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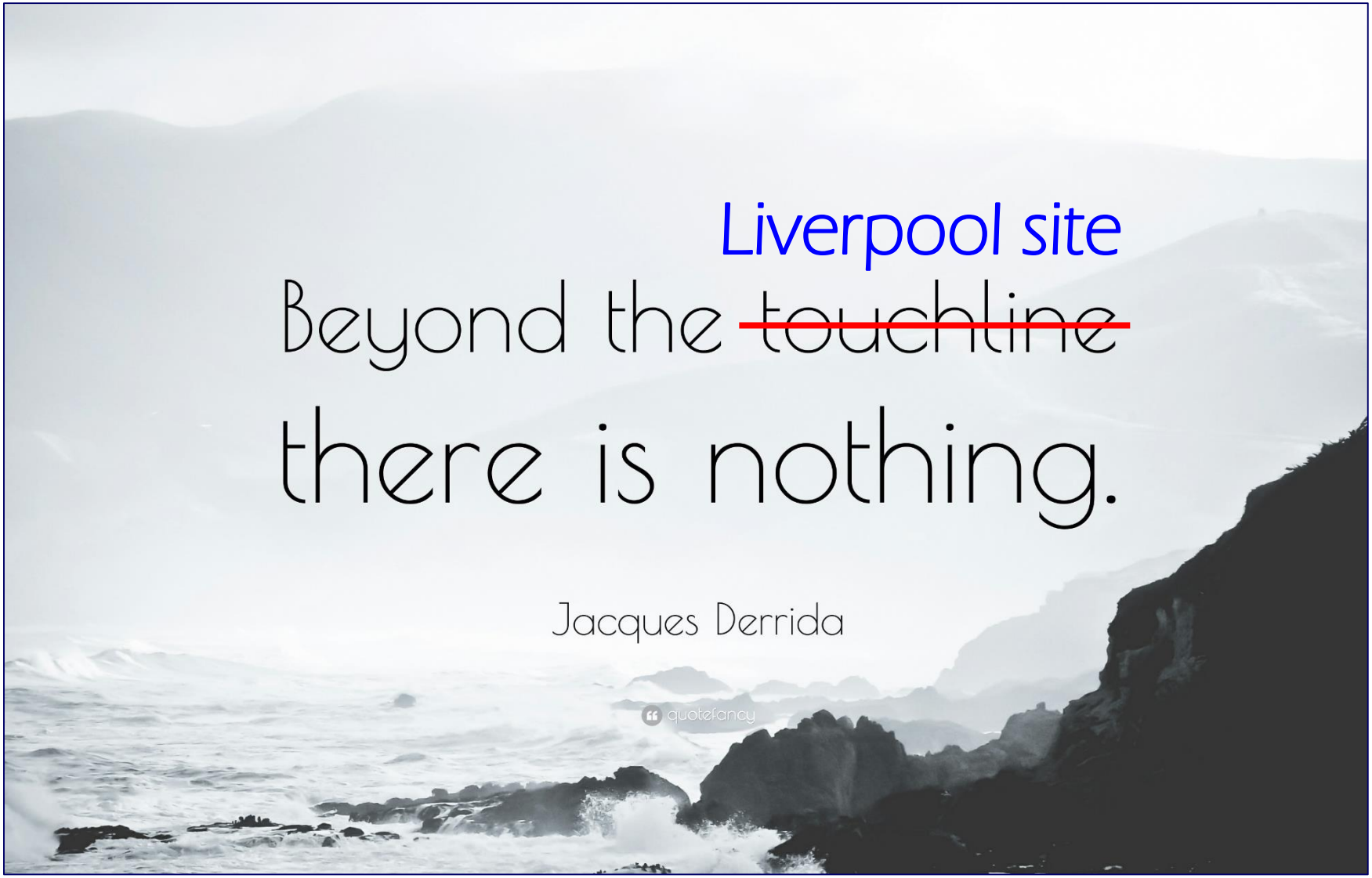
ASST Fatebenefratelli Sacco

GAP

Beyond Liverpool site: pharmacological support for the management of polypharmacy in HIV-positive patients

Dario Cattaneo
Unit of Clinical Pharmacology
ASST Fatebenefratelli Sacco, Milano

My disclosure…



…However, it may fail in atypical patients….

