PL 6. Pharmacology of Antiretroviral Therapy.

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August 2014

UNIVERSITY OF LIVERPOOL

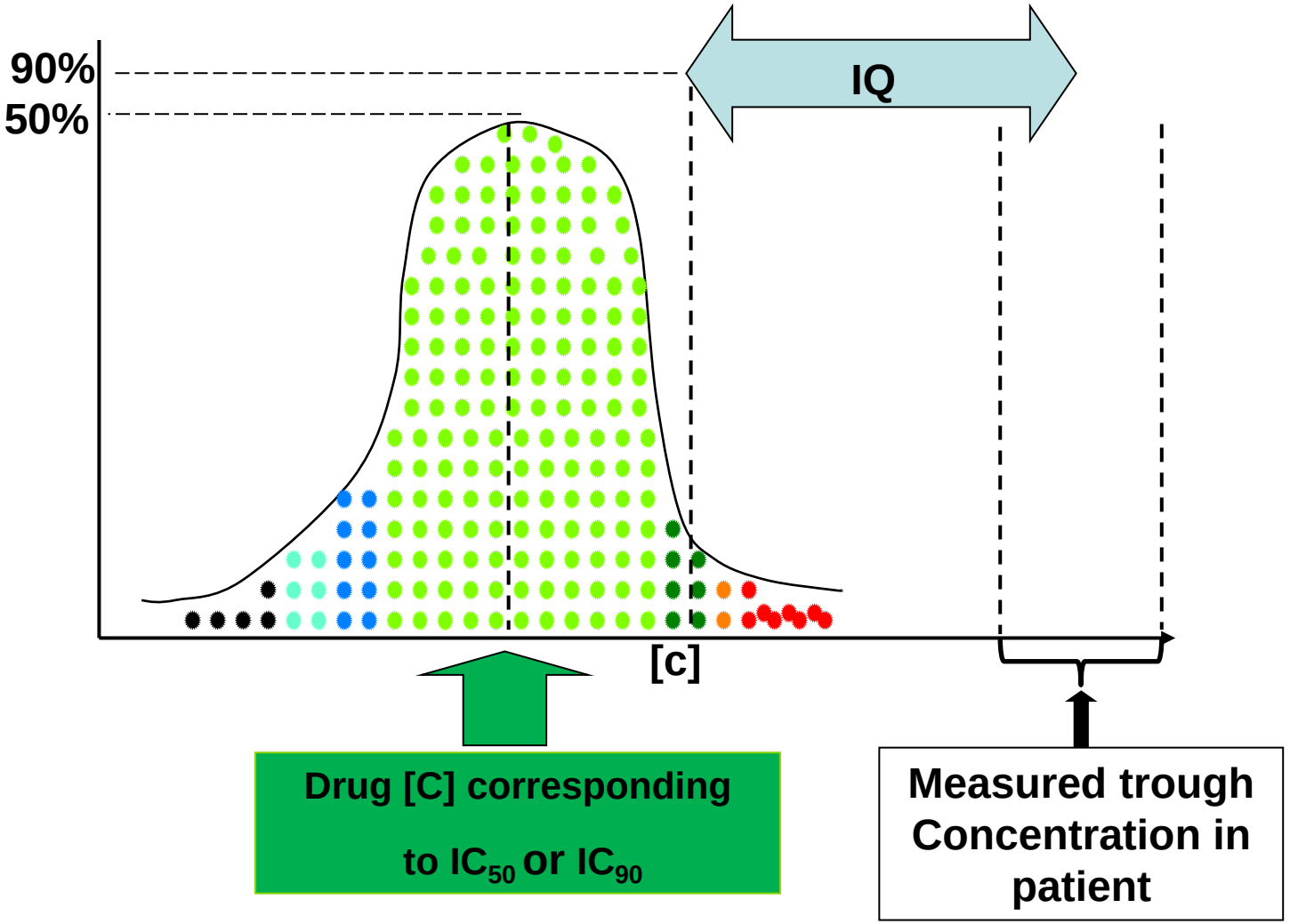
LHPG

Overview

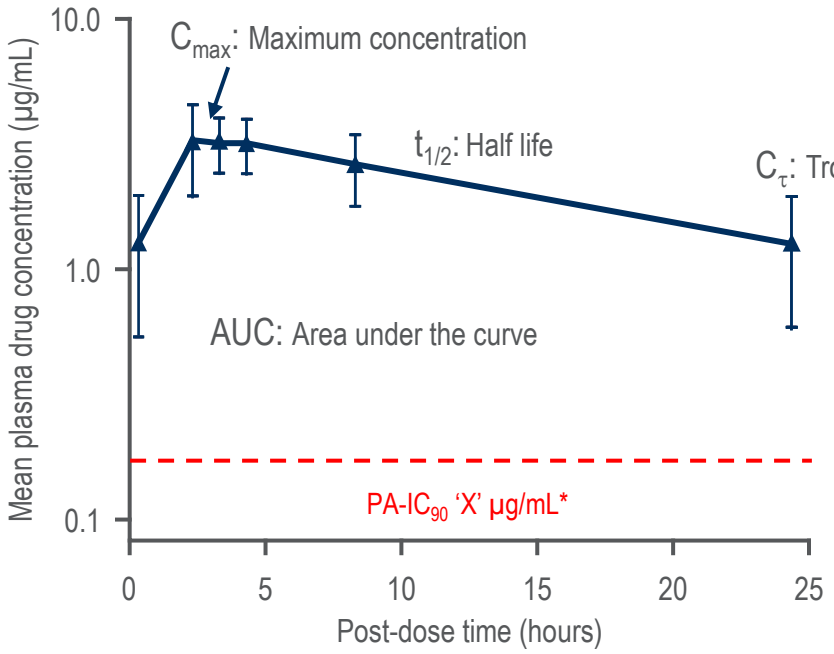
1. Some general principles
2. Why drug interactions occur
3. There are more risky ARVs and more risky co-meds for DDIs
4. DDIs are not going away with an Aging Population.
5. DDIs: we need management strategies.
6. What is on the horizon?

Durable suppression of HIV-1 replication requires delivery of drug to target cells at concentrations that exceed the susceptibility of the virus strain(s) infecting the patient

In vitro susceptibility and target trough concentrations



Pharmacological profile of a QD drug



Clearance = Dose/AUC

*PA-IC_{90} - Protein-adjusted 90% inhibitory concentration

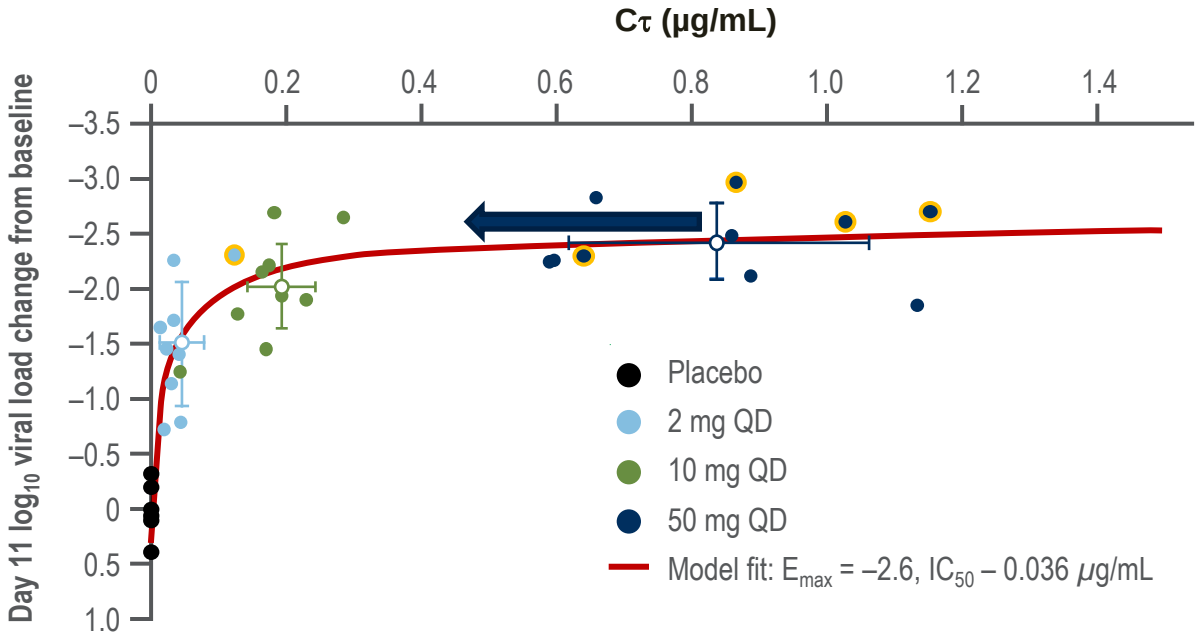
The Inhibitory Quotient is defined as C_τ/PA–IC_{90}

- Drug concentrations in plasma over a dosing interval at steady state.
- All drug levels are well above the in-vitro PA-IC_{90}

Personal communication/data from Professor D Back

RELATIONSHIP BETWEEN DTG TROUGH CONCENTRATION & VIRAL LOAD REDUCTION

Phase IIa, dose-ranging, placebo-controlled, 10-day monotherapy study



Subjects with HIV-1 RNA <50 c/mL are represented by orange-bordered circles

Open circles with lines denote mean standard deviation

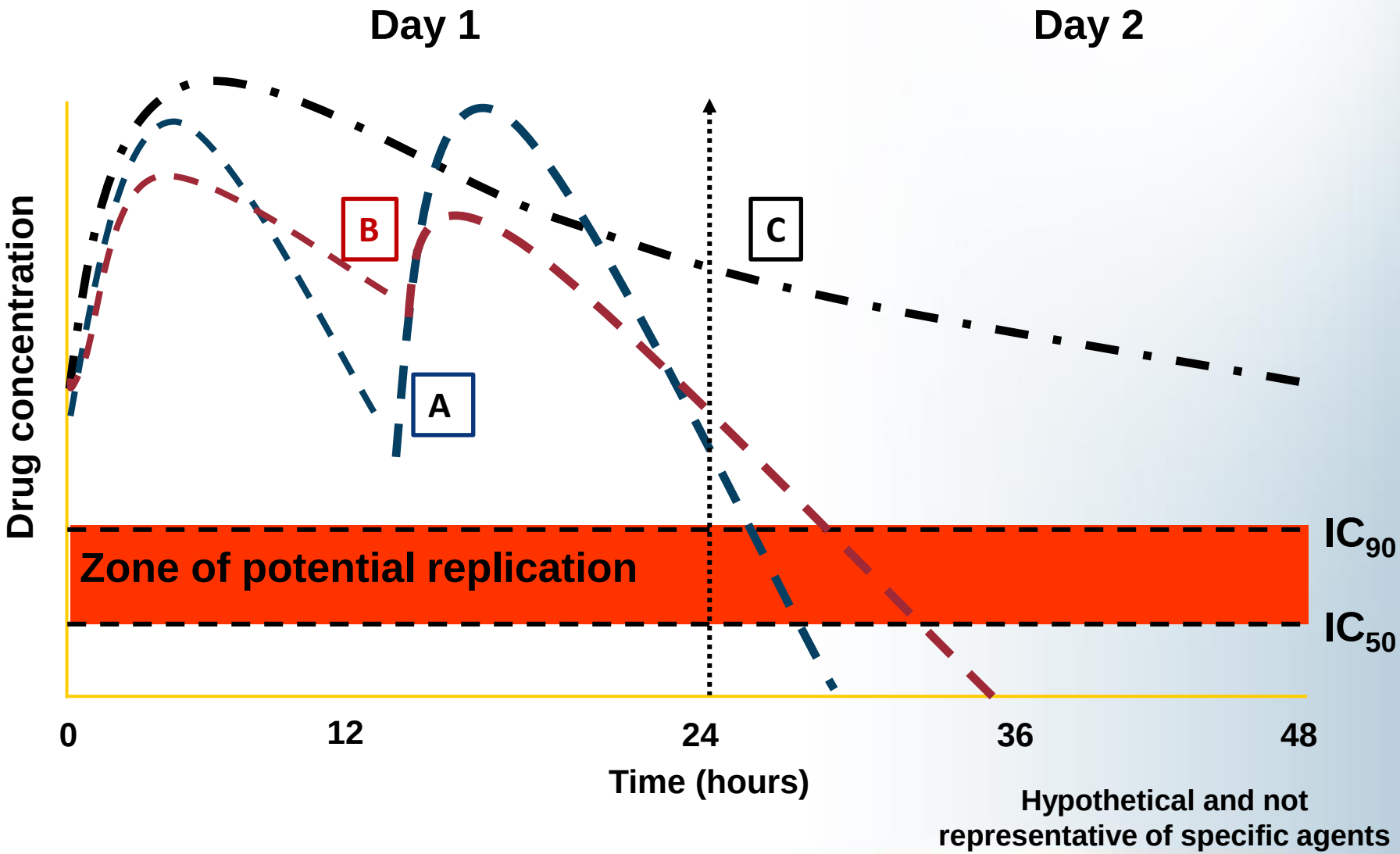
DTG is associated with a well characterised exposure-response relationship

