New issues in management of drug-drug interactions

Catia Marzolini

Division of Infectious Diseases & Hospital Epidemiology
www.hiv-druginteractions.org

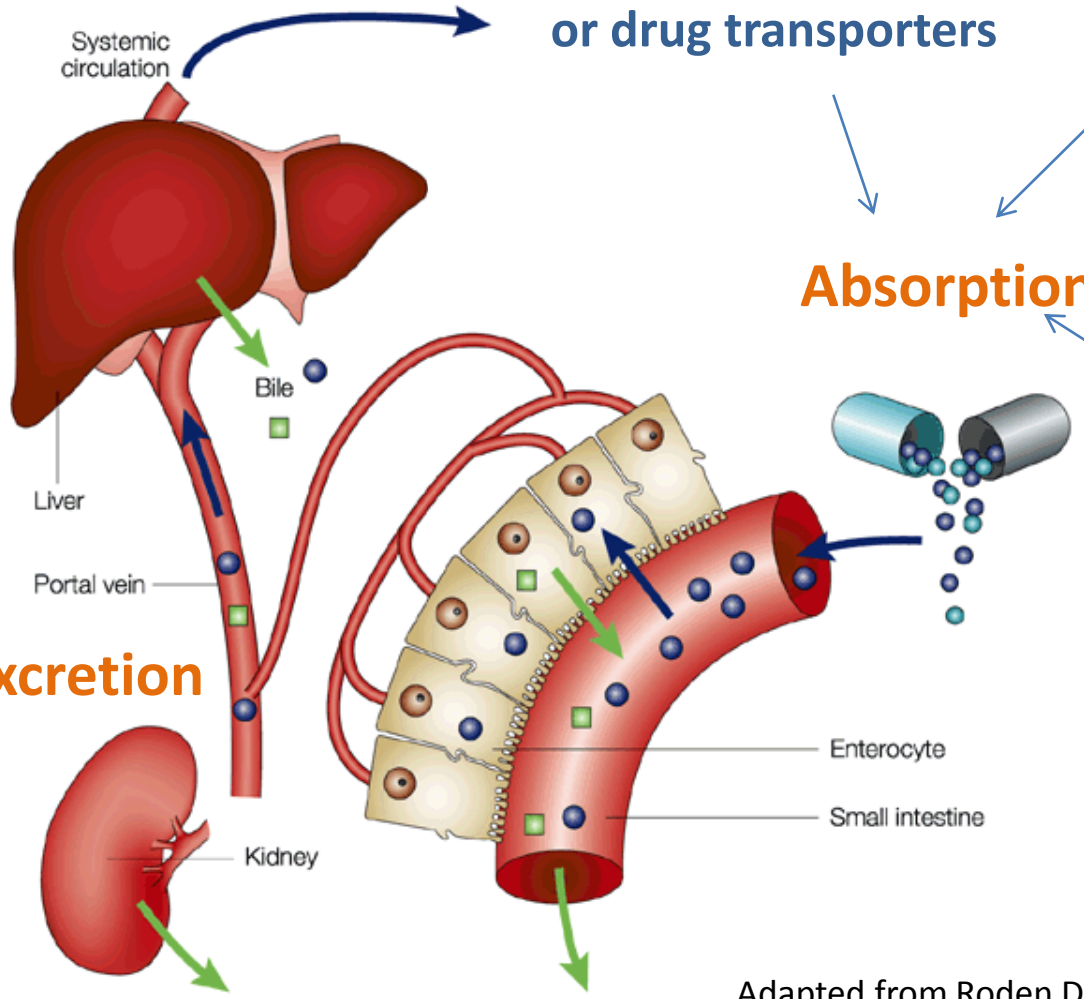
University Hospital Basel

UNIVERSITY OF LIVERPOOL

Presentation outline

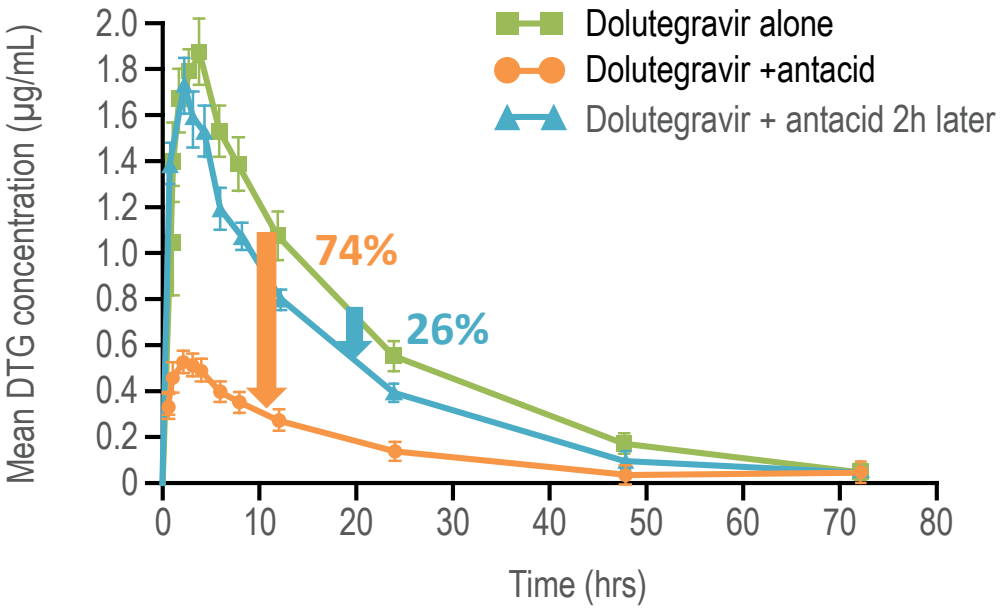
- mechanisms of drug-drug interactions
- drug-drug interactions in the older HIV patient
- management of drug-drug interactions in the treatment of co-morbidities

Mechanisms of PK drug-drug interactions

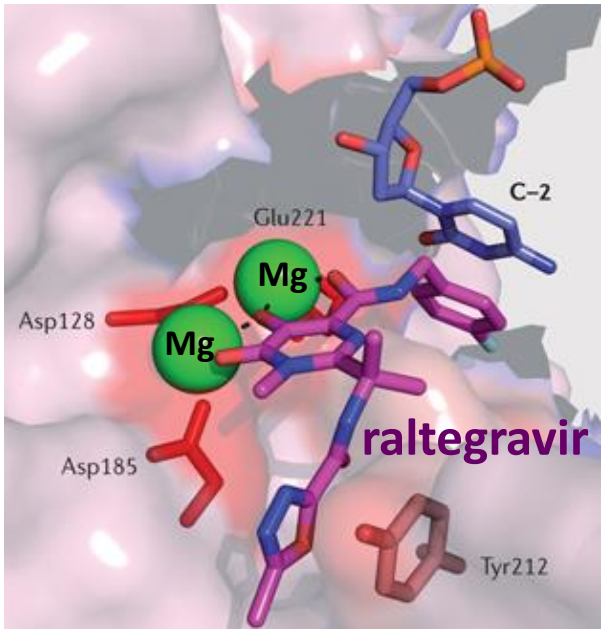


Adapted from Roden DM et al. Nat Rev 2002

Mechanism of interaction specific to integrase inhibitors



Binding of integrase inhibitors



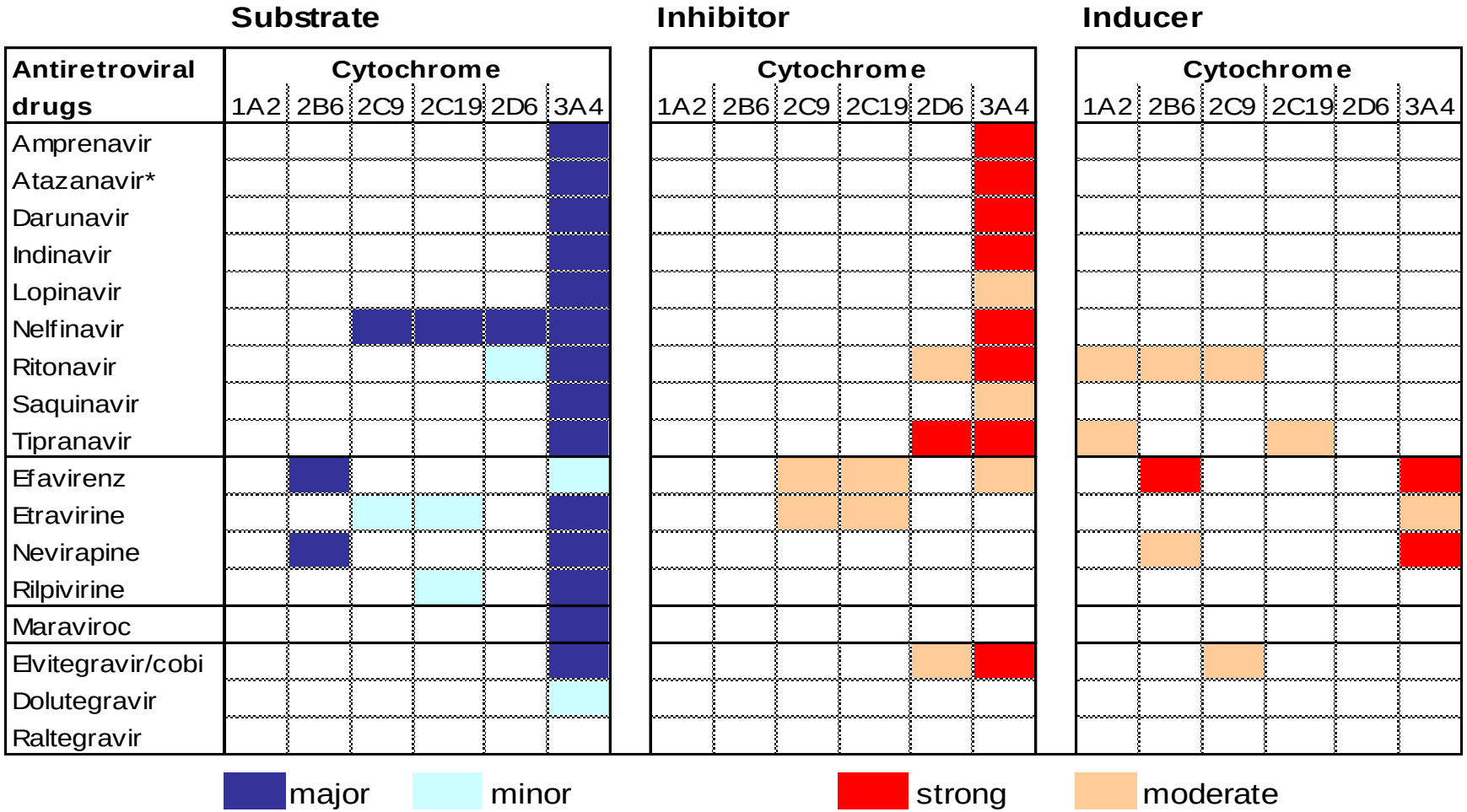
Chelation of integrase inhibitors with divalent cations (magnesium, calcium, iron, aluminium)

Cave: mineral supplements, antacids

➔ Separate intake integrase inhibitors with drugs containing divalent cations

Adapted from Patel P et al. JAC 2011, Pommier Y et al. Nat Rev 2005

Metabolism of antiretroviral drugs



atazanavir, indinavir inhibit UGT1A1

ritonavir induces glucuronidation

tipranavir, etravirine induce UGT1A1

NRTIs: renal elimination (FTC, 3TC, TDF)
glucuronidation (AZT, ABC)

raltegravir is a substrate of UGT1A1

elvitegravir is substrate of UGT1A1, UGT1A3 (minor)

dolutegravir is mainly metabolized by UGT1A1

http://pharmacoclin.hug-ge.ch/actualites.html

Are we always anticipating all metabolic DDI?

