CNS pharmacology of antiretroviral drugs and relevant interactions between antiretroviral and CNS drugs

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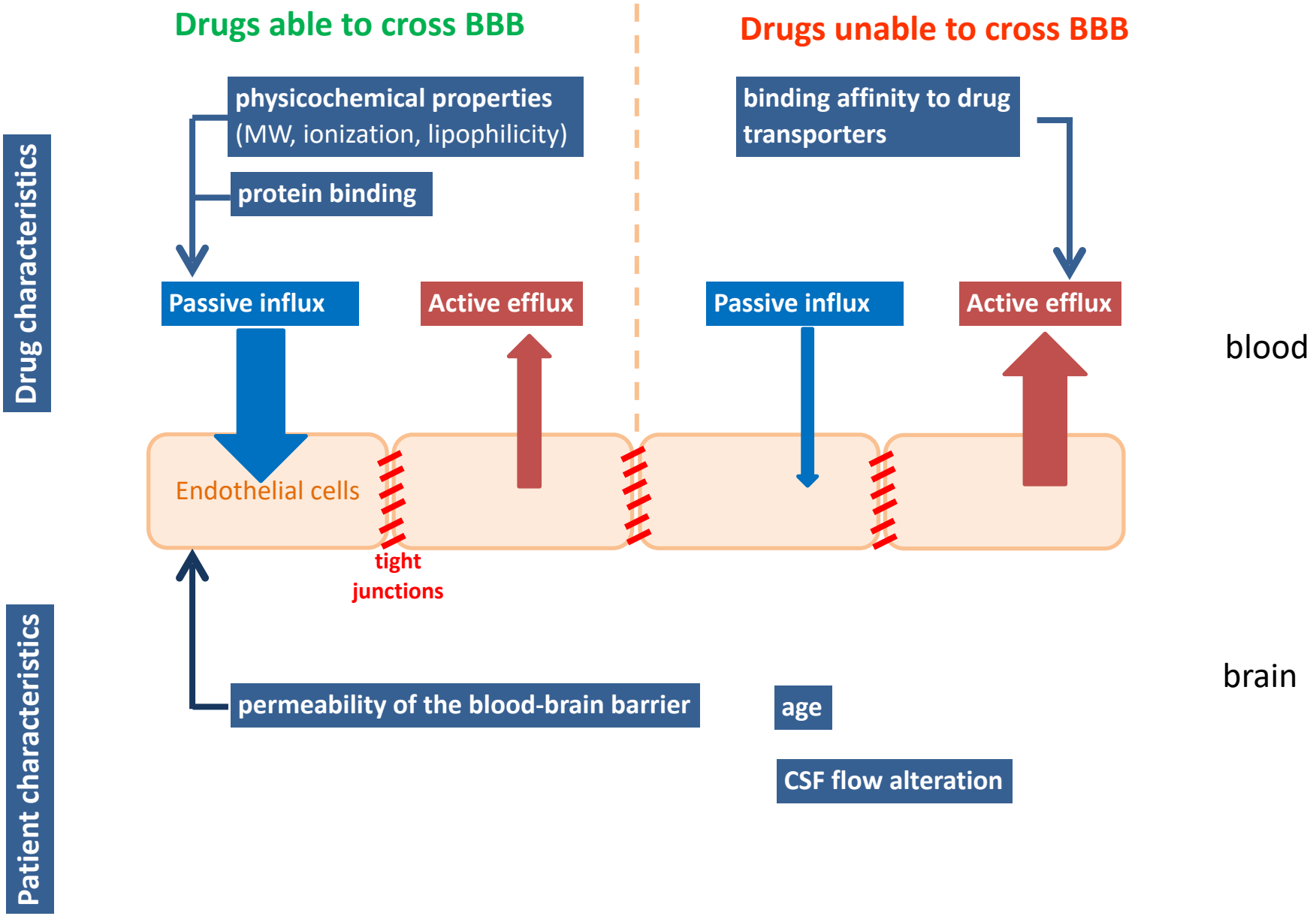
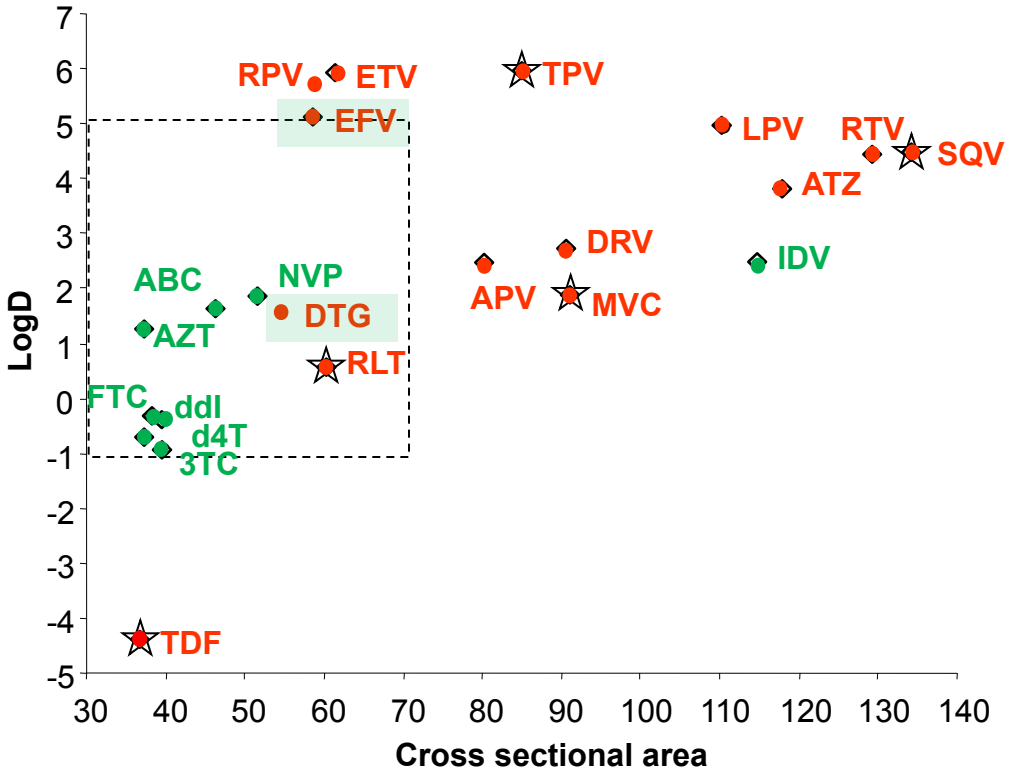
Presentation outline

- penetration of antiretroviral drugs (ARV) in CNS
- CSF ARV concentrations and IC50/IC95
- ARV penetration effectiveness and PD effects
- open questions
- drug-drug interactions between ARV and CNS drugs
- combination of ARV and CNS drugs and risk of QT interval prolongation

Factors determining drug entry in the brain



Prediction of blood-brain permeation of HIV drugs



charged at physiological pH ☆

BBB+ : passive influx > efflux

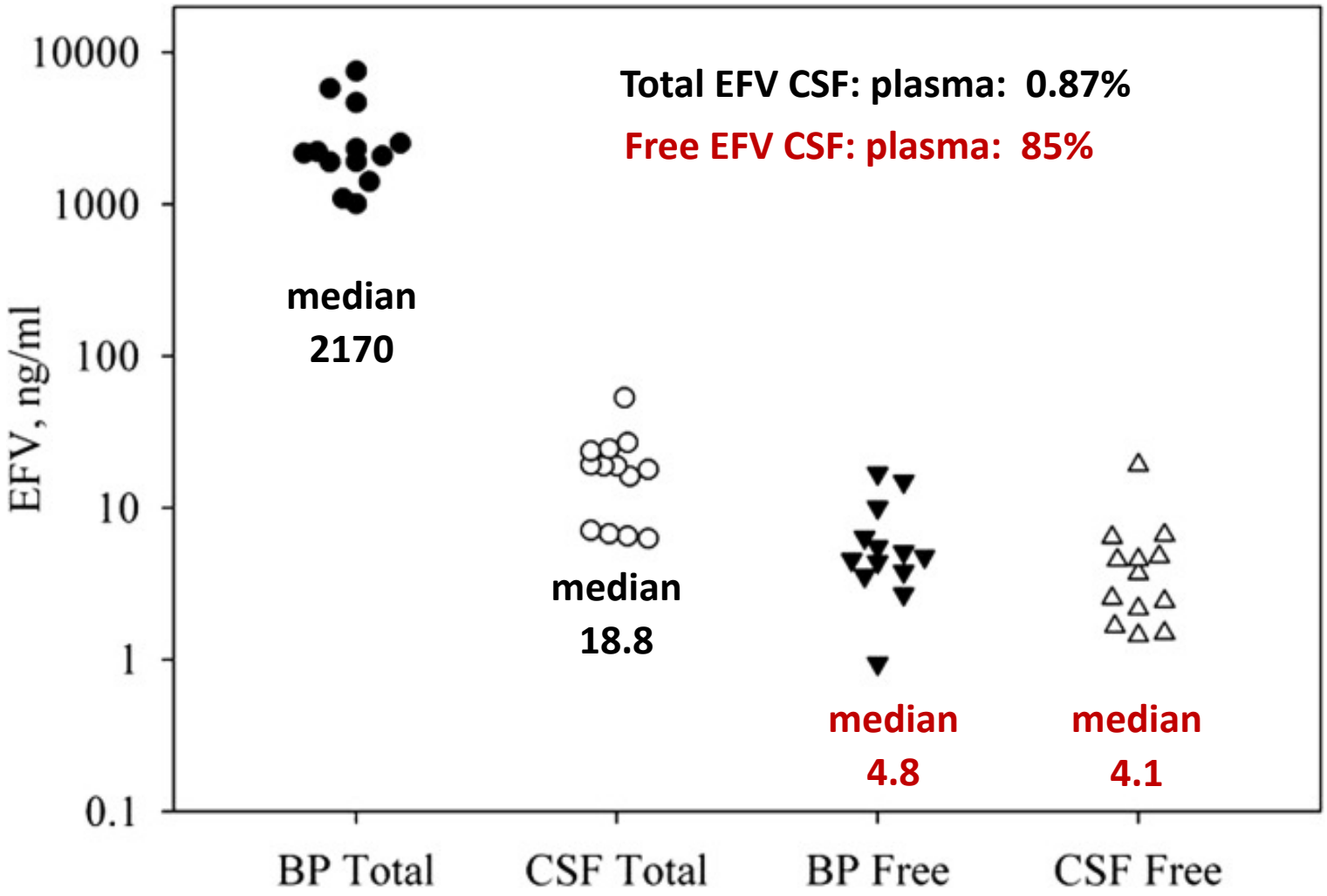
BBB- : passive influx < efflux

clinical data: CSF/plasma (%)

Abacavir (ABC)	36%
Didanosine (ddI)	23%
Dolutegravir (DTG)	0.5%
Emtricitabine (FTC)	43%
Lamivudine (3TC)	15%
Stavudine (d4T)	32%
Tenofovir (TDF)	4%
Zidovudine (AZT)	75%
Efavirenz (EFV)	0.5%
Etravirine (ETV)	4%
Nevirapine (NVP)	46%
Rilpivirine (RPV)	1.4%
Amprenavir (APV)	1%
Atazanavir (ATZ)	1.5%
Darunavir (DRV)	0.9%
Indinavir (IDV)	17%
Lopinavir (LPV)	0.3%
Ritonavir (RTV)	0.2%
Saquinavir (SQV)	0.1%
Tipranavir (TPV)	na
Raltegravir (RLT)	6%
Maraviroc (MVC)	4%

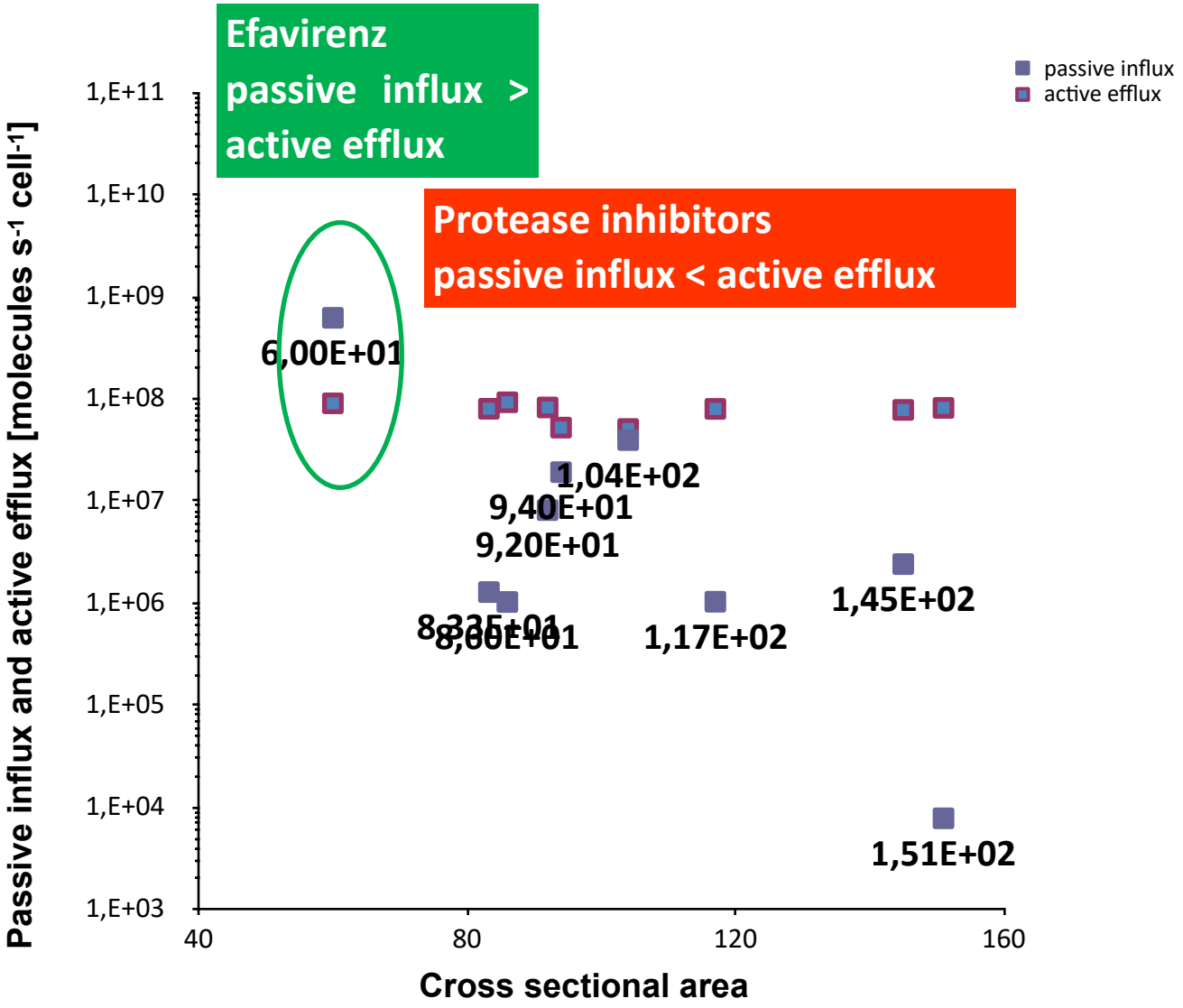
Marzolini C et al. Mol Pharm 2013

Protein free EFV CSF:plasma ratio



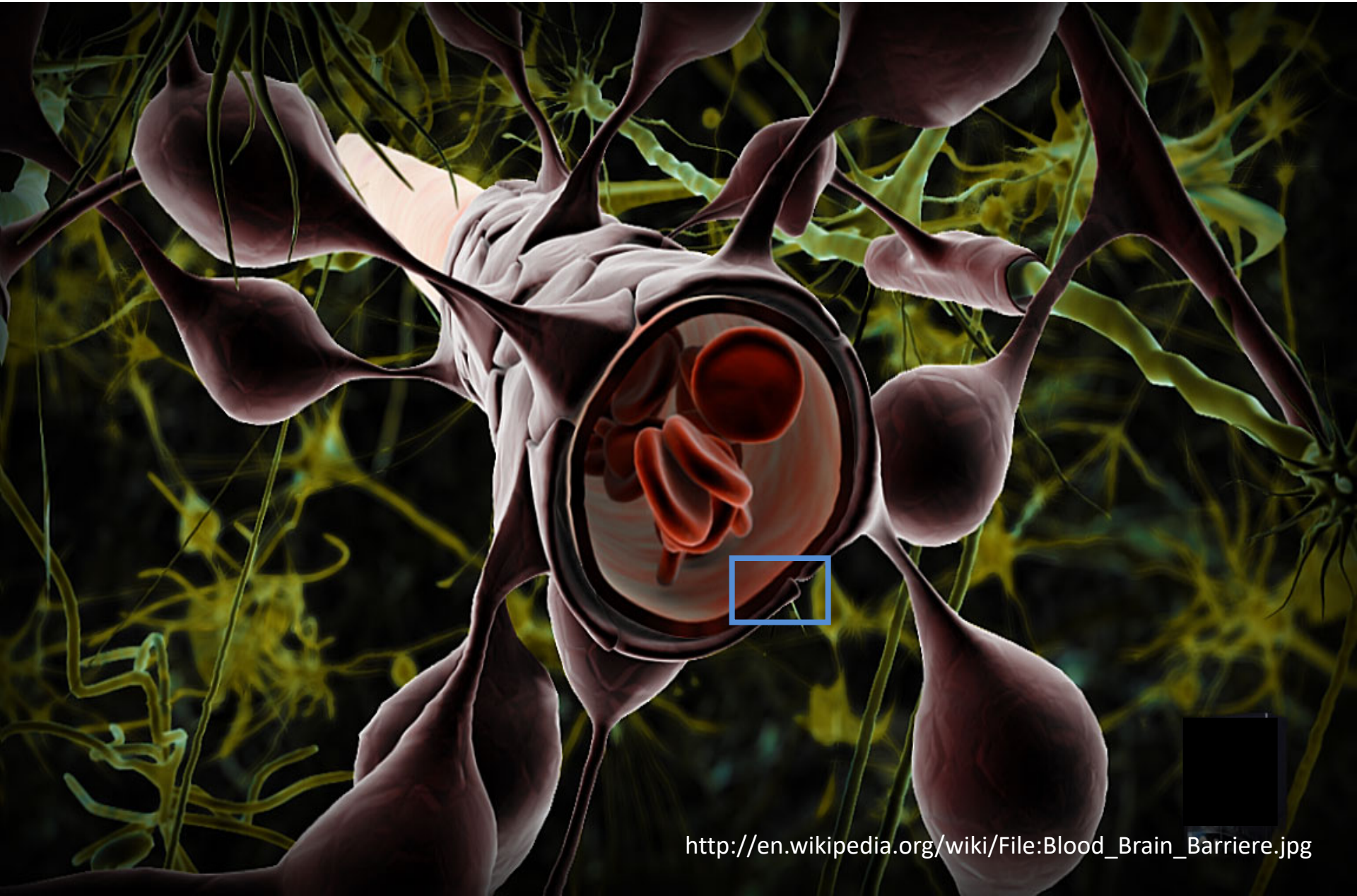
Avery LB et al. Antimicrob Agents Chemother 2013