c/mL, copies/mL; Emax, maximum effect

Adapted from Min S, et al. AIDS 2011; 25:1737–45

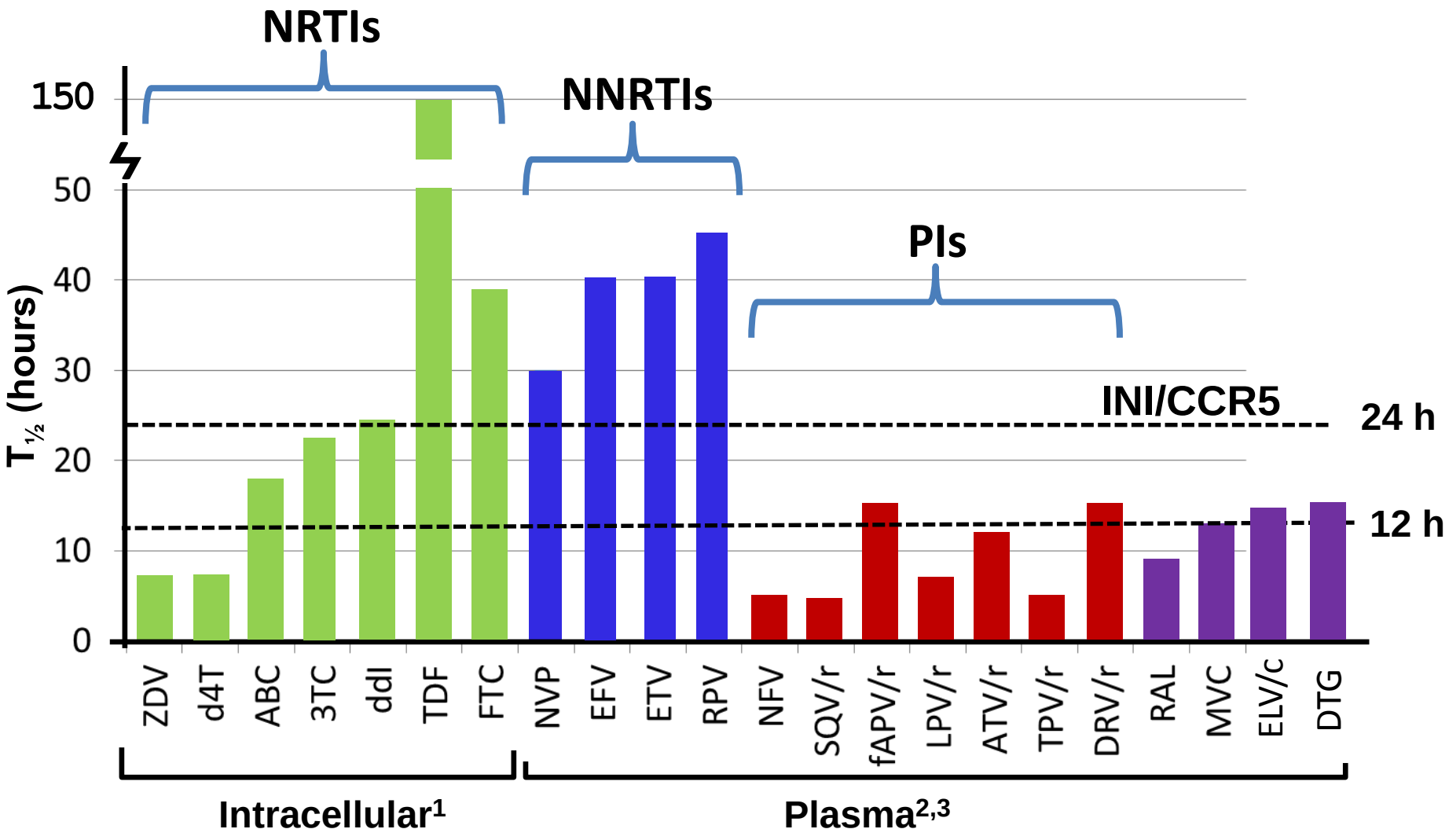
Whether you give a drug once or twice/three times a day is largely governed by the **Half Life:** this parameter is the key to **Forgiveness**

PK of HIV Drugs With Different Half-lives



Adapted from Taylor S et al AIDS 2007; 21: 1673-1682

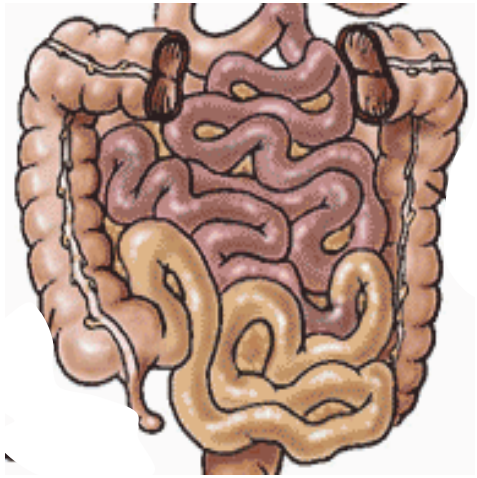
Antiretroviral drug half-lives



Created from 1. Anderson PL, et al. J Antimicrob Chemother. 2011:66:240–50. 2. Summary of Product Characteristics. Available at: http://www.medicines.org.uk/emc/. 3. Ford J, et al. Antimicrob Agents and Chemother. 2004;48:2388–93; www.hiv-druginteractions.org

Why Drug-Drug Interactions (DDIs) occur

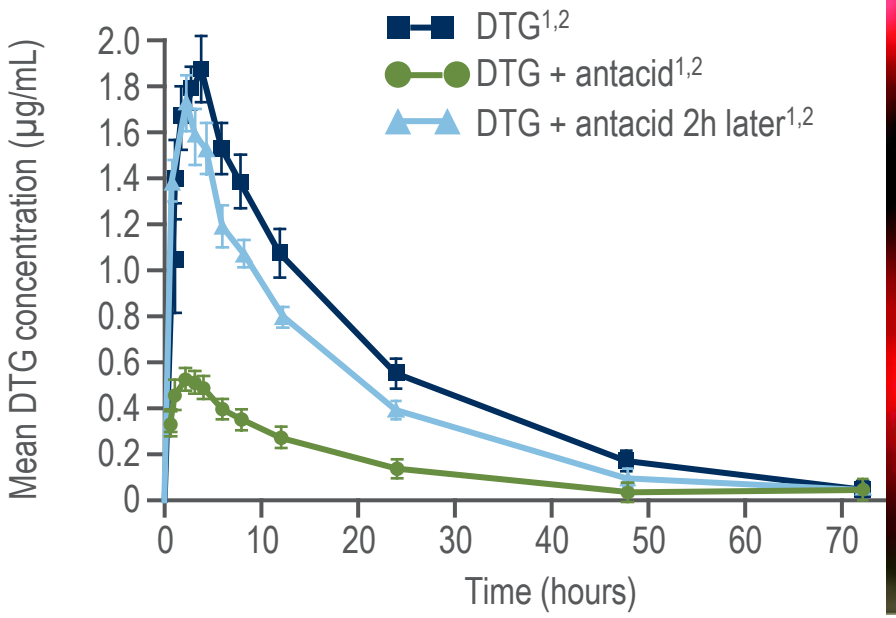
Mechanisms of DDIs: Absorption

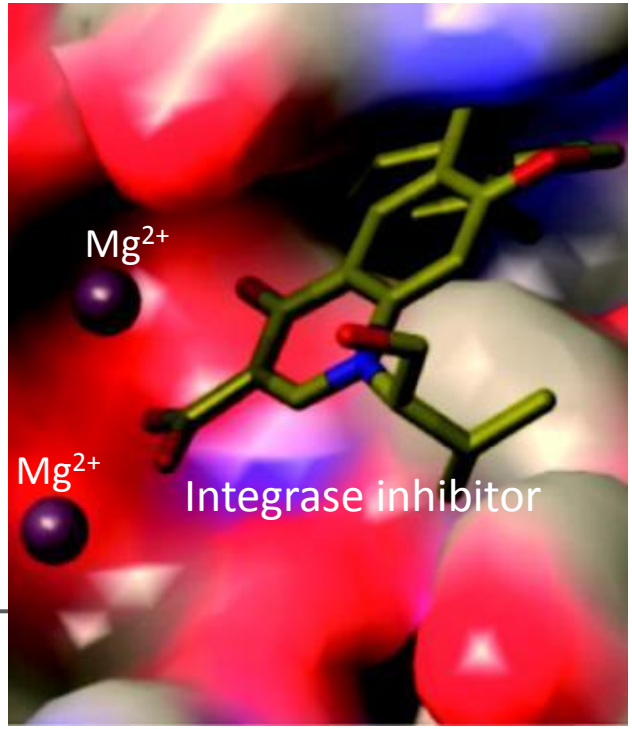


3 Distinct mechanisms

- Chelation with cations
- Change in gastric pH
- Altered enzymes or transporters in enterocyte