- 47 year old man
- HIV + since 2004
- severely depressed since the death of girlfriend

Antiretroviral treatment

- atazanavir 300 mg QD
  ritonavir 100 mg QD
  tenofovir 300 mg QD
  emtricitabine 200 mg QD

} well suppressed (<20 copies/ml)
562 CD4 cell counts

Antidepressant

- fluvoxamine starting dose of 50 mg which was increased gradually to 150 mg/day

Case presentation

- the patient complains of palpitations, tachycardia, panick attacks and insomnia a few days after starting fluvoxamine.
- question: potential drug-drug interaction?

Metabolic pathways of the aministered drugs

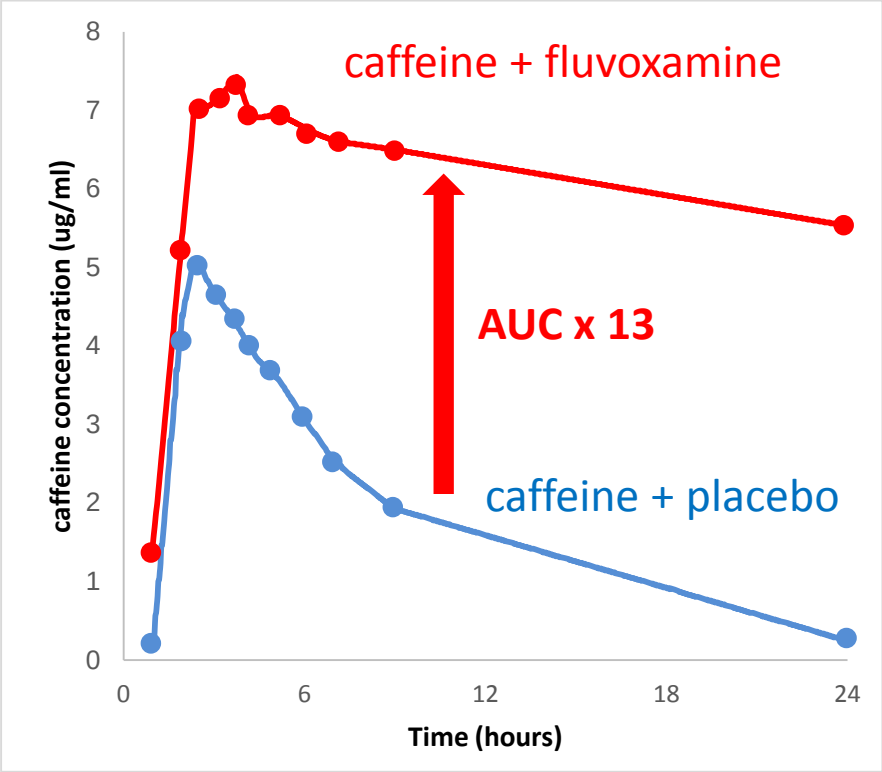
- atazanavir: substrate CYP3A4, inhibitor CYP**3A4**
  ritonavir: substrate CYP3A4, inhibitor CYP**3A4**, 2D6
  tenofovir: renally eliminated
  emtricitabine: renally eliminated
- fluvoxamine: substrate CYP2D6, 1A2, inhibitor CYP**1A2**, 2C9, 2C19, 3A4.

- the patient drinks roughtly 5 cups of **coffee**/day

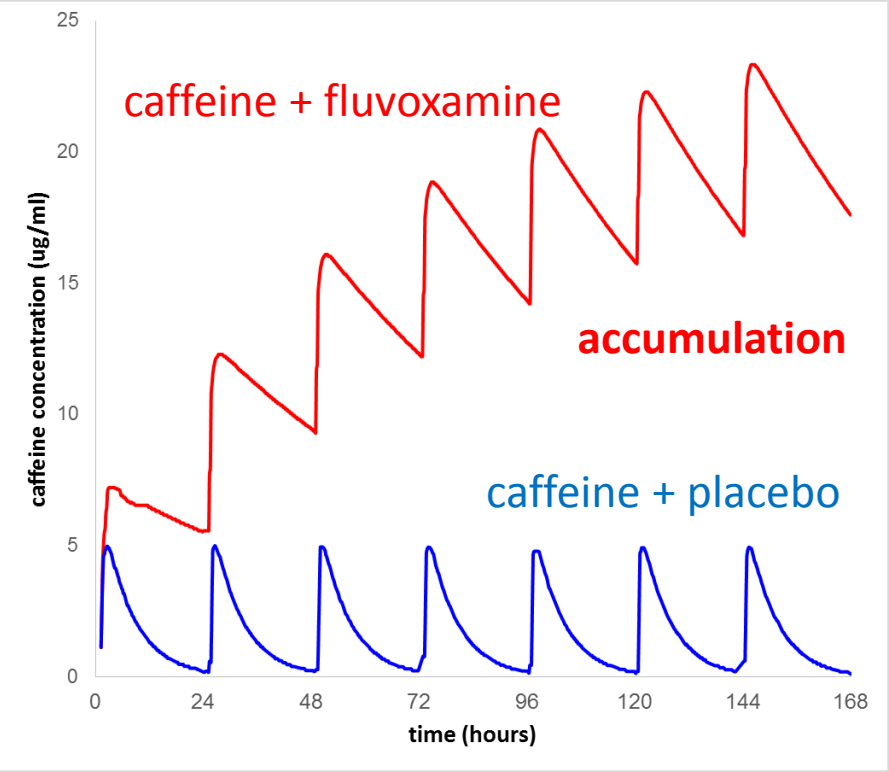
Interaction fluvoxamine caffeine

Caffeine: substrate CYP1A2 (major) and 3A4.

Plasma caffeine concentration with and without fluvoxamine

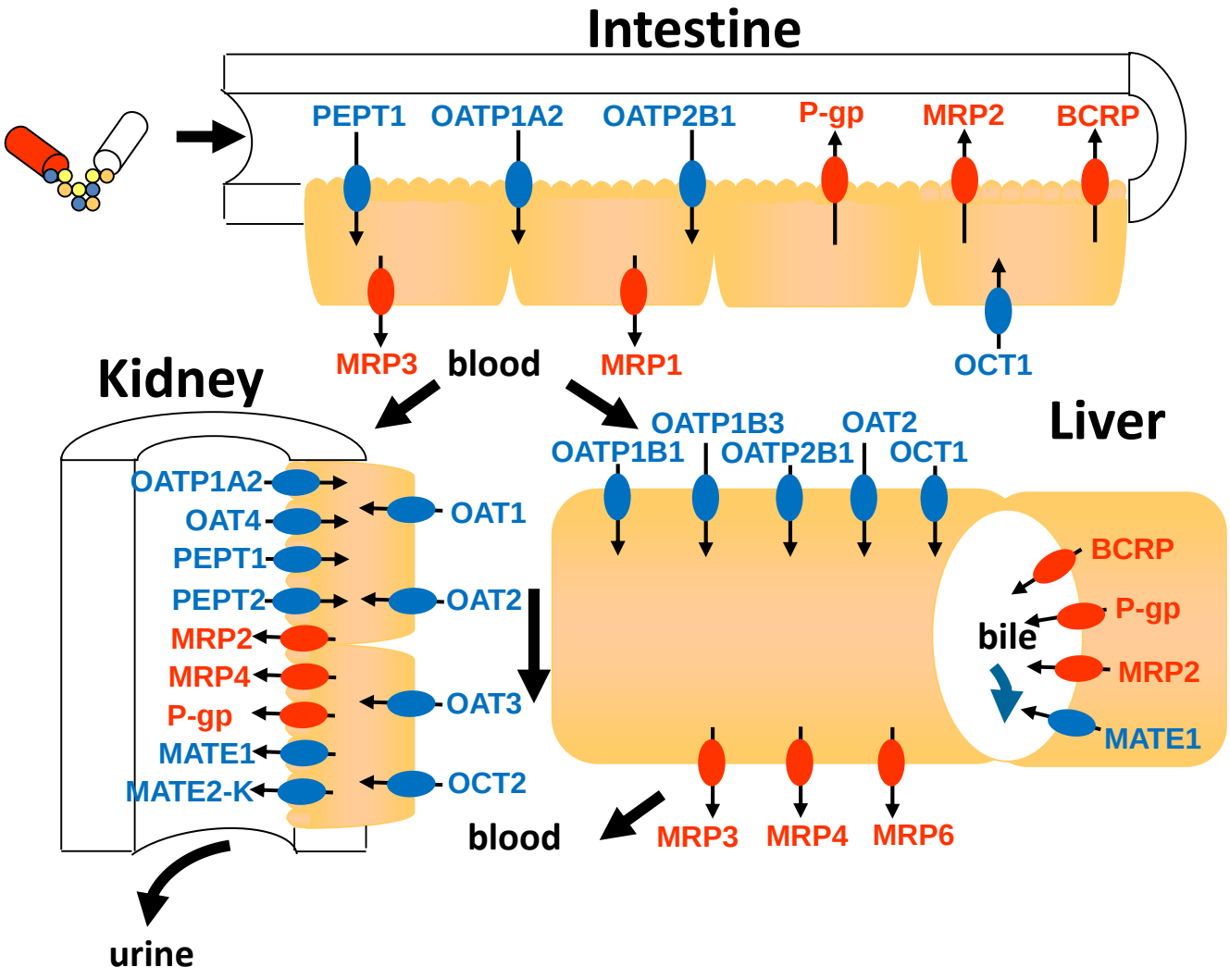


Simulated plasma caffeine concentration ± fluvoxamine treatment over 7 days



Culm-Merdek K et al. BJCP 2005

Drug transporters



Marzolini C et al. In: Drug Interactions in Infectious Diseases 2011

Antiretroviral drugs are substrates and/or inhibitors of drug transporters (in vitro data)