Passive influx and active efflux of antiretroviral drugs



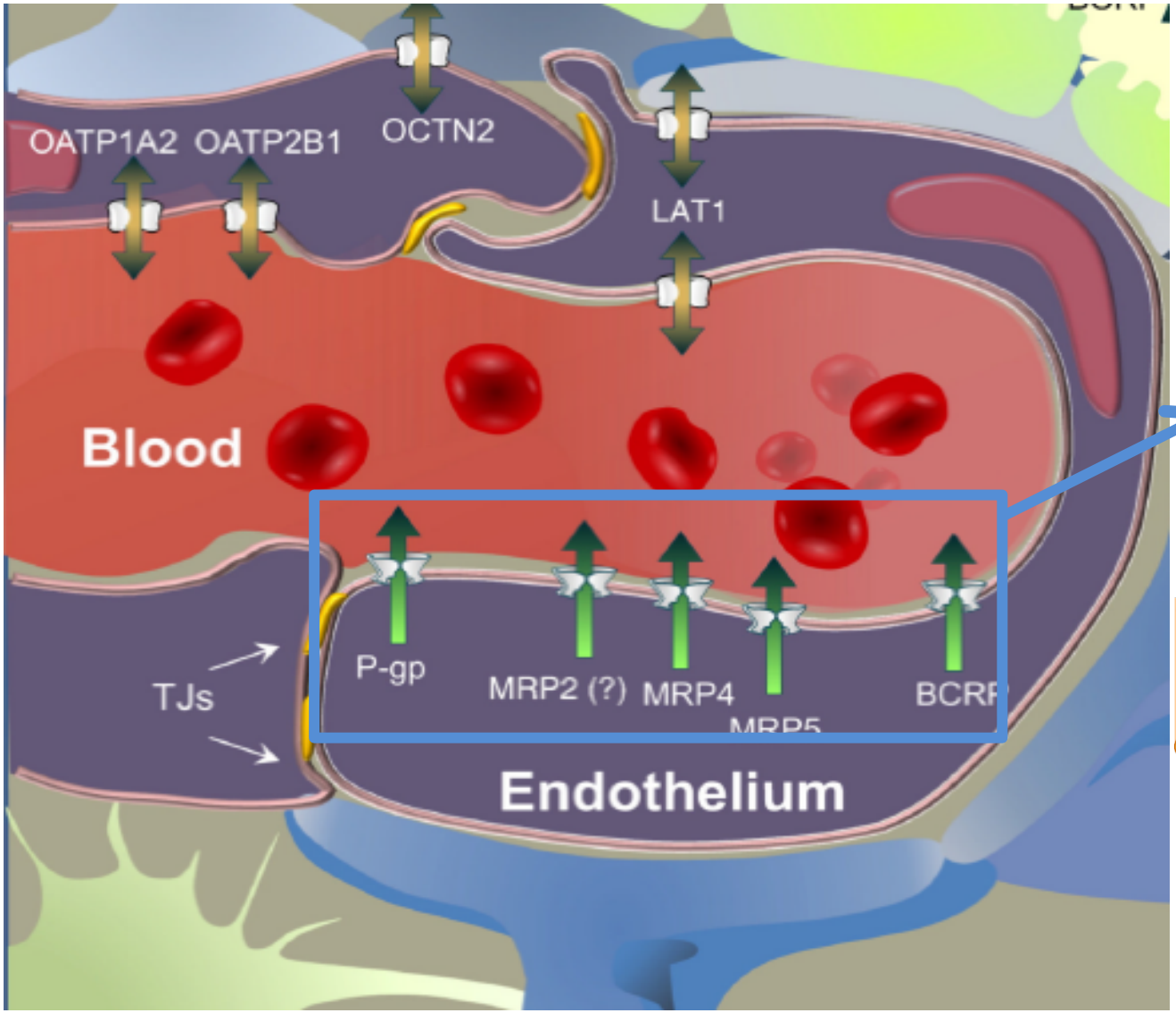
Marzolini C et al. Mol Pharm 2013

Blood-brain barrier

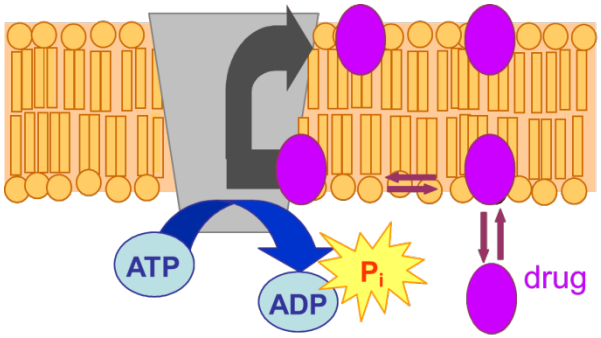


http://en.wikipedia.org/wiki/File:Blood_Brain_Barriere.jpg

Transporters expressed at the blood-brain barrier



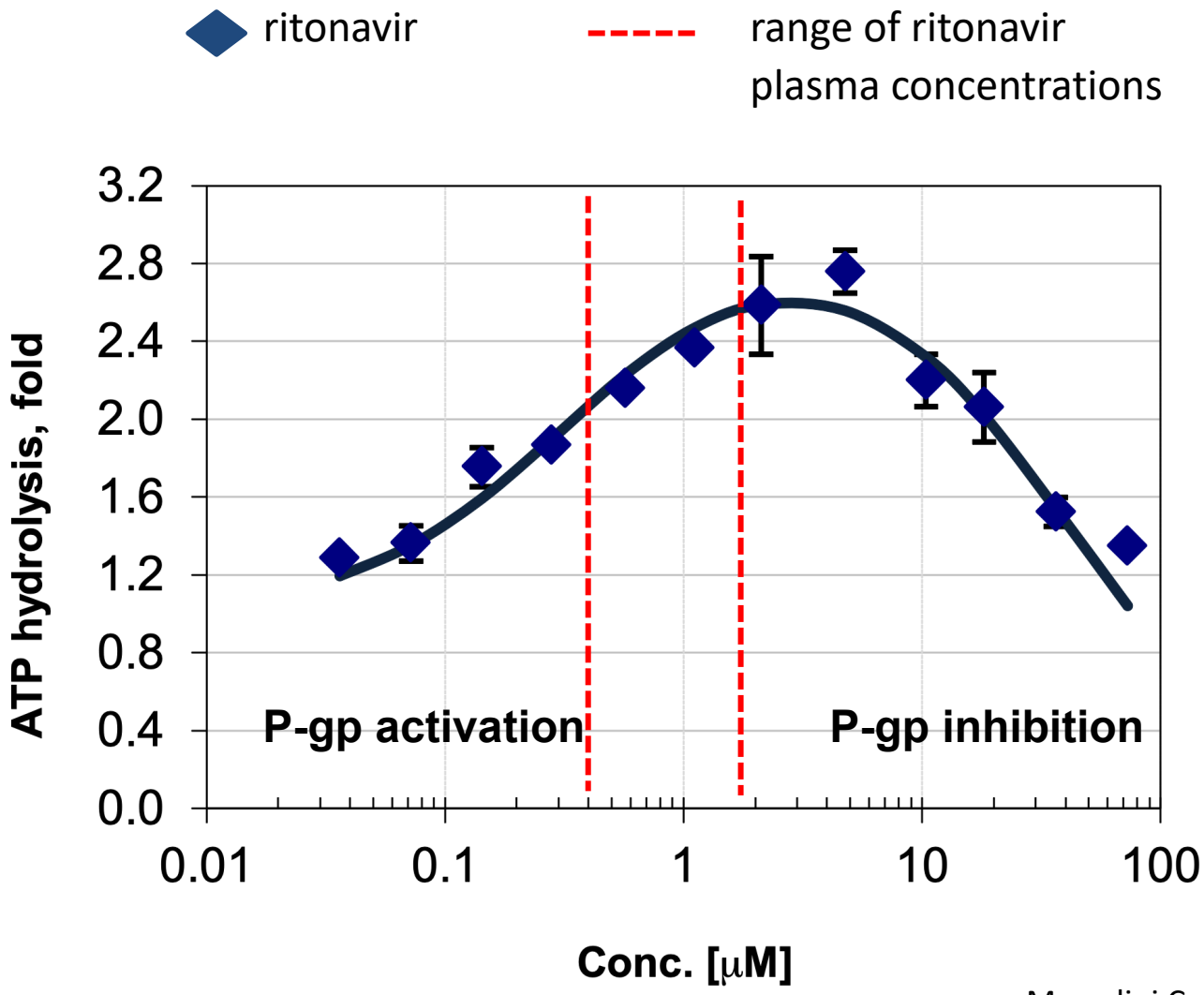
Efflux transporters use hydrolysis of ATP as an energy source to export drug out of the cell



Eyal S et al. Pharmacol Ther 2009, Marzolini C et al. Mol Pharm 2013

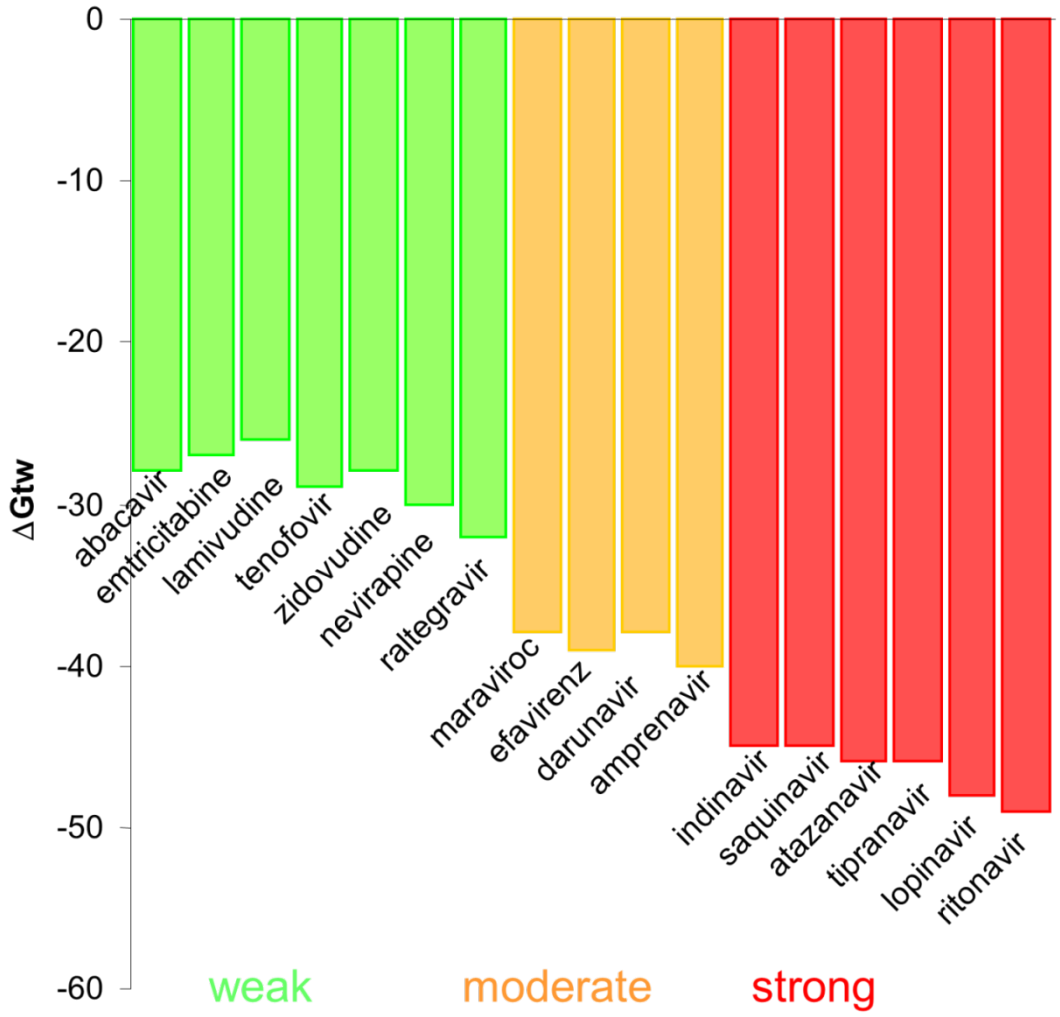
Interaction of ARV with efflux transporters

P-gp ATPase activity profile of ritonavir



Marzolini C et al. Mol Pharm 2013

Binding affinities of antiretroviral drugs to P-gp

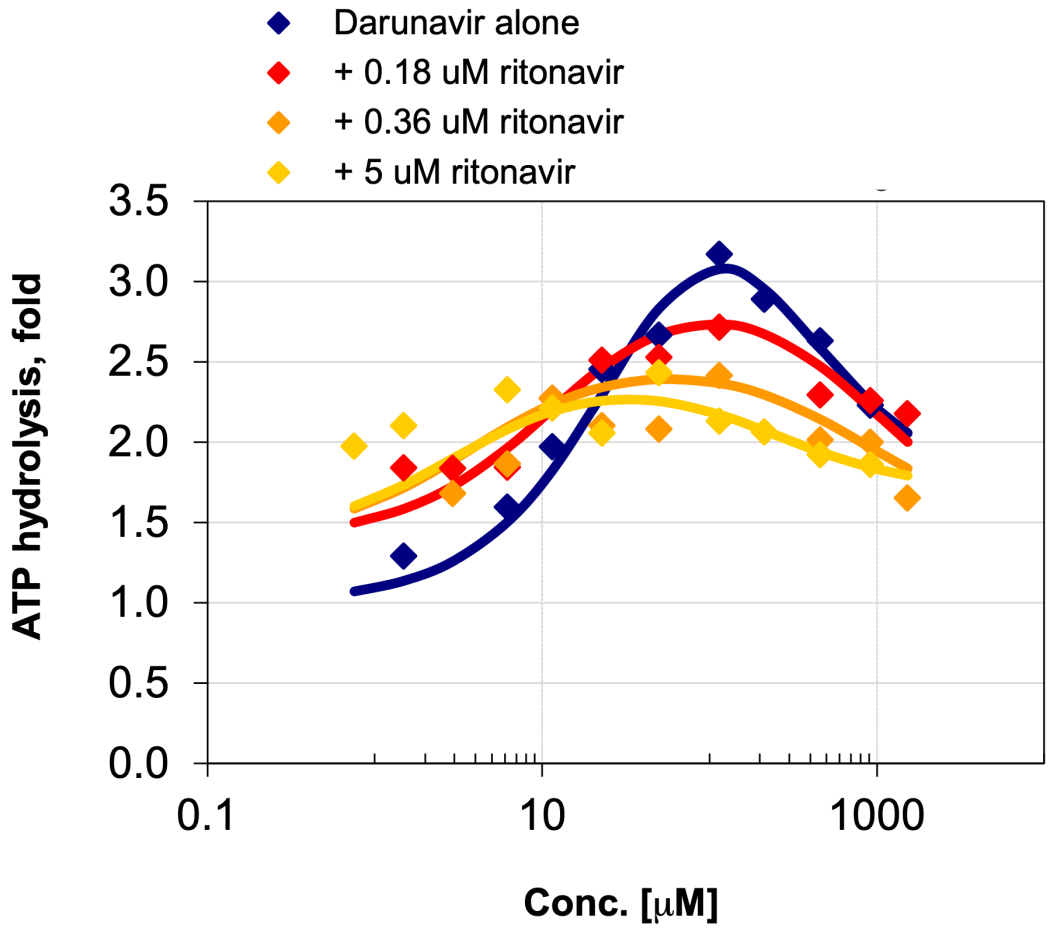


Protease inhibitors have strong binding affinities to efflux transporters and thus have a higher tendency to modulate the activity of efflux transporters