Chelation with Cations: Integrase Inhibitor and Antacids *(polyvalent cations)*



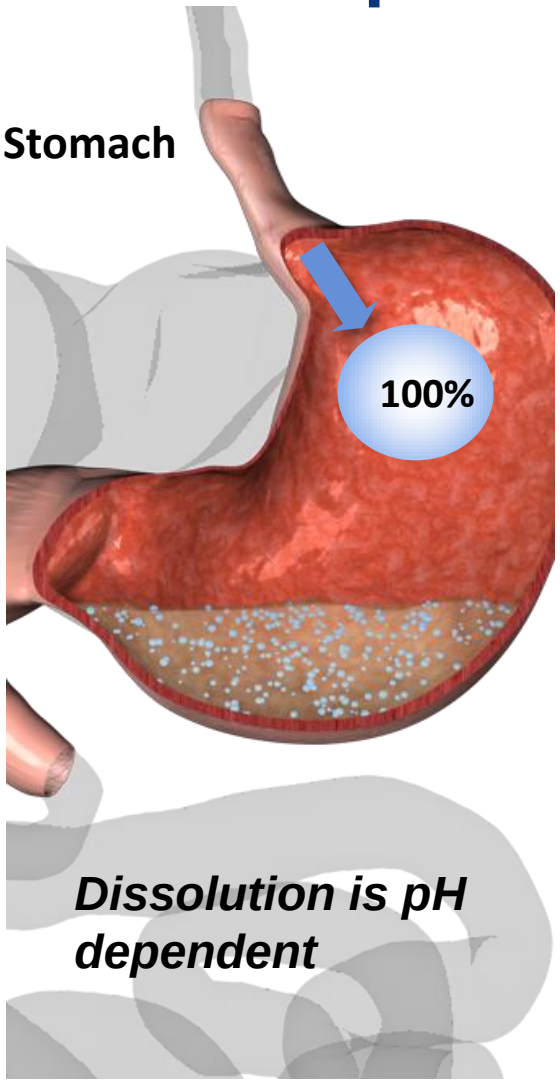


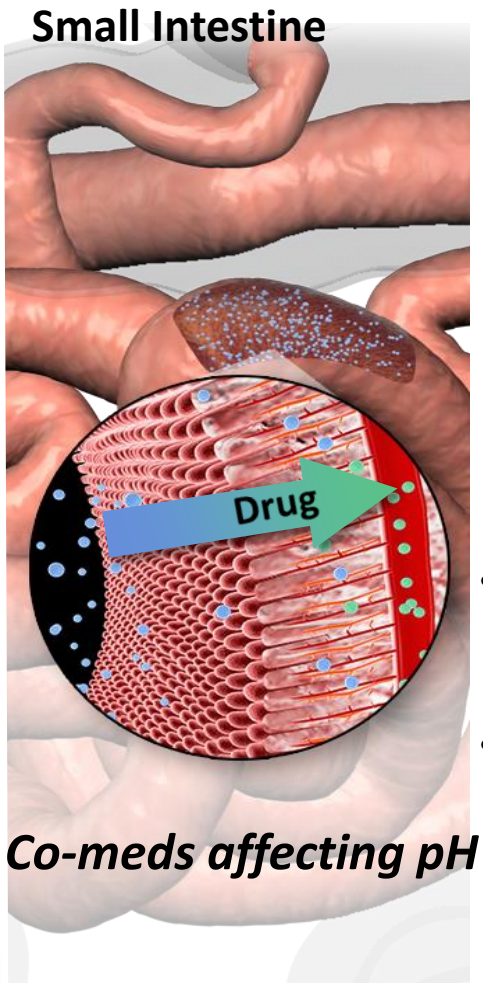
Dolutegravir should be taken 2 hours before or 6 hours after taking antacids containing polyvalent cations[1,2]

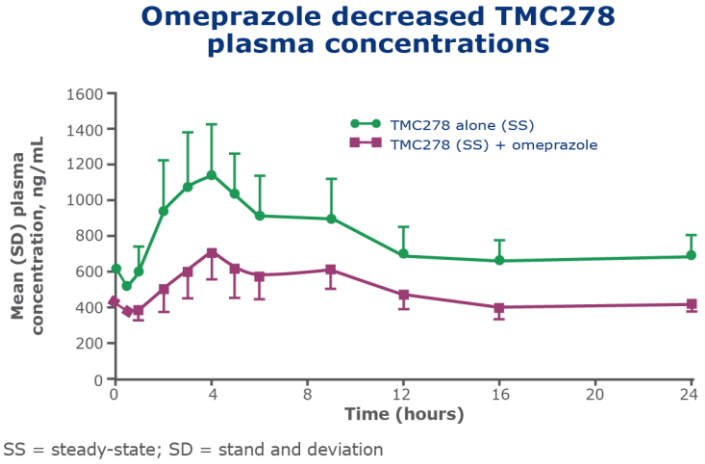
Values shown are GLS mean ratio (90% CI)
*DTG given as 50 mg QD in study

1. Adapted from Patel P, et al. J Antimicrob Chemother 2011;66:1567–72
2. Adapted from Song I, et al. ICAAC 2009. Abstract A1-1305

Change in Gastric pH: Rilpivirine & Proton Pump Inhibitors





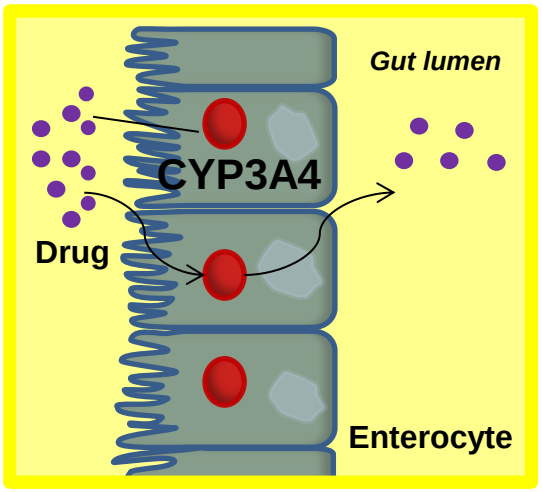


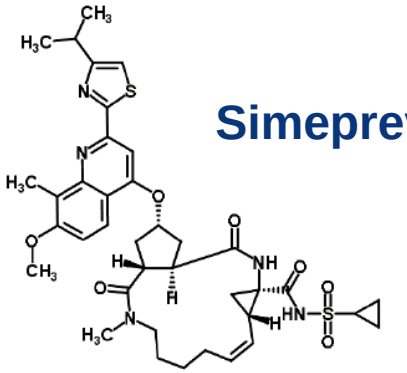
- Co-administration of Omeprazole 20 mg reduced rilpivirine exposure by 40%
- Combination of rilpivirine with PPIs is contraindicated[1]

1. Crauwels H, et al. HIV9 2008.

Altered Enzyme Activity: CYP3A4 inhibition

(A) Intestine – drug metabolized

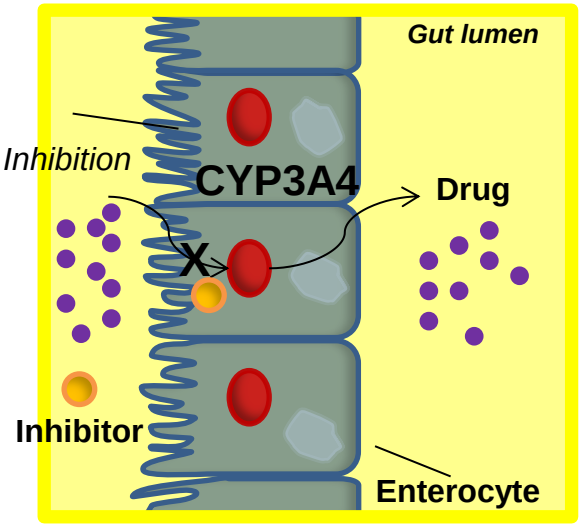




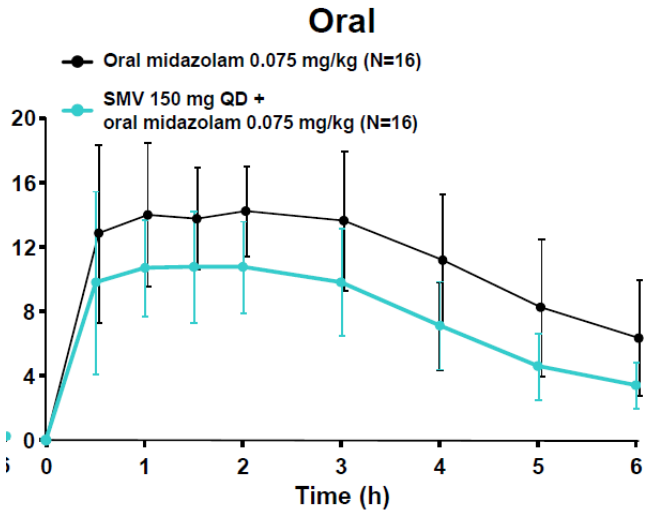
Simeprevir

Simeprevir is a mild inhibitor of CYP3A4 in intestine but not in the liver.

(B) Intestine – inhibition



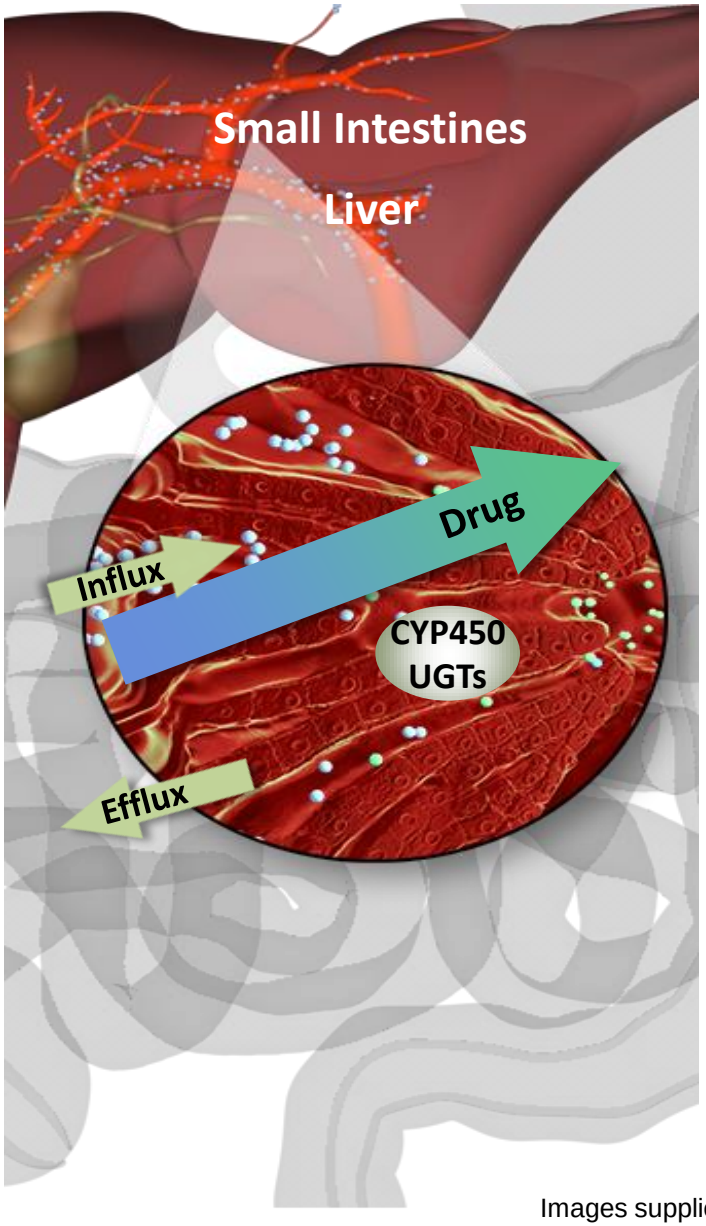
So Simeprevir increases the exposure (AUC) of Oral Midazolam by 45%.



Ouwerkerk-Mahadevan S EASL 2014

Mechanisms of DDIs: Hepatic Clearance

- **Enzyme & transporter induction or inhibition**
- **Inducers:** *rifampicin, rifabutin, efavirenz, nevirapine, phenytoin, carbamazepine, SJW, dexamethasone,*
- **Inhibitors:** *ritonavir, cobicistat, macrolide antibiotics, cimetidine, omeprazole, ketoconazole, GFJ, verapamil, sertraline, fluoxetine, cyclosporine, telaprevir, boceprevir.*



Questions?

