Pharmacology of antiretroviral drugs in the aging patient and drug-drug interactions

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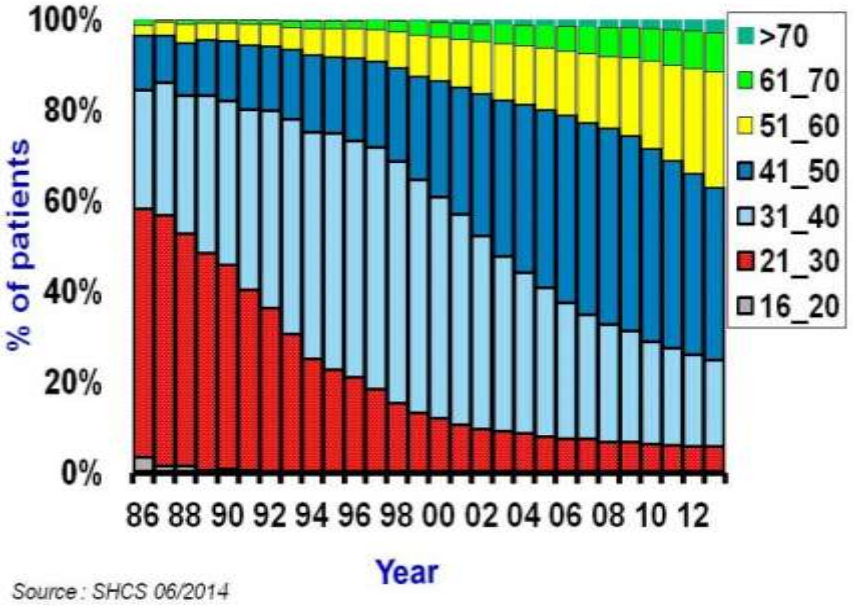
Presentation outline

- Aging of HIV population and prevalence of comorbidities
- Age related physiological changes and impact on drug pharmacokinetics and pharmacodynamics
- Risk for DDI and DDI of interest in the aging HIV population

Aging of HIV population and comorbidities

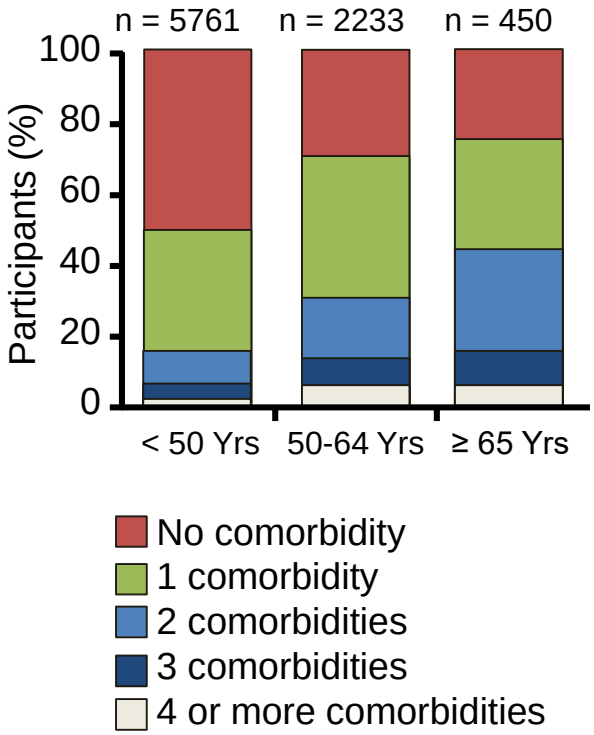
Age distribution of active patients by year in the SHCS, 1986-2013



Source : SHCS 06/2014

- proportion of older HIV-infected individuals has increased in recent years

Number of non-AIDS comorbidities stratified by age



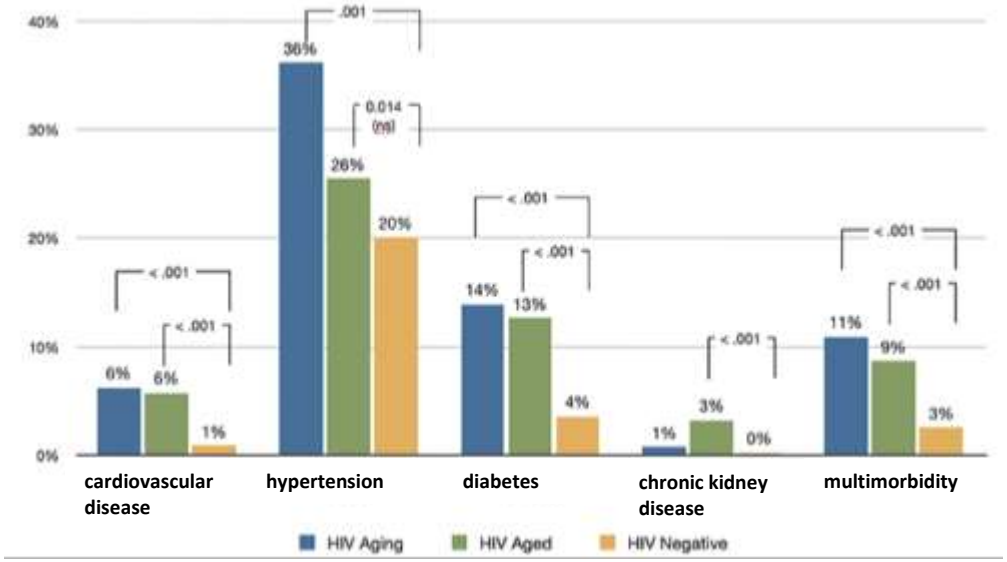
- number of comorbidities increases with older age

SWISS HIV COHORT STUDY

Hasse B et al. CID 2011

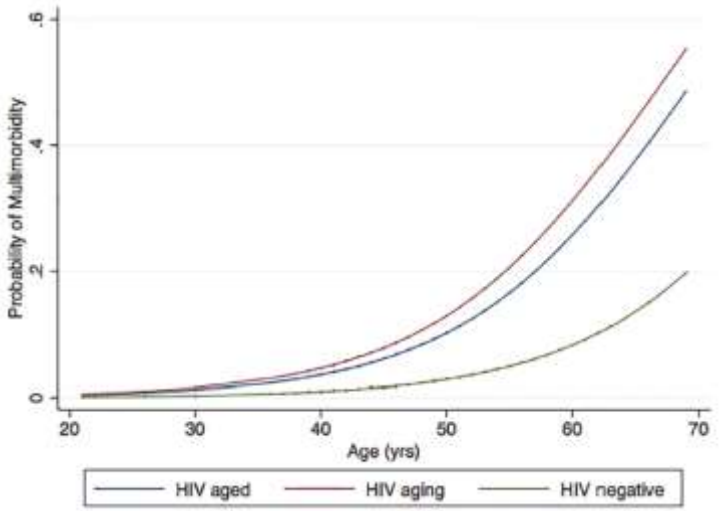
Prevalence of comorbidities in HIV+ vs HIV- individuals

Prevalence of comorbidities and multimorbidity



Higher rates of comorbidities and multimorbidity in HIV infected individuals compared to age matched uninfected individuals