Marzolini C et al. Mol Pharm 2013

Impact of ARV combination on P-gp efflux

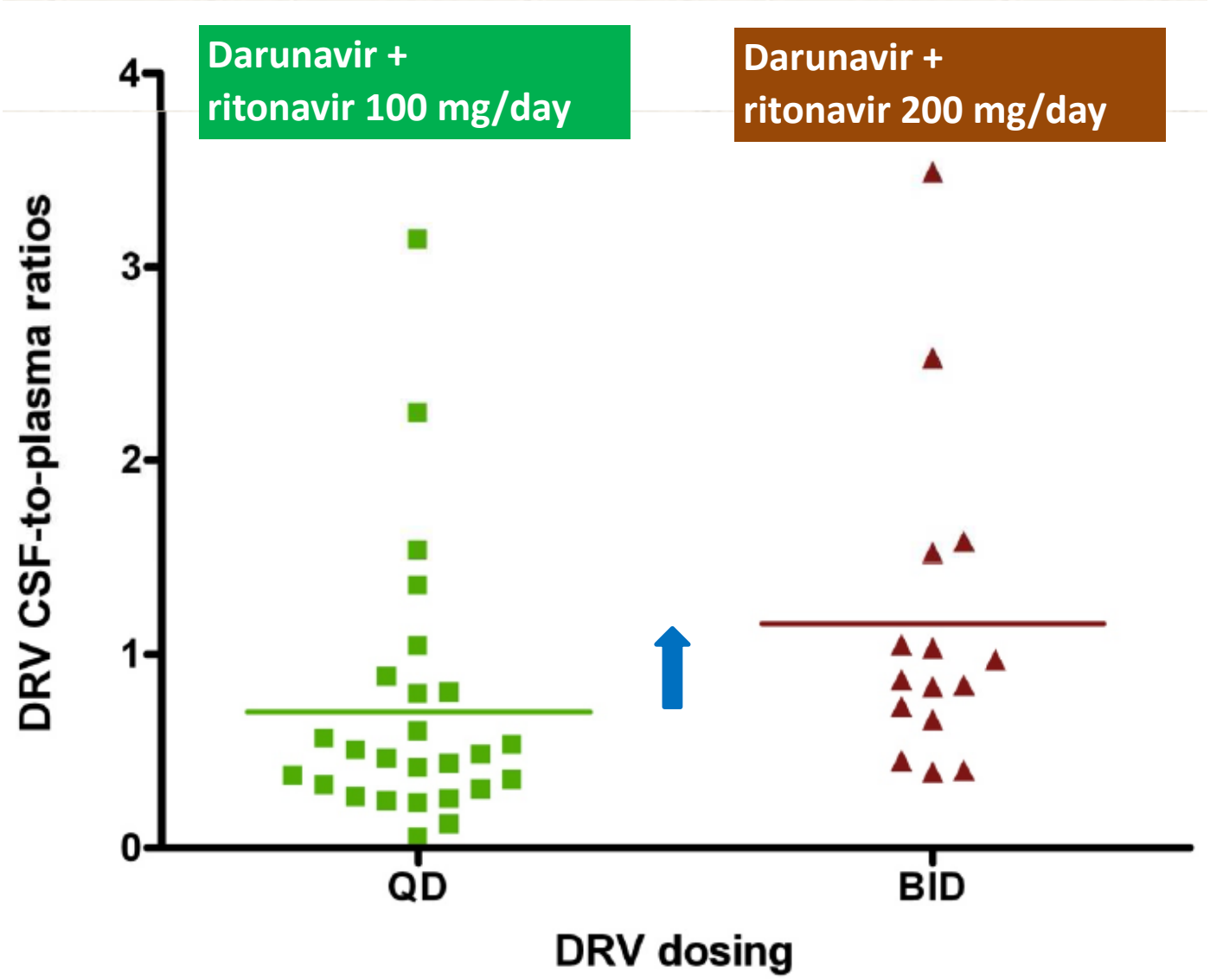
P-gp ATPase activity profile of darunavir without/with ritonavir



The protease inhibitor with the highest binding affinity will occupy the transporter binding sites and slow down the efflux rate of the coadministered drug.

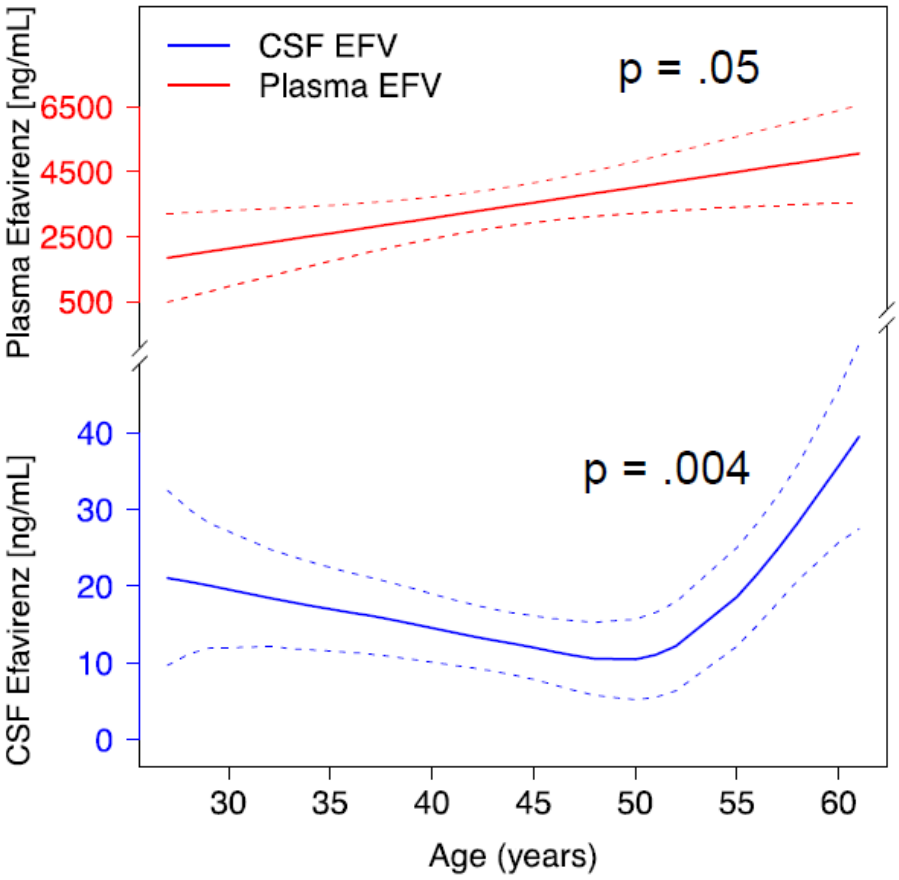
Marzolini C et al. Mol Pharm 2013

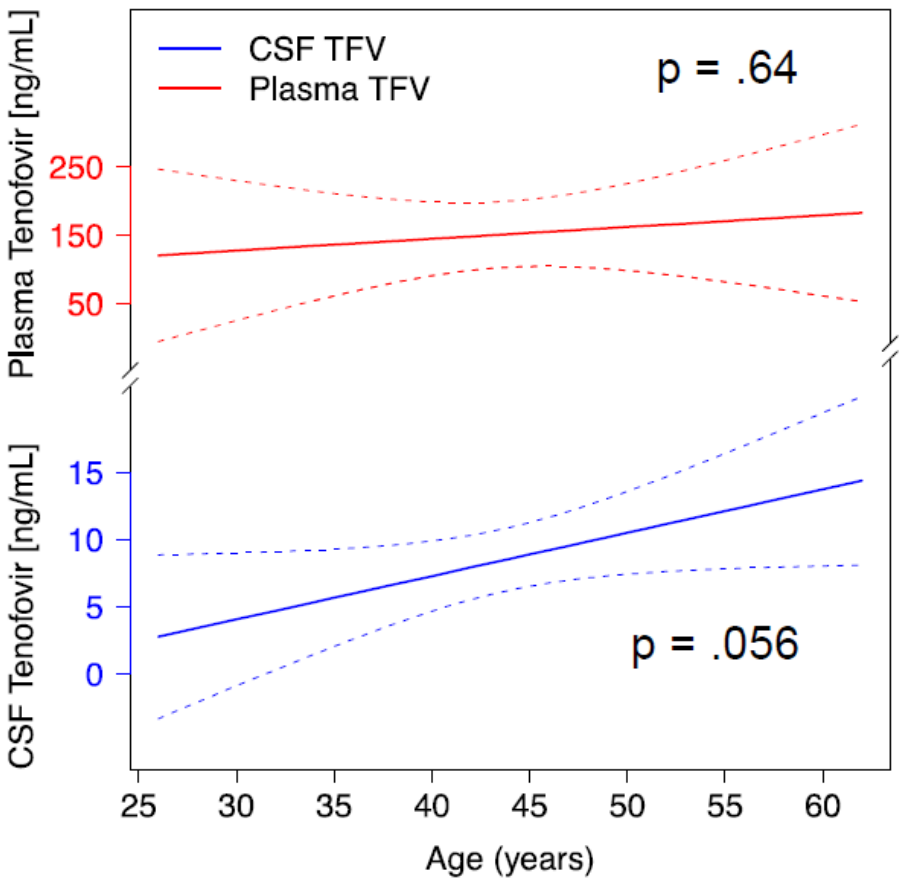
Darunavir CSF: plasma ratio with ritonavir boosting



Calcagno A et al. AIDS 2012

Older age and drug concentrations in CSF



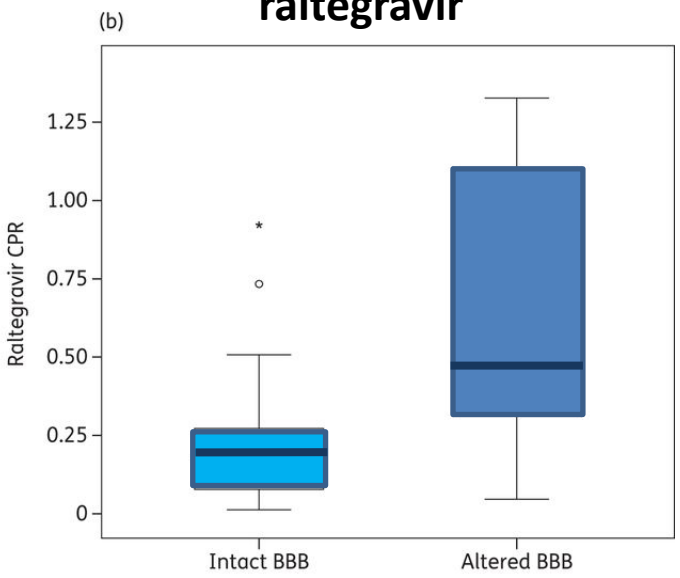


Older age was associated with greater antiretroviral drugs exposure in the CNS. This could be explained by a reduced drug efflux, permissive BBB or altered CSF flow.

Croteau D et al. CROI 2012

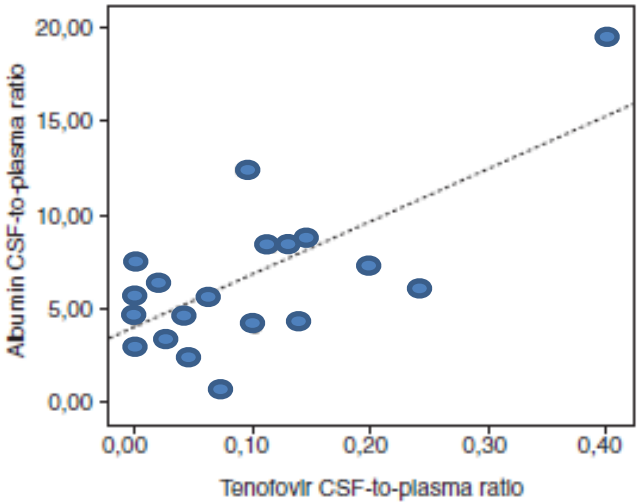
CSF concentrations in patients with altered BBB

raltegravir

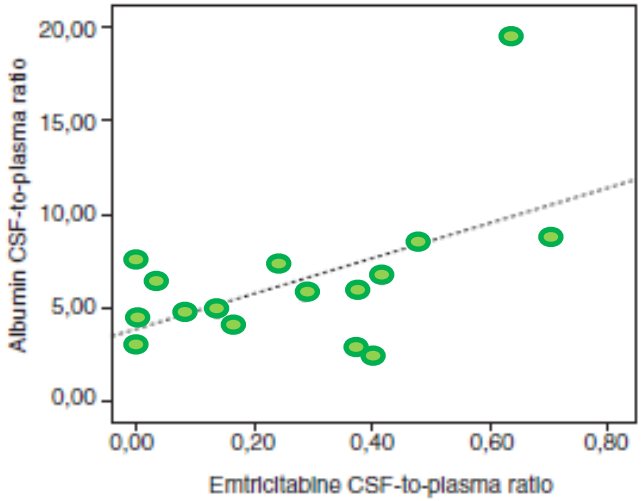


Clinical significance unclear: total drug levels bound to proteins might be higher but not the free drug levels

tenofovir



emtricitabine



Calcagno A et al. JAC 2014; Calcagno A et al. AIDS 2011

CSF drug concentrations relative to IC50

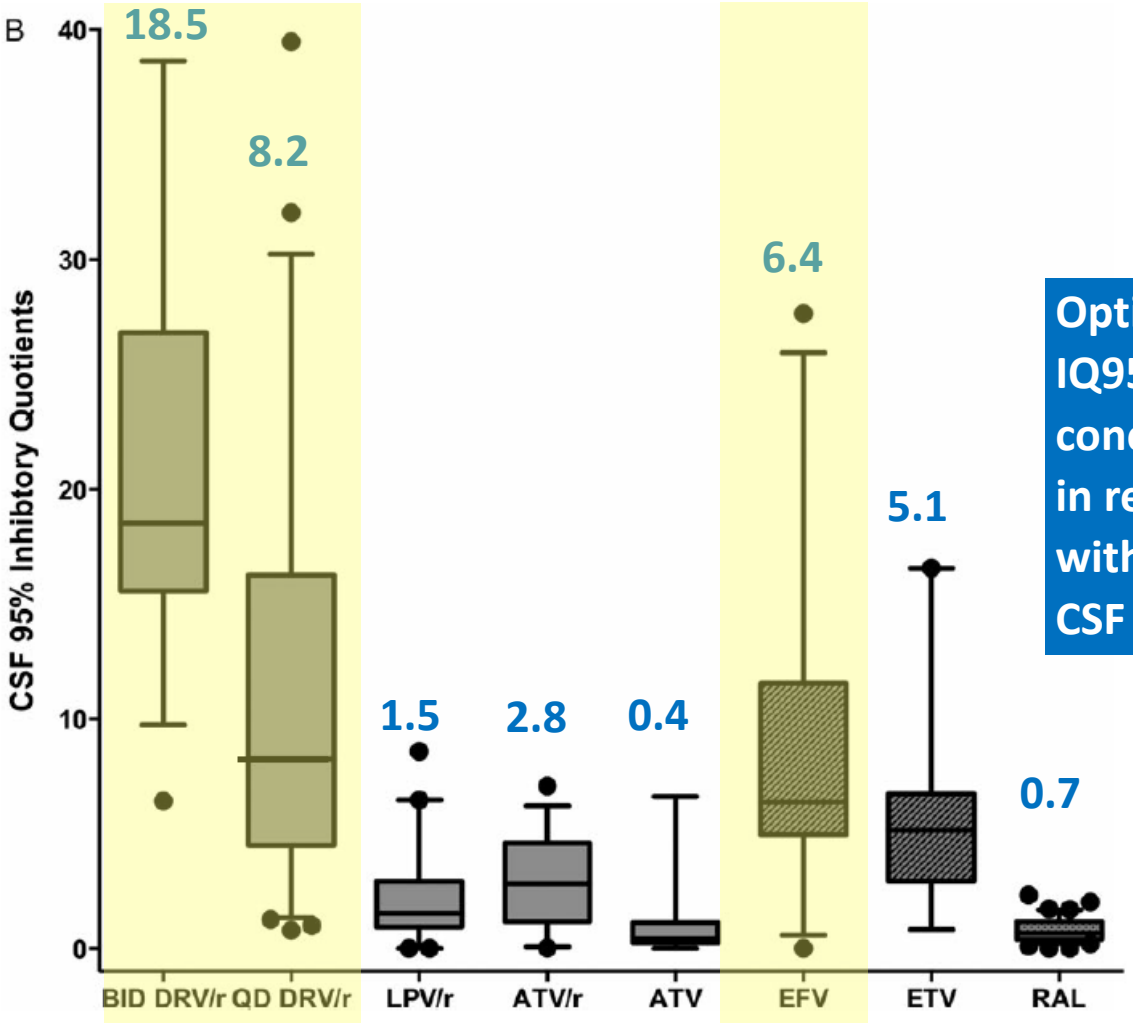
	Drug	IC50 [ng/ml]	pharmacokinetics data	Reference
NRTI	Abacavir	70	CSF trough above IC50 for 85% of dose interval	Capparelli EV. AAC 2005
	Lamivudine	NA	Total CSF concentrations above IC50	Foudraine N. Lancet 1998
	Stavudine	52	Total CSF concentrations above IC50	Haworth SJ. JAIDS 1998
	Tenofovir	11.5	Total CSF concentrations did not exceed IC50 in 77% of patients	Best BM. JAIDS 2012
	Zidovudine	0.5-641.4	Total CSF concentrations above IC50	Foudraine N. Lancet 1998
NNRTI	Efavirenz	0.51	Unbound and total CSF concentrations above IC50	Best B. JAC 2011 Cusini A. JAIDS 2013
		0.36	Total CSF concentrations above IC50	Avery L. DMD 2013
		1.3	Total CSF concentrations above IC50 (protein free) by 12 fold	Yilmaz A. AAC 2012
	Etravirine	0.39-2.4	Total CSF concentrations above IC50	Tiraboschi J. JAC 2012
		0.9	Total CSF concentrations above IC50 but unbound CSF is below IC50 but did not seem to affect in vivo activity.	Nguyen A. JAC 2013
	Rilpivirine	0.27	Total CSF concentrations above IC50	Mora-Peris B. JAC 2014