	OATP				OAT				OCT		PEPT		Pgp	BCRP	MRP			
	1A2	1B1	1B3	2B1	1	2	3	4	1	2	1	2			1	2	4	5
Antiretrovirals																		
Amprenavir		X	X										X	X	X			
Atazanavir		X	X	X									X	X	X	X		
Darunavir		X	X										X			X		
Indinavir	X	X	X	X					X	X			X		X	X		
Lopinavir		X	X	X									X	X		X		
Nelfinavir	X	X		X					X	X			X	X		X		
Ritonavir	X	X	X	X					X	X			X	X	X	X		
Saquinavir	X	X	X	X					X	X			X	X	X	X		
Tipranavir				X									X					
Efavirenz														X	X	X		
Nevirapine															X	X		
Abacavir									X	X				X				
Didanosine																		
Emtricitabine									X	X					X	X		
Lamivudine									X	X								
Stavudine																		
Tenofovir									X	X								
Zidovudine					X	X	X	X	X	X				X				

Substrates

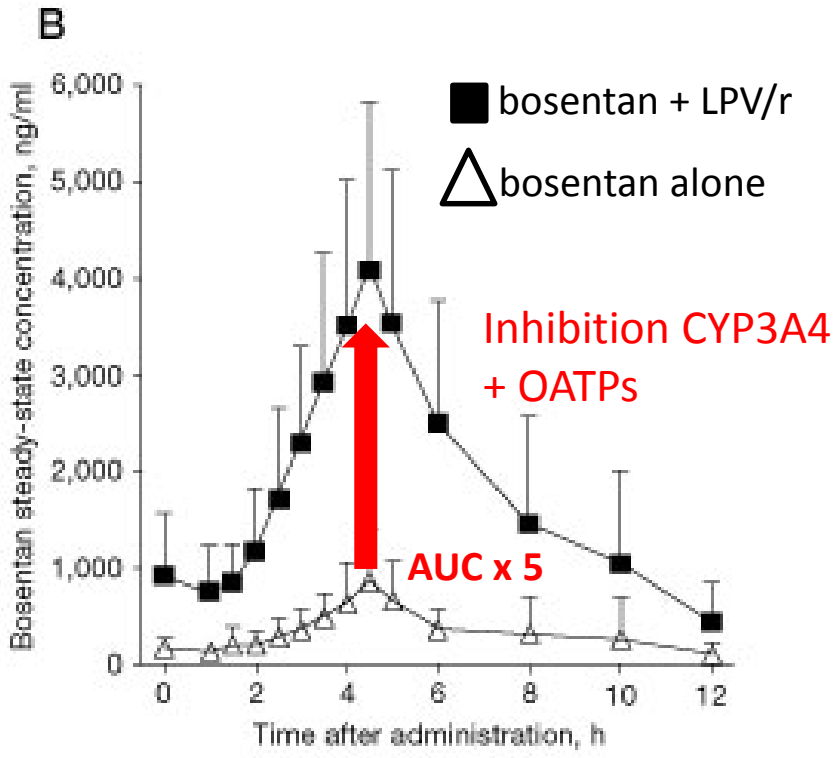
Inhibitors **x**

Marzolini C et al. In: Drug Interactions in Infectious Diseases 2011

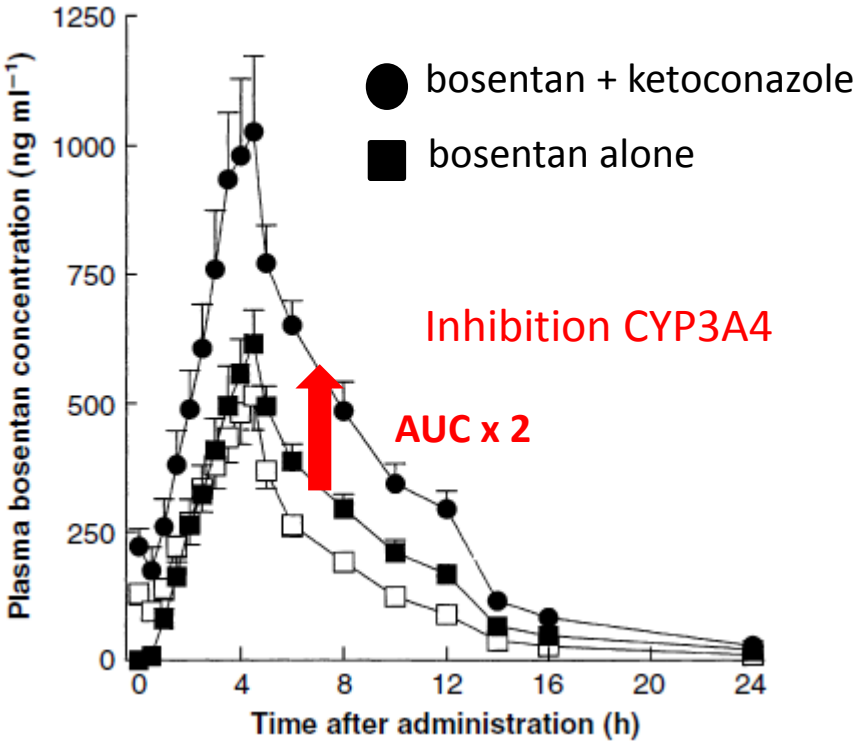
Drug-drug interactions involving both cytochromes and drug transporters can have profound effects

Example: bosentan + lopinavir/ritonavir

Bosentan: metabolized by CYP3A4, 2C9 (1)
substrate OATP1B1, OATP1B3 (2)



Lopinavir/r: substrate and inhibitor CYP3A4
substrate (3) and inhibitor
OATP1B1, OATP1B3 (4)

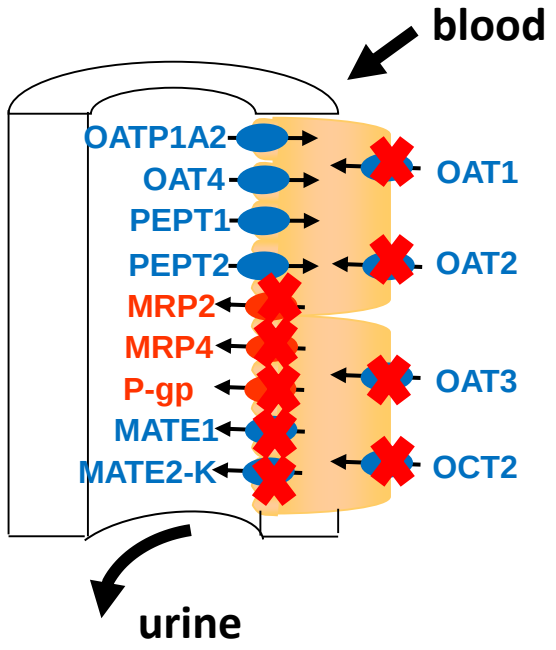


1) Dingemasse J et al. Antiviral Ther 2010, 2) Treiber A et al. DMD 2007, 3) Hartkoorn RC et al. Pharmacogenetics & Genomics 2010, 4) Annaert P. et al. Xenobiotica 2010

Drug interactions at the renal level

- **Glomerular filtration**
  passive process affected by hemodynamic changes
- **Tubular reabsorption**
  passive and transporter-mediated processes
- **Tubular secretion**
  transporter-mediated process

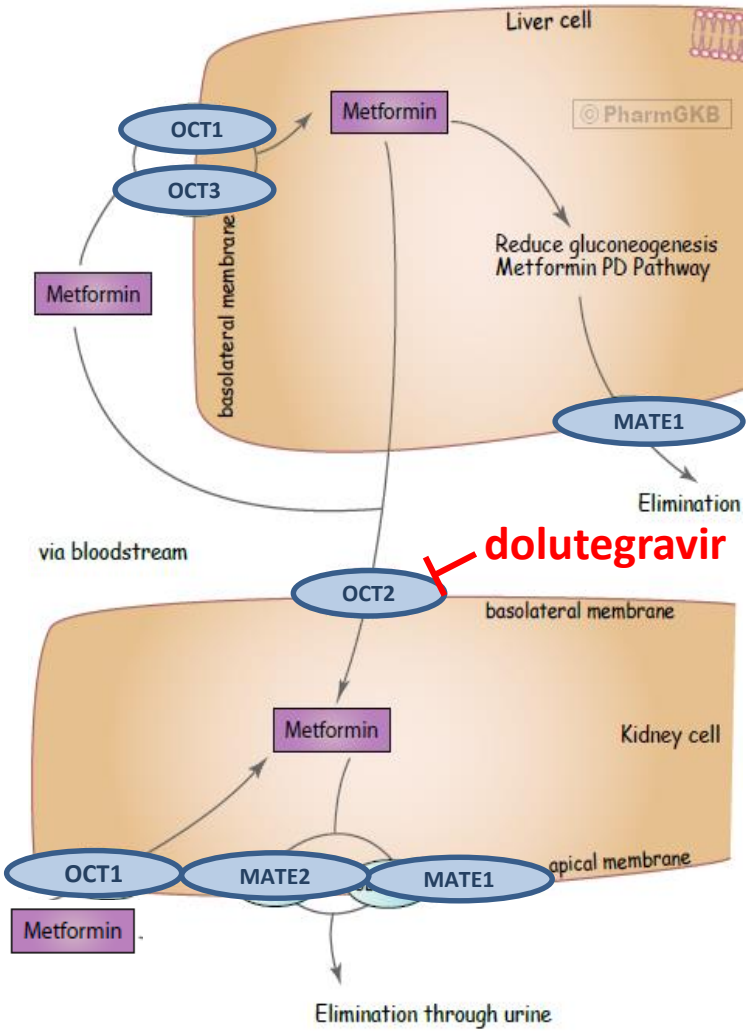
competitive inhibition of tubular secretion is the most common mechanism of drug-drug interaction at the renal level.