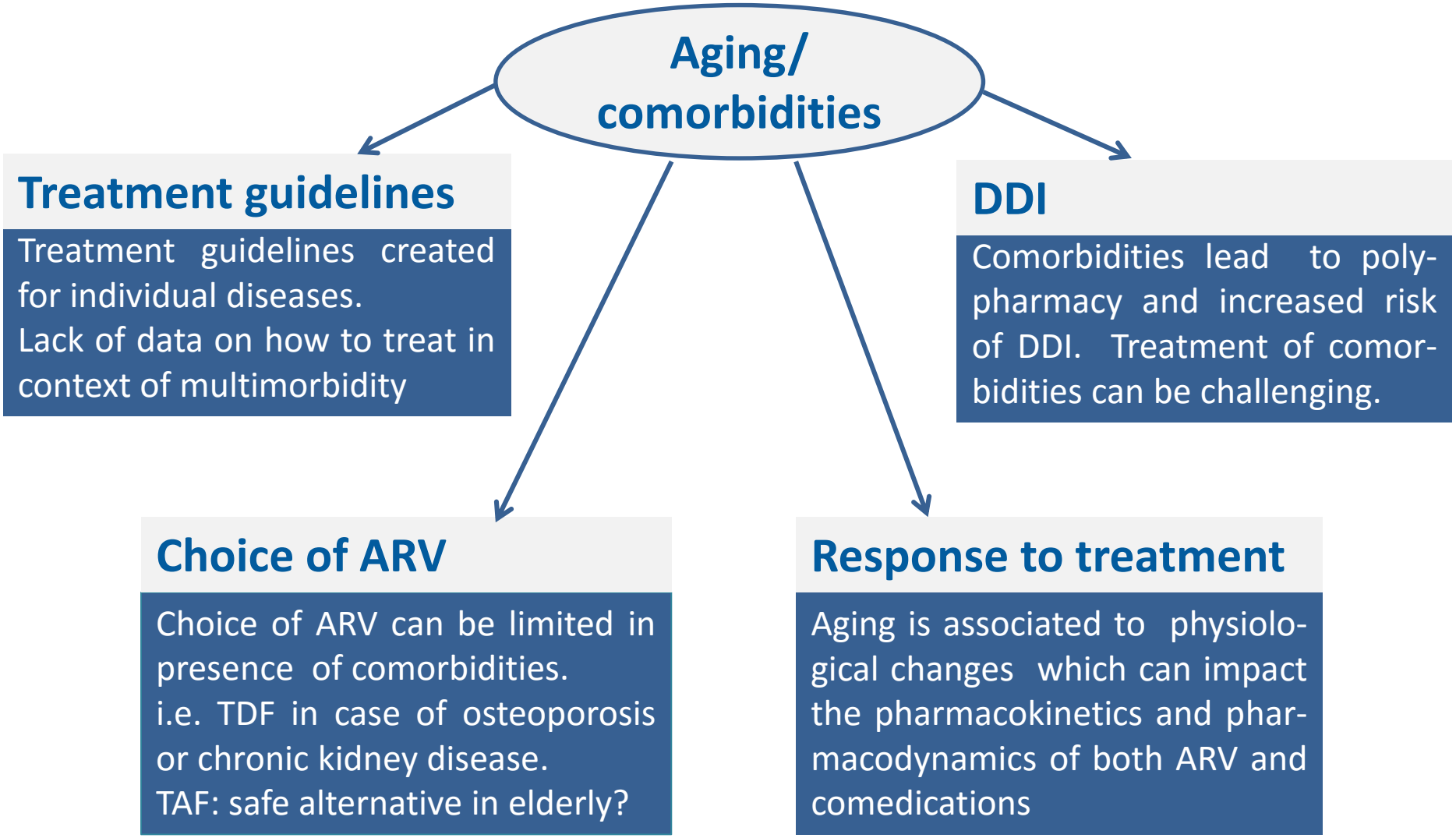
Probability for multimorbidity according to HIV status and duration of infection



Risk of multimorbidity is higher in individuals with longer duration of HIV infection relative to uninfected individuals and also to individuals who seroconverted at older ages

Guaraldi G et al. PLoS One 2015

Aging and comorbidities pose therapeutic challenges



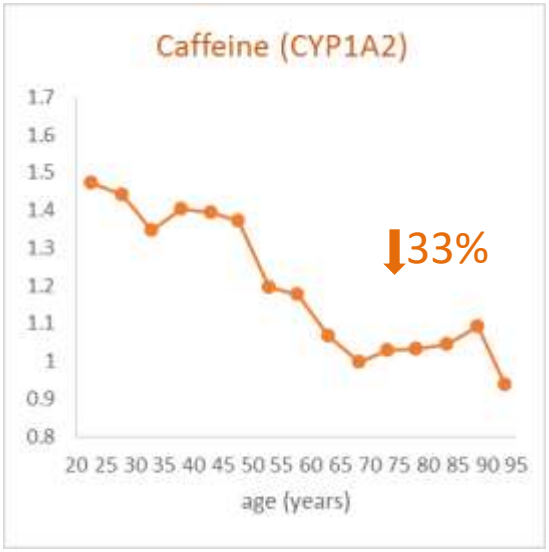
Age related pharmacokinetics changes

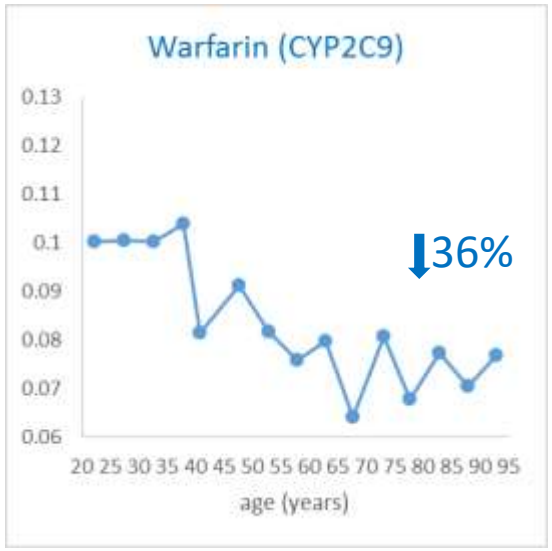
PK parameter	Altered physiology with aging	Comments
Absorption	↑ gastric pH ↓ GI mobility ↓ GI blood flow	↓ absorption (atazanavir, rilpivirine) rate of absorption may be delayed
Distribution	↓ albumin ↑ body fat ↓ lean muscle and total body water	↑ free fraction of drugs ↑ Vd of lipophilic drugs (PI, NNRTI) ↑ plasma concentration of hydrophilic drugs
Metabolism	↓ hepatic mass ↓ hepatic blood flow (≈40%)	reduced hepatic CL (PI, NNRTI) of note: decrease in hepatic mass will impact low hepatic extraction drugs (capacity limited) decrease in blood flow will impact high hepatic extraction drugs (flow limited)

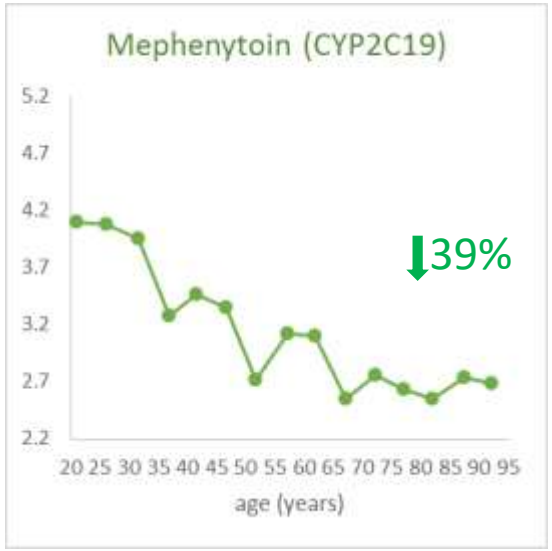
Schoen JC et al. Expert Opin Drug Metab Toxicol 2013; Winston A et al. Curr Opin Infect Dis 2015

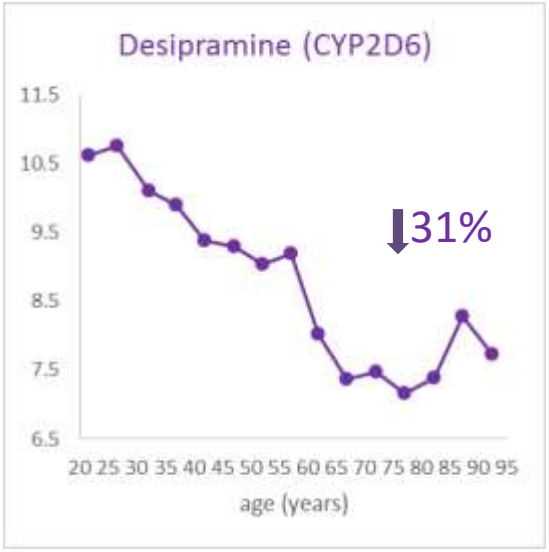
Impact of age on drug clearance

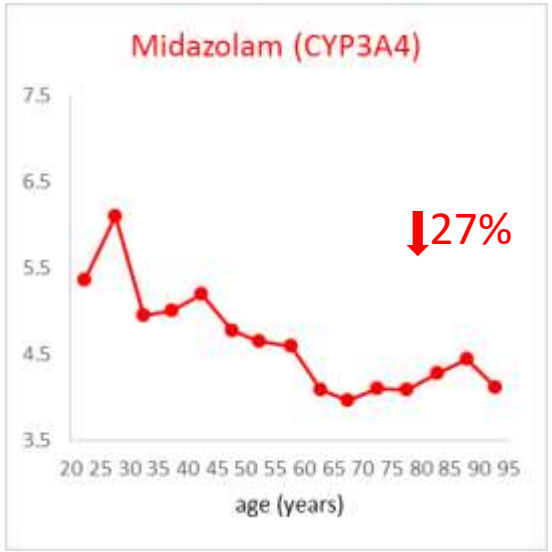
Predicted total drug clearance (ml/min kg)











adapted from Polasek TM et al. BJCP 2012

Age related pharmacokinetics changes

PK parameter	Altered physiology with aging	Comments
Elimination	↓ GFR ↓ renal blood flow ↓ kidney mass	drug accumulation for renally cleared drugs (NRTI)

Serum creatinine is commonly used to estimate renal function using the equations: Cockcroft-Gault, MDRD or CKD-EPI

Cave: estimation of renal function using serum creatinine **may be inaccurate in elderly** as daily creatinine production may be reduced due to decreased muscle mass and/or due to decreased dietary protein intake ➔ overestimation of renal function