CSF drug concentrations relative to IC50

	Drug	IC50 /95 [ng/ml]	pharmacokinetics data	References
PI	Indinavir	18-70	Total CSF concentrations above IC95	Polis MA. AIDS 2003
		15-61	Unbound CSF concentrations above IC95	Haas DW. AAC 2003
	Atazanavir	1	Total CSF concentrations near IC50 in 16% pts	Best BM. AIDS 2009
		1	Total CSF concentrations below IC50 in 17% pts	Cusini A. JAIDS 2013
	Lopinavir	1.9	Total CSF concentrations above IC50	Capparelli EV. AIDS 2005
	Darunavir	12-55	Total CSF concentrations above IC50	Yilmaz A. AIDS Res Hum Retrovir 2009
		1.78	Unbound CSF concentrations above IC50	Croteau D. JAC 2013
	Saquinavir	42-55	CSF concentrations below IC50	Yilmaz A. BMC Infect Dis 2006
INI	Raltegravir	3.2 (IC_{50}) 9-15 (IC_{95})	Total CSF concentrations above IC50 but total CSF concentrations above IC95 in roughtly 50% pts	Croteau D. AAC 2010 Yilmaz A. PLoS One 2009
	Dolutegravir	0.2	Total CSF concentrations above IC50	Letendre S. CID 2014
	Maraviroc	0.57	Total CSF concentrations above IC90	Yilmaz A. AIDS 2009

CSF inhibitory quotients of various antiretroviral drugs

Inhibitory quotient (IQ95) = CSF drug concentration / IC95



Optimal CSF drug exposure : IQ95 >1 and detectable CSF concentrations of all drugs in regimen was associated with decreased probability of CSF escape

Calcagno A et al. CID 2015

Correlation CPE score and CNS HIV RNA or NC testing

Reference	n	Higher CPE* => CSF VL	Higher CPE => NC testing
Cysique et al. Neurology 2009	37	**Lower CSF VL**	**Better NC tests**
Tozzi et al. JAIDS 2009	185	Not done	**Better NC tests**
Marra et al. AIDS 2009	79	**Lower CSF VL**	**Worse NC tests**
Winston et al. CID 2010	30	Not done	**Better NC tests**
Smurzynski et al. AIDS 2011	2636	Not done	**Better NC tests with > 3 drugs**
Arendt et al. CROI 2011	3883	**Lower CSF VL**	**Better NC tests**
Garvey et al. HIV Clin Trials 2011	101	Not done	**No effect**
Rourke et al. CROI 2012	545	Not done	**Better NC tests**
Robertson et al. CID 2012	860	Not done	**No effect**
Ciccarelli et al. Antivir Ther 2013	101	Not done	**Better NC tests**
Kahouadji et al. HIV Med 2013	54	Not done	**Worse NC tests**
Cross et al. S Afr Med 2013	69	Not done	**No effect**
Ellis et al. CID 2014	49	**No effect**	**No effect**
Vassallo et al. AIDS 2014	246	Not done	**Stable or better NC tests**
Casado et al. J Neurovirol 2014	67	Not done	**Trend toward benefit**
Caniglia et al. Neurology 2014	61938	Not done	**Worse NC tests**

* Letendre S et al. Arch Neurol 2008

Comparative analysis of ARV neurotoxicity

Toxicity risk of 15 ARV on cultures of rat neurons (considering drug concentrations achieved in CSF)

Drugs with significant risk of neurotoxicity

Drugs with low risk of neurotoxicity

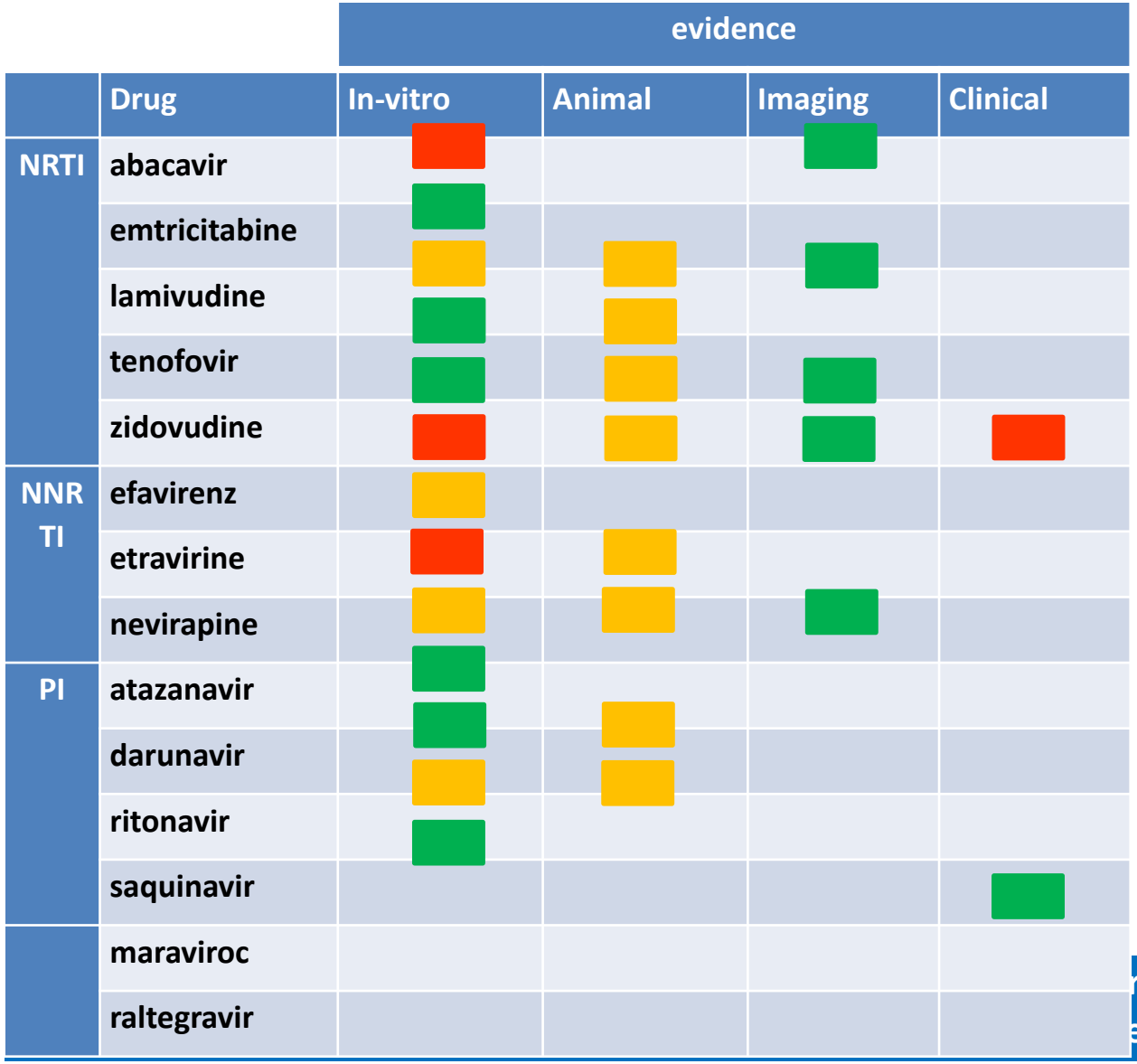
Drugs with negligible risk of neurotoxicity

Neurotoxic effect for 8-OH-EFV (10 times more toxic than EFV) using rat neuronal cultures

Tovar-Y-Romo LB et al. JPET 2012

Robertson K et al. J Neurovirol 2012

Summary of available evidence for ARV neurotoxicity



Likely to cause toxicity at clinical doses/ reasonable evidence of toxicity

Some evidence of toxicity at clinical doses

Possible evidence of toxicity not significant at clinical doses or conflicting reports or significant toxicity unlikely at clinical doses

rk. Studies are needed to estations of HAND.

adapted from Underwood J et al. AIDS 2015

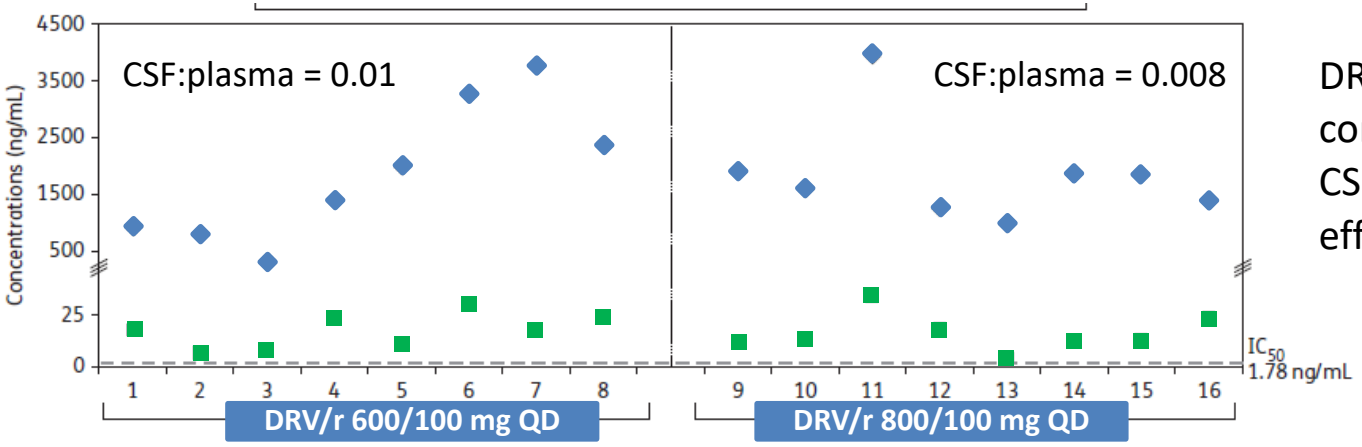
PI monotherapy

Reference	Drug regimen	Study design	Patients baseline	CSF escape	Intervention
Vernazza AIDS 2007	**ATV/r** MT	single MT arm 24 weeks	On cART or IDV/r MT VL suppressed CD4: ND	**3/20** all pts asympto-matic	reintroduction cART -> persistent CSF escape in 2 pts
Katlama AIDS 2010	**DRV/r** MT DRV/r cART	Randomized Controlled 96 weeks	On cART VL suppressed CD4: 232 MT CD4: 212 cART	**2/102** mild neurological symptoms	reintroduction cART -> CSF VL undetectable, clinical resolution
Gutmann AIDS 2010	**LPV/r** MT LPV/r cART	Randomized Controlled 48 weeks	On cART VL suppressed CD4: **160** both arms	**6/42** (also blood failure) Neurol. symptoms	reintroduction cART -> VL resuppression
Santos PLoS One 2013	**LPV/r** MT LPV/r cART	Cross-sectional	On cART VL suppressed CD4: 186 MT CD4: 169 cART	**3/17**	ND

LPV/r, DRV/r MT: **no negative effects on NC performance** (Perez Valero et al. CID 2014; Santos et al. PLoS One 2013)

ARV dose reduction

Plasma and **CSF** levels: DRV/r **600**/100 QD vs DRV/r **800**/100 QD + NRTIs



DRV dose reduction gives comparable plasma and CSF levels and comparable efficacy.

Yacovo M. JAC 2015

CSF levels of EFV, 8-OH EFV when dosed at 400 mg vs 600 mg QD+ NRTIs

GM	EFV plasma	EFV CSF	CSF:plasma	8OH EFV CSF
EFV 400 mg	**1956** ng/ml	**16.5** ng/ml	**0.83**	**5.08** ng/ml → 11/14 > 3.3 ng/ml
EFV 600 mg	**2567** ng/ml	**19.5** ng/ml	**0.71**	**3.08** ng/ml → 7/14 > 3.3 ng/ml (toxicity threshold)

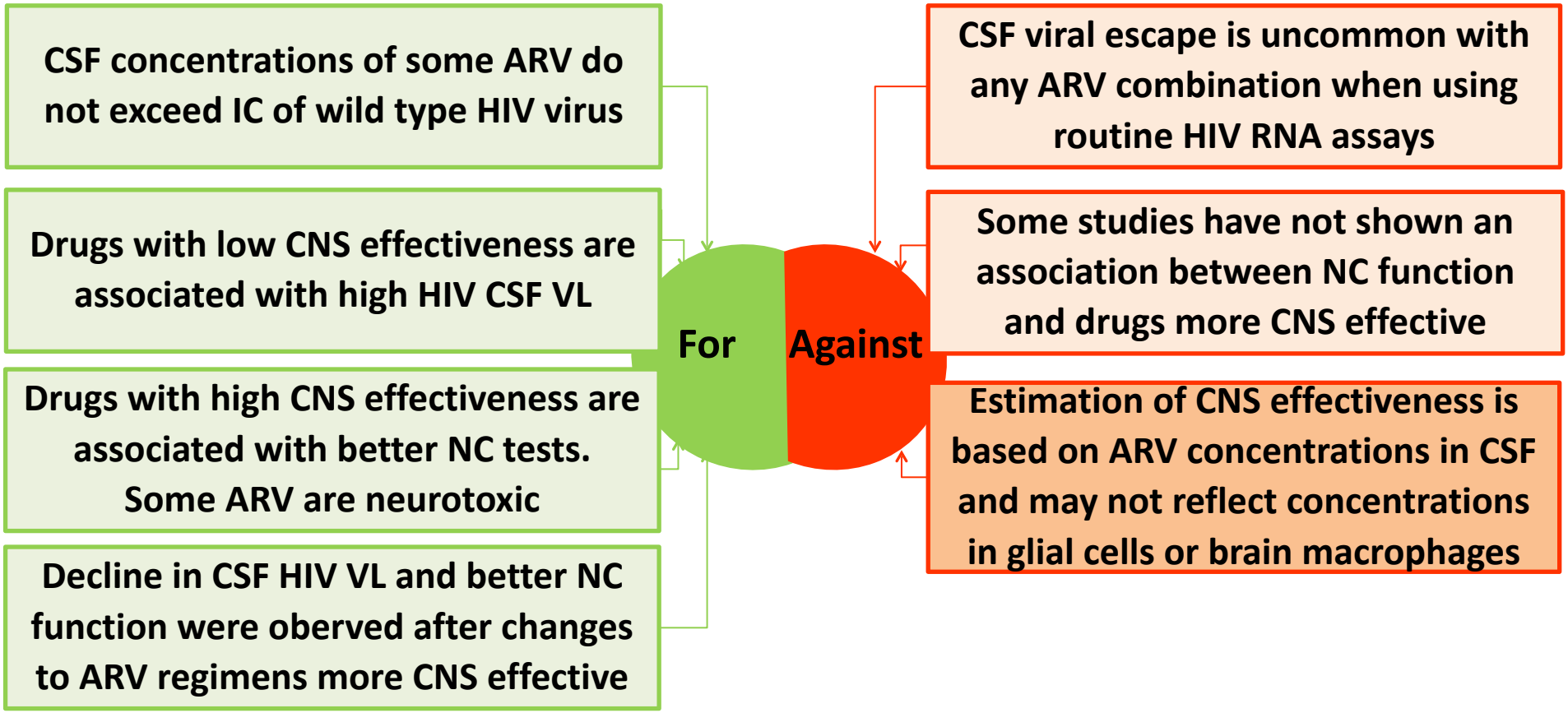
all > IC50 0.51 ng/ml

no statistical difference

CSF EFV concentrations were adequate with both dose however exposure of 8-OH EFV was still within the range associated with toxicities.