Marzolini C et al. In drug interactions in infectious diseases 2011

Inhibition of metformin elimination by dolutegravir

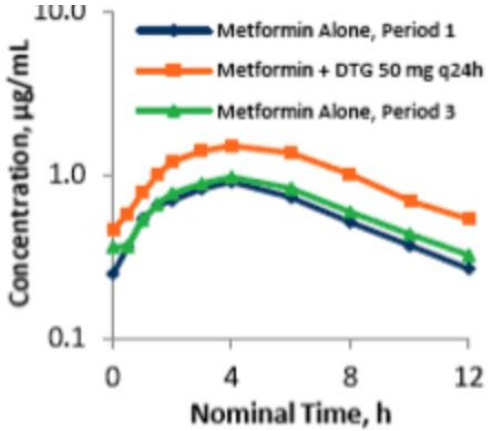
Metformin elimination pathway

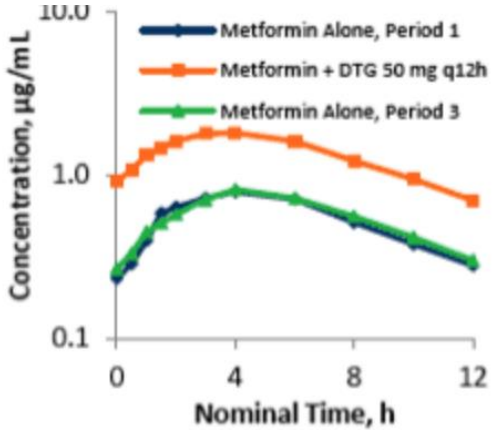


Adapted from PharmGKB

DDI study in healthy volunteers

1) Metformin 500 mg BID + dolutegravir 50 mg QD
2) Metformin 500 mg BID + dolutegravir 50 mg BID





DTG 50 mg QD	Met +DTG/Met alone
AUC	**1.79**
Cmax	**1.66**
DTG 50 mg BID	**Met +DTG/Met alone**
AUC	**2.45**
Cmax	**2.11**

Zong J et al. Glasgow Conference 2014

Prediction and clinical relevance of DDI

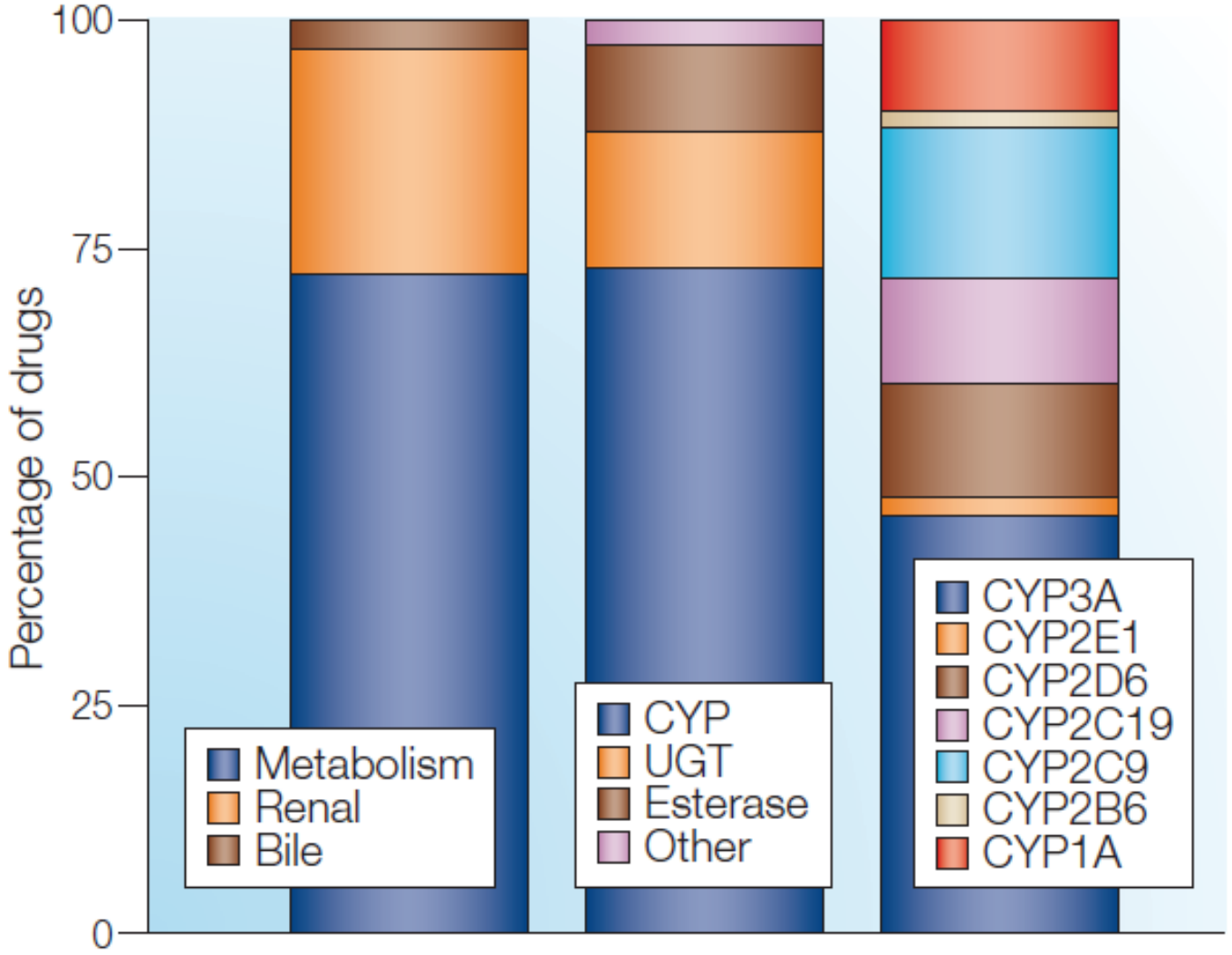
Prediction based on:

- metabolic pathway of drugs (*in vitro* data)
- DDI study with same inhibitor or inducer or victim drug with similar metabolic pathway

Clinical significance depends on:

- potency and concentration of inhibitor/inducer
- therapeutic index of the victim drug
- presence of active or toxic metabolites
- extent of metabolism through affected enzyme/ elimination through affected renal transporter

Routes of elimination of the top most prescribed drugs

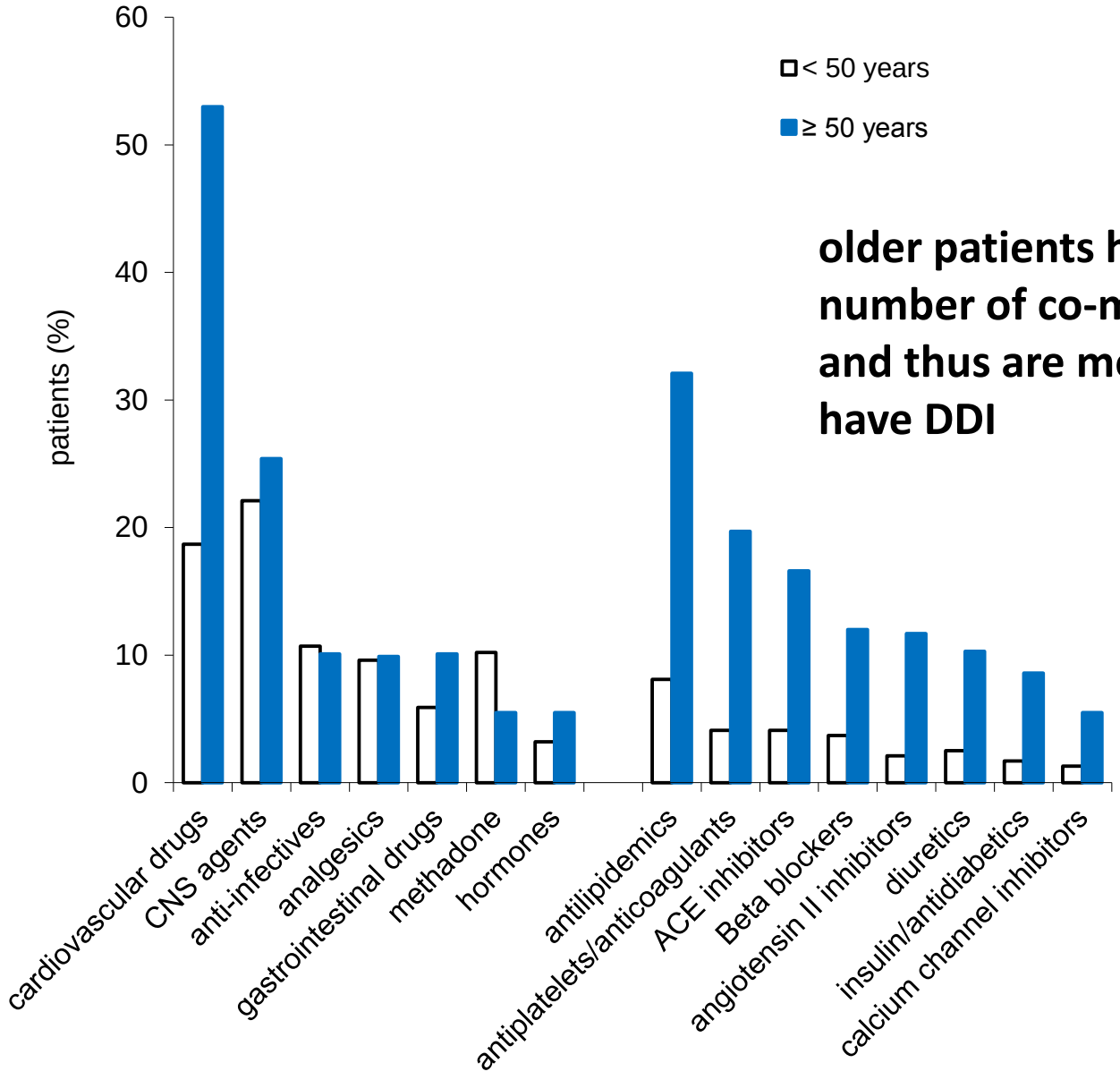


Wienkers LC et al. Nat Rev Drug Discov 2005

Presentation outline

- mechanisms of drug-drug interactions
- drug-drug interactions in the older HIV patient
- management of drug-drug interactions in the treatment of co-morbidities