Schoen JC et al. Expert Opin Drug Metab Toxicol 2013; Winston A et al. Curr Opin Infect Dis 2015

Dose adjustments in case of impaired renal function

		eGFR[i] (mL/min)				Haemodialysis
		≥ 50	30-49	10-29	< 10	
NRTIs						
ABC		300 mg q12h	No dose adjustment required			
ddI[ii]	≥ 60 kg	400 mg q24h	200 mg q24h	150 mg q24h	**> 60 kg: 100 mg/24h**	
	< 60 kg	250 mg q24h	125 mg q24h	100 mg q24h	**< 60 kg: 75 mg/24h**	
d4T	> 60 kg	30 mg q12h	15 mg q12h	15 mg q24h	15 mg q24h	15 mg q24h[iv]
	< 60 kg	40 mg q12h	20 mg q12h	20 mg q24h	20 mg q24h	20 mg q24h[iv]
FTC		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h
3TC		300 mg q24h	150 mg q24h	100 mg q24h[iii]	50-25 mg q24h[iii]	50-25 mg q24h[iii], [iv]
TDF[v], [vi]		245 mg q24h	245 mg q48h	Not recommended (245 mg q72-96h, if no alternative)	Not recommended (245 mg q7d, if no alternative)	245 mg q7d[iv]
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h
ABC/3TC		600/300 mg q24h	Use individual drugs			
ZDV/3TC		300/150 mg q12h				
ABC/3TC/ZDV		300/150/300 mg q12h				
TDF/FTC		245/200 mg q24h	245/200 mg q48h	Use individual drugs		

EACS guidelines 2015

Available data on PK of ARV in older HIV patients

ARV	Pharmacokinetics in older HIV patients
PI	increase in exposure of ritonavir and some boosted PI (ATV, LPV): impact on the magnitude of a drug-drug interaction?
NNRTI	no clear evidence of an age effect on exposure of NNRTI
NRTI	emtricitabine exposure shown to be increased, some data showed altered tenofovir levels
INI	raltegravir exposure not modified

Limitations of current studies:

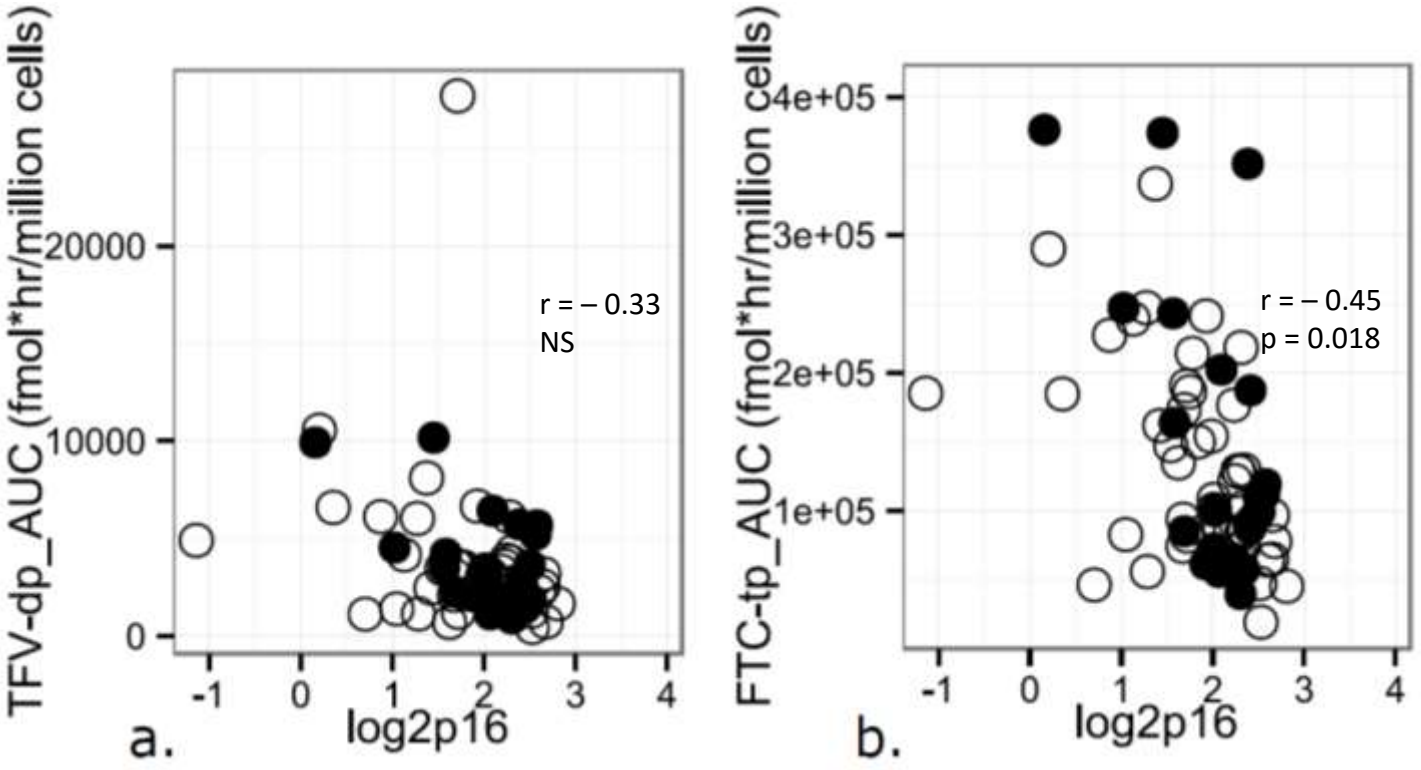
- small amount of patients > 65 years
- exclusion of individuals with significant comorbidities or frailty
  ➔ possible underestimation of magnitude of pharmacokinetic changes
- data on tolerance/toxicity are missing

Winston A et al. J Antimicrob Chemother 2013; Crawford K et al. AIDS Res Hum Retrovir 2010; Avihingsanon A et al. AIDS Res Hum Retroviruses 2013; Dumond JB et al. HIV Med 2013; Kakuda TN et al. Clin Pharmacol Ther 2010; Vera JH et al. HIV Clin Trials 2015

T-cell senescence marker and TDF/FTC metabolites

- small study found negative correlation between expression of T-cell senescence marker ($p16^{INK4a}$) and FTC intracellular triphoshate as well as endogenous nucleotide.

  Senescence alteration of cellular transport of nucleotides and/or alteration of phosphorylation activity?



Dumond JB et al. Antiviral Ther 2016

Age related pharmacodynamic changes

- Age-related changes in the affinity of some medications to receptor sites or in the number of receptors
  - ➔ affect efficacy or increase sensitivity to certain drugs
- Aging can affect the regulation of some physiological processes (i.e renal hemodynamics)

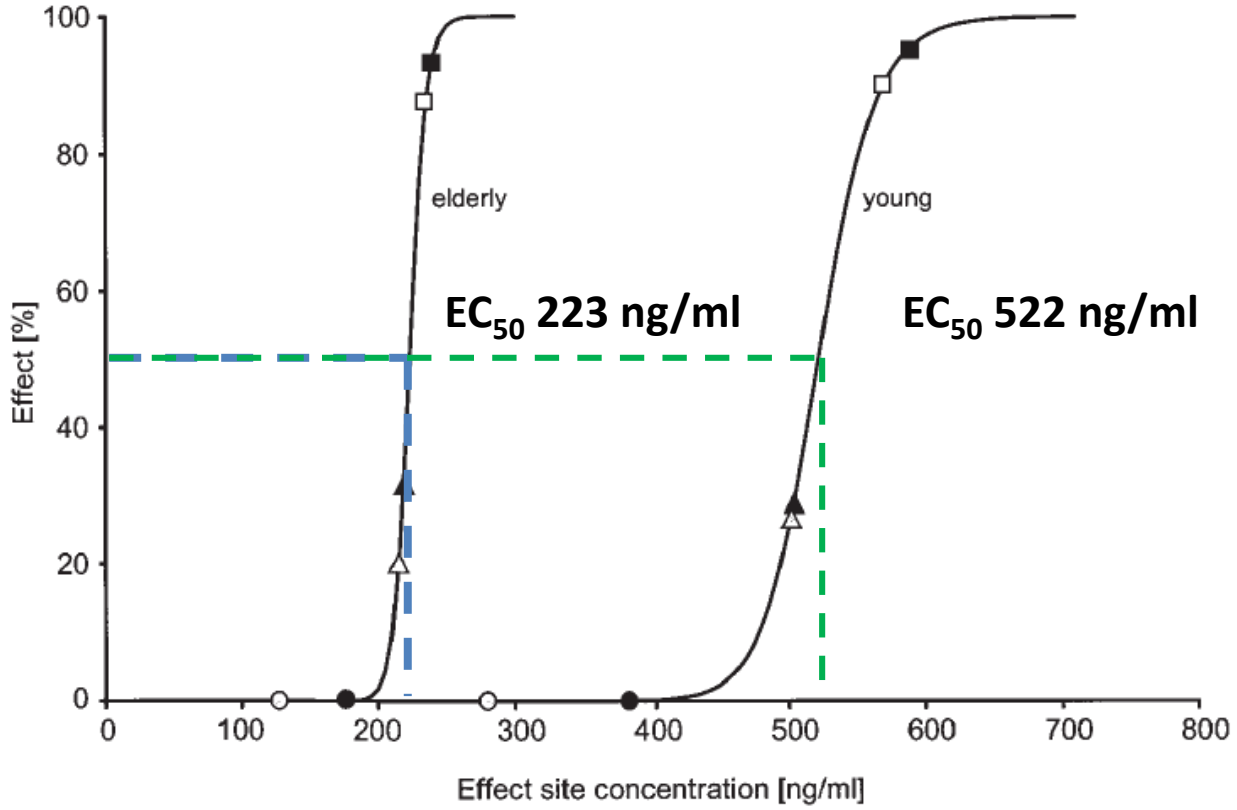
Drug class	Potential PD issues	Comments
Antihypertensives	orthostatic hypotension	use with caution, start with lower dose
Benz		ort ose
ß-blockers	ß-receptors less responsive	may require ↑ ß-blocker doses to have same effect
Diuretics	↑ sensitivity drug action	monitor blood pressure and electrolytes
Anticholinergic agents	↑ sensitivity (agitation, confusion, decompensation of glaucoma, dry mouth, constipation, urinary retention…)	avoid