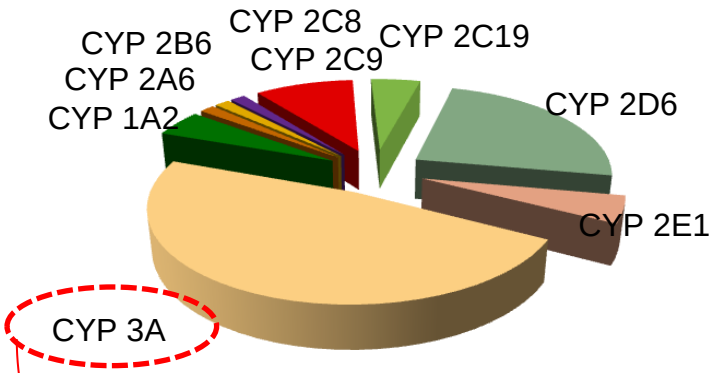
- **Impact of Liver disease on a DDI *(Healthy subjects v patients with HCV)***
- **Impact of Pharmacogenetics on a DDI**

CYP=cytochrome P450;

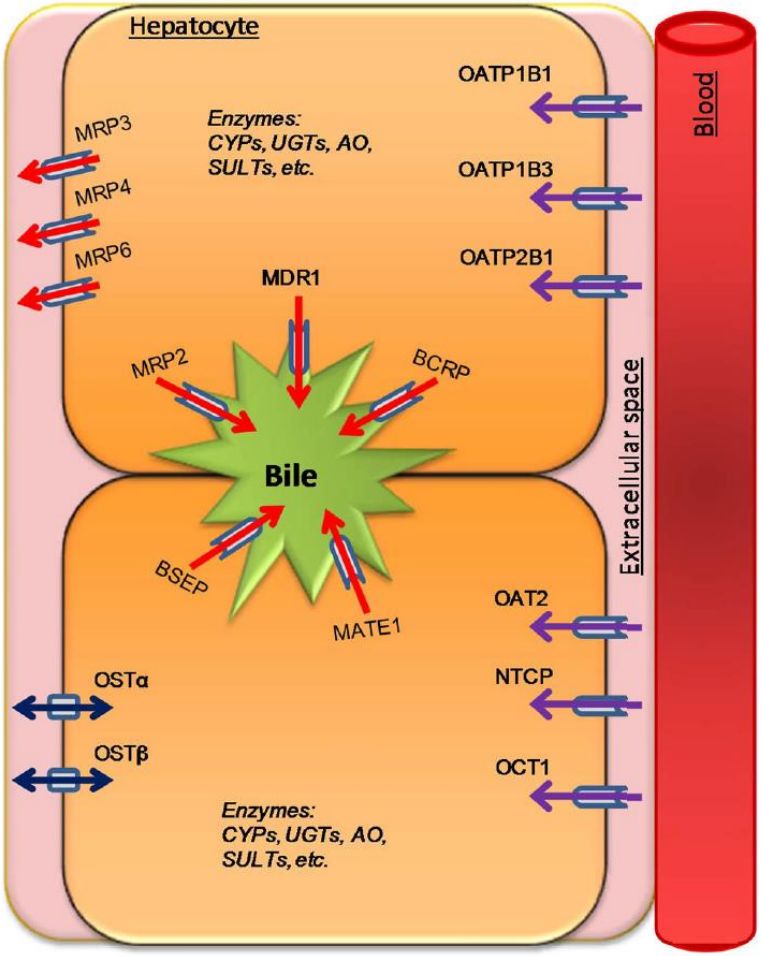
Images supplied by Vertex Pharmaceuticals Inc, February 2011.

The Importance of Hepatic Enzymes & Transporters

Proportion of drugs that are substrates for major CYP enzymes

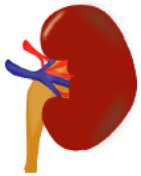


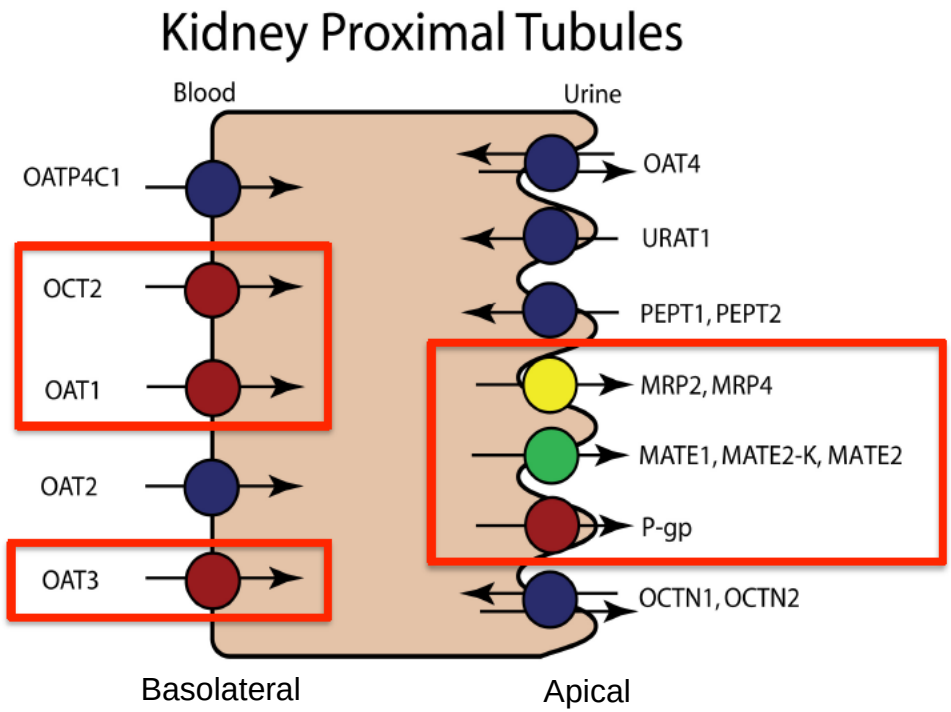
CYP 3A isozymes are the most abundant in the liver



Li R et al Clin Pharmacokinetic 2014; 53: 659-678.

Mechanisms of DDIs: Renal Clearance



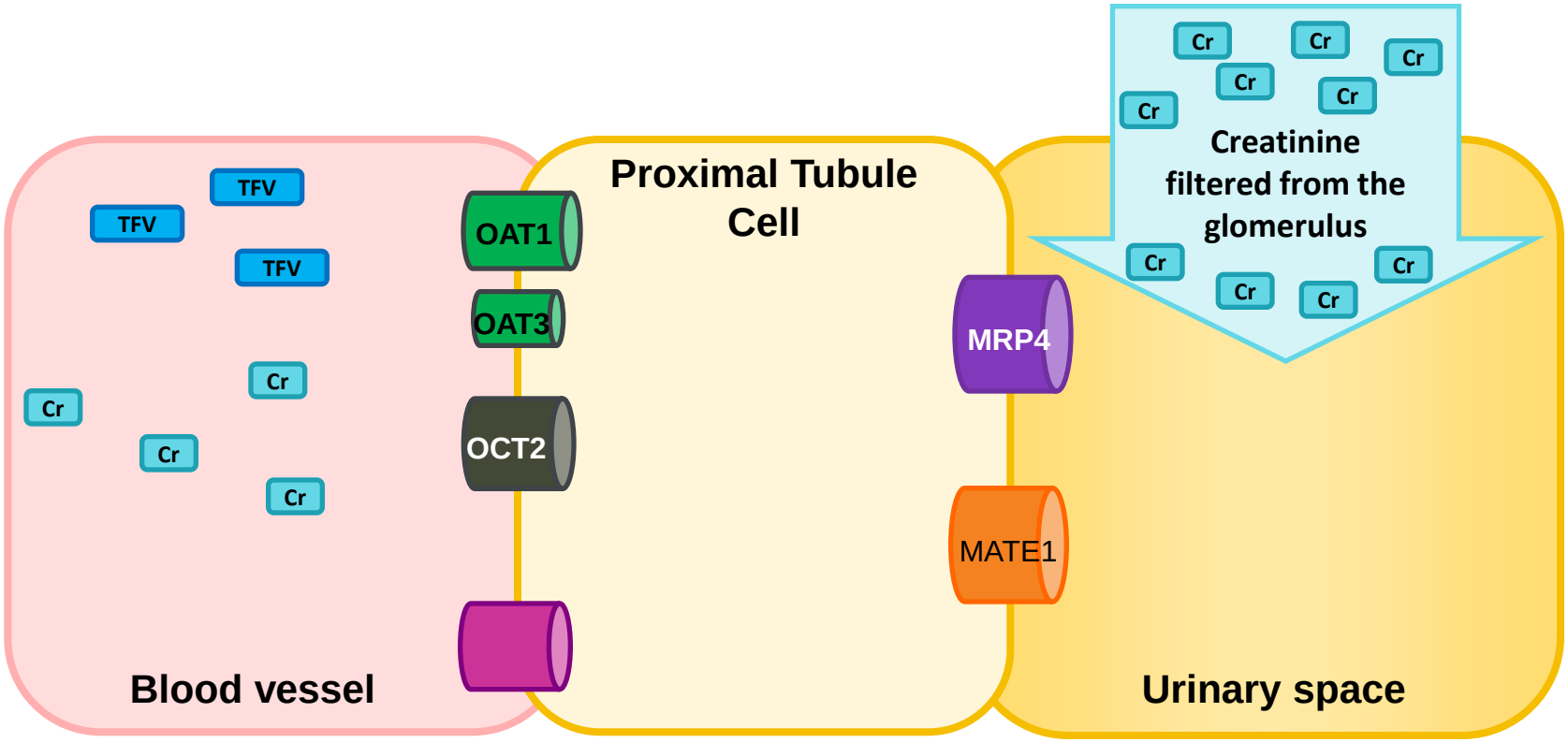


INTERNATIONAL TRANSPORTER CONSORTIUM

Giacomini KM, et al. Nat Rev Drug Discov. 2010 Mar;9(3):215-36.
Zamek-Gliszczynski et al., Clin Pharmacol Ther 92: 553-556, 2012.

Active Tubular Secretion of Creatinine and Tenofovir

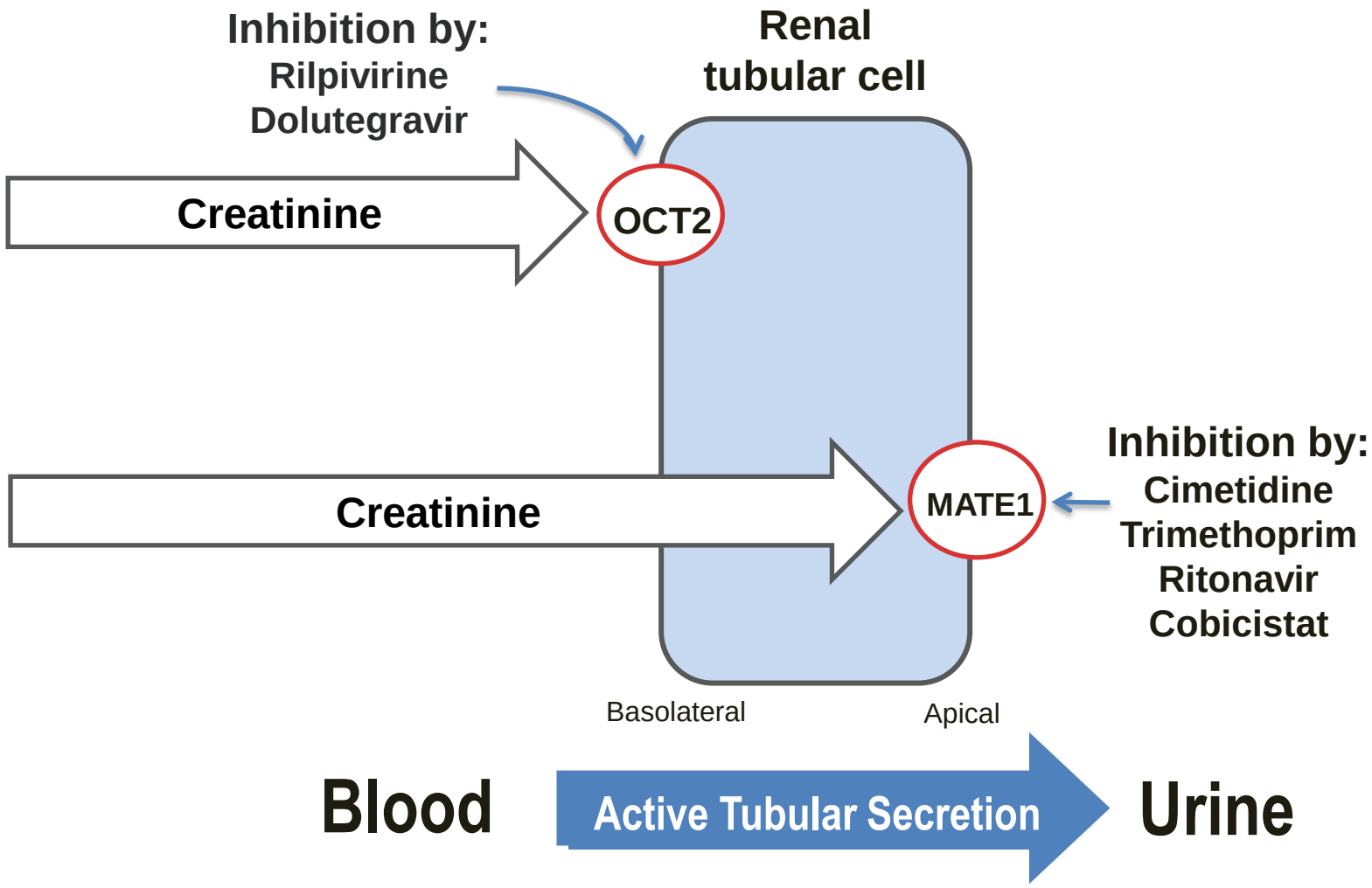
- A small percentage of creatinine is secreted via the proximal tubule.
- Some TFV is secreted via proximal tubule