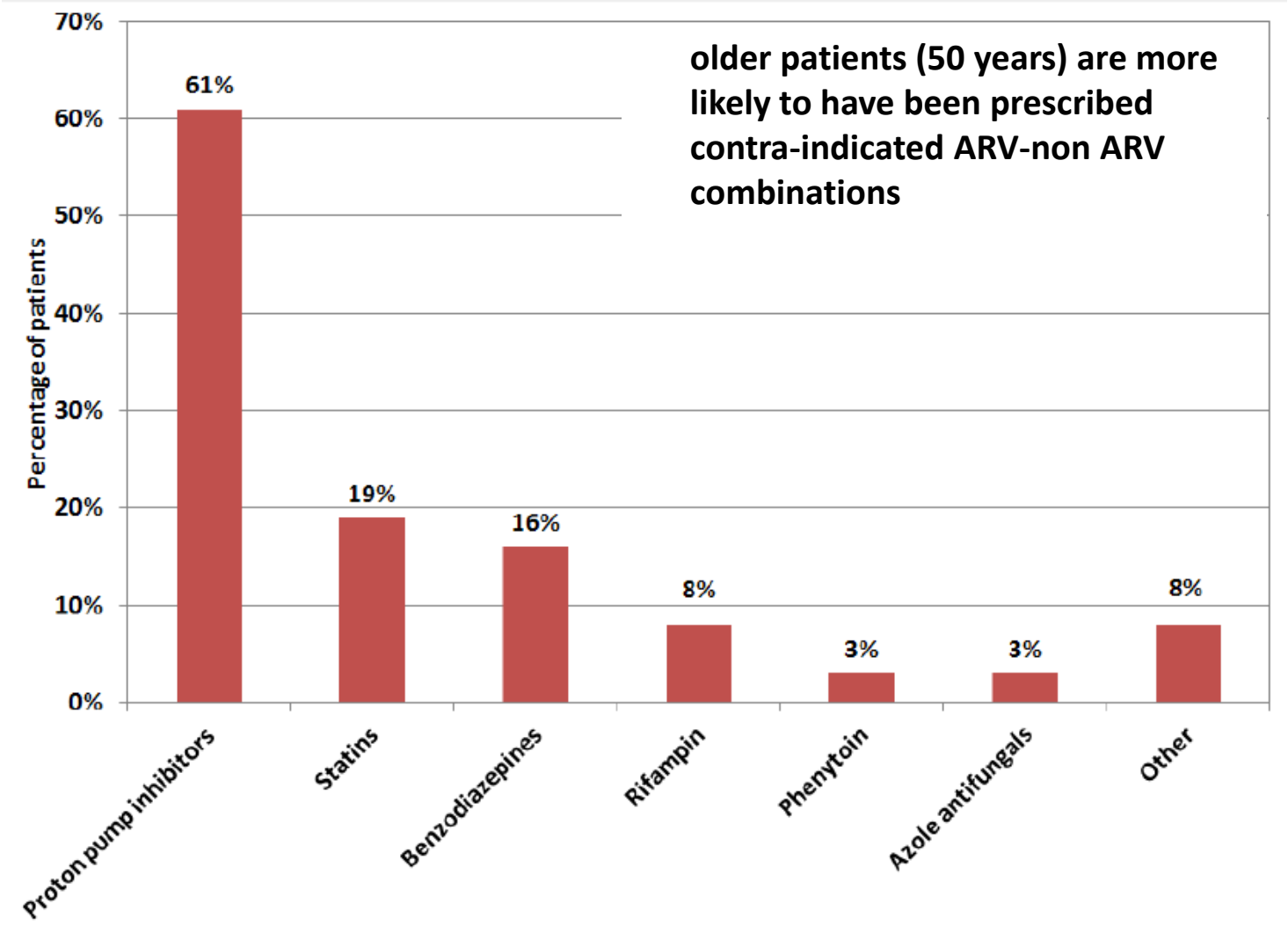
HIV population is aging ➔ increased risk of DDI



older patients have a higher number of co-medications and thus are more likely to have DDI

Marzolini C et al. J Antimicrob Chemother 2011

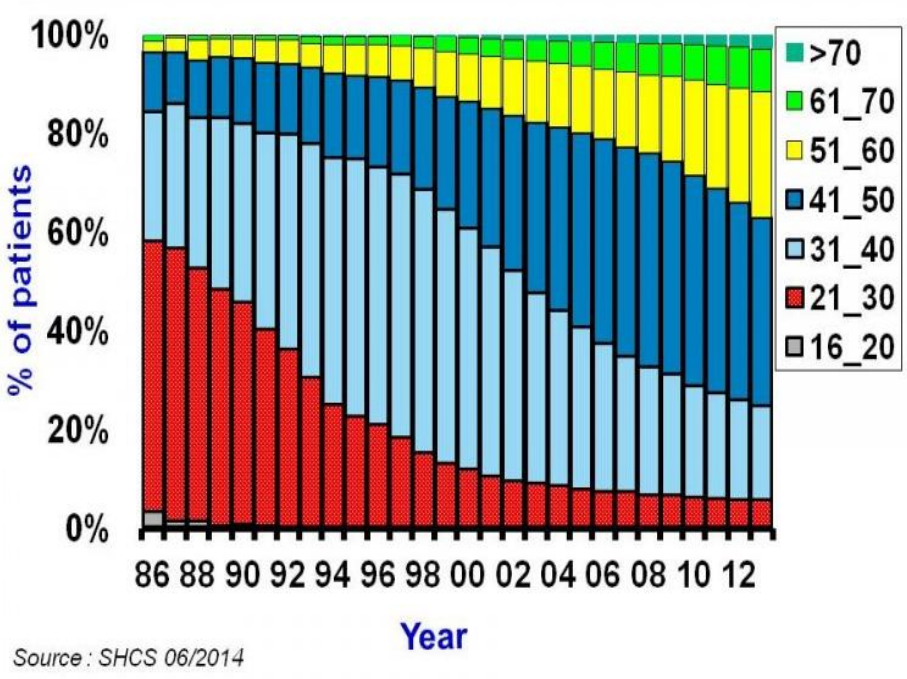
Contra-indicated ARV/non-ARV drug combinations



Holtzman C et al. J Gen Intern Med 2013

Aging and effect on pharmacokinetics

Age distribution of active patients by year in the SHCS, 1986-2013



Source : SHCS 06/2014

proportion of individuals >65 y where PK effects related to age will be noticeable is growing

Table 1. Age-related changes in drug pharmacokinetics and potential effects on antiretroviral drugs

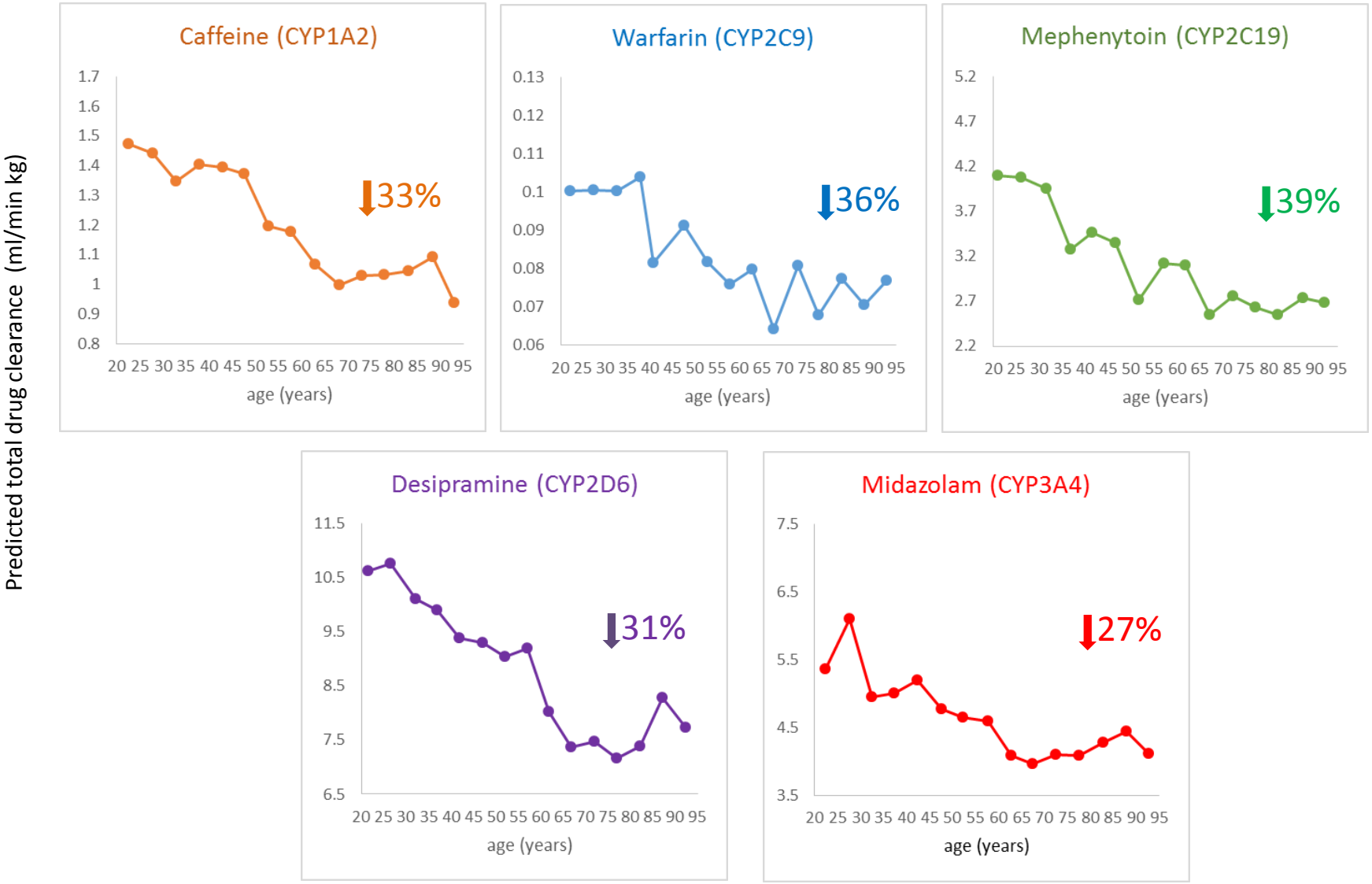
Potential age-related changes to pharmacokinetic characteristics	Potential effects on plasma drug exposure*
Liberation and absorption (absorption rate, bioavailability)	
↑ gastric pH	↓/↑ PIs*
↓ gastric emptying	↑ Rilpivirine*
↓ GI p-gp and CYP activity	↑ Maraviroc
Distribution (volume of distribution)	
↓ albumin	↑ PIs
↑ body fat %	↑ NNRTIs
↓ lean muscle %	↑ Maraviroc
	↑ INSTIs
Metabolism (clearance)	
↓ albumin	↑ PIs*
↓ liver mass	↑ NNRTIs*
↓ hepatic CYP activity	↑ Maraviroc*
	↑ INSTIs
Excretion (clearance)	
↓ renal function	↑ NRTIs** (particularly tenofovir)

➔ mainly ↑ in ARV exposure with ↑ risk of drug toxicity

Winston A et al. Curr Opin Infect Dis 2014

SWISS HIV COHORT STUDY

Aging and predicted effect on drug clearance



adapated from Polasek TM et al. BJCP 2012

Available data of age on ARV pharmacokinetics

- Increase in exposure of ritonavir and some boosted PI: impact on the magnitude of a drug-drug interaction?