Winston A et al. CID 2015

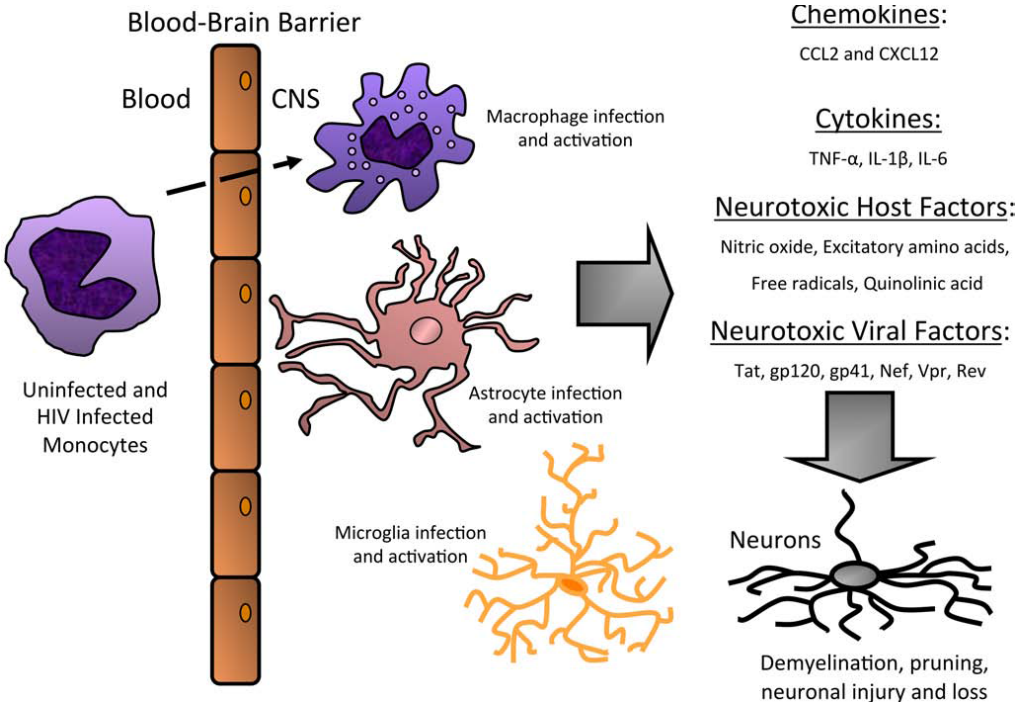
Are some ARV more effective in the CNS than others?



Adapted from Nightingale S et al. Lancet Neurol 2014

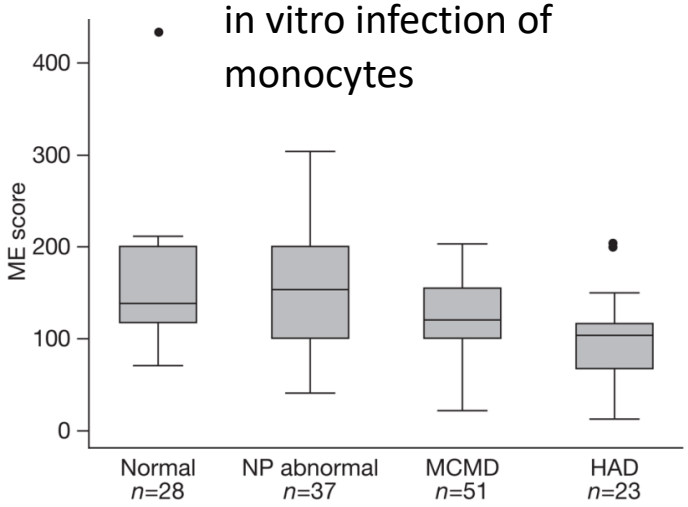
ARV monocyte efficacy score linked to NC impairment

Monocytes and HIV neuropathology



Correlation between monocyte efficacy (ME) scores and cognitive status

ARV with higher ME score inhibit more effectively in vitro infection of monocytes

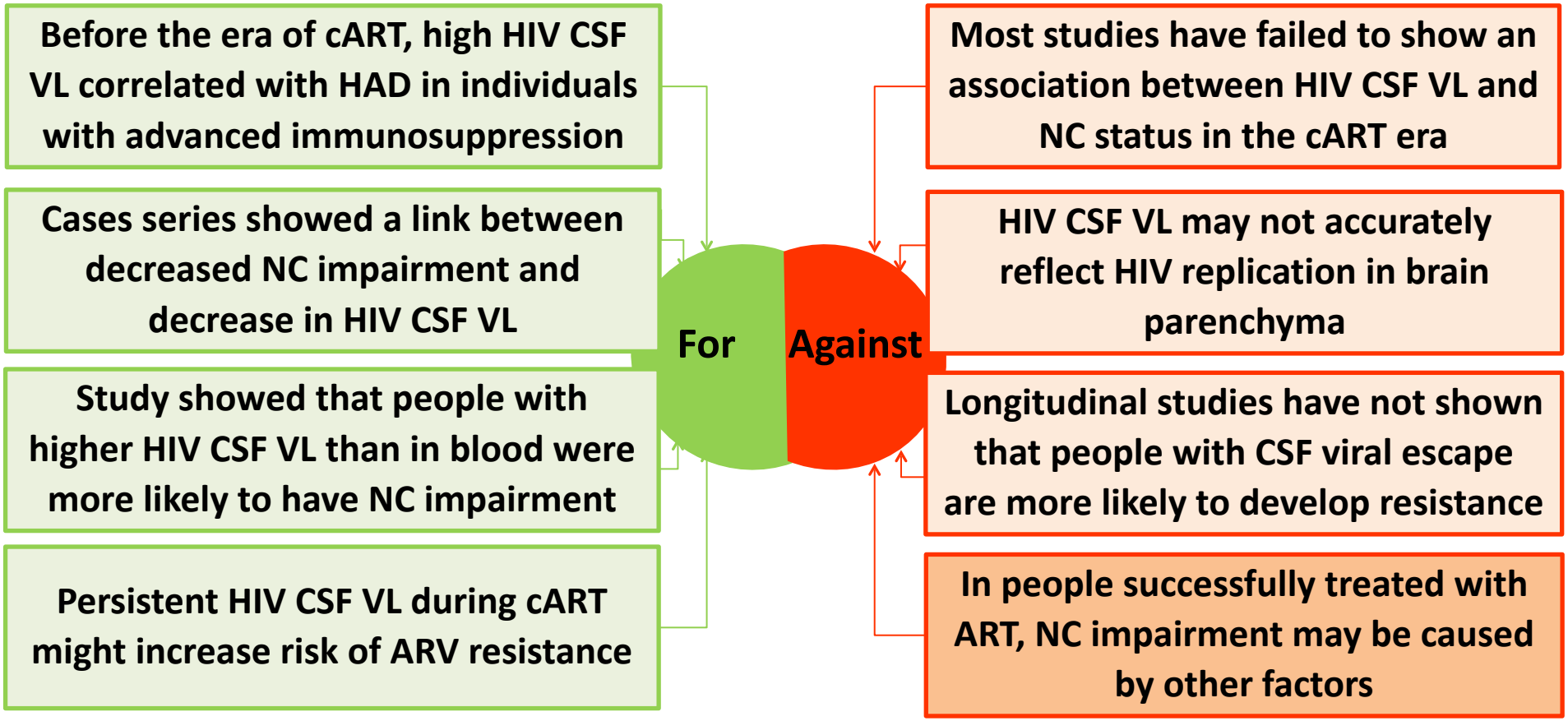


ARV effective concentration inhibiting HIV infection of monocytes

ARV	ABC	FTC	3TC	TDF	AZT	EFV	NVP	IDV	RTV	SQV	MVC
EC50 nM	300	80	20	20	20	10	50	60	120	50	0.5
ME score (1/EC50)x1000	3	12.5	50	50	50	100	20	17	8.3	20	2000

Williams D et al. Curr HIV Res 2014; Shituma C et al. Antivir Ther 2012

Is HIV RNA in CSF a useful clinical tool ?



Adapted from Nightingale S et al. Lancet Neurol 2014

Factors implicated in pathogenesis of HAND in cART era

ongoing neuroinflammation

antiretroviral drugs factors

patient factors

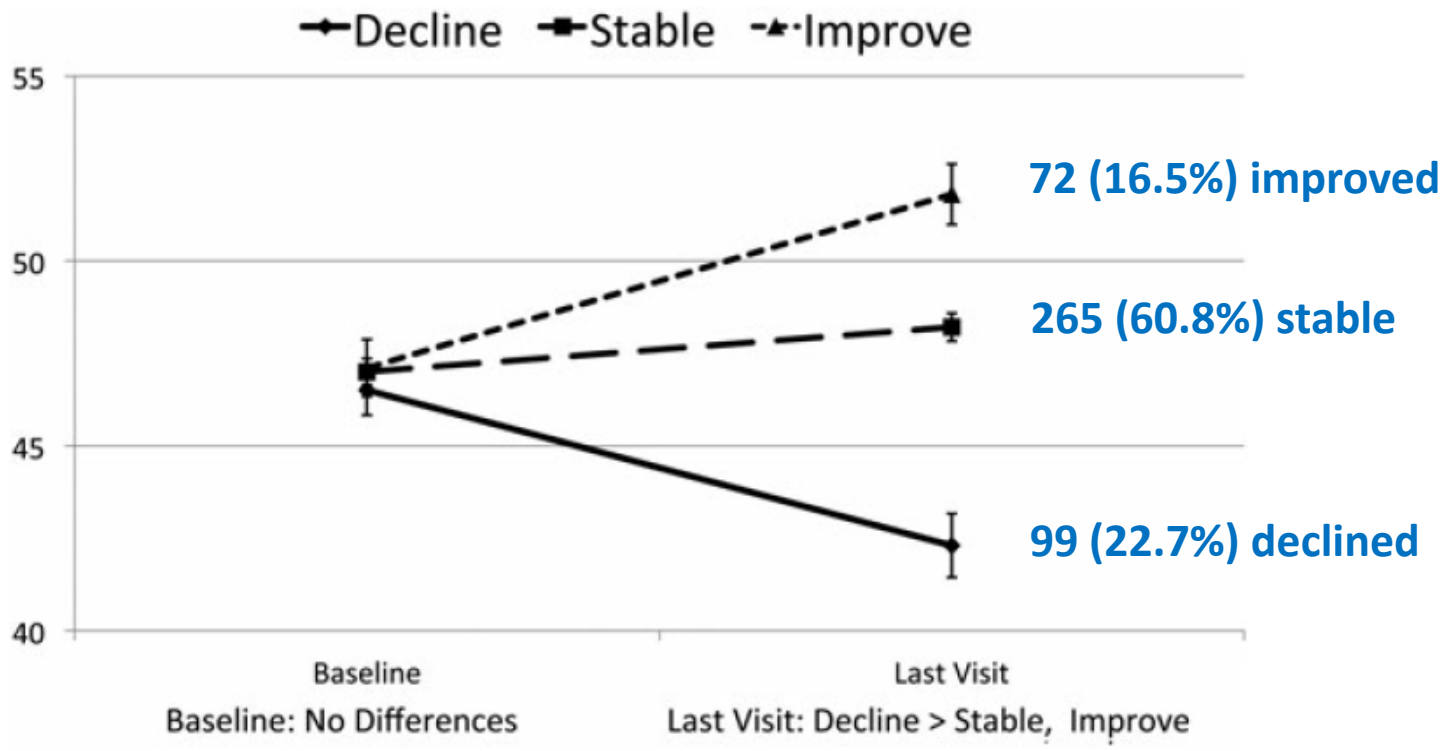
Pathogenic mechanisms	Corresponding clinical risk factors
Persistent immune activation	Nadir CD4 cell count
Immune-reconstitution	Nadir CD4 cell count
Antiretroviral toxicity	Type of antiretroviral therapy (e.g. efavirenz?)
Inadequate exposure to ART in the CNS	Type of antiretroviral therapy
Accelerated brain ageing	Age
Neurodegeneration	Family history of dementia and other neurodegenerative diseases
Coinfections	Hepatitis C
	Syphilis
	CMV
Comorbidities and lifestyle factors	Cardiovascular disease
	Diabetes
	Clinical depression
	Drug and alcohol abuse
	Smoking

CNS infections acquired during primary HIV infection, education level, use of psychoactive drugs (methamphetamine)

Adapted from Winston A & Vera JH. Curr Opin HIV AIDS 2014

Neurocognitive change in cART era: data from CHARTER

Longitudinal study evaluating incidence and predictors of NC change over 16-72 months in 436 HIV infected patients.



Predictors of NC declines or improvements included factors specific to HIV and its treatment, factors related to health status, baseline demographics, intelligence quotient, non-HIV related comorbidities, current depressive symptoms and lifetime psychiatric diagnoses.

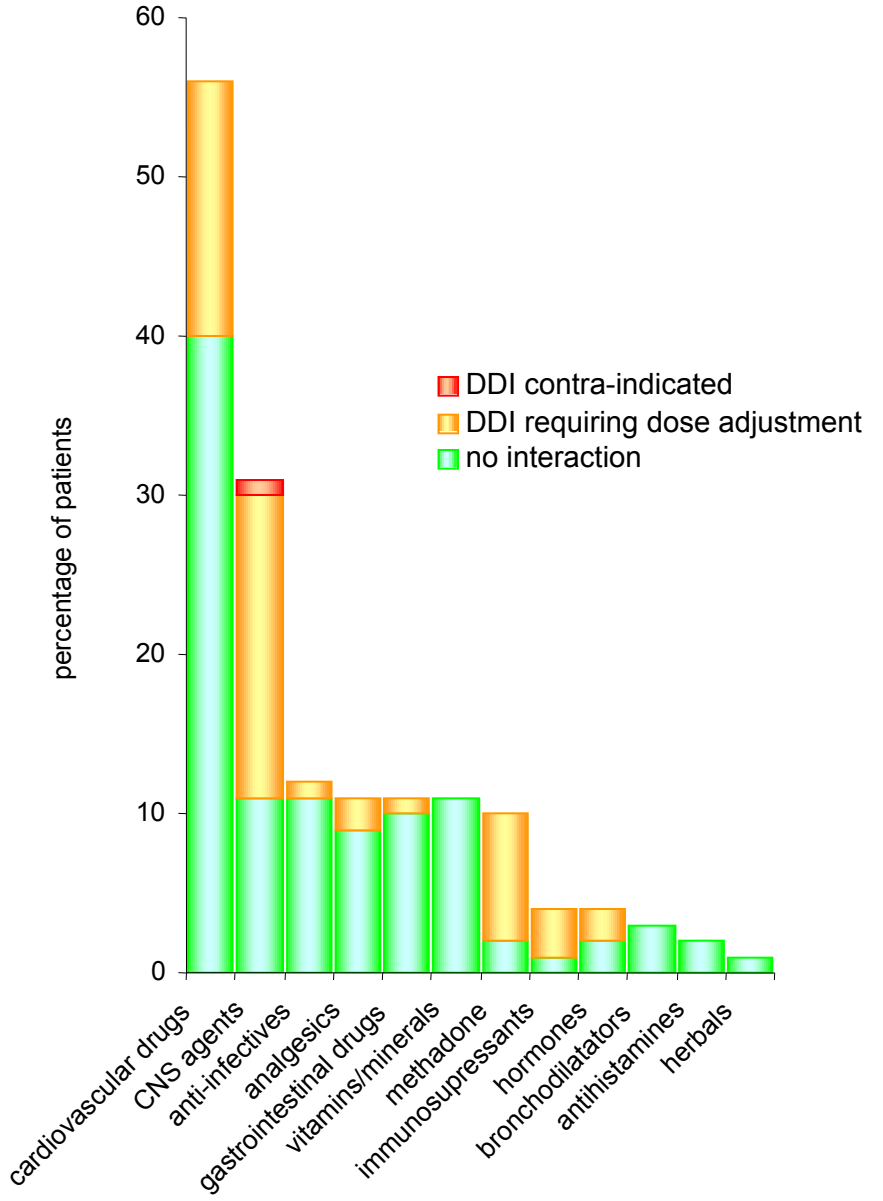
Heaton RK et al. Clin Infect Dis 2015

Some other open questions

- What are the target drug concentrations in CNS?
- What role may ARV neurotoxicity have on neurocognitive function?
- To which extent do comorbidities contribute to HAND?
- Would earlier initiation of ART protect CNS?(CD4 cell count seems to be an important predictor of neurocognitive performance)
- Evidence of low level of CNS inflammatory reactions: are these immune reactions driven by persistent local HIV infection or by other mechanisms?