German P et al. J Acquir Immune Defic Syndr 2012;61:32–40
Lepist EI, Ray AS. Expert Opin Drug Metab Toxicol 2012;8:433–48

GILEAD – with permission

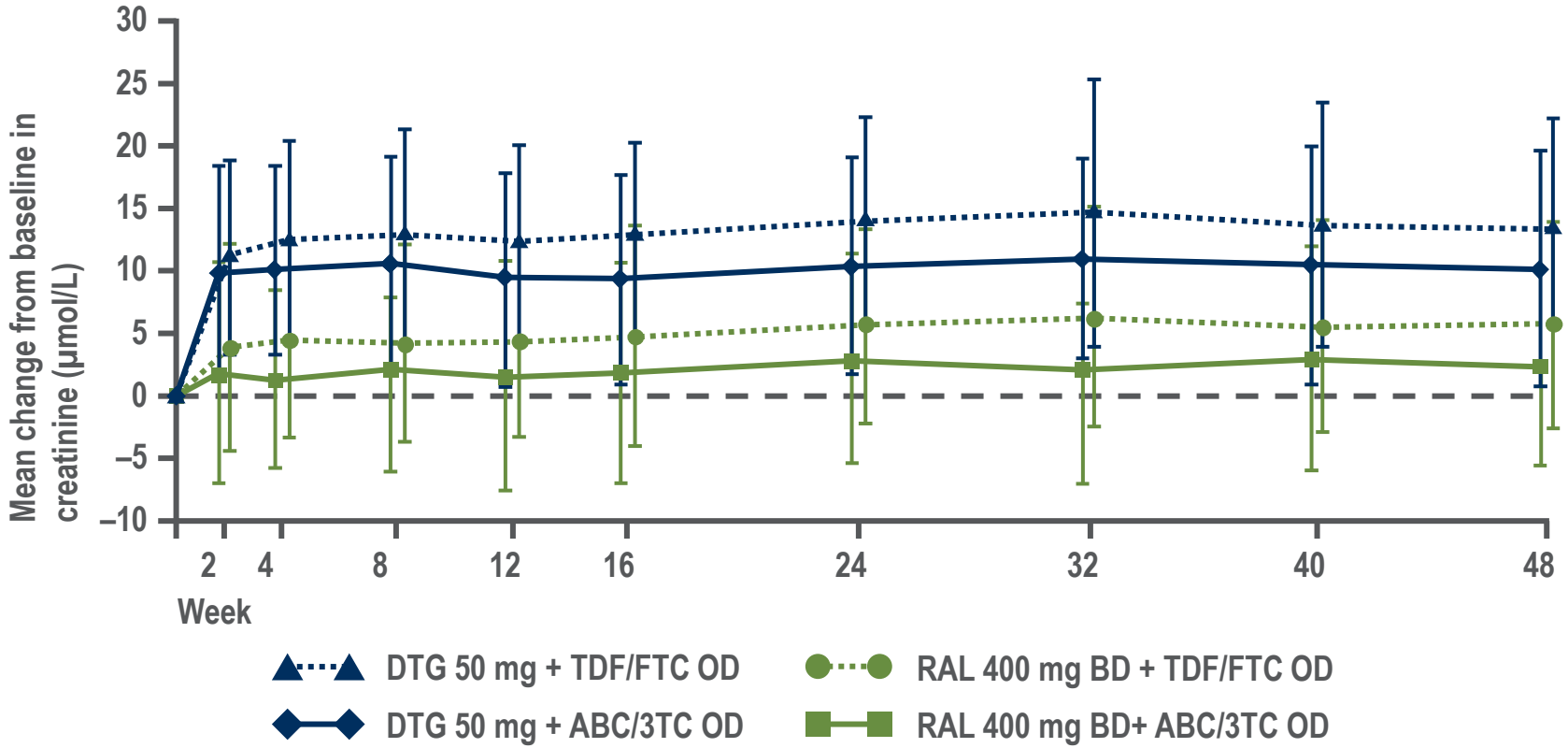
Drugs interfering with Creatinine tubular transporters



CR, creatinine

Adapted from Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724

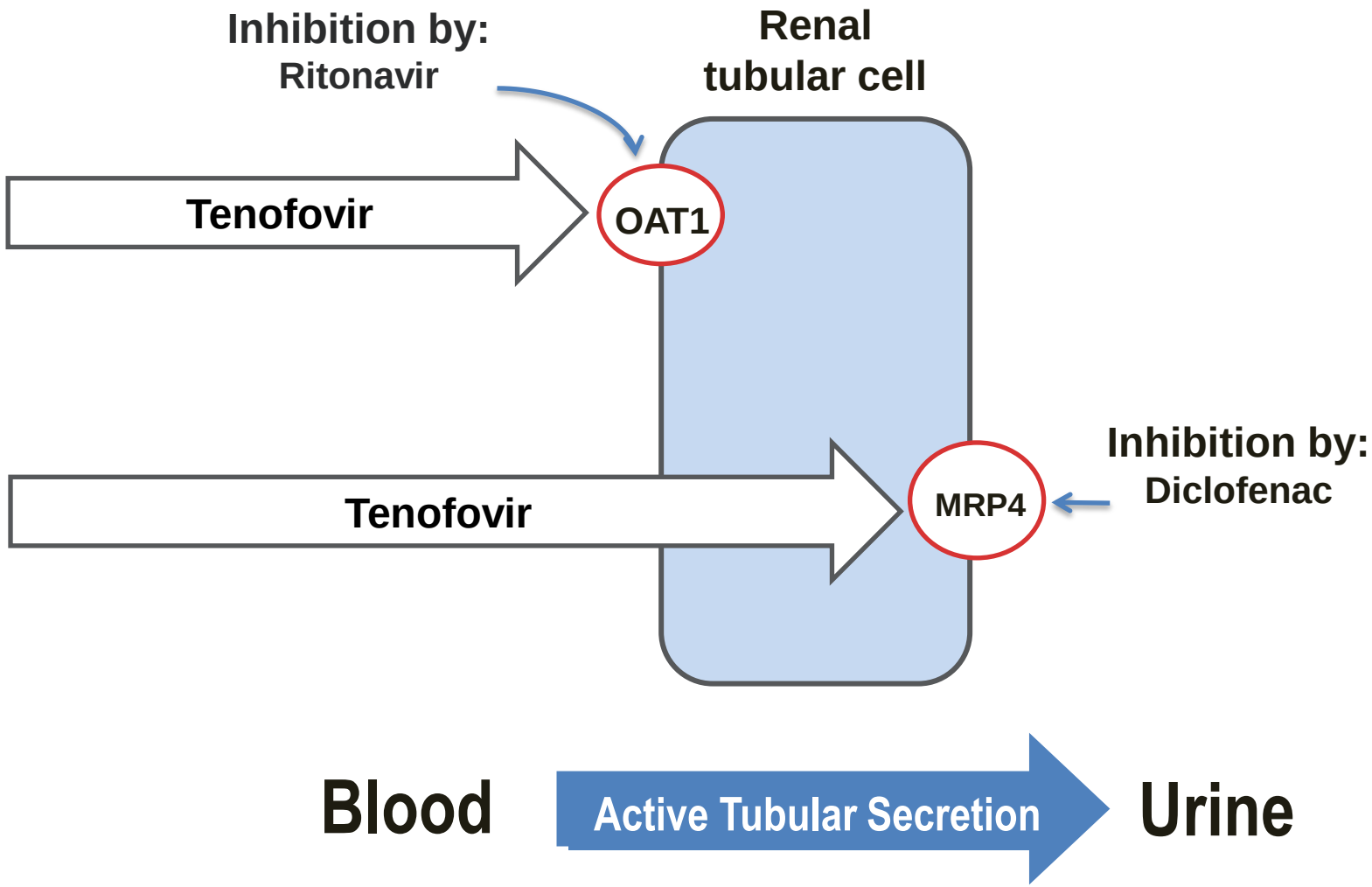
SPRING 2: Change in serum creatinine levels to 48 weeks



Subjects receiving each NRTI background, n (%)	DTG	RAL
TDF/FTC	242 (59)	247 (60)
ABC/3TC	169 (41)	164 (40)

Adapted from Curtis LD, et al. IAS 2013. Poster TUPE282

Drugs interfering with Tenofovir tubular transport



CR, creatinine

Adapted from Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724

Boosted PIs increase tenofovir exposure

Table 1: effects of protease inhibitors on tenofovir, Geometric mean ratio (90% confidence intervals)

Protease Inhibitor	Effect on Tenofovir (GMR; 90%CI) Cmax	AUC	Cmin
Lopinavir (7)	1.15 (1.07-1.22)	1.32 (1.25-1.38)	1.51 (1.37-1.66)
Atazanavir (8)	1.34 (1.20-1.51)	1.37 (1.30-1.45)	1.29 (1.21-1.36)
Darunavir (9)	1.24 (1.08-1.42)	1.22 (1.10-1.35)	1.37 (1.19-1.57)

Should the dose of tenofovir be reduced to 200-250mg/day, when combined with protease inhibitors?.

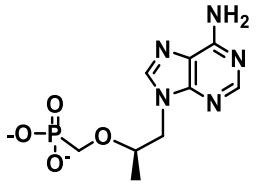
Andrew Hill, Saye Khoo, David Back, Department of Molecular and Clinical Pharmacology, Liverpool University, UK
Anton Pozniak, Marta Boffito, St Stephens Centre, Chelsea and Westminster Hospital, London, UK

International Workshop on HIV Clinical Pharmacology, Washington, USA, May 2014 [poster]

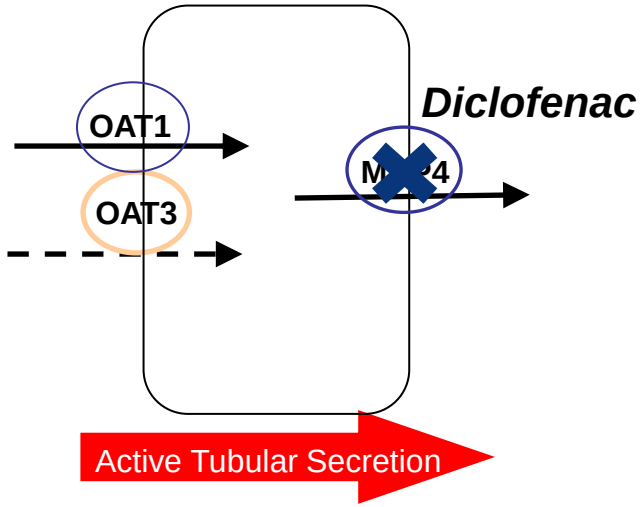
Acute kidney injury caused by tenofovir disoproxil fumarate and diclofenac co-administration

M Bickel,[1] P Khaykin,[1] C Stephan,[1] K Schmidt,[1] M Buettner,[2] K Amann,[2] T Lutz,[3] P Gute,[3] A Haberl,[1] H Geiger,[4] HR Brodt[1] and O Jung[4]

- Retrospective analysis of 89 patients with diclofenac prescriptions
- 68.5% treated with TDF regimen
- 31.5% treated with TDF-sparing regimen
- 13 patients (14.6%) developed AKI after initiating diclofenac. ALL were TDF-treated patients.