Effects can be aggravated by inhibition of metabolism by PI/r, cobicistat

Wooten JM et al. South Med J 2012

Effect of age on the PD of midazolam

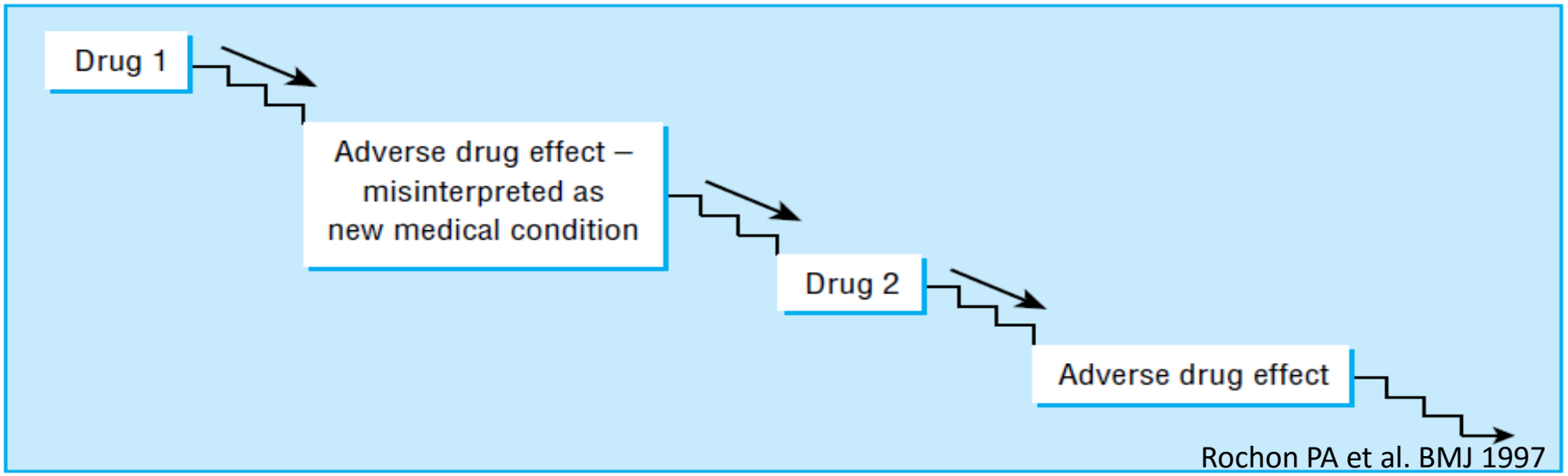
- assessment of the concentration-hypnotic/sedative effect relationship of midazolam in young (24-28 years) and elderly (67-81 years)



- total dose of midazolam needed to reach sedation in younger was about twice that needed in elderly.

Albrecht S et al. Clin Pharmacol Ther 1999

Adverse drug reactions and the prescribing cascade



Rochon PA et al. BMJ 1997

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

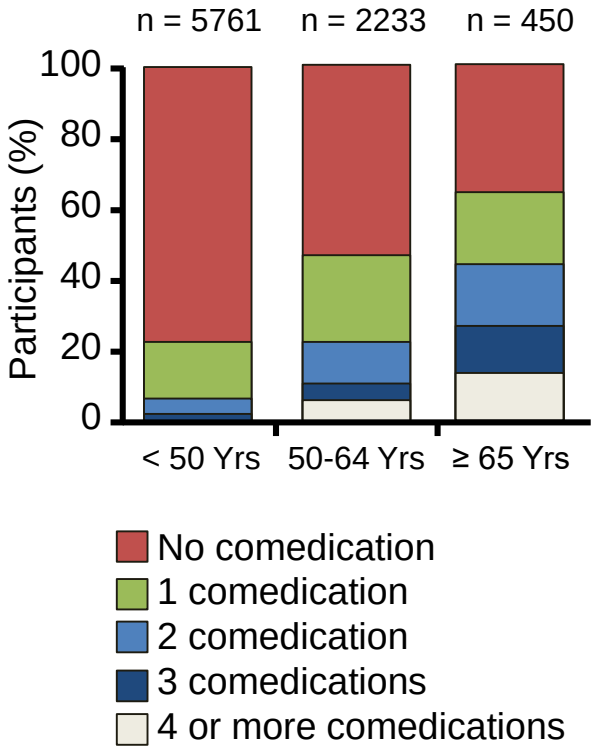
By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel

STOPP/START criteria for potentially inappropriate prescribing in older people: version 2

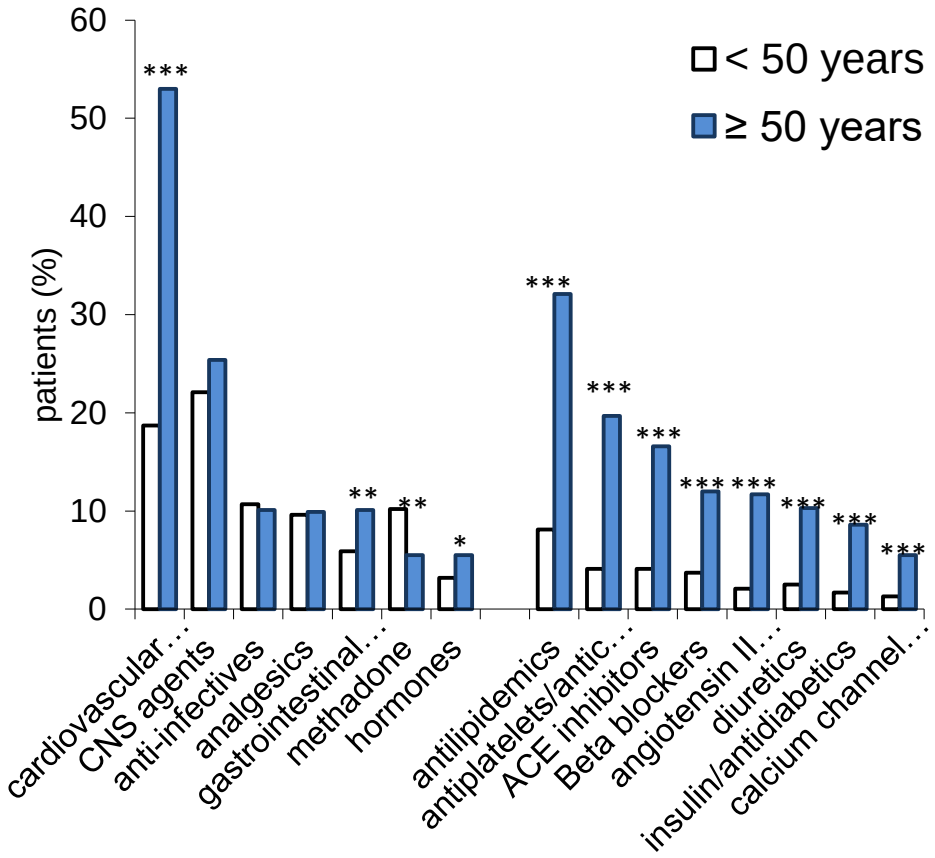
American Geriatrics Society. J Am Geriatr Soc 2015; O'Mahony D et al. Age Aging 2015