Winston A et al. J Antimicrob Chemother 2013, Crawford K et al. AIDS Res Hum Retrovir 2010

- PK study: 6 pts on TDF + FTC + EFV and 6 pts on TDF + FTC + ATV/r
  ➔ TDF AUC ↓ 8-13%, FTC and RTV AUC ↑ 19-78%, ATV AUC ↓ 12%

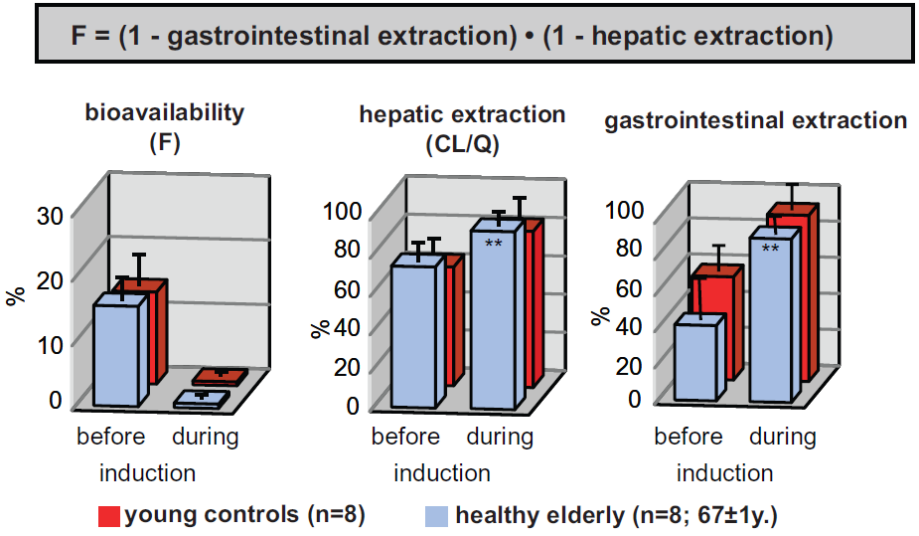
Dumond JB et al. HIV Med 2013

Limitations of current studies:

- small amount of patients > 65 years, exclusion of individuals with significant co-morbidities or frailty ➔ possible underestimation of magnitude of pharmacokinetic changes.
- data on tolerance/toxicity are missing.

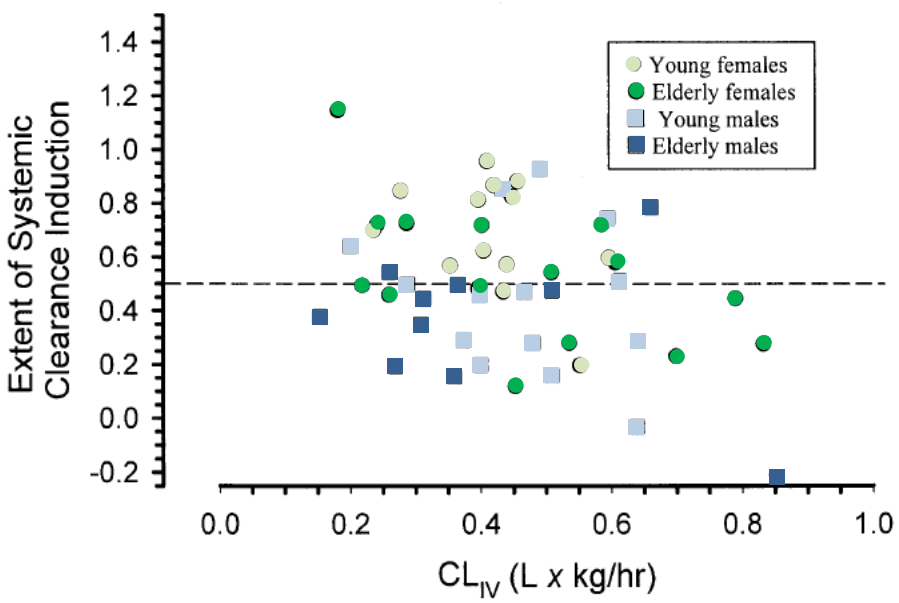
Effect of age on CYP induction/inhibition potential

Induction



Disposition of verapamil in young and elderly subjects before and during induction by rifampicin

Fromm MF et al. BCJP 1998



Extent of midazolam induction resulting from rifampicin treatment is independent of the baseline systemic clearance

Gorski JC et al. Clin Pharmacol Ther 2003

Inhibition

Although clarithromycin concentrations are greater in elderly individuals than in young, intestinal and hepatic CYP3A4 are inhibited to a similar extent as in the young.

Quinney SK et al. BJCP 2007

Presentation outline

- mechanisms of drug-drug interactions
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Case presentation

- 46 year old HIV-infected male
- HIV CDC C3 (PCP in 2005)
- HIV infection controlled (CD4: 912 cells/mm3; VL <20 copies/ml)
- viral mutation: M184V

  - darunavir/r (600/100 mg BID)
  - emtricitabine + tenofovir (200 + 300 mg QD)

- diagnosed with stage IV B Hodgkin's lymphoma
- planned to give BEACOPP (6 cycles)

  - bleomycin (10000 U/m^2)
  - etoposide (200 mg/m^2)
  - doxorubicin (35 mg/m^2)
  - cyclophosphamide (1250 mg/m^2)
  - vincristine (1.4 mg/m^2)
  - procarbazine (100 mg/m^2)
  - prednisone (40 mg/m^2)

Kurz M & Marzolini C. Int J STD AIDS 2014

How would you manage

- stop the antiviral therapy
- reduce doses of cytostatic agents
- omit protease inhibitors and switch to a non PI regimen

How would you manage

- stop the antiviral therapy

  not a good option in our patient (previous AIDS with severe immunosuppression)

- reduce doses of cytostatic agents

  no recommendations on how to adjust, risky given the advanced stage of the Hodgkin Lymphoma.

- ✓ omit protease inhibitors and switch to a non PI regimen

  PI have been shown to increase the incidence and severity of chemotherapy related side effects due to inhibition of drug metabolizing enzymes.

Leveque D et al. Pharm World Sci 2009, Vaccher E et al. Cancer 2001, Cingolani A et al. AIDS 2010, Kotb R et al. Eur J Haematol 2006

DDI potential with patient's chemotherapy

Drug	Metabolism	Comment
Bleomycin	non-CYP mediated metabolism	✓
Etoposide	CYP3A4 + non-CYP metab. + UGT; 45% unchanged in urine	↑ level with CYP3A4 inhibitor ↓ level with CYP3A4 inducer
Doxorubicin	non-CYP metabolism	✓
Cyclophosphamide	CYP2B6 (activation) >> CYP3A4 (inactivation, neuro-toxic metabolite)	↑ active metab. with CYP2B6 inducer ↑ neurotoxicity with CYP3A4 inducer ↑ active metab. with CYP3A4 inhibitor
Vincristine	CYP3A5 >> CYP3A4	↑ level with CYP3A4/5 inhibitor ↓ level with CYP3A4/5 inducer
Procarbazine	CYP2B6 (activation)	↑ active metab. with CYP2B6 inducer

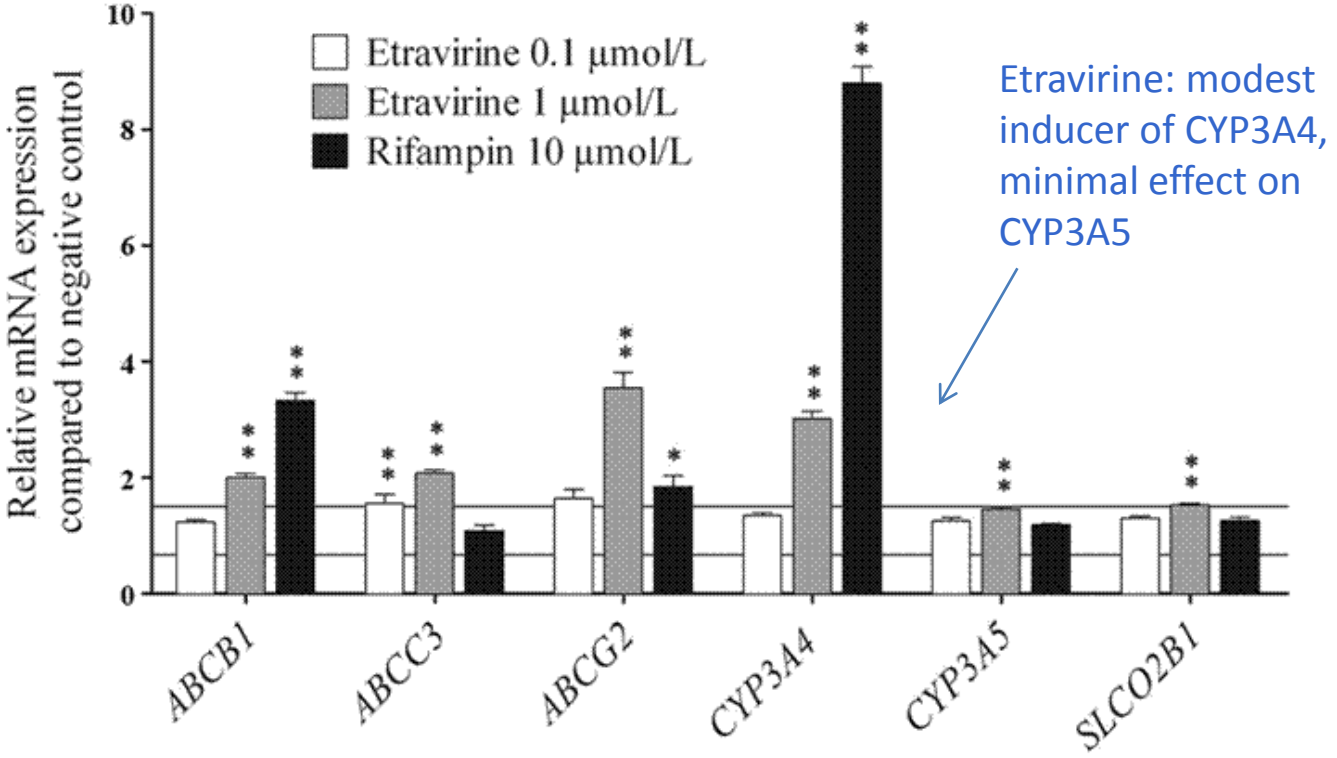
Switch to a non PI regimen: options

Raltegravir: UGT1A1 substrate ➔ no DDI with chemotherapy

However, patient has M184V which requires treatment intensification

Would you add etravirine?