Tenofovir



NSAID	IC50 MRP4 [uM]
Celecoxib	35
Diclofenac	**0.006**
Ibuprofen	26.3
Indomethacin	6.1
Naproxen	42.3
Piroxicam	216

Acute renal failure and liver toxicity in an HIV/hepatitis C coinfected patient receiving telaprevir and boosted atazanavir

AIDS 2014, **28**:1537–1543

Eva Van den Eynde, Elena Ferrer and Daniel Podzamczer, *HIV Unit, Infectious Diseases Service, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain.*

- HIV/HCV co-infected male patient on ATV/r + TDF/FTC started TVR and within 1 week experienced progressive deterioration in renal function. Note: ATV/r is only PI recommended for use with TVR.
- TDF/FTC switched to ABC/3TC and TVR stopped. Abnormal liver function tests.

- Mechanisms?

  i) TVR inhibition of renal OCT2 - <u>increased serum creatinine</u>
  ii) TVR inhibition of tenofovir renal elimination – <u>increased serum tenofovir.</u>
  iii) TVR inhibition of ATV clearance – <u>increased atazanavir.</u>

There are more risky ARVs and more risky co-meds for DDIs

Antiretrovirals and Interaction Potential

Highest potential	Moderate Potential	Low Potential
Boosted PIs Perpetrators – enzyme and transporter Inhibition	**Rilpivirine** Victim of enzyme inhibition and induction. Also absorption.	**Raltegravir** Victim of few induction and absorption interactions
EVG/cobi Perpetrators – enzyme and transporter inhibition	**Maraviroc** Victim of enzyme inhibition and induction.	**Most NRTIs**
Efavirenz, nevirapine, etravirine Perpetrators – enzyme and transporter induction	**Dolutegravir** Victim of enzyme inhibition and absorption interactions	

www.hiv-druginteractions.org

Polypharmacy and Risk of Antiretroviral Drug Interactions Among the Aging HIV-Infected Population

Carol Holtzman, PharmD[1], Carl Armon, PhD[2], Ellen Tedaldi, MD[3], Joan S. Chmiel, PhD[4], Kate Buchacz, PhD[5], Kathleen Wood, BSN[2], John T. Brooks, MD[5], and the HOPS Investigators

[1]Temple University School of Pharmacy, Philadelphia, PA, USA; [2]Cerner Corporation, Vienna, VA, USA; [3]Temple University School of Medicine, Philadelphia, PA, USA; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [5]Centers for Disease Control and Prevention, Atlanta, GA, USA.

- N = 3674

- ARV – Non-ARV Interactions identified with the University of Liverpool web site www.hiv-druginteractions.org

- 261 (7%) prescribed at least 1 contraindicated ARV – drug combination
  - *Proton pump inhibitors with atazanavir*
  - *Simvastatin or lovastatin with boosted PI*
  - *Benzodiazepines and boosted PI*
- 1239 (34%) prescribed at least one ARV-drug combination with moderate or high evidence of interaction.

J Gen Intern Med
DOI: 10.1007/s11606-013-2449-6
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www.hiv-druginteractions.org

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Lipid-Lowering Treatment Selector

Charts reviewed February 2014. 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
Statins	Atorvastatin	↑	↑	↑153%	↑	↑490%	↑	↓43%	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Fluvastatin	↔	↔	↔	↑	↔	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Lovastatin	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	Pravastatin	↔	↑81%	↔	↑	↔	↓50%	↓44%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Rosuvastatin	↑213%	↑48%	↑8%	↑	↑107%	↑	↔	↑	↔	↔	↔	↔	↑ 48%	↔	↔	↔	↔	↔	↔
	Simvastatin	↑	↑	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Fibrates	Bezafibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Clofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ ⇑	↔
	Fenofibrate	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	Gemfibrozil	↓	↓	↓	↓	↓41%	↓	↔	↔	↔	↔	↔	⇑	↔	↑	↔	↔	↔	↔	↔
	Ezetimibe	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour Legend

- No clinically significant interaction expected
- These drugs should not be coadministered.
- Potential interaction which may require a dosage adjustment or close monitoring.
- Potential interaction predicted to be of weak intensity (<2 fold ↑AUC or <50% ↓AUC). No *a priori* dosage adjustment is recommended.

Text Legend

↑ Potential increased exposure of the lipid-lowering drug
↓ Potential decreased exposure of the lipid-lowering drug
↔ No significant effect

⇑ Potential increased exposure of HIV drug
⇓ Potential decreased exposure of HIV drug

Drug-drug interactions between HIV drugs and non-HIV drugs [i]

EACS Guidelines 2012

	Non-HIV drugs	ATV	DRV	LPV	RTV [ii]	EFV	ETV	NVP	MVC	RAL
CARDIOVASCULAR DRUGS	atorvastatin	↑	↑	↑	↑	↓	↓	↓*	↔	↔
	fluvastatin	↔*	↔*	↔*	↔*		↑*		↔*	↔*
	pravastatin	↔*	↑	↔	↔	↓	↓*	↔*	↔	↔
	rosuvastatin	↑	↑*	↑	↑	↔	↑*	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓	↓*	↓*	↔	↔
	amlodipine	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔
	diltiazem	↑[iii]	↑*	↑	↑	↓	↓*	↓	E*	↔
	metoprolol	↑*	↑*	↑*	↑*	↔*	↔*	↔*	↔*	↔*
	verapamil	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	E*	↔*
	warfarin	↑ or ↓*	↓	↓	↓	↑ or ↓*	↑*	↑ or ↓*	↔*	↔*
CNS DRUGS	diazepam	↑*	↑*	↑*	↑*	↓*	↑*	↓*	↔*	↔*
	midazolam	↑	↑	↑	↑	↑			↔	↔
	triazolam	↑	↑	↑	↑	↑			↔*	↔*
	citalopram	↑*	↑*	↑*	↑*	↓*	↑*	↓*	↔*	↔*
	mirtazapine	↑*	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔*
	paroxetine	↑*	↓	↑*	↑	↔	↔	↔*	↔*	↔*
	sertraline	↑*	↓	↑*	↑	↓	↓*	↓*	↔*	↔*
	pimozide	↑	↑	↑	↑	↑			↔*	↔*
	carbamazepine	↑D	↑	↑D	↑	↓D	D	↓D	D	D
	lamotrigine	↔**	↔*	↓	↓	↔*	↔*	↔*	↔*	↔*
	phenytoin	D	D	D	↓	↓D	D	↓D	D	D

www.hiv-druginteractions.org

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Cytotoxic Treatment Selector

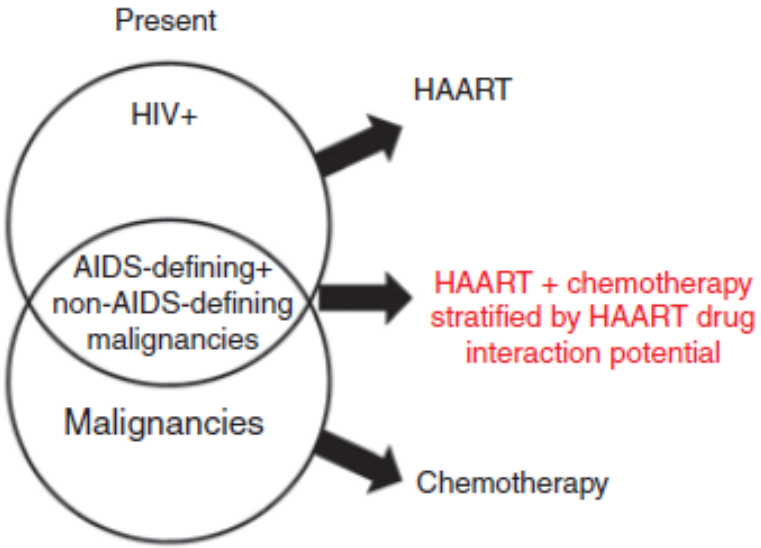
Charts revised February 2014. Full information available at www.hiv-druginteractions.org and www.hiv-druginteractionslite.org

		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	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↑	↑	↔[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]	↔[g]	↑[cg]	↔[bg]
Plant Alkaloids	Docetaxel	↑	↑	↑	↑	↑	↑	↓	↓	↓	↑?	↑?	↔	↑	↔	↔	↔	↔	↔	↔[b]
	Etoposide	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[b]
	Irinotecan	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[b]
	Paclitaxel	↑	↑	↑	↑	↑	↑	↑	↓⇓	↔	⇓	⇓	⇓	↑	⇓	↔	↔	↔	↔	↔[b]
	Vinblastine	↑	↑	↑	↑	↑	↑	↓	↓⇓	↓	⇓	⇓	⇓	↑	⇓	↔	↔	↔	↔	↔[b]
	Vincristine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[b]

Also Tyrosine Kinase Inhibitors (eg: dasatinib, everolimus, imatinib, lapatinib – have complex interaction profile)

Pharmacotherapy in Cancer Patients With HIV/AIDS

JH Beumer[1,2], R Venkataramanan[2,3] and MA Rudek[4]



Newer antiretrovirals such as raltegravir may become standard of care in patients with multiple comorbidities due to their reduced interaction potential as compared with NNRTIs and PIs

Received 6 December 2013; accepted 7 January 2014; advance online publication 19 February 2014. doi:10.1038/clpt.2014.10

- DDIs are not going away with an aging HIV population.

Considerations in Management of the Older HIV Patient

- **Co-morbid conditions**
  - *eg., cardiovascular, hepatic, metabolic*
  - *may be exacerbated by effects of HIV or its treatment*
- **Greater medication use**
  - *overlapping side effects or potential interactions between ARVs and concomitant medications*

Association of Age With Polypharmacy and Risk of Drug Interactions With Antiretroviral Medications in HIV-Positive Patients

Annals of Pharmacotherapy
47(11) 1429–1439
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DOI: 10.1177/1060028013504075
aop.sagepub.com
SAGE

Alice Tseng, PharmD, FCSHP, AAHIVP[1,3], Leah Szadkowski, MSc[2], Sharon Walmsley, MD, MSc, FRCPC[1,2,3], Irving Salit, MD, FRCPC[1,3], and Janet Raboud, PhD[2,3]

Medication	Age < 50 years (n=498)	Age > 50 years (n=416)
Cardiovascular	127 (26%)	271 (65%)
Antidepressants/ Psychotropics	199 (40%)	224(54%)
Gastrointestinal	243 (49%)	276 (66%)
Narcotics/Analgesics	113 (23%)	164 (39%)
Systemic hormonal	49 (10%)	67 (16%)

Summary of ARV PK studies in older subjects

- There is an increase in exposure (~20%) of **RTV** and some **boosted PIs** (DRV, LPV): This could increase the impact of a drug-drug interaction.

- No clear evidence of an age effect on exposure of **NNRTIs** *but* changes in protein binding could increase unbound concentration (EFV & CNS).

- There is an increase in **FTC** exposure (> 30%) in older patients; some data show altered **TFV** which could be further increased by an interaction at the renal level.