Older HIV patients and risk of drug-drug interactions

Number of non-HIV co-medications stratified by age



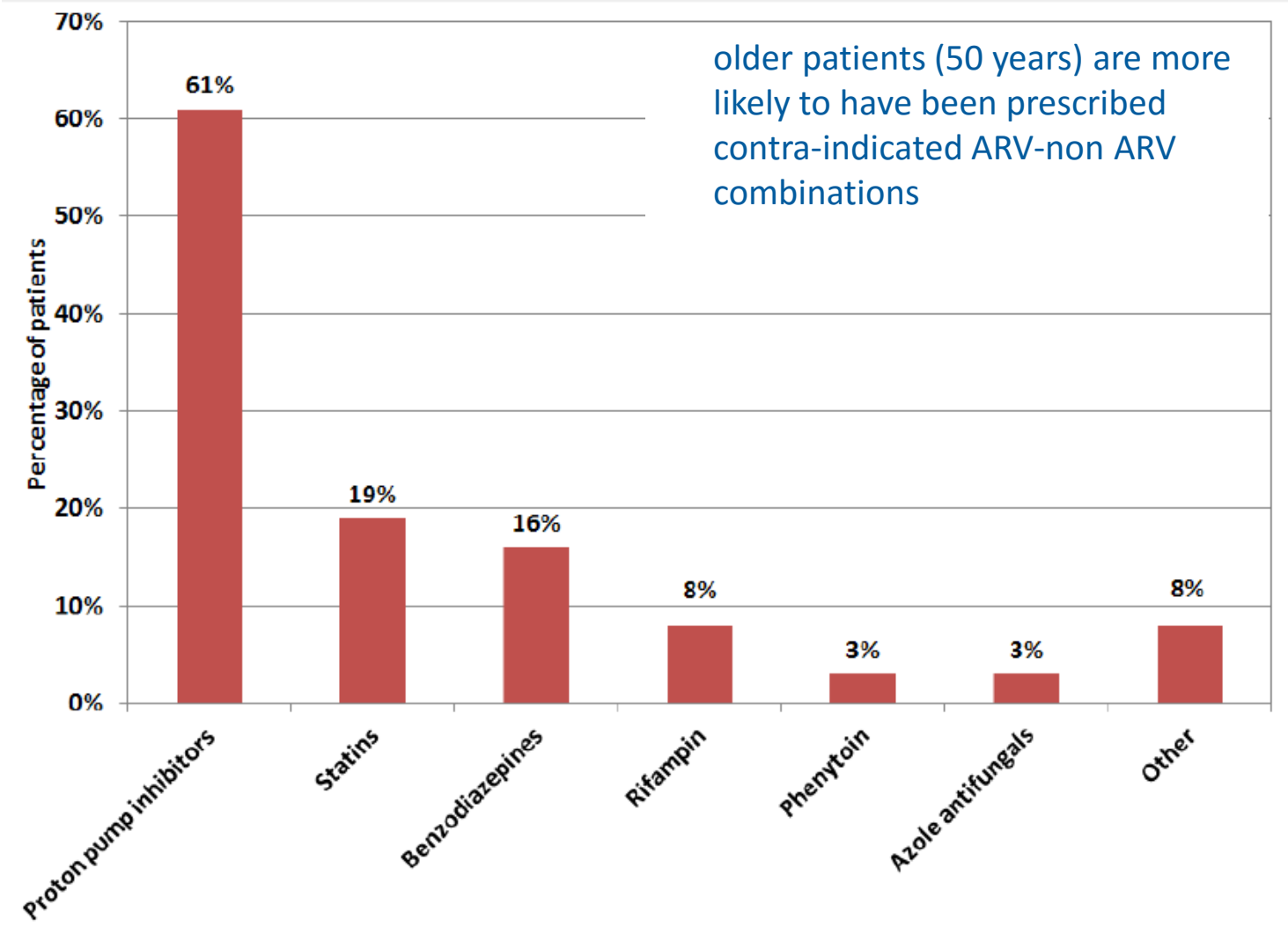
Prescribed therapeutic classes



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

Hasse B et al. CID 2011; Marzolini C et al. J Antimicrob Chemother 2011

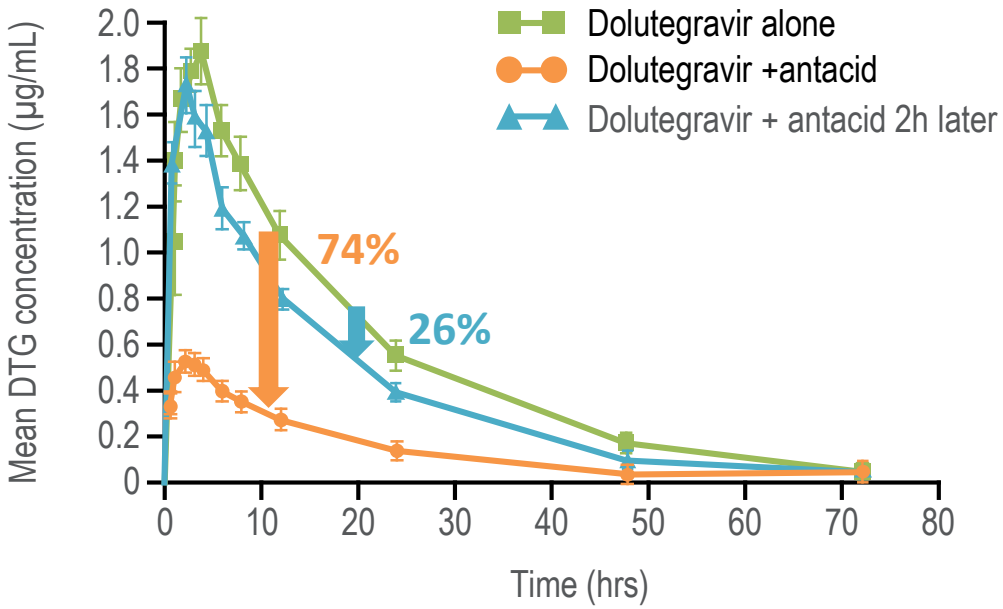
Contra-indicated ARV/non-ARV drug combinations



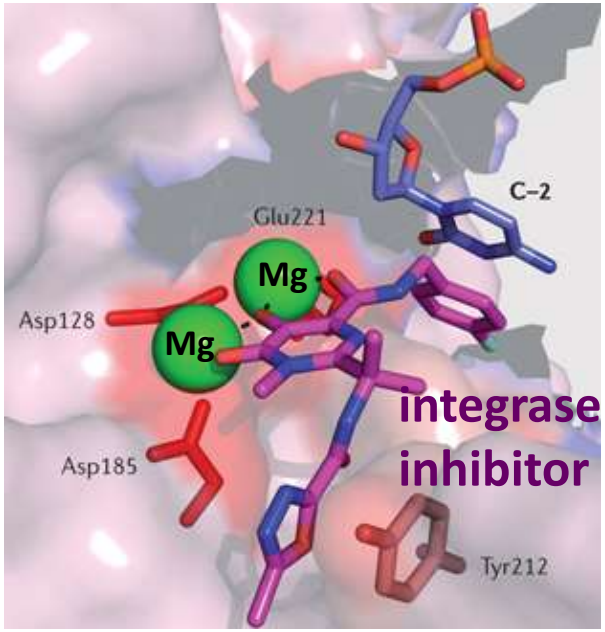
Holtzman C et al. J Gen Intern Med 2013

Selected DDI of interest in the aging population

- First-line therapy for osteoporosis consists of biphosphonates: no DDI with ARV
  However biphosphonates are often given with calcium supplementation
  Cave: calcium impairs absorption of HIV 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

Virologic Failure with a Raltegravir-Containing Antiretroviral Regimen and Concomitant Calcium Administration

Jennie L. Roberts, B.S., Jennifer J. Kiser, Pharm.D., Jason T. Hindman, Pharm.D., M.B.A., and Amie L. Meditz, M.D.