Drug-drug interactions between ARV and CNS drugs

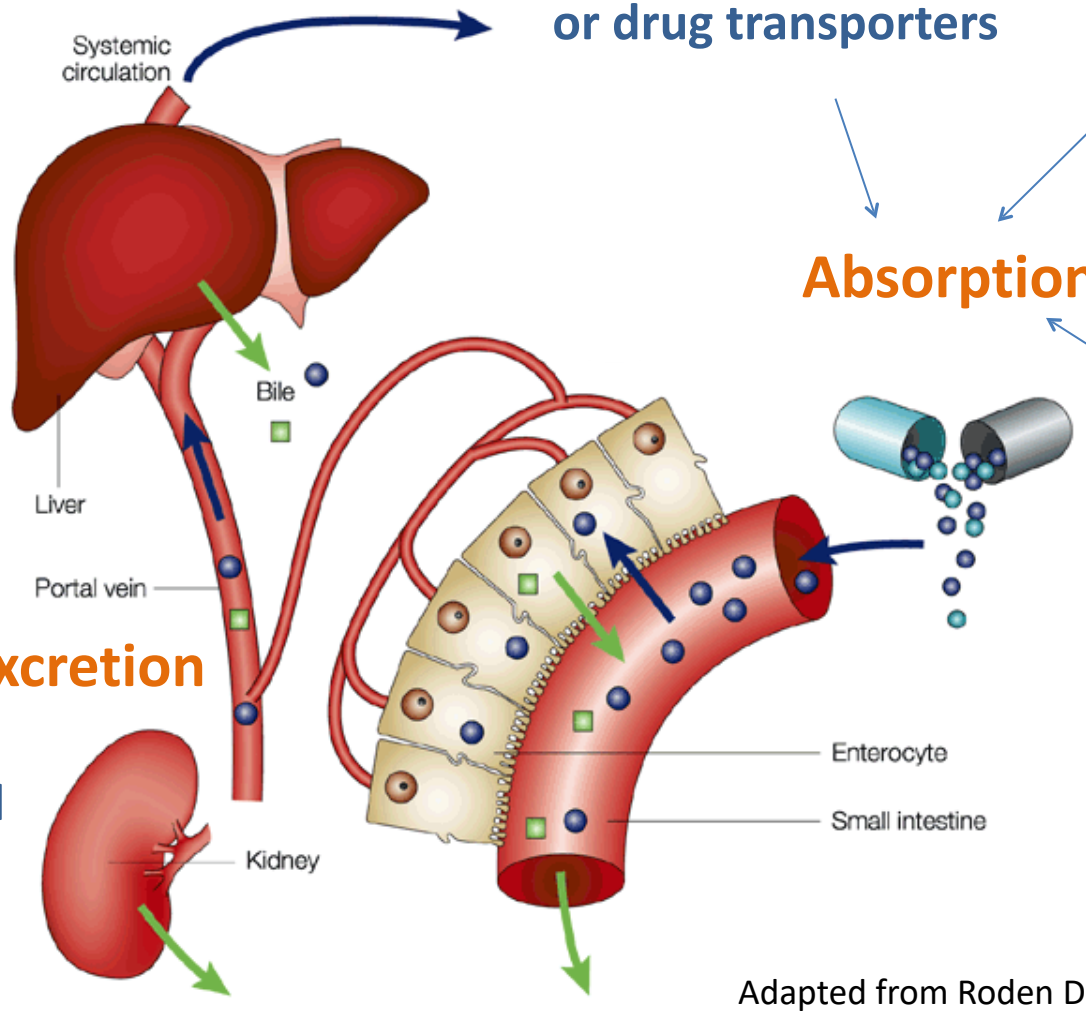
Prevalence of drug-drug interactions in the SHCS



- 1497 prescriptions analyzed
- 31% patients received CNS drug
  (anxiolytics (13%); antidepressants (12%);
  antipsychotics (3%); anticonvulsants (3%)
- 599 (40%) had at least one potential drug-drug interaction.
  Overall, DDI with:
  - antidepressants 23%
  - anxiolytics 17%
  - antipsychotics 6%
- HIV population is aging and has a higher risk for drug-drug interactions

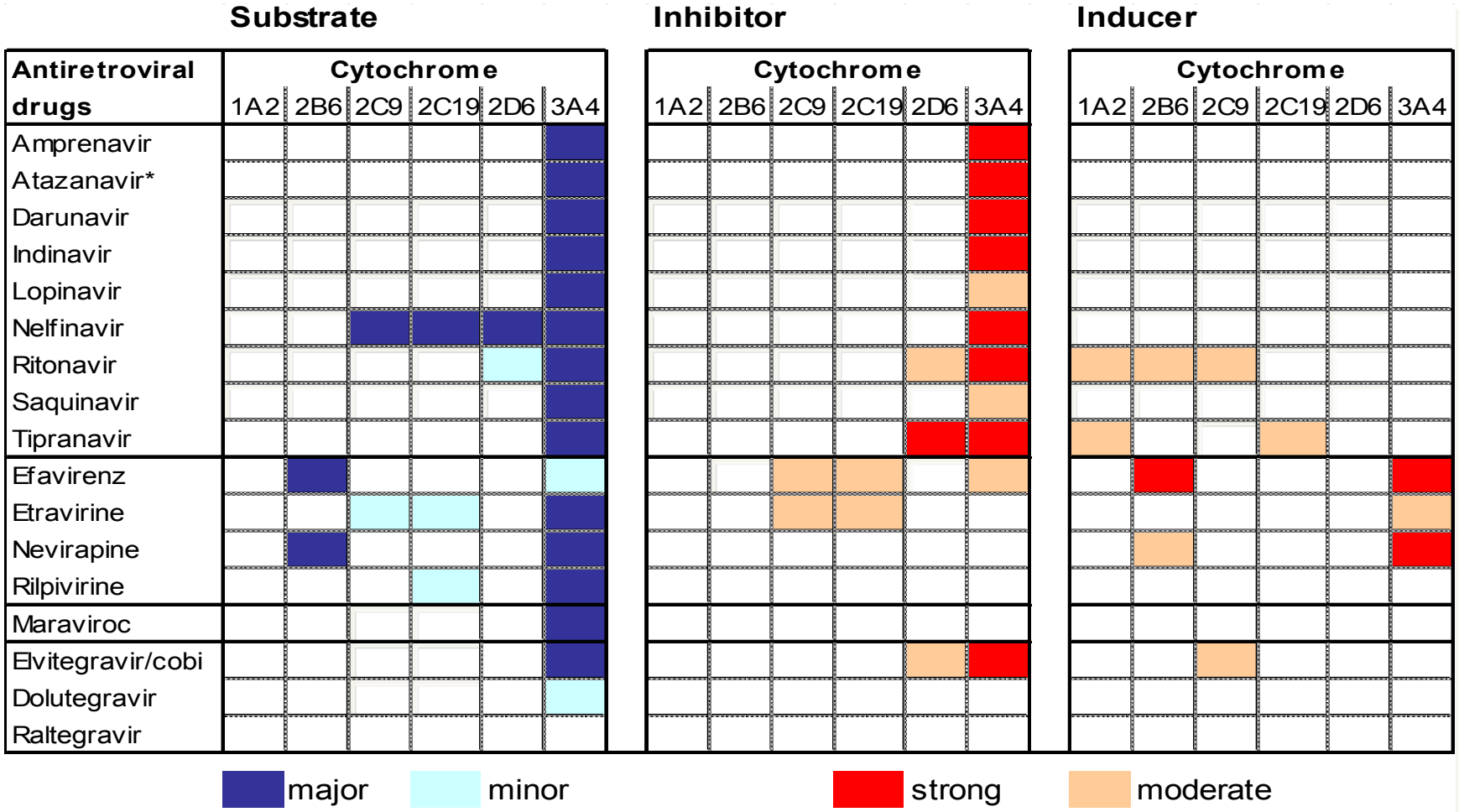
Marzolini C et al. Antiviral Therapy 2010
Marzolini C et al. J Antimicrob Chemother 2011

Mechanisms of PK drug-drug interactions



Adapted from Roden DM et al. Nat Rev 2002

Metabolism of antiretroviral drugs



atazanavir, indinavir inhibit UGT1A1

ritonavir induces glucuronidation

tipranavir, etravirine induce UGT1A1

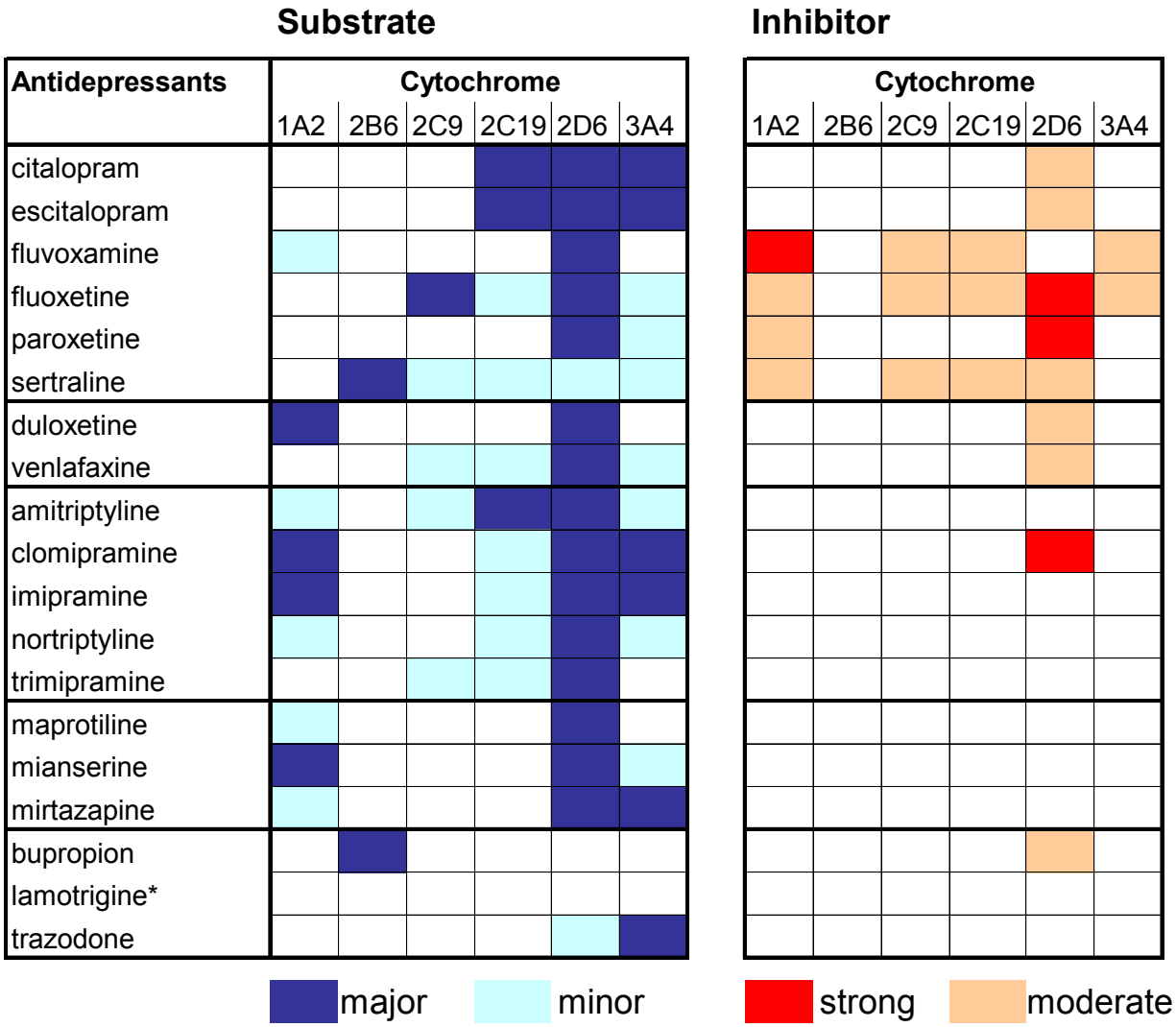
raltegravir is a substrate of UGT1A1

elvitegravir is substrate of UGT1A1, UGT1A3 (minor)

dolutegravir is mainly metabolized by UGT1A1

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

Metabolism of antidepressants

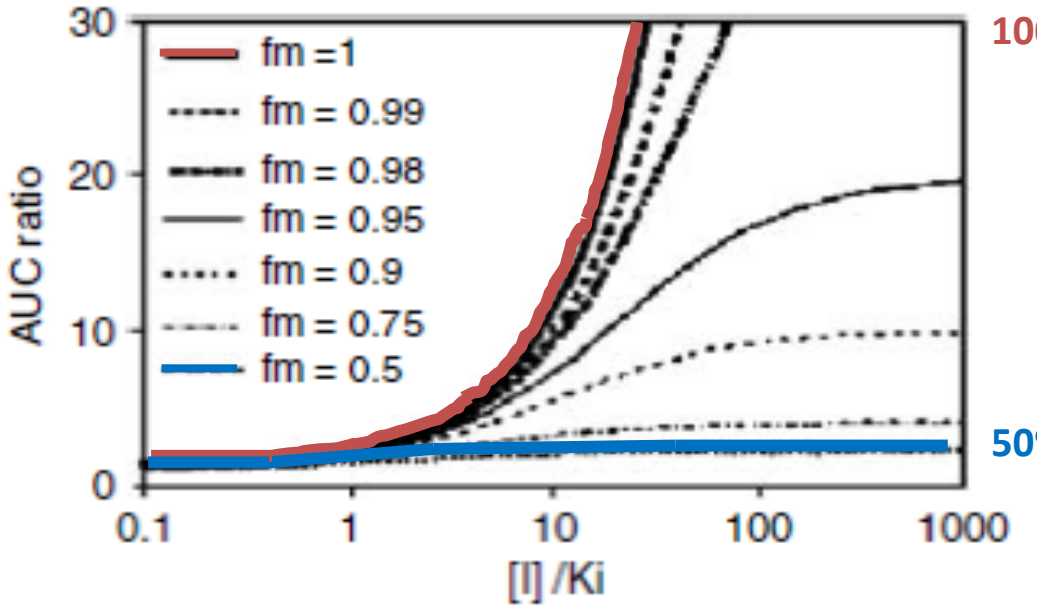


* lamotrigine is glucuronidated

http://pharmacoclin.hug-ge.ch/actualites.html
Spina E et al. Clinical Therapeutics 2008

Clinical significance of drug-drug interactions

- potency and concentration of the inhibitor or inducer
- therapeutic index of the „victim“ drug
- presence of active or toxic metabolites
- extent of metabolism through the affected enzyme