Crawford K et al AIDS Res Hum Retrovirus 2010; 26; Ahmed A et al EACS Belgrade 2011; Cevik M et al EACS Belgrade 2011; di Perri G et al IWCPHT Amsterdam 2013; Schoen JC et al, Expert Opin Drug Metab Toxico 2013; 9: 573-588

DDIs: we need management strategies.

Drug Interaction Resources

- **hivinsite.ucsf.edu.**

  Updated drug interaction database and interactive tool to assess DDIs

- **www.aidsinfo.nih.gov**

  DHHS guidelines for use of ARVs with updated interaction tables

- **www.hivclinic.ca.**

  Updated drug interaction tables. Downloadable.

- **www.eacsociety.org**

  European guidelines including drug interaction tables.

- **www.hivmedicationguide.com**

  Updated interactive drug interaction database. Apps (iPhone; iPad)

- **Micromedex.com.**

  Comprehensive database (subscription required)

- **www.lexi.com**

  Lexi-interact database (subscription required)

- **www.hiv-druginteraction.org;**
- **www.hep-druginteraction.org.**

www.hiv-druginteractions.org

LATEST ARTICLES

Drug Interactions - Dolutegravir and methadone

Drug Interactions - Elvitegravir/cobicistat and methadone.

Drug Interactions - Dolutegravir and prednisone.

Case Report - Atazanavir/ritonavir and charcoal.

Review - ART and cardiovascular disease.

Drug Interactions - Tenofovir and diclofenac.

Click here for previous news items

SITE UPDATES

Interactions with Dolutegravir Dolutegravir (Tivicay®), an integrase inhibitor, was licensed in America a few months ago and i...

>>more

New Presentation - Interactions with Stribild
A new presentation on Drug-Drug Interactions with Stribild has been adde...

>>more

New cytotoxics added as comedications
Ten new cytotoxic drugs have been added to the interaction charts - dasatinib, erlotinib, evero...

>>more

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DRUG INTERACTION CHARTS

Now Includes Dolutegravir

Access our comprehensive, user friendly, free, drug interactions charts

CLICK HERE

Providing clinically useful, reliable, up-to-date evidence-based information

To view low bandwidth version click here

INTERACTIONS ON MOBILE DEVICES

HIV iCharts - we want your opinions

Recent changes to the Apple operating system have caused issues with the update feature of the HIV iCharts app. We are taking this opportunity to investigate alternative options for accessing our drug interaction information on mobile devices and would be grateful if you could take a few minutes to answer a few short questions and to give us any comments.

Click here to take the survey

TREATMENT SELECTOR TABLES

Treatment Selector Tables - now with dolutegravir

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.

INTERACTION CHARTS FOR YOUR SMART PHONE AND TABLET

HIV iChart - an interaction app for mobile devices

iOS7 - We have recently become aware that the update function on the app may not work properly with iOS7 on some devices. We are currently working to determine the nature and extent of the problem and to rectify this.

Free for **Apple** and **Android** devices.
Now optimised for iPads

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EDITORIAL SPONSORSHIP

We are pleased to announce Editorial Sponsorship from BHIVA, EACS and the International Congress on Drug Therapy in HIV (Glasgow).

British HIV Association BHIVA

EACS European AIDS Clinical Society

HIV Drug Therapy Glasgow 2014

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ASSOCIATED SITES

www.hep-druginteractions.org

A reliable guide to drug-drug interactions in the treatment of hepatitis.

HIV DRUG THERAPY

Portal providing emerging data, clinical updates and meeting reviews.

BRITISH SOCIETY FOR NANOMEDICINE

Website of the British Society of

Do common medicines information resources identify drug interactions between the most frequently prescribed medicines in primary care in the UK and antiretrovirals?

N Marshall[1], S Sonecha[2], C Okoli[3], C Smith[4], M Boffito[2]
1.Royal Free London NHS Foundation Trust, London, UK
2.Chelsea and Westminster NHS Foundation Trust, London, UK
3.North Middlesex University Hospital, London, UK
4.Research Department of Infection and Population Health, UCL, London, UK
Correspondence: Neal.Marshall@nhs.net

- The UKs most commonly prescribed non-ARV medicines (2010-2012) were identified using the ABPIs 'top products in the UK' website.
- The ere ide d
- DDIs the

Clinic letters should recommend clinicians consult www.hiv-druginteractions.org as the preferred source for identifying DDIs

Table 3: Outcomes against audit standards

Audit standard	eBNF 66	SPC for ARV	SPC for nARV	Liverpool DDI website	P
100% of potential, clinically significant DDIs will be identified by the medicines resource. (n=20).	60% (12)	75% (15)	70% (14)	100% (20)	0.010
Each medicines resource gives clear and appropriate advice on 100% of potential, clinically significant DDIs (category A and B from table 3).	20% (4)	60% (12)	65% (13)	100% (20)	<0.0001

A stepwise approach to DDI management

Note all co-medications (prescribed, OTC and herbal products)

Consult pharmacist and online resources

Consider the nature of any interaction and whether an alternative to an ‘interacting drug’ is possible.

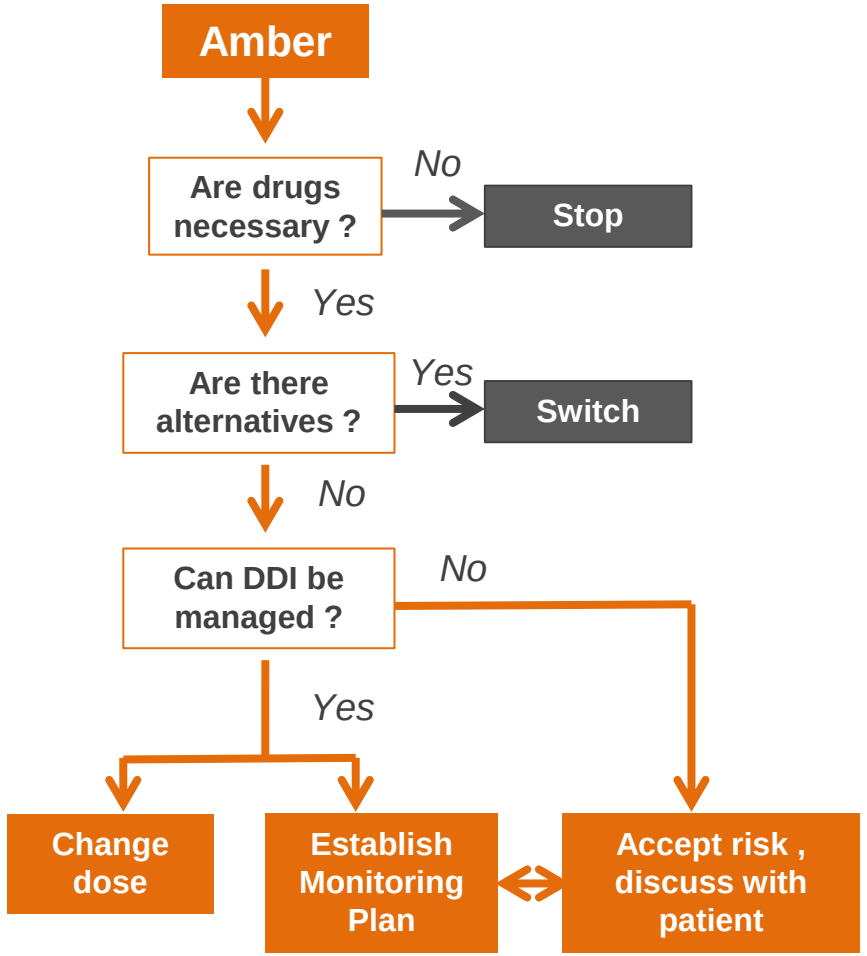
Some interactions can be managed by dose adjustment with careful monitoring

OTC: over the counter

A stepwise approach to DDI management

- Ask key questions

- No clinically significant interaction or interaction not anticipated.
- Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration.
- Interaction likely – do not co-administer

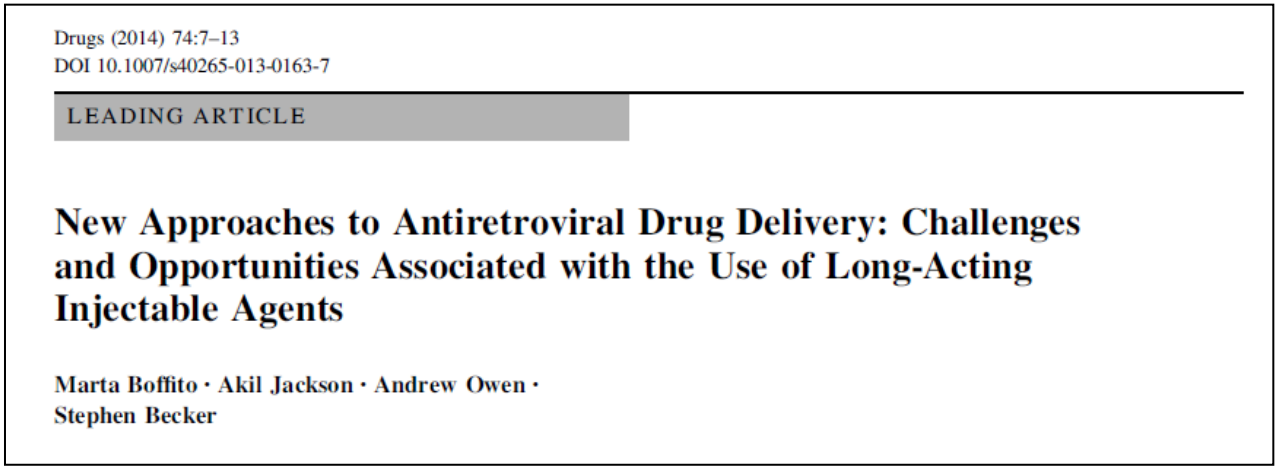


What is on the horizon?

Long-acting formulations

- Have been used to improve adherence and prevent missed doses/treatment fatigue in several therapeutic areas
- Contraception: (Depo Provera)
- Schizophrenia: 6 long-acting antipsychotics available (e.g. risperidone, olanzapine, aripiprazole)
- Hypogonadism: (testosterone undecanoate)

New approaches to antiviral drug delivery



Drugs (2014) 74:7–13
DOI 10.1007/s40265-013-0163-7

LEADING ARTICLE

New Approaches to Antiretroviral Drug Delivery: Challenges and Opportunities Associated with the Use of Long-Acting Injectable Agents