Pharmacotherapy 2011

calcium carbonate 1 g–vitamin D_3 400 IU 3 times/day was started for prevention of osteoporosis associated with long-term glucocorticoid use. After 10 months of an undetectable plasma HIV-1 RNA level and clinical evidence of a high level of adherence, he subsequently developed detectable HIV-1 RNA levels with documented resistance to raltegravir. His antiretroviral therapy was changed back to a protease inhibitor–based regimen, and his HIV-1 RNA level rapidly resuppressed. Calcium binding to the divalent metal ion–chelating motif of raltegravir may have led to subtherapeutic raltegravir levels in this patient. It is important for clinicians to be aware of the potential interaction between polyvalent cation–containing agents, such as calcium,

Drug-drug interactions with anticoagulants

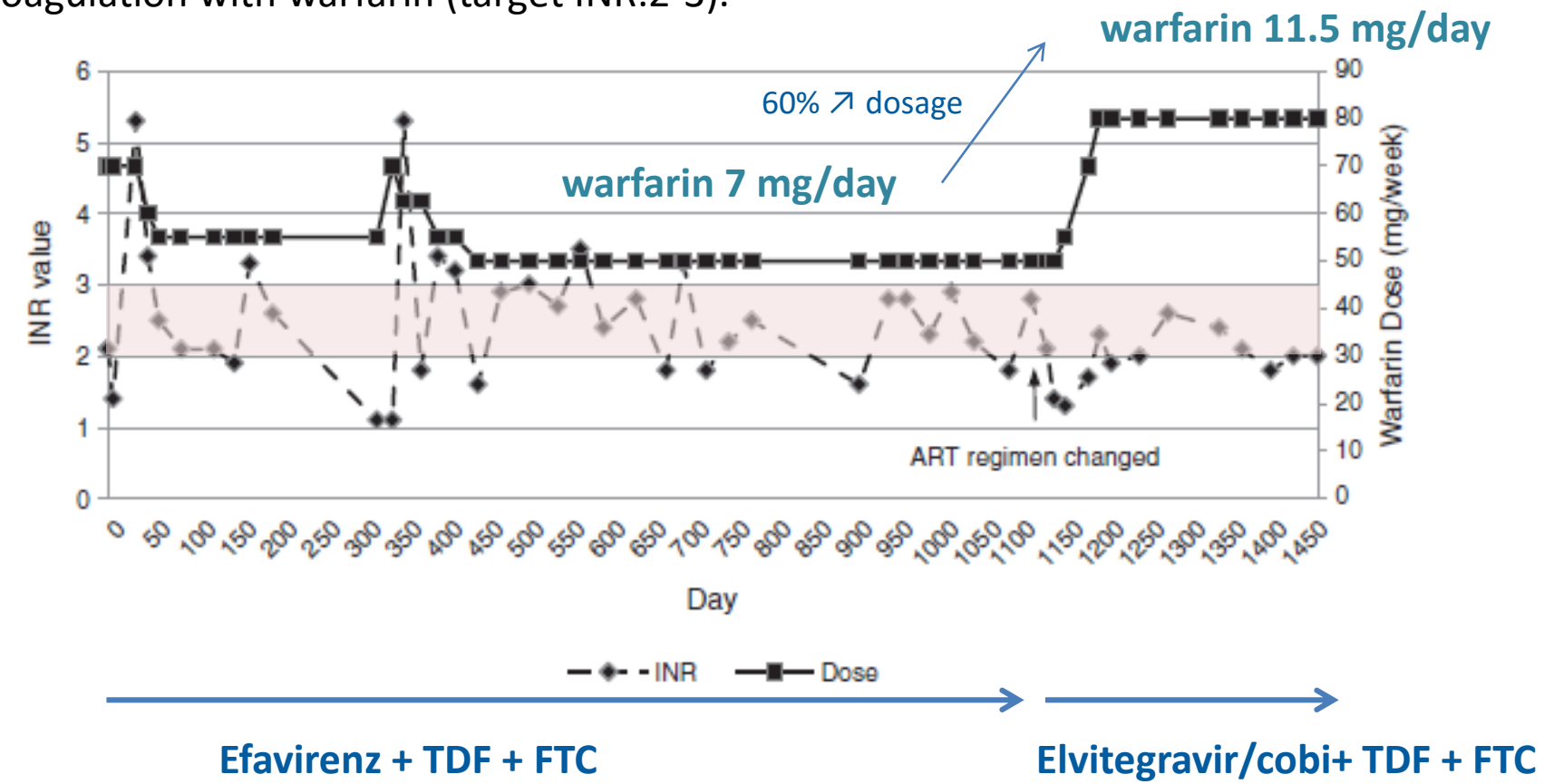
- **acenocoumarol**: substrate CYP2C9 (major), CYP1A2, CYP2C19
- **phenprocoumon**: substrate CYP2C9, CYP3A4
- **warfarin**: CYP2C9 (S-enantiomer, more potent); CYP3A4, CYP1A2, CYP2C19 (R-enantiomer)
- **apixaban, rivaroxaban**: substrates CYP3A4, P-gp,
- **edoxaban**: substrate P-gp, eliminated renally and through biliary secretion
- **dabigatran**: prodrug substrate P-gp, mainly eliminated renally

anticoagulants	ATV/r	DRV/c	DRV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL
acenocoumarol	↓	↔	↓	↓	↓	↓	↑	↓	↔	↔	↔	↓	↔
phenprocoumon	↑↓	↑	↑↓	↑↓	↑↓	↓	↑↓	↓	↔	↔	↔	↑↓	↔
warfarin	↓	↑	↓	↓	↓	↑↓	↑↓	↓	↔	↔	↔	↓	↔
heparine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
apixaban	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔
rivaroxaban	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔
edoxaban	↑	↑	↑	↑	↑	↔	↑	↔	↔	↔	↔	↑	↔
dabigatran	↑	↑	↑	↑	↑	↔	↑	↔	↔	↔	↔	↑	↔

- **cave:** when switching pharmacokinetic booster:
  ritonavir and cobicistat: equally potent inhibitors of CYP3A
  ritonavir induces CYP2C9, CYP2C19, CYP1A2 whereas **cobicistat does not**
  however cobicistat can be co-formulated with EVG which induces CYP2C9

Interaction between warfarin and elvitegravir/cobicistat

HIV-infected patient with bilateral lower extremity deep venous thromboembolism requiring anticoagulation with warfarin (target INR:2-3).



warfarin: CYP2C9 (S-enantiomer, more potent); CYP3A4, CYP1A2, CYP2C19 (R-enantiomer)

Good BL et al. AIDS 2015

Cobicistat versus ritonavir and differences in DDI profile

Therapeutic class	Drug	Metabolic pathway/comments	RTV	Cobi
Anaethetics	**propofol**	UGT1A9, UGT1A8 + CYP2B6	↓	↔
Analgesics	**diamorphine**	deacetylation + UGT2B7, UGT1A1	↓	↔
	dihydrocodeine	CYP2D6 + UGT2B7 > CYP3A4	↓↑	↑
	hydromorphone	UGT2B7	↓	↔
	morphine	UGT2B7, UGT1A1	↓	↔
	pethidine	CYP2B6 > CYP3A4	↓	↑
Antibacterials	**sulfadiazine**	CYP2C9	↓	↔
Anti-coagulants	**acenocoumarol**	CYP2C9 > CYP1A2, CYP2C19	↓	↔
	eltrombopag	UGT1A1, UGT1A3 + CYP1A2, CYP2C8	↓	↔
	phenprocoumon	CYP2C9, CYP3A4	↓↑	↑
	warfarin	CYP2C9 > CYP1A2, CYP3A4, CYP2C19	↓	↑
Anticonvulsants	**lamotrigine**	UGT1A4	↓	↔
	valproate	UGT1A6, UGT1A9, UGT2B7 + CYP2C9, CYP2C19	↓	↔
Antidepressants	**agomelatin**	CYP1A2	↓	↔
	bupropion	CYP2B6	↓	↔
	duloxetine	CYP2D6, CYP1A2	↓↑	↑
	sertraline	CYP2B6 > CYP2C9, CYP2C19, CYP2D6, CYP3A4	↓	↑
Anti-diabetics	**gliclazide**	CYP2C9 > CYP2C19	↓	↔
	glimepiride	CYP2C9	↓	↔
	glipizide	CYP2C9	↓	↔
	nateglinide	CYP2C9 > CYP3A4	↓↑	↑
	rosiglitazone	CYP2C8 > CYP2C9	↓	↔
	tolbutamide	CYP2C9 > CYP2C8, CYP2C19	↓	↔
Antiprotozoals	**amodiaquine**	CYP2C8	↑	↔
	atovaquone	glucuronidation	↓	↔
	proguanil	CYP2C19 > CYP3A4	↓	↔
Antipsychotics	**asenapine**	UGT1A4, CYP1A2, CYP3A4	↓	↑
	olanzapine	CYP1A2, UGT1A4	↓	↔
Antiretrovirals	**efavirenz**	cobicistat administered 150 mg QD is	*	D
	etravirine	not sufficient to overcome induction by	*	D
	nevirapine	EFV, ETV, NVP	*	D
Beta-blockers	**carvedilol**	UGT1A1, UGT2B4, UGT2B7 + CYP2D6	↓↑	↑
	oxprenolol	glucuronidation	↓	↔
Bronchodilators	**theophylline**	CYP1A2	↓	↔
Contraceptives/HRT	**estradiol**	CYP3A4, CYP1A2 + glucuronidation	↓	↑
	ethinylestradiol	CYP3A4 > CYP2C9, glucuronidation	↓	↑
	norethisterone	CYP3A4, glucuronidation	↓	↑
Cytotoxics	**anastrozole**	CYP3A4 + UGT1A4	↓↑	↑
	dacarbazine	CYP1A2 > CYP2E1	↓	↔
	droloxifene	glucuronidation	↓	↔
	epirubicin	UGT2B7	↓	↔
	formestane	partly glucuronidation	↓	↔
	procarbazine	CYP2B6, CYP1A2	↓	↔
Gastrointestinal agents	**alosetron**	CYP1A2 > CYP2C9, CYP3A4	↓	↔
Anti-hypertensives	**irbesartan**	glucuronidation + CYP2C9	↓	↔
	labetalol	UGT1A1, UGT2B7	↓	↔
	losartan	CYP2C9	↓	↔
	torasemide	CYP2C9	↓	↔
Immunosuppressants	**mycophenolate**	UGT1A9, UGT2B7	↓	↔
Lipid lowering agents	**gemfibrozil**	UGT2B7	↓	↔
	pitavastatin	UGT1A3, UGT2B7 > CYP2C9, CYP2C8	↓	↔
Parkinsonism agents	**apomorphine**	glucuronidation, sulfation	↓	↔
	rasagiline	CYP1A2	↓	↔
	ropinirole	CYP1A2	↓	↔
Other	**dexmedetomidine**	UGT1A4, UGT2B10, CYP2A6	↓	↔