www.hiv-druginteractions.org

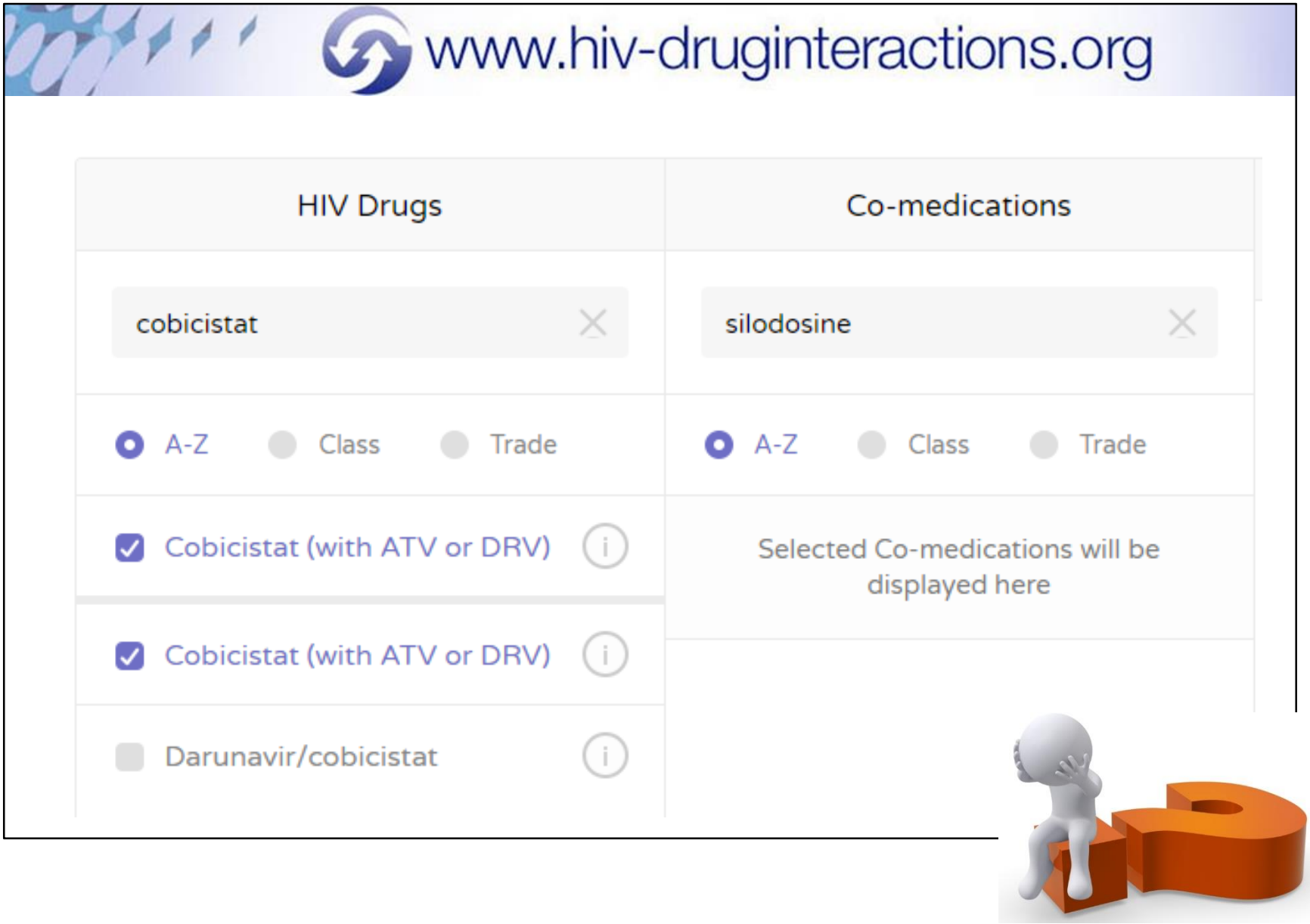
Class:	Drug:	HIV Drug:
Antibacterials	Rifampicin	Efavirenz

Coadministration of rifampicin (600 mg) with efavirenz (600 mg) decreased efavirenz Cmax (20%), AUC (26%), and Cmin (32%). The dose of efavirenz should be increased to 800 mg/day in most patients

AIDS 2011, Vol 25 No 3

Paradoxically elevated efavirenz concentrations in HIV/tuberculosis-coinfected patients with *CYP2B6* 516TT genotype on rifampin-containing antituberculous therapy

…or may have missing medications….



Beyond Liverpool site: pharmacological support for the management of polypharmacy in HIV-positive patients

Do not forget that PK/PD of many drugs may change in elderly patients….

Drug Metabolism Reviews, 2009; 41(2): 67–76

informa
healthcare

REVIEW ARTICLE

Pharmacokinetics and drug metabolism in the elderly

Ulrich Klotz

Pharmacodynamic Changes in the Elderly

Clin Pharmacokinet 1998 Jul; 35 (1): 49-64

..elderly patients are at risk of polypharmacy, DDIs and ADRs…

Hospitalizations Due to Adverse Drug Events in the Elderly—A Retrospective Register Study

- ✓ 290 admission to the Emergency Department

		Medication-related admission
Age	54-74 yrs 75-84 yrs 85-95 yrs	18,9% 21,8% 35,4%
Polypharmacy	Yes No	28,2%* 10,7%

*Odd Ratio 3.3 [1,5-6,9], p=0.01

- Laatikainen, Frontiers Pharmacol 2016 -

..what happens at discharge???

✓ 70 Italian internal medicine and geriatric wards (2765 pts >65 yrs)

	At admission	At discharge
Number of patients	2712	2314
Age (mean ± SD)	79.1 (7.4)	79.0 (7.5)
Female (%)	1419 (52.3)	1221 (52.8)
Number of drugs (mean ± SD)	5.1 (2.8)	6.1 (2.9)
Number of diagnoses (mean ± SD)	5.0 (2.7)	6.2 (2.7)
Number of patients with at least one potential DDI at hospital discharge		
Overall		622 (73.7)
Patients with new DDI at discharge		423 (50.1)
Severe		223 (26.4)

- Pasina, Pharmacoepidemiol Drug Safety 2013 -

How to verify the appropriateness of medications in the elderlies?

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

International Journal of Clinical Pharmacology and Therapeutics, Vol. 46 – No. 2/2008 (72-83)

STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation

P. Gallagher[1], C. Ryan[2], S. Byrne[2], J. Kennedy[2] and D. O'Mahony[3]

ISSN 0946-1965

- Reduction in prescribing of PIMs in 70% of patients
- Reduction in PPOs in 31.6% of patients
- 33.3% reduction in ADRs

PPOs: potential prescribing omissions;
PIMs: potentially inappropriate medications

..what about HIV patients??

PHARMACOTHERAPY accp

Explore this journal >

Original Research Article