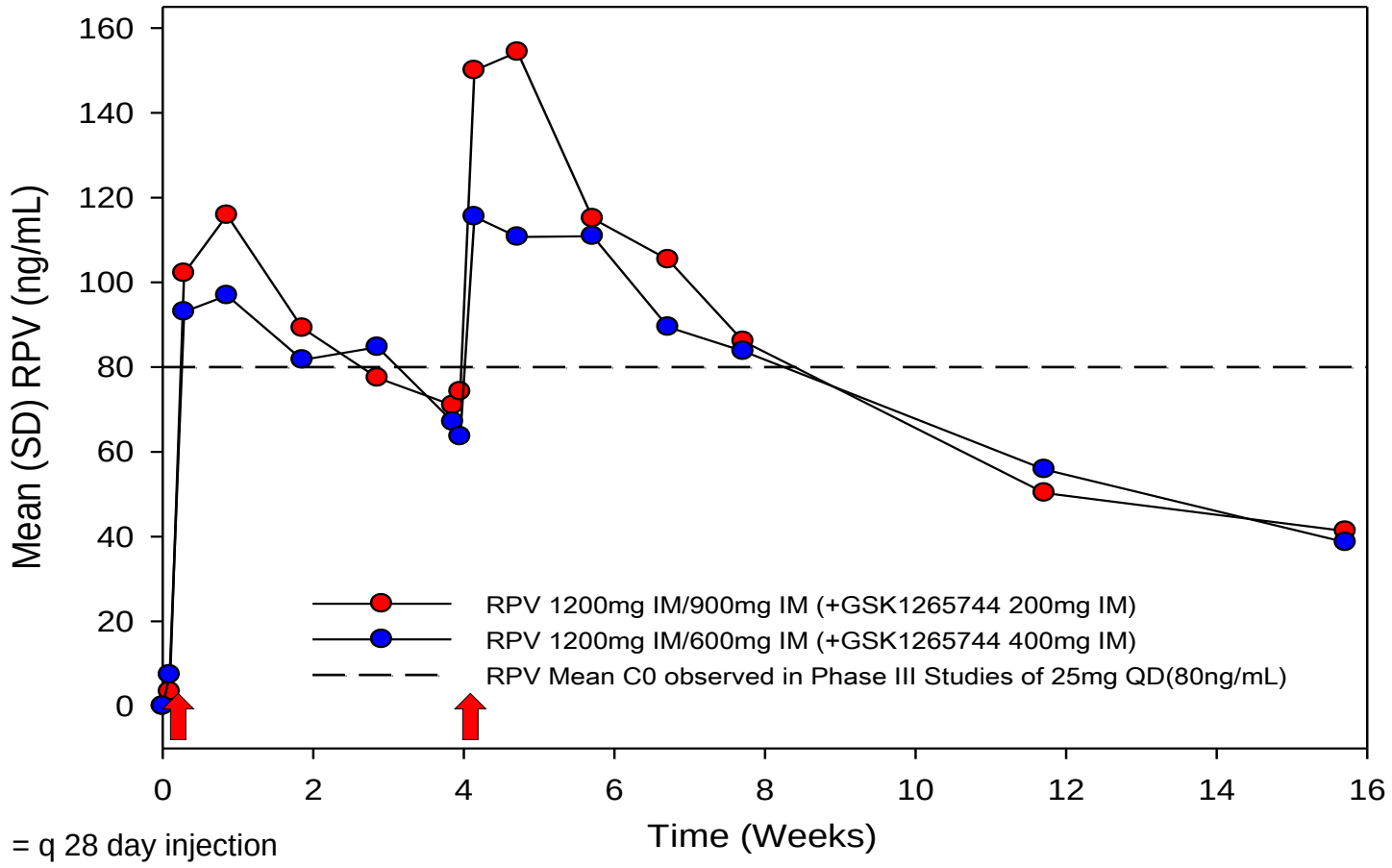
Marta Boffito · Akil Jackson · Andrew Owen · Stephen Becker

- Main focus on *prevention* but interest also in *treatment*
- 2 drugs in clinical trials (PK and PK-PD):
  - *Rilpivirine*
  - *GSK-1265744 (Cabotegravir)*

Boffito M, et al. Drugs 2014;74:7–13

Mean rilpivirine plasma concentrations

- Rilpivirine plasma concentrations following long-acting injections are comparable to oral 25mg/day in HIV patients

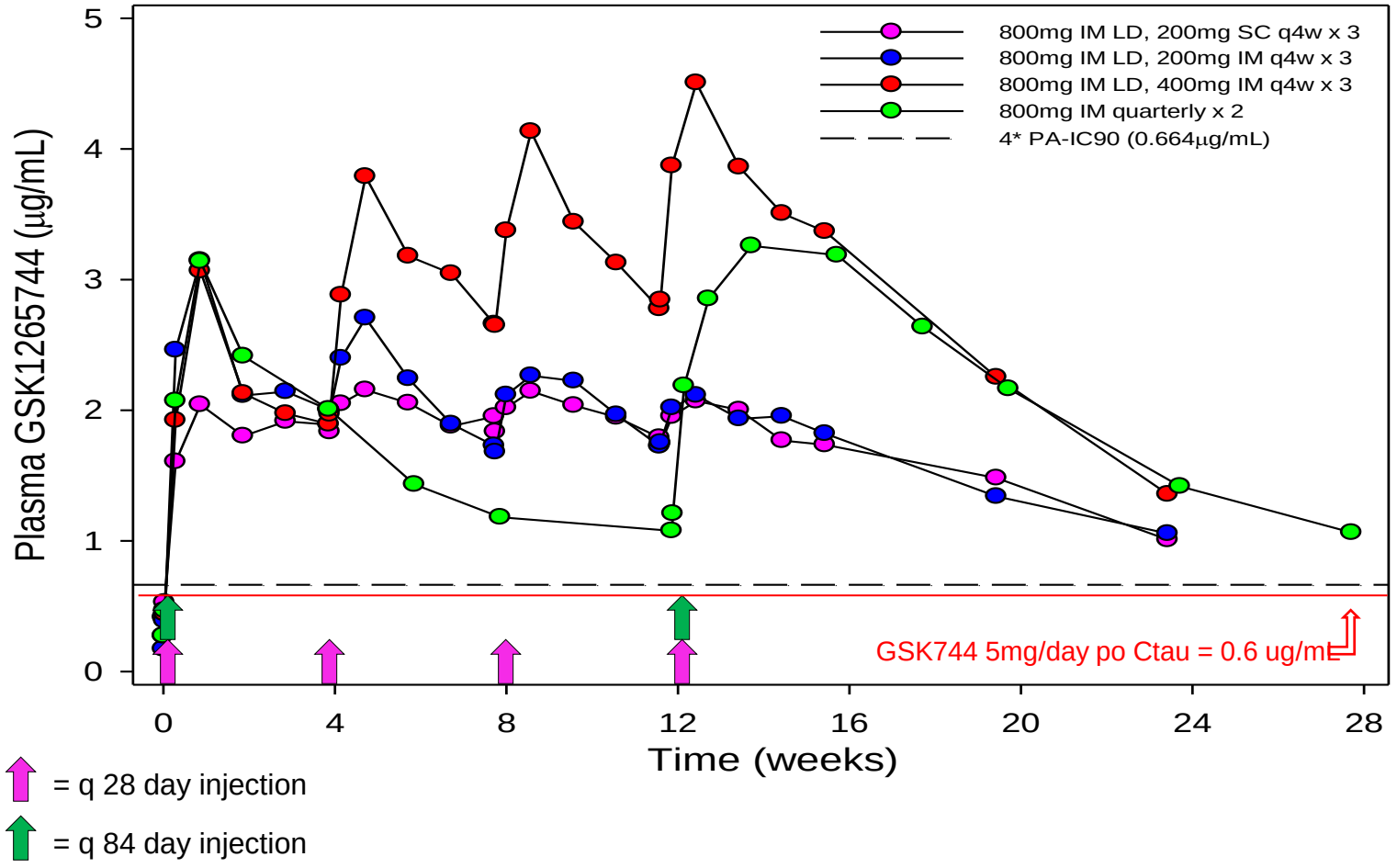


Spreen W et al. 7th IAS 2013, Kuala Lumpur, Malaysia. Abstract WEAB0103

GSK1265744 LA every 4 weeks or 12 weeks

Regimens achieve plasma concentrations >4 x PA-IC90

- Mean GSK1265744 plasma concentration profiles



Spreen W et al. 7th IAS 2013, Kuala Lumpur, Malaysia. Abstract WEAB0103

Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial

*ENCORE1 Study Group**

	Efavirenz 400 mg		Efavirenz 600 mg		Difference (95% CI)	p value
	N	n (%)	N	n (%)		
Modified intention-to-treat analysis	302	94·1% (91·5 to 96·7)*	285	92·2% (89·2 to 95·2)*	1·8 (−2·1 to 5·8)	0·36
Stratified by baseline BMI (kg/m²)						
≤22	104	99 (95·2%)	113	101 (89·4%)	5·81% (−1·20 to 12·8)	..
>22–25	111	103 (92·8%)	91	84 (92·3%)	0·49% (−6·80 to 7·78)	..
>25	105	99 (94·3%)	105	100 (95·2%)	−0·95% (−6·98 to 5·07)	0·47
Stratified by ethnic origin						
African	118	107 (90·7%)	116	103 (88·8%)	1·88% (−5·90 to 9·70)	..
Asian	106	103 (97·2%)	103	99 (96·1%)	1·05% (−3·83 to 5·94)	..
Other	97	92 (94·8%)	90	83 (92·2%)	2·62% (−4·45 to 9·69)	0·82

BMI=body-mass index. *Data are % (95% CI). Other includes white and Aboriginal and Torres Strait Islander.

Table 2: **Primary endpoint stratified by baseline body-mass index and ethnic origin**

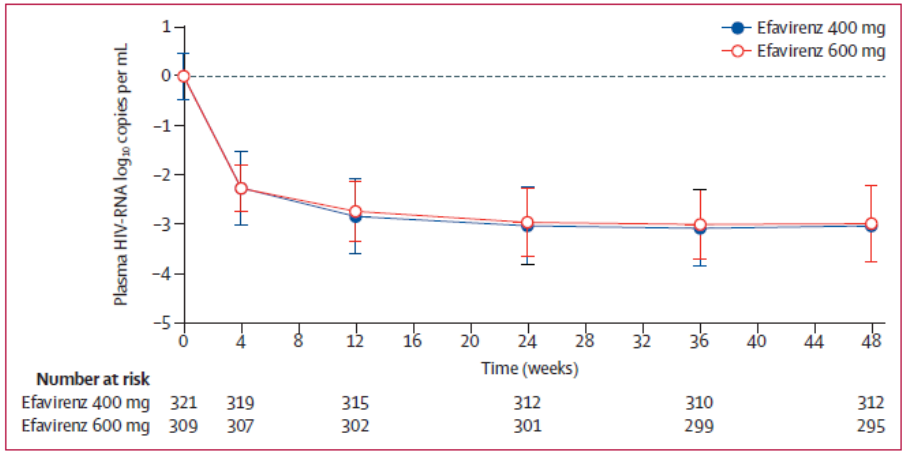


Figure 3: **Mean change in HIV-RNA viral load from baseline to week 48 for the modified intention-to-treat population**

Data are presented as mean (SD) $\log_{10}$ copies per mL.

Nanomedicines for HIV therapy

Heterogeneity in response to HIV treatments has been attributed to several causes including variability in pharmacokinetic exposure. Nanomedicine applications have a variety of advantages compared with traditional formulations, such as the potential to increase bioavailability and specifically target the site of action.

Studies ongoing with EFV and LPV

Grateful Thanks


Prof David Back


Prof Saye Khoo


Prof Andrew Owen


Dr Gerry Davies
(Wellcome Trust Research Fellow)


Dr Marco Siccardi
(Lecturer in Pharmacology)


Dr Phil Martin
(Post-doctoral Research Associate)


Dr Neill Liptrott
(Post-doctoral Research Associate)


Dr Lee Tatham
(Post-doctoral Research Associate)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Christina Chan
(1st Year PhD Student)

Tyrosine kinase Inhibitors & antiretrovirals

Protein Kinase Inhibitors	Considerations with Antiretrovirals
CYP3A4 Substrates eg: dasatinib, everolimus, imatinib, lapatinib	PIs may ↑ levels via CYP3A4 inhibition EFV, NVP may ↓levels via CYP3A4 induction
CYP3A4 Inhibitors eg: dasatinib, everolimus, imatinib, lapatinib	NNRTIs, MVC levels may ↑
UGT1A1 Inhibitors eg: erlotinib, nilotinib	Potential for ↑ bilirubin levels. RAL levels may ↑(unlikely clinically relevant)
QT Interval Prolongation eg: dasatinib, lapatinib, nilotinib, sunitinib	Increased risk for QT prolongation with PIs, rilpivirine
Myelosuppression eg: dasatinib, everolimus, imatinib, sunitinib	Increased risk for myelosuppression with ZDV
Nephrotoxicity eg: sunitinib	Increased risk for nephrotoxicity with TDF
Hepatotoxicity eg: imatinib, lapatinib, sunitinib	Increased risk for hepatotoxicity with some ARVs