Differences in DDI profile with co-medications:

- drugs glucuronidated and/or metabolized by inducible CYPs and without CYP3A involvement
  ➔ ↓ RTV and ↔ Cobi
- drugs glucuronidated and/or metabolized by inducible CYPs > CYP3A
  ➔ ↓ RTV and ↑Cobi
- drugs whose metabolism is subject to induction or inhibition
  ➔ ↑↓ RTV and ↑Cobi

Marzolini C et al. JAC 2016
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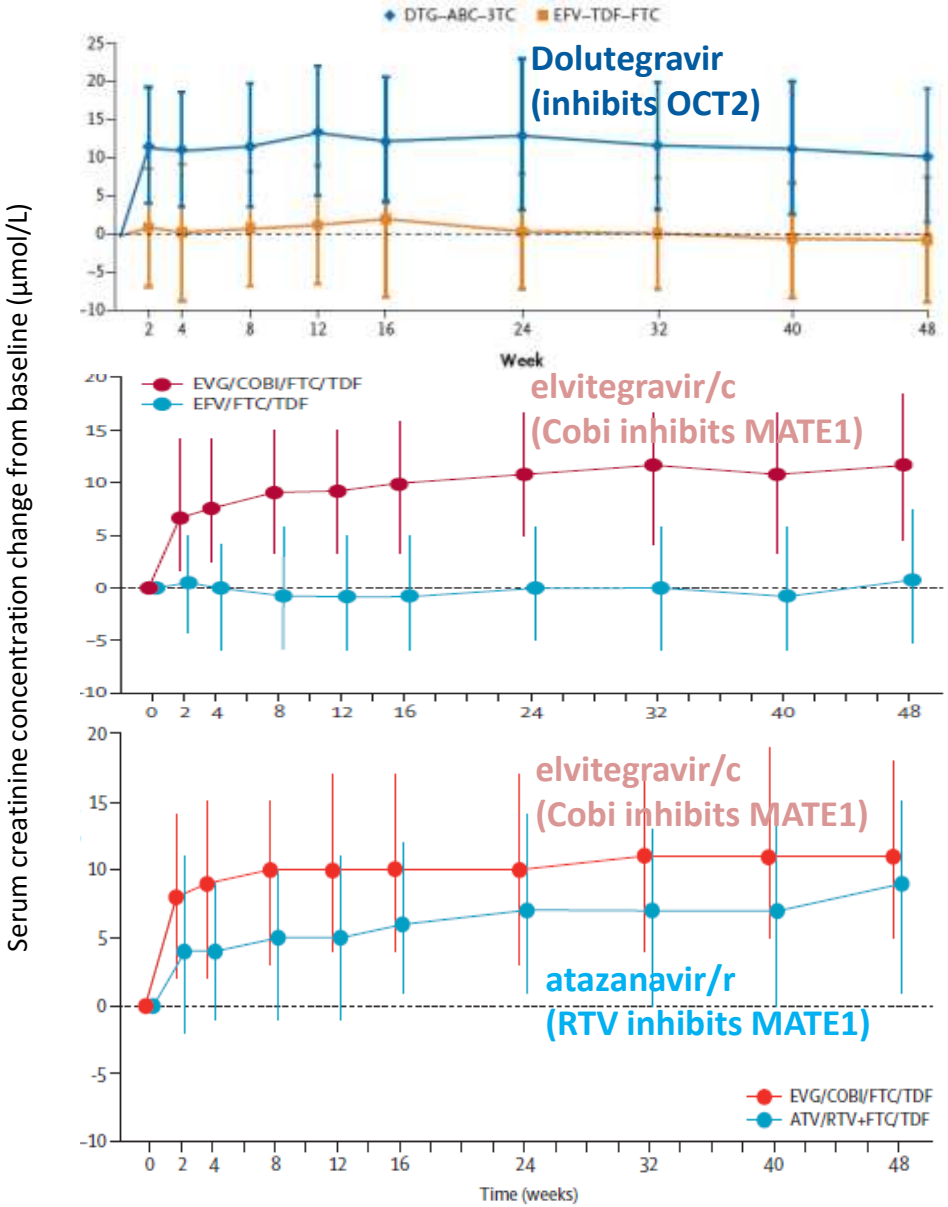
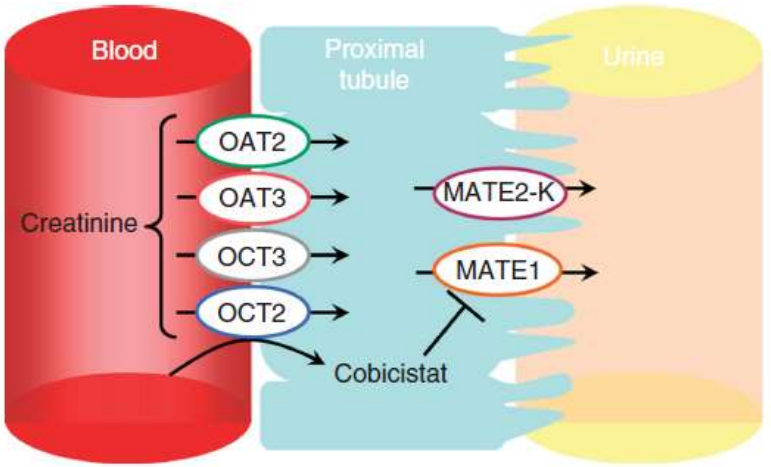
DDI at the level of the kidney



Renal transporters involved in active tubular secretion of creatinine



OCT2 mediated uptake of cobicistat into proximal tubule cells facilitates inhibition of MATE1

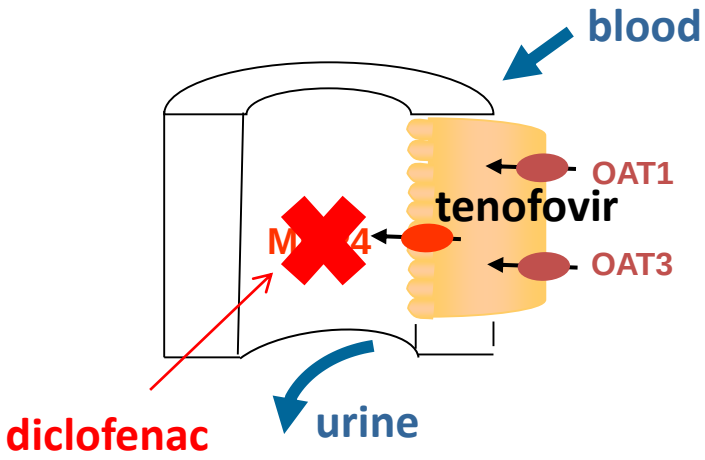
Walmsley S et al. NEJM 2013; Sax P et al. Lancet 2012; deJesus E et al. Lancet 2012; Lepist EI et al. Kidney Int 2014

Cumulative risk factors leading to acute renal failure

- 70-year old HIV-infected patient well controlled with darunavir/r + TDF + FTC
- co-morbidities: hypertension treated with lisinopril
  dyslipidemia treated with pravastatin
- patient is hospitalized for **anuric acute renal failure**
- five days before admission, patient suffered from nausea, diarrhea, vomiting. He took diclofenac for abdominal pain.