Induction of CYP and transporters by etravirine



Zembruski N et al. AAC 2011

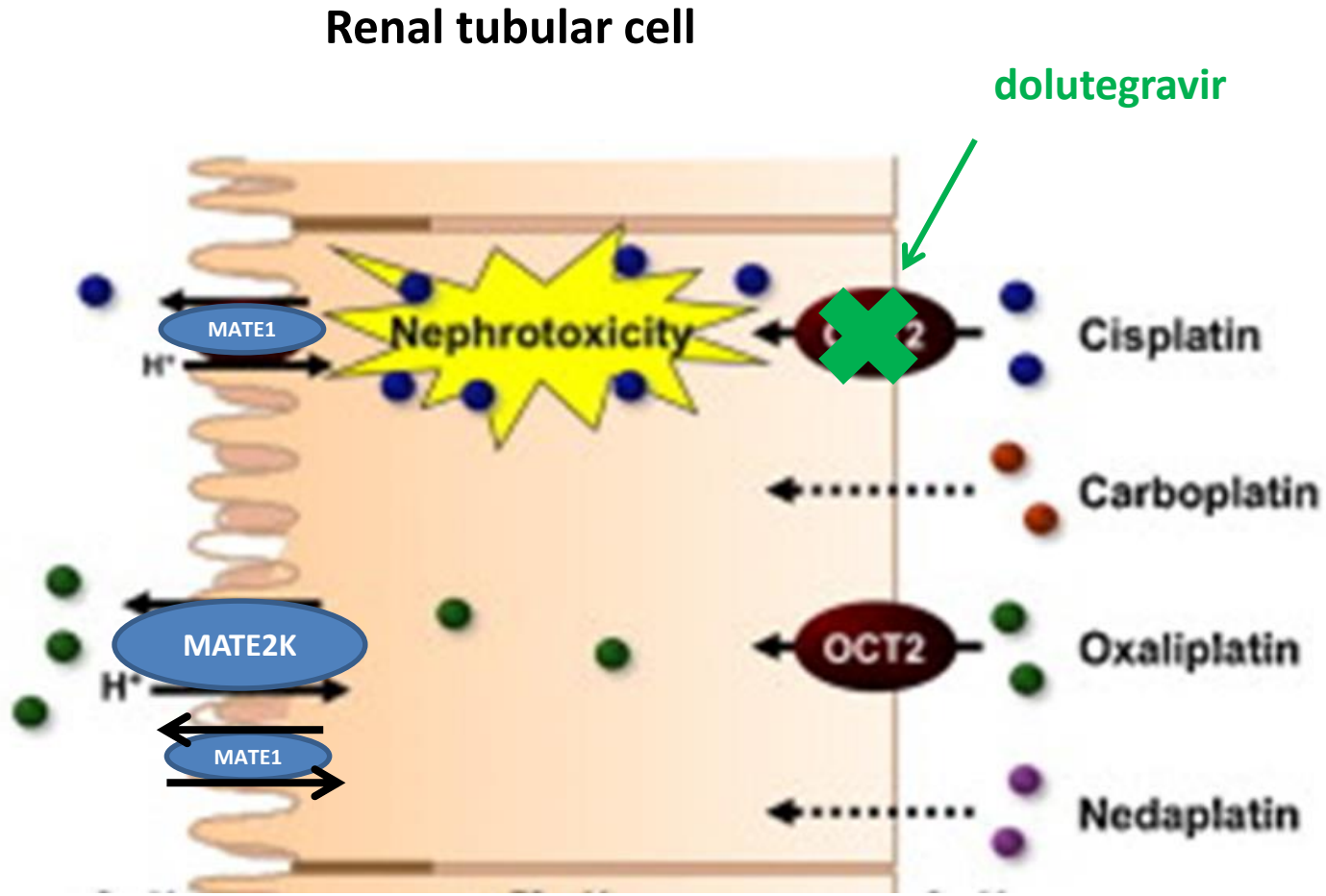
Predicted DDI with patient's new ARV regimen

Drug	Metabolism	Comment
Bleomycin	non-CYP mediated metabolism	✓
Etoposide	**CYP3A4** + non-CYP metab. + UGT; 45% unchanged in urine	decrease in etoposide levels predicted to be modest
Doxorubicin	non-CYP metabolism	✓
Cyclophosphamide	CYP2B6 (activation) >> **CYP3A4** (inactivation, neuro-toxic metabolite)	no effect on active metabolite but could increase neurotoxic metabolite
Vincristine	**CYP3A5 >>> CYP3A4**	decrease in vincristine levels predicted to be weak
Procarbazine	CYP2B6 (activation)	✓

==> etravirine is unlikely to significantly impair the activity of chemotherapy

Outcome: - VL remained suppressed
- no major toxicities related to chemotherapy
- complete remission

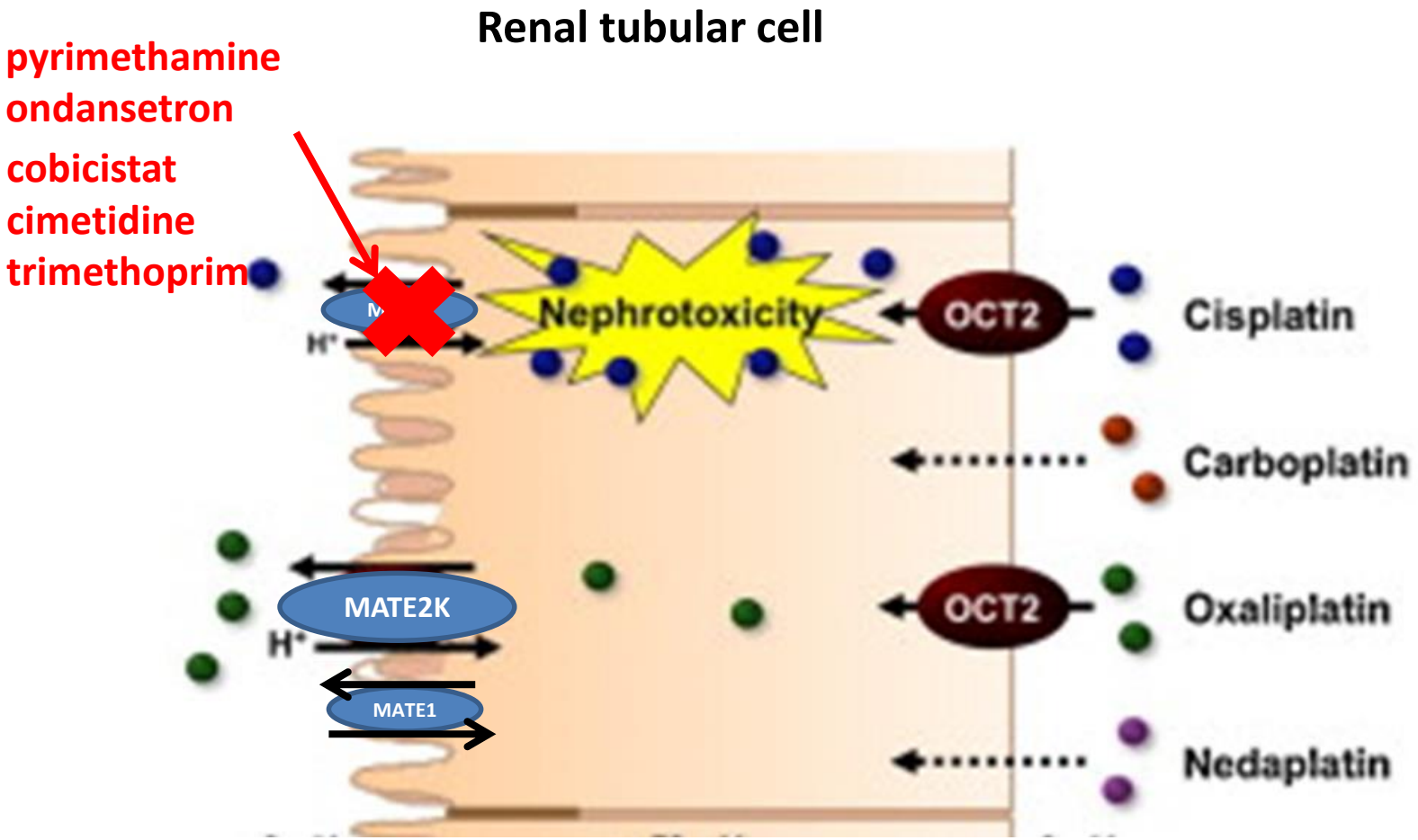
Beneficial drug-drug interaction



Mice lacking Oct1/2 had less cisplatin related nephrotoxicity Franke RM et al. Clin Cancer Res 2010

Adapted from Yanezawa A et al. Biochem Pharmacol 2011, Yokoo S et al. Biochem Pharmacol 2007