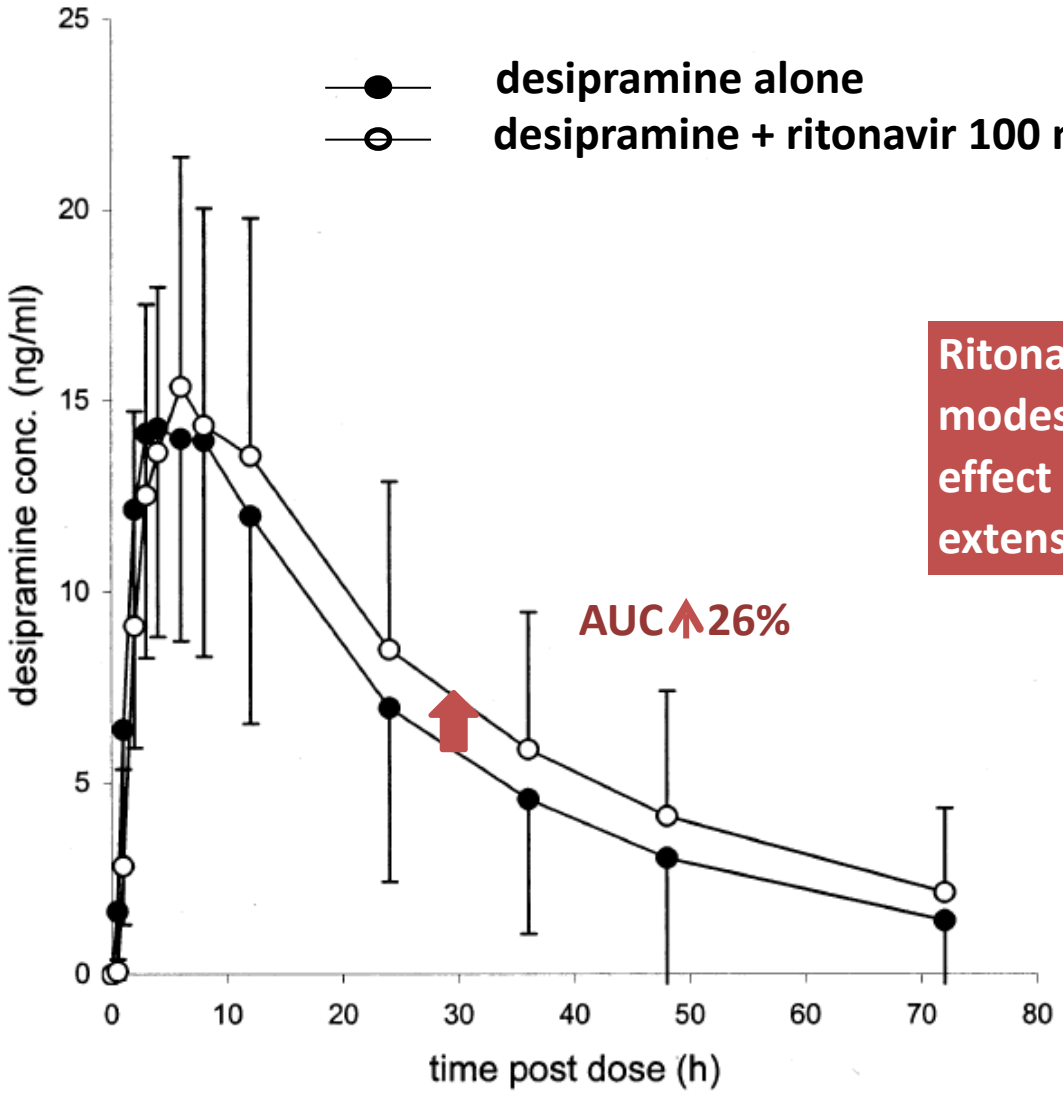


100% eliminated by CYP2D6

50% eliminated by CYP2D6

Ito K et al. Drug Metab Dispos 2005

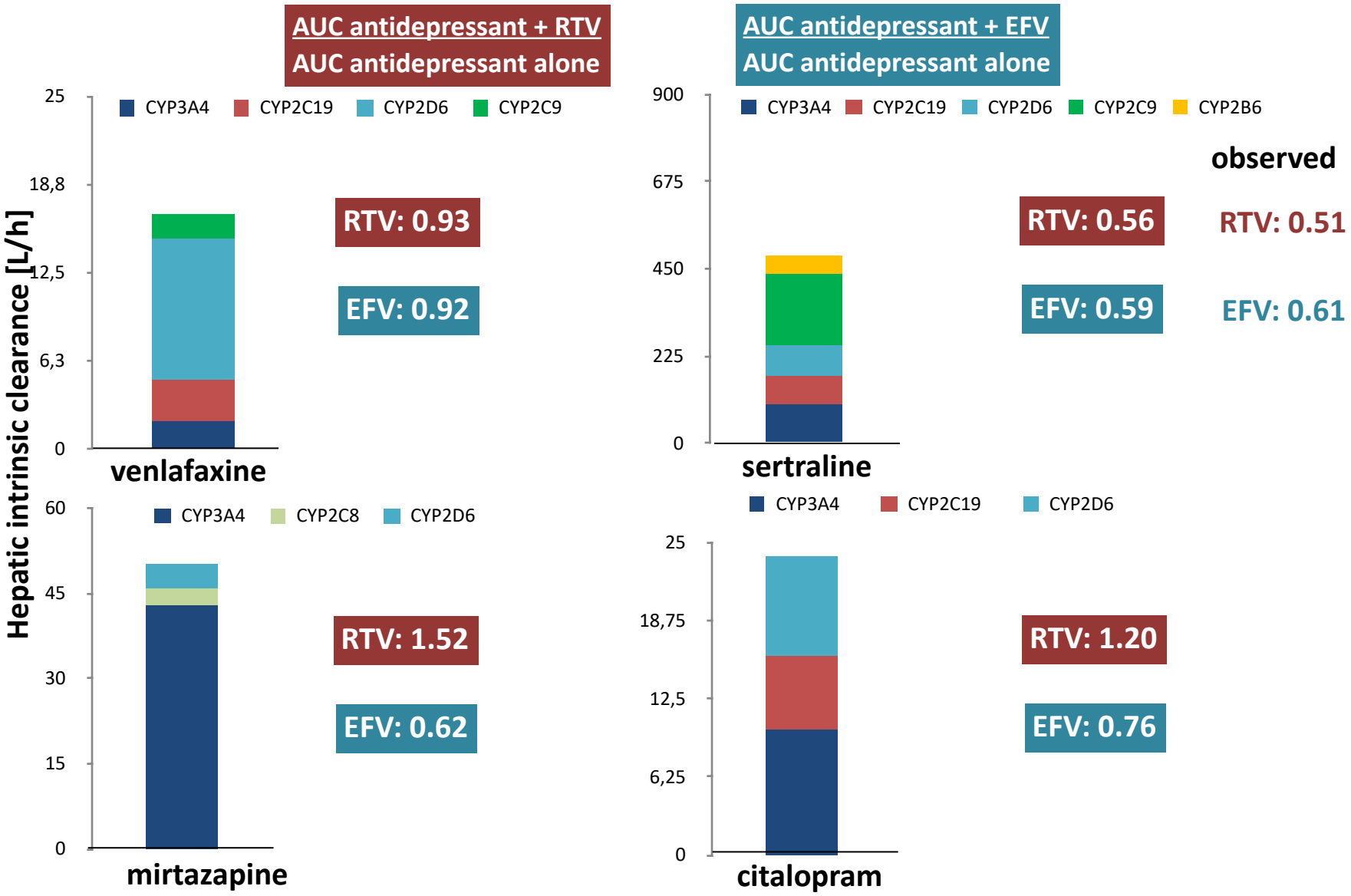
CYP2D6 inhibition by ritonavir



Ritonavir 100 mg BID modest inhibitory effect on CYP2D6 in extensive metabolizers

Aarnoutse RE et al. CPT 2005

Prediction of DDI with antidepressants using PBPK



adapted from Siccardi M, Marzolini C et al. Clin Pharmacokinet 2013

Potential DDI between ARV and antidepressants

	antidepressants	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
SSRI	citalopram	↑ [a]	↑	↑	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
SSRI	escitalopram	↑ [a]	↑	↑	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
SSRI	fluvoxamine	↑	↑	↑	↑	↑	↑	↔	↔	E	↔	↔	↑	↔	↔	↔	↔	↔	↔
SSRI	fluoxetine	↑	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SSRI	paroxetine	↑↓?	↓39%	↓50%	↑↓?	↑↓?	↑↓?	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔	↔	↔	↔
SSRI	sertraline	↓	↓49%	↓	↓	↓	↓	↓39%	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
SNRI	duloxetine	↑↓	↑↓	↑↓	↑↓	↑↓	↑↓	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SNRI	venlafaxine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	D	↑	↔	↔	↔	↔	↔	↔
TCA	amitriptyline	↑ [a]	↑	↑	↑	↑ [a]	↑ [ab]	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TCA	clomipramine	↑ [a]	↑	↑	↑	↑ [a]	↑ [ab]	↓	↓	↓	↔ [a]	↔	↑	↔	↔	↔	↔	↔	↔
TCA	desipramine	↑ [a]	↑	↑	↑	↑5%	↑ [a]	↔	↔	↔	↔ [a]	↔	↑	↔	↔	↔	↔	↔	↔
TCA	doxepin	↑	↑	↑	↑	↑	↑ [b]	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TCA	imipramine	↑ [a]	↑	↑	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
TCA	nortriptyline	↑ [a]	↑	↑	↑	↑ [a]	↑ [ab]	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TCA	trimipramine	↑	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TeCA	maprotiline	↑	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TeCA	mianserine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
TeCA	mirtazapine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
Others	bupropion	↓	↓	↓	↓	↓57%	↓	↓55%	↔	↓	↔	↔	↑?	↔	↔	↔	↔	↔	↔
Others	lamotrigine	↓32%	↓	↓	↓	↓50%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Others	nefazodone	↑	↑	↑	↑	↑	↑	↓ E	↓ E	↓ E	E	E	↑	↔	↔	↔	↔	↔	↔
Others	St John's wort	D	D	D	D	D	D	D	D	D	D	D	D	↔	↔	↔	↔	↔	↔
Others	trazodone	↑	↑	↑	↑	↑	↑ [b]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔

EACS guidelines 2014; www.hiv-druginteractions.org

Potential DDI between ARV and antipsychotics

	antipsychotics	ATV/r	DRV/c	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
atypical antipsychotic	amisulpride	↔[a]	↔	↔	↔	↔	↔[a]	↔[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	aripiprazole	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	asenapine	↓	↑	↓	↓	↓	↓	↓	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	clozapine	↑[a]	↑	↑	↑	↑	↑[a]	↑[ab]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔[d]
	olanzapine	↓	↔	↓	↓	↓	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	paliperidone	↑[a]	↑	↑	↑	↑	↑[a]	↑[a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	quetiapine	↑[a]	↑	↑	↑	↑	↑[a]	↑[a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔[d]
	risperidone	↑[a]	↑	↑	↑	↑	↑[a]	↑[a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
phenothiazine	chlorpromazine	↑[a]	↑	↑	↑	↑	↑[a]	↑[ab]	↔	↔	↔	↔[c]	↔	↑	↔	↔	↔	↔	↔	↔[d]
	fluphenazine	↑[a]	↑	↑	↑	↑	↑[a]	↑[a]	↔	↔	↔	↔[c]	↔	↑	↔	↔	↔	↔	↔	↔[d]
	perphenazine	↑[a]	↑	↑	↑	↑	↑[a]	↑[ab]	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[d]
	pimozide	↑[a]	↑	↑	↑	↑	↑[a]	↑[a]	↑	↓	↓	↔[c]	↔	↑	↔	↔	↔	↔	↔	↔
	prochlorperazine	↑[a]	↑	↑	↑	↑	↑[a]	↑[ab]	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔[d]
	thioridazine	↑[a]	↑	↑	↑	↑	↑[a]	↑[ab]	↓	↓	↓	↔[c]	↔	↑	↔	↔	↔	↔	↔	↔[d]
Others	haloperidol	↑[a]	↑	↑	↑	↑	↑[a]	↑[ab]	↓	↓	↓	↔[c]	E	↑	↔	↔	↔	↔	↔	↔
	sulpiride	↔[a]	↔	↔	↔	↔	↔[a]	↔[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

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Potential DDI between ARV and anxiolytics/hypnotics

	anxiolytics/hypnotics	ATV/r	DRV/c	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	EVG/c	RAL	ABC	FTC	3TC	TDF	ZDV
anxiolytics	alprazolam	↑[a]	↑	↑[a]	↑[a]	↑[b]	↑[a]	↑[a]	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	bromazepam	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	buspirone	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	clorazepate	↑	↑	↑	↑	↑[b]	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	diazepam	↑	↑	↑	↑	↑[b]	↑	↑	↓	↑	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
hypnotics	chlordiazepoxide	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	estazolam	↑	↑	↑	↑	↑[b]	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	flunitrazepam	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	flurazepam	↑	↑	↑	↑	↑[b]	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lormetazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	temazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	triazolam	↑	↑	↑	↑	↑	↑	↑	↑	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	valerian	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	zaleplon	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	zolpidem	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔
	zopiclone	↑	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↑	↔	↔	↔	↔	↔	↔

Where to check for DDI with antiretroviral agents

Drugs selection

Protease Inhibitor	NNRTI	NRTI	Entry and Integrase Inhibitors
☐ Atazanavir	☐ Delavirdine	☐ Abacavir	☐ Dolutegravir
☐ Cobicistat (with ATV or DRV)	☐ Efavirenz	☐ Didanosine (ddI)	☐ Elvitegravir/cobicistat
☑ Darunavir	☐ Etravirine	☐ Emtricitabine (FTC)	☐ Maraviroc
☐ Fosamprenavir	☐ Nevirapine	☐ Lamivudine (3TC)	☐ Raltegravir
☐ Indinavir	☐ Rilpivirine	☐ Stavudine (d4T)	
☐ Lopinavir		☐ Tenofovir	
☐ Nelfinavir			
☐ Ritonavir			
☐ Saquinavir			
☐ Tipranavir			

select the antiretroviral drug (s)

select the co-medication (s)

Antidepressants	Antiretrovirals (Protease Inhibitors)
☐ Amitriptyline	☐ Atazanavir
☐ Bupropion	☐ Cobicistat (with ATV or DRV)
☐ Citalopram	☑ Darunavir
☐ Clomipramine	☐ Fosamprenavir
☐ Desipramine	☐ Indinavir
☐ Doxepin	☐ Lopinavir
☐ Duloxetine	☐ Nelfinavir
☐ Escitalopram	☐ Ritonavir
☐ Fluoxetine	☐ Saquinavir
☐ Fluvoxamine	☐ Tipranavir
☐ Imipramine	
☐ Lithium	
☐ Maprotiline	
☐ Mianserin	
☐ Mirtazapine	
☐ Nefazodone	
☐ Nortriptyline	
☐ Paroxetine	
☑ Sertraline	
☐ Trazodone	

Commentary on drug-drug interaction

Antidepressants	Darunavir
Sertraline	☐
Antiretrovirals (Protease Inhibitors)	**Darunavir**
Darunavir	n/a

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Summary

Note: this interaction was studied using a darunavir/ritonavir dose lower than that licensed. Coadministration of sertraline (50 mg once daily) and darunavir/ritonavir (400/100 mg twice daily) decreased sertraline AUC, Cmax and Cmin by 49%, 44% and 49%,respectively. There was no significant change in darunavir exposure. If coadministering, dose titrate sertraline based on a clinical assessment of antidepressant response. Patients on a stable dose of sertraline who start treatment with darunavir/ritonavir should be monitored for antidepressant response.

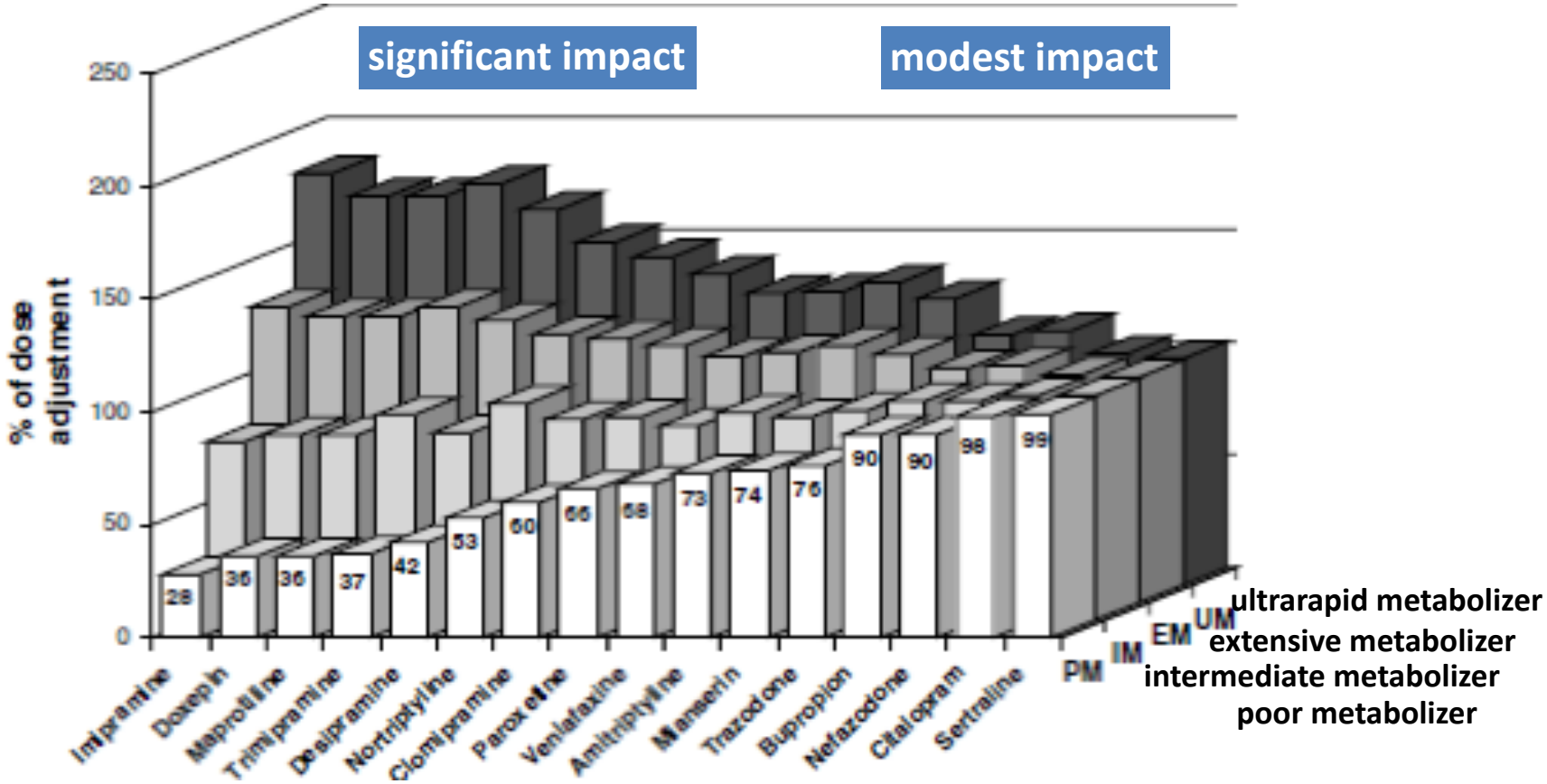
Description

Coadministration of sertraline (50 mg once daily) and darunavir/ritonavir (at a dose lower than recommended or with a different dosing regimen) decreased both sertraline AUC and Cmin by 49%; Cmax decreased by 44%. Darunavir AUC and Cmin were unchanged, but Cmax decreased by 6%. If SSRIs are coadministered with darunavir and low dose ritonavir, the recommended approach is a dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with darunavir coadministered with low dose ritonavir should be monitored for antidepressant response.
Prezista Summary of Product Characteristics, Janssen-Cilag Ltd, June 2012.