Question: what is your explanation for the anuric acute renal failure?

interaction between diclofenac and tenofovir



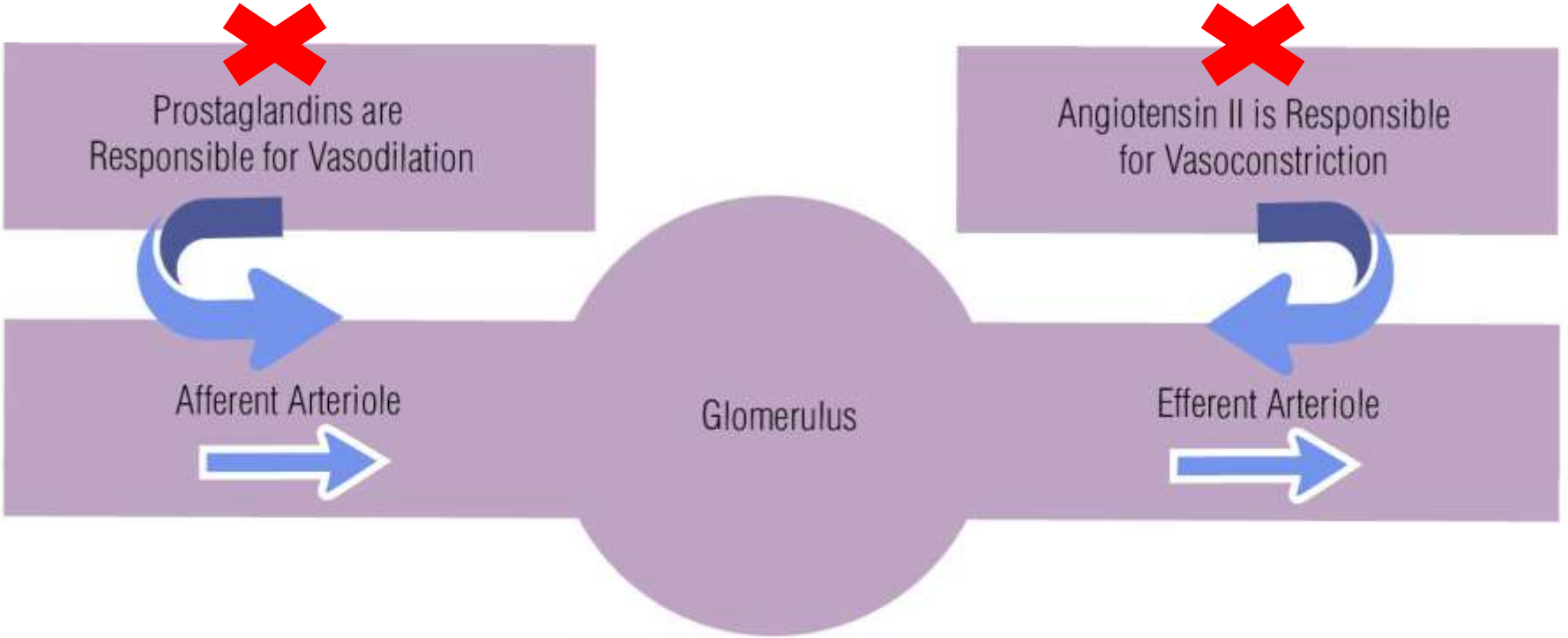
NSAID	IC50 MRP4 [uM]
Celecoxib	35
Diclofenac	**0.006**
Ibuprofen	26.3
Indomethacin	6.1
Naproxen	42.3
Piroxicam	216

Bickel M et al. HIV Med 2013, El-Sheikh A et al. JPET 2007

Hemodynamics of blood flow through glomerulus

NSAID inhibits production of prostaglandins

Angiotensin converting enzyme (ACE) inhibitor blocks production of angiotensin II



The purpose is to maintain adequate filtration pressure and preserve GFR

Renal hemodynamic responses decline with age

Risk factors for drug-induced nephrotoxicity

Drug related risk factors

- altered intraglomerular hemodynamics
- tubular cell toxicity
- nephrolithiasis
- thrombotic microangiopathy
- acute interstitial nephritis
- glomerulonephritis
- rhabdomyolysis
- drug dose and duration of treatment, rate of infusion (iv administration)

Patient related risk factors

- **older age**
- underlying renal insufficiency
- volume depletion (i.e.diarrhea, vomiting, poor oral intake, fever)
- diabetes
- heart failure

Preventive measures

- avoid nephrotoxic drug combinations
- ensure adequate hydration before and during therapy with potential nephrotoxic drugs
- monitor renal function
- inform the patient

+ early intervention

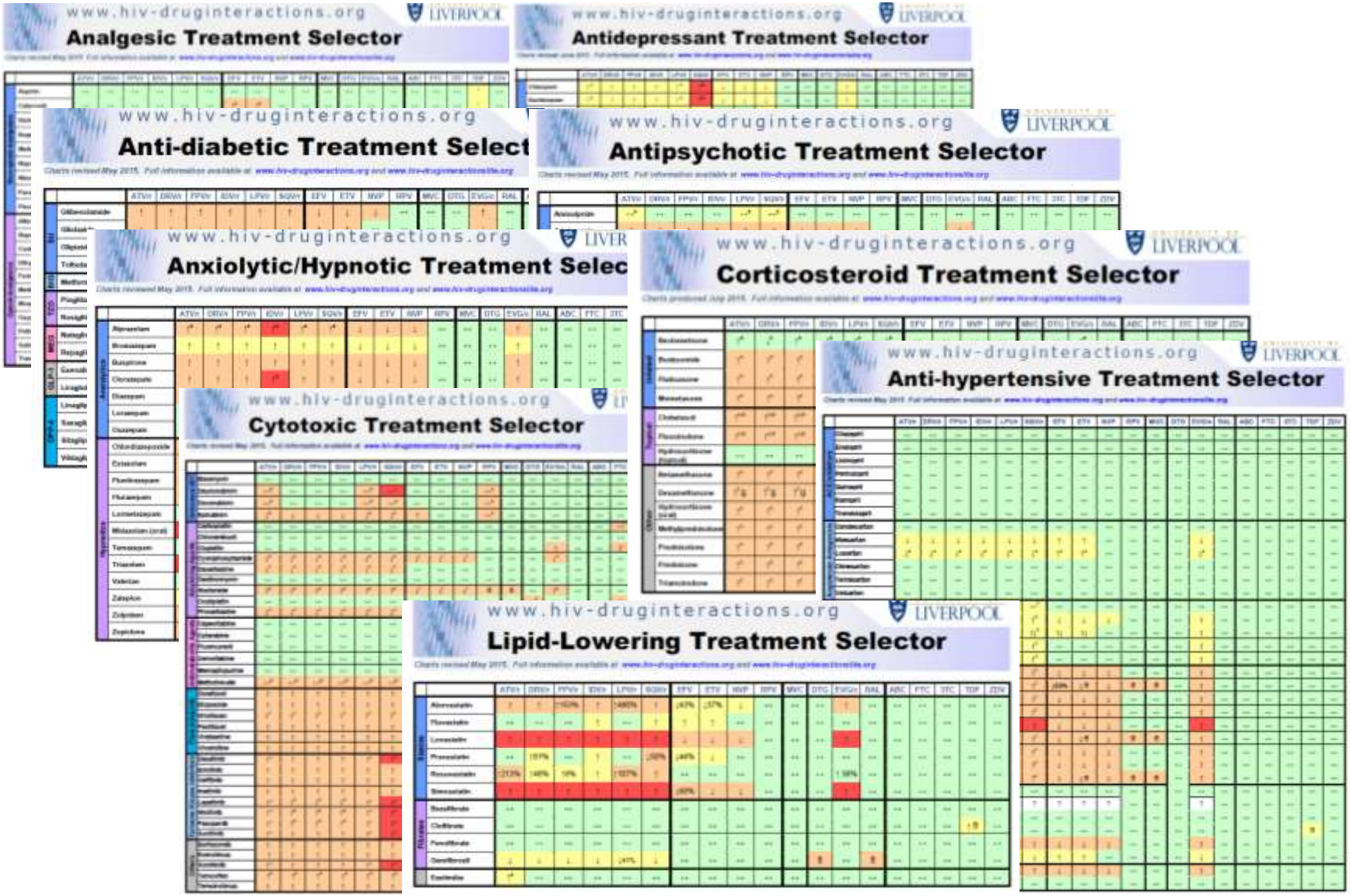
Naughton C. Am Fam Physician 2008

Other DDI of interest in the aging patients

Drug class	ARV	comment
Steroids	PI, Cobi	increase risk of Cushing syndrome (inhibition of steroids metabolism). If possible avoid PI/r, cobi. Beclomethasone: preferred agent (for inhalation)
Antidepressants	PI, Cobi	avoid tricyclic antidepressants as can cause anticholinergic effets, sedation and orthostatic hypotension. Side effects reinforced by inhibition of metabolism
Benzodiazepines	PI, Cobi	avoid due to increased sensitivity in elderly (increased risk of cognitive impair-ment, falls and fractures). Side effects reinforced by inhibition of metabolism
Calcium channel blockers	PI, Cobi	PI/r, cobi can increase hypotensive effect of CCB (inhibition of metabolism). Decrease dosage and slowly titrate with close monitoring
Peripheral alpha blockers	PI, Cobi	avoid due to risk of orthostatic hypotension. Side effect reinforced by inhibition of metabolism
Statins	PI, Cobi	can significantly increase exposure of some statins and thus increase risk of rhabdomylosis. Follow dosage recommendations
NSAID	TDF	avoid long term use and closely monitor renal function

Burgess MJ et al. HIV AIDS 2015; Nachega JB et al. AIDS 2012; American Geriatrics Society. J Am Geriatr Soc 2015

Drug-drug interactions tables



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