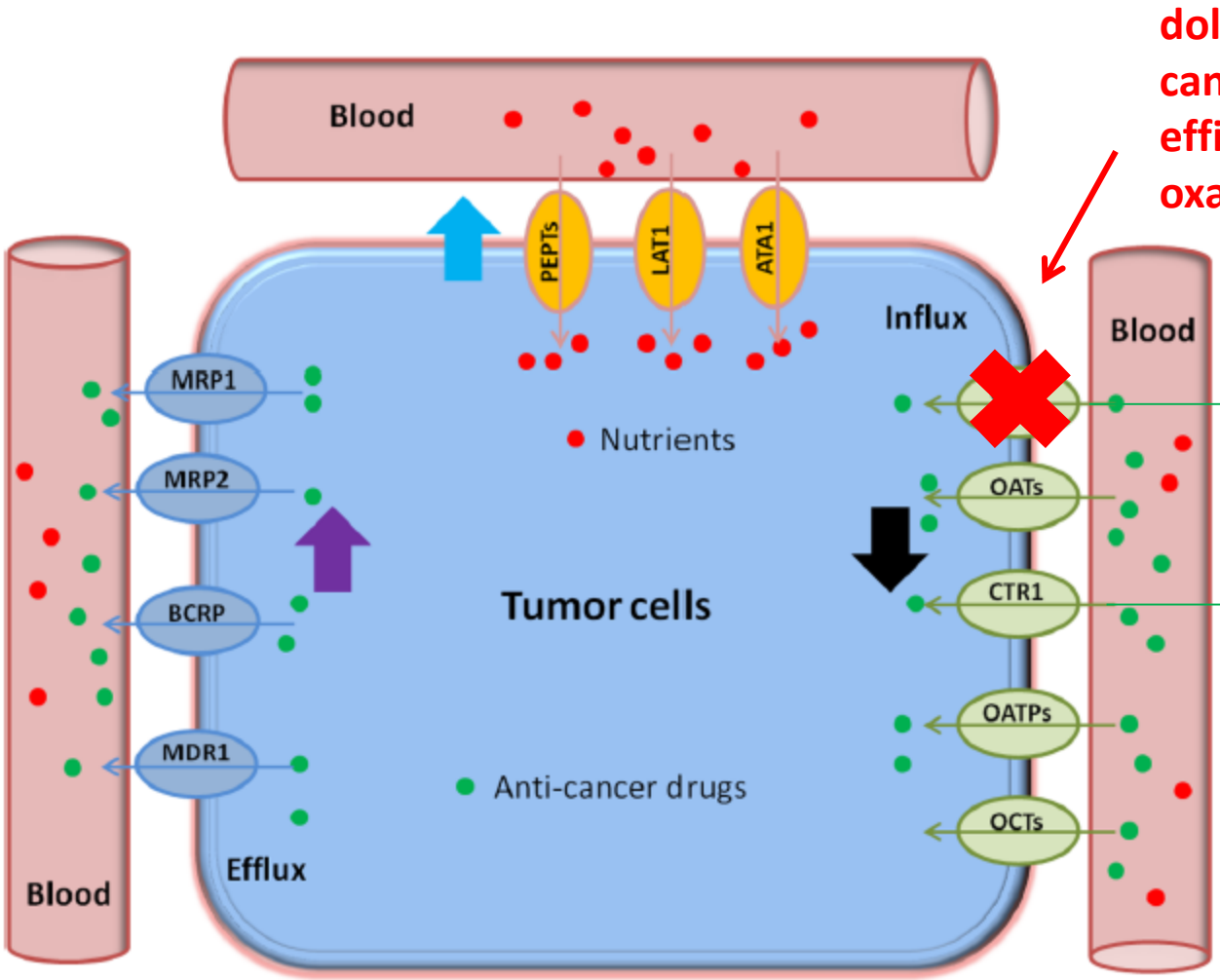
Deleterious drug-drug interaction



Ondansetron enhanced cisplatin related nephrotoxicity Li Q et al. Toxicol Appl Pharmacol 2013

Yanezawa A et al. Biochem Pharmacol 2011, Nakamura T et al. Biochem Pharmacol 2010

Transporters expression in tumor cells



Inhibitor of OCT2 antagonized oxaliplatin efficacy Morrow CJ et al. Cancer Res 2010

Inhibitor of OCT2 had no effect on cisplatin uptake in cancer cells Sprowl J et al. CPT 2013

Li Q et al. Molecular and Cellular Therapies 2014

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www.hiv-druginteractions.org

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Meeting Report - HIV2014, Glasgow

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Meeting Report - 54th ICAAC, Washington

Case Report - Atazanavir/ritonavir and telaprevir.

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TREATMENT SELECTOR TABLES

Treatment Selector Tables

New tables for Contraceptives/HRT and Recreational Drugs

We have produced a series of printable tables showing interactions between key antiretrovirals and drugs used to treat a range of common comorbidities.
The tables can be accessed from the Printable Chart & Treatment Selector sub menu on the Interaction Charts menu.

Click here for the new Contraceptive/HRT table.

Click here for the new Recreational Drug table.

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Cytotoxic Treatment Selector

Charts updated January 2015. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org

		ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
Anti-tumour ABT	Bleomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Daunorubicin	↔[a]	↔	↔	↔	↔[a]	↔[a]	↔	↔	↔	↔[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Doxorubicin	↔[a]	↔	↔	↔	↔[a]	↔[a]	↔	↔	↔	↔[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Epirubicin	↓[a]	↓	↓	↓	↓[a]	↓[a]	↑	↔	↔	↔[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
Alkylating Agents	Carboplatin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[h]	↔[h]	↔[ch]	↔[b]
	Chlorambucil	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Cisplatin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↑[h]	↑[h]	↔[ch]	↔[b]
	Cyclophosphamide	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[f]	↓[f]	↓[f]	↔	↔	↔	↓[d]	↔	↔	↔	↔	↔	↔[b]
	Dacarbazine	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔[b]
	Dactinomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Ifosfamide	↑[e]	↑[e]	↑[e]	↑[e]	↑[e]	↑[e]	↓[f]	↓[f]	↓[f]	⇓	⇓	↔	↑[e]	↔	↔	↔	↔	↔[c]	↔[b]
	Oxaliplatin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[i]	↔	↔	↔	↑	↑	↔[c]	↔[b]
	Procarbazine	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↓[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
Antimetabolite Agents	Capecitabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑?	↑?	↑?	↔[b]
	Cytarabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Fluorouracil	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑?	↑?	↑?	↔[b]
	Gemcitabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Mercaptopurine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔[b]
	Methotrexate	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↔[g]	↑[cg]	↔[bg]
Plant Alkaloids	Docetaxel	↑	↑	↑	↑	↑	↑	↓	↓	↓	↑?	↑?	↔	↑	↔	↔	↔	↔	↔	↔[b]
	Etoposide	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[b]
	Irinotecan	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[b]
	Paclitaxel	↑	↑	↑	↑	↑	↑	↑	↓⇓	↔	⇓	⇓	⇓	↑	⇓	↔	↔	↔	↔	↔[b]
	Vinblastine	↑	↑	↑	↑	↑	↑	↓	↓⇓	↓	⇓	⇓	⇓	↑	⇓	↔	↔	↔	↔	↔[b]
	Vincristine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[b]
Inhibitors	Dasatinib	↑*	↑	↑	↑	↑*	↑*	↓	↓	↓	⇑+	⇑	↔	↑	↔	↔	↔	↔	↔	↔
	Erlotinib	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	⇑	↑	⇑	↔	↔	↔	↔	↔
	Gefitinib	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔

Clinical studies of new cytostatics in HIV patients

A Phase 1/Pharmacokinetic Study of Sunitinib in Combination With Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus-Positive Patients With Cancer

AIDS Malignancy Consortium Trial AMC 061

Cancer 2014

Michelle A. Rudek, PharmD, PhD[1]; Page C. Moore, PhD[2]; Ronald T. Mitsuyasu, MD[3]; Bruce J. Dezube, MD[4]; David Aboulafia, MD[5]; John Gerecitano, MD, PhD[6]; Ryan Sullivan, MD[7]; Mary E. Cianfrocca, DO[8]; David H. Henry, MD[9]; Lee Ratner, MD, PhD[10]; Missak Haigentz, Jr., MD[11]; Afshin Dowlati, MD[12]; Richard F. Little, MD[13]; Susan Percy Ivy, MD[12]; and John F. Deeken, MD[14]

➔ dose reduction of sunitinib to 37.5 mg in patients receiving PI based ART

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ORIGINAL REPORT

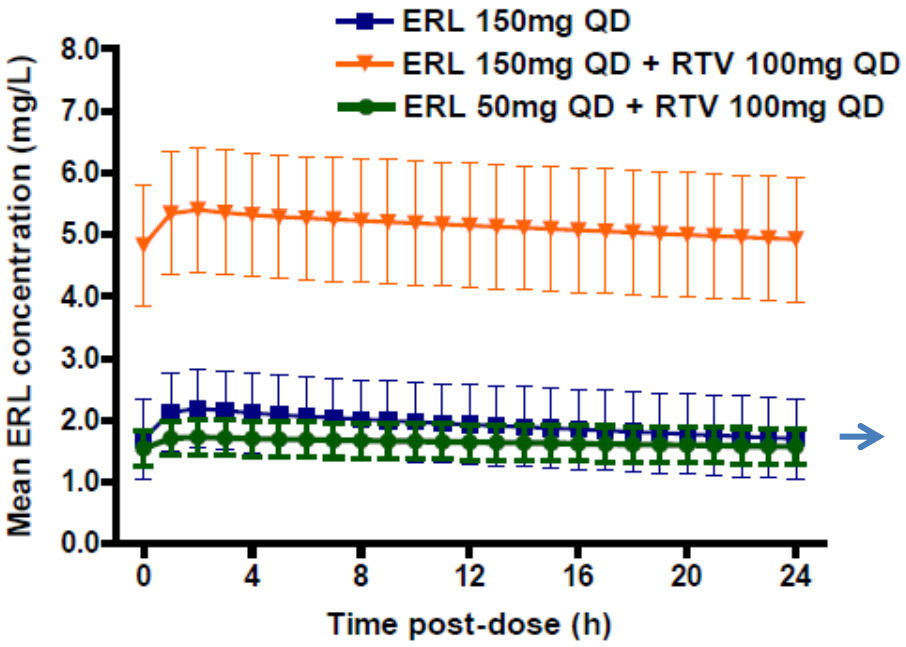
Phase II Trial of Imatinib in AIDS-Associated Kaposi's Sarcoma: AIDS Malignancy Consortium Protocol 042

Henry B. Koon, Susan E. Krown, Jeannette Y. Lee, Kord Honda, Suthee Rapisuwon, Zhenghe Wang, David Aboulafia, Erin G. Reid, Michelle A. Rudek, Bruce J. Dezube, and Ariela Noy

➔ ARV did not significantly alter imatinib metabolism

DDI simulation with the new anti-cancer drug erlotinib

Erlotinib is mainly metabolized by CYP3A4.
Ritonavir is a strong inhibitor of CYP3A4.



→ suggest erlotinib dose reduction to 50 mg QD when co-administered with ritonavir

GMR (90% CI) for PK of ERL + RTV vs. ERL 150mg QD

	ERL150mg QD + RTV 100mg QD	ERL 50mg QD + RTV 100mg QD
C_{trough}	3.01 (2.74-3.31)	0.97 (0.88-1.06)
C_{max}	2.51 (2.33-2.71)	0.81 (0.75-0.87)
AUC_{0-24}	2.74 (2.52-2.98)	0.88 (0.81-0.96)

Molto J et al. IWCPHT 2014

Summary

- DDI with antiretroviral agents are common, affect mainly the co-medication and are mostly manageable but some DDI can be very challenging (i.e. cytostatics, immuno-suppressive drugs….).
- A good understanding of the mechanism of drug action and elimination is essential to optimally manage drug-drug interactions.

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