Coadministration of sertraline (50 mg once daily) and darunavir/ritonavir (400/100 mg twice daily) was studied in 13 subjects. There was no significant change in darunavir exposure and sertraline exposure was decreased. Darunavir Cmax increased by 1%; AUC and Cmin decreased by 2% and 6%, respectively. Sertraline Cmax, AUC and Cmin decreased by 44%, 49% and 49%, respectively. If sertraline or paroxetine is co-administered with darunavir/ritonavir, the recommended approach is a careful dose titration of the SSRI based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with darunavir/ritonavir should be monitored for antidepressant response.
Prezista Prescribing Information, Tibotec Inc, June 2012.

Pharmacogenetics of antidepressants

Impact of CYP2D6 phenotype on antidepressant dose adjustment



Kirchheiner J et al. Mol Psychiatry 2004

Genetic impacts the magnitude of drug-drug interaction

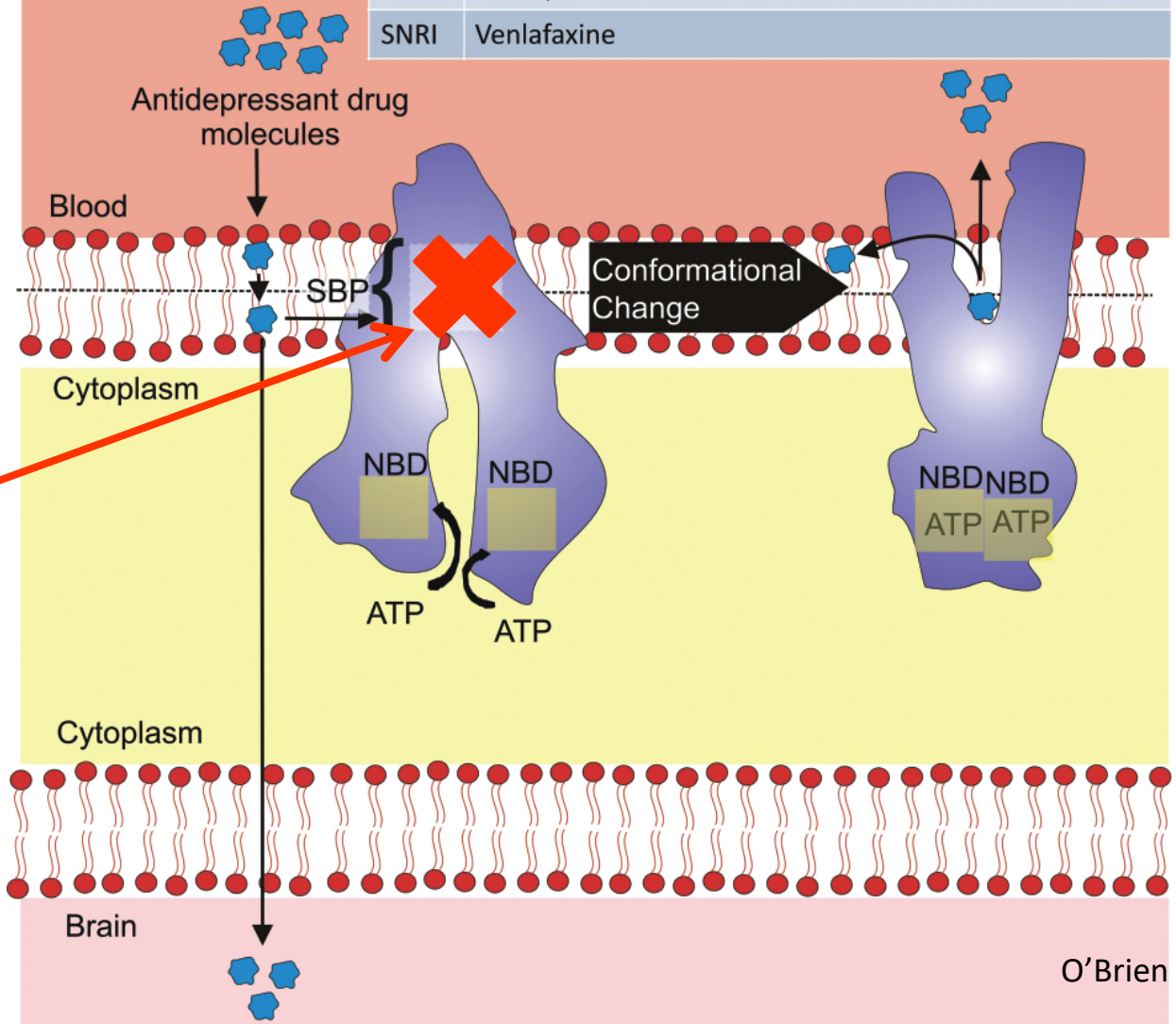
	venlafaxine AUC (nmol/l h)		
	venlafaxine alone	venlafaxine + ketoconazole	change
EM	2771 (2238)	3472 (3064)	**+ 21%**
PM	6496 (2931)	9987 (4360)	**+ 70%**

drug-drug interactions may be of greater magnitude in individuals lacking functional CYP2D6 genes

Lindh JD et al. Eur J Clin Pharmacol 2003

P-gp inhibition by PI: improved antidepressant effect?

Potential P-gp substrate antidepressants	
TCAs	Amitriptyline, Desipramine, Doxepine, Imipramine, Nortripyline, Trimipramine
SSRIs	Citalopram, Fluoxetine, Fluvoxamine, Paroxetine
SNRI	Venlafaxine



protease inhibitors

O'Brien et al. BJCP 2012

QT interval prolongation

- some psychotropes have the potential to delay cardiac repolarization, an effect that can be measured as prolongation of QT interval.
- QT interval is heart rate dependent (shortened with increasing heart rate), therefore a correction factor is generally used (QTc).
- excessive QTc interval prolongation can be proarrhythmic and prompt a potentially fatal ventricular tachyarrhythmia known as torsade de pointes (TdP).

Trinkley KE et al. Curr Med Res & Opinion 2013

Risk factors for drug induced TdP

- drug prolonging QTc in presence of host risk factors

  (e.g. female gender, electrolyte abnormalities, pre-existing prolongation of QT interval, bradycardia, myocardial ischemia, congestive heart failure, history of arrhythmias, genetic variants affecting cardiac ion channels)

- drug-drug interactions:

  1) drug prolonging QTc + drug prolonging QTc (PD interaction)

  2) drug prolonging QTc + metabolic inhibitor (PK interaction)

  3) drug prolonging QTc & metabolic inhibitor + drug prolonging QTc (PK + PD interaction)

Trinkley KE et al. Curr Med Res & Opinion 2013

ARV and co-administration of drug prolonging QT

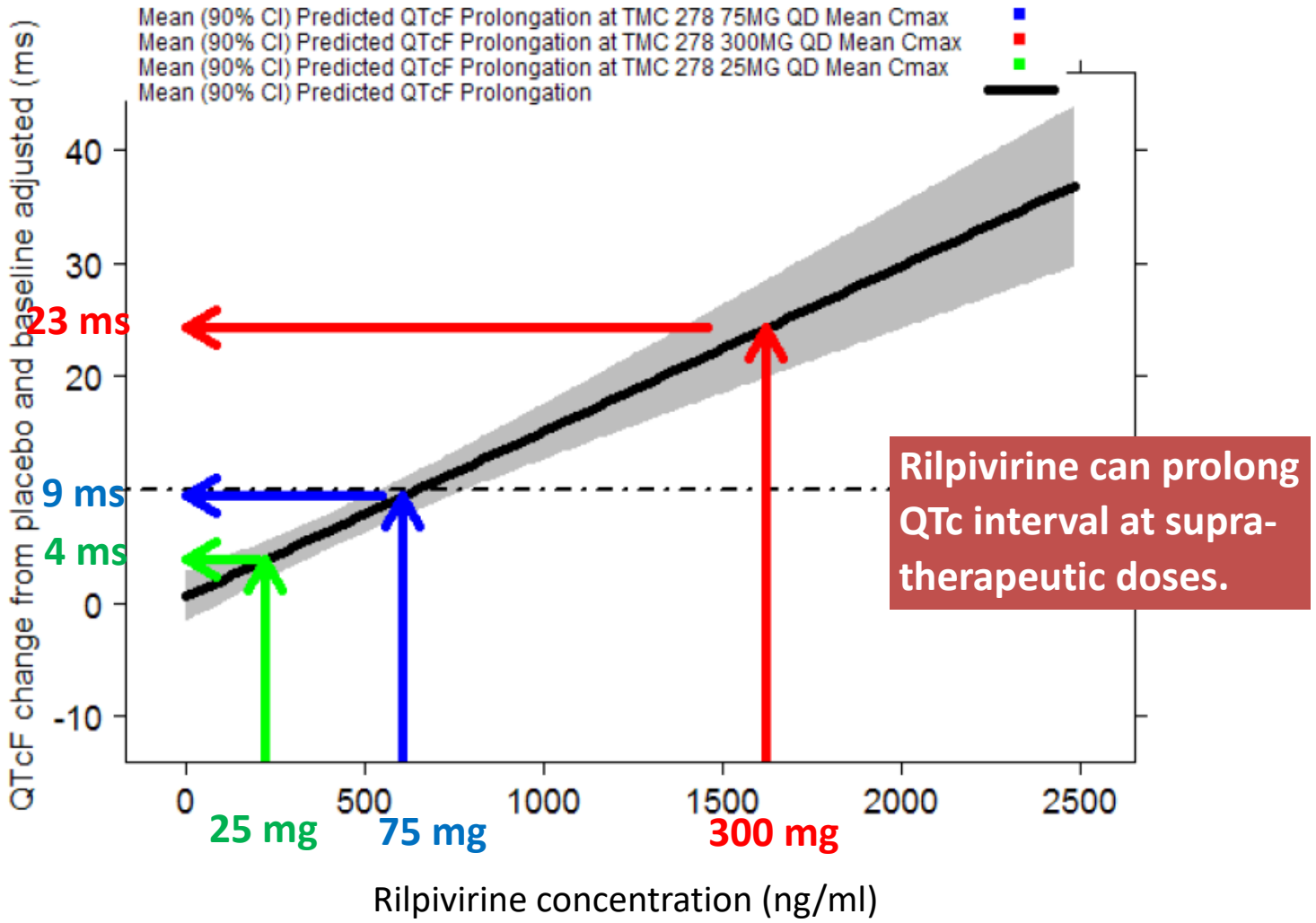
Saquinavir: dose dependent prolongation of QT and PR intervals in healthy volunteers receiving boosted saquinavir.
Concomitant use with other drugs that prolong the QT and PR intervals is contra-indicated or in patients with risk factors.

Atazanavir: dose dependent asymptomatic prolongation of PR interval observed in clinical studies.
Caution when prescribing with other drugs that prolong the QT and PR intervals or in patients with risk factors.

Lopinavir: modest asymptomatic prolongation of PR interval and moderate elevation of QTc interval observed in clinical studies. Reports of cardiac events. **Caution when prescribing with other drugs that prolong the QT and in patients with risk factors**.

Individual drugs SPCs

Rilpivirine and risk of QTc interval prolongation



FDA access data 2011

Thorough QT/QTc study

- Study conducted early in clinical development to determine whether the effect on QTc interval should be intensively investigated during later stages.
- Interpretation of the QT/QTc interval prolongation in study:

Around mean increases of 5 ms* or less ➔ drug does not appear to cause TdP

(*or with the upper bound of 95% CI for the largest time-matched mean effect of the drug < 10ms)

Above 5 ms* ➔ threshold of regulatory concern

(*or with the upper bound of 95% CI for the largest time-matched mean effect of the drug ≥ 10ms)

>20 ms ➔ drug has a substantially increased risk of being proarrhythmic

FDA (2005). E14: the clinical evaluation of QT/QTc interval prolongation and pro-arrhythmic potential for non-arrhythmic drugs

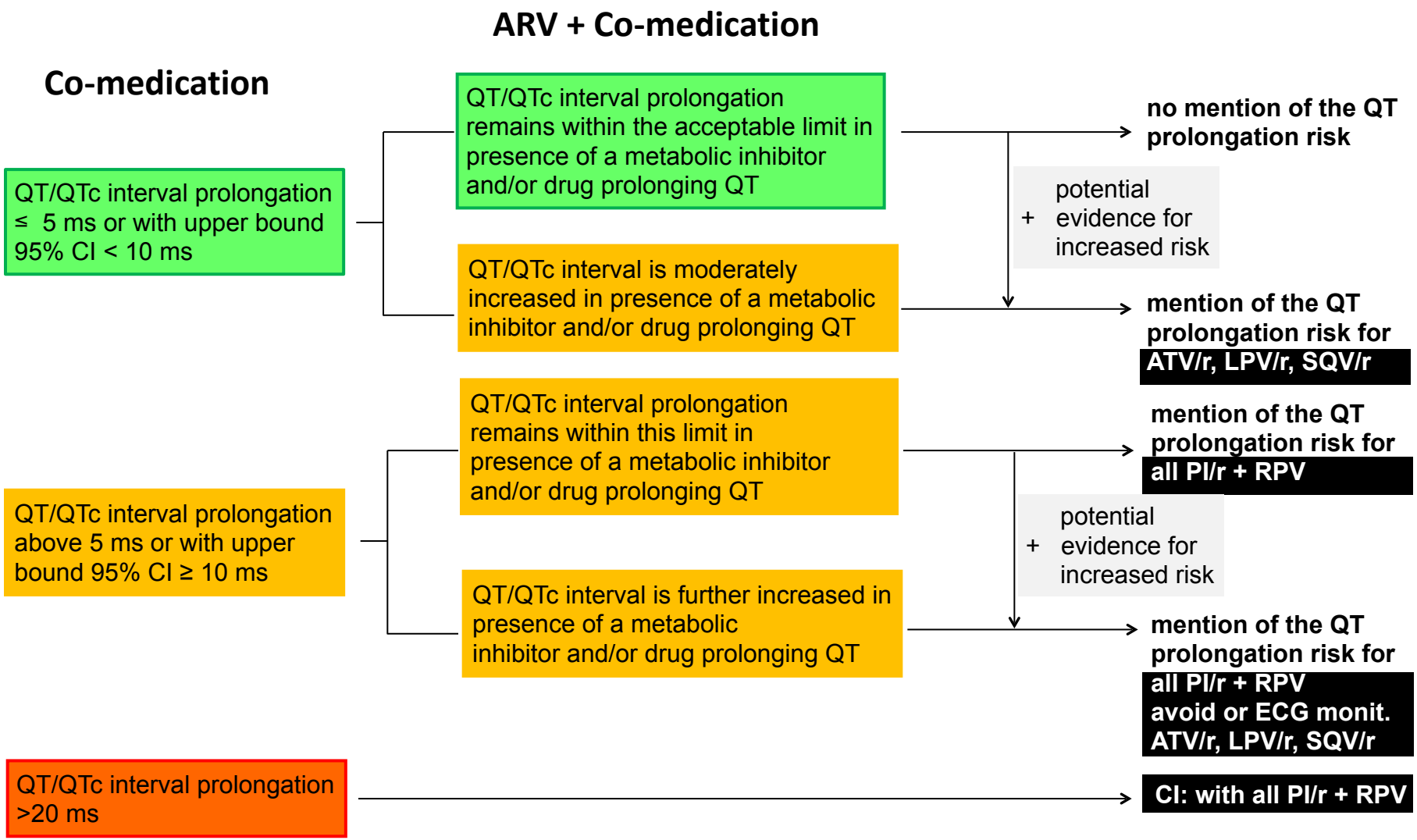
Evaluation of the risk

- The absolute increase in risk of TdP with QT related DDI is often difficult to assess. Patient-related risk factors do considerably impact the absolute risk.

- Data on the extent of QT/QTc interval prolongation in the presence of a metabolic inhibitor or another drug prolonging QTc should be taken into consideration to evaluate the risk of cardiac events.

- Other considerations:
  - Does drug block hERG channel or Ikr current in vitro?
  - Is there evidence of dose/concentration response in clinical and/or lab data?
  - Do clinical studies show consistent results for QT prolongation or report serious cardiovascular event?
  - Consider the gradation of the risk described in www.AZCERT.org

Decision tree to code the QT interval prolongation risk



Permission of www.hiv-druginteractions.org

ARV + antidepressants and coding of QT risk

Antidepressants with QT risk coding	Antidepressants without QT risk coding
citalopram	fluvoxamine
escitalopram	fluoxetine
amitriptyline	paroxetine
clomipramine	sertraline
desipramine	duloxetine
imipramine	venlafaxine
nortriptyline	doxepin
	trimipramine
	maprotiline
	mianserine
	mirtazapine
	bupropion
	nefazodone

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Saye Khoo

Marco Siccardi

SWISS HIV COHORT STUDY

Members of the SHCS
co-workers of all HIV clinics