TC/DTG) for simplification (HLAB5701 negative)

…during the study reports occasional use of mephedrone (injecting)

Case 3

September 2015 – presents:

Agitated, **nervous**, **anxious** and **paranoid**

Wants to **come off Triumeq** due to **side effects…**

Case 3

Explains that the week before :

-**Resigned from work** after feeling very confused, with episodes of difficulty speaking, agitation and confusion

-**Attended A&E** department for onset of confusion, paresthesias in both arms, dry mouth, anxiety ++ and “near to death” feeling, discharged with flucloxacillin for thrombophlebitis ..

Case 3

From history and physical examination:

- No clear signs of cerebral vascular accidents/TIAs
- No previous history of mental health issues/panic attacks
- Not typical ABC/Triumeq side effects

ABC SPC

Anorexia, nausea, vomiting, diarrhea
Headache
Rash
Fever, lethargy, fatigue
Hypersensitivity reactions

Case 3

Only when asked about *Chems*:

Injected crystal meth and mephedrone at least 5 times in the previous week and in other occasions in the previous month

Followed long discussion about: *Chems* adverse effects, come-down post use, unlikelihood of current symptoms being related to Triumeq

Still refused to continue on Triumeq

-> Switched to Truvada + raltegravir

-> Diazepam 2.5 mg for 2-3 days

-> Referred to Chemsex support / health advisors

Any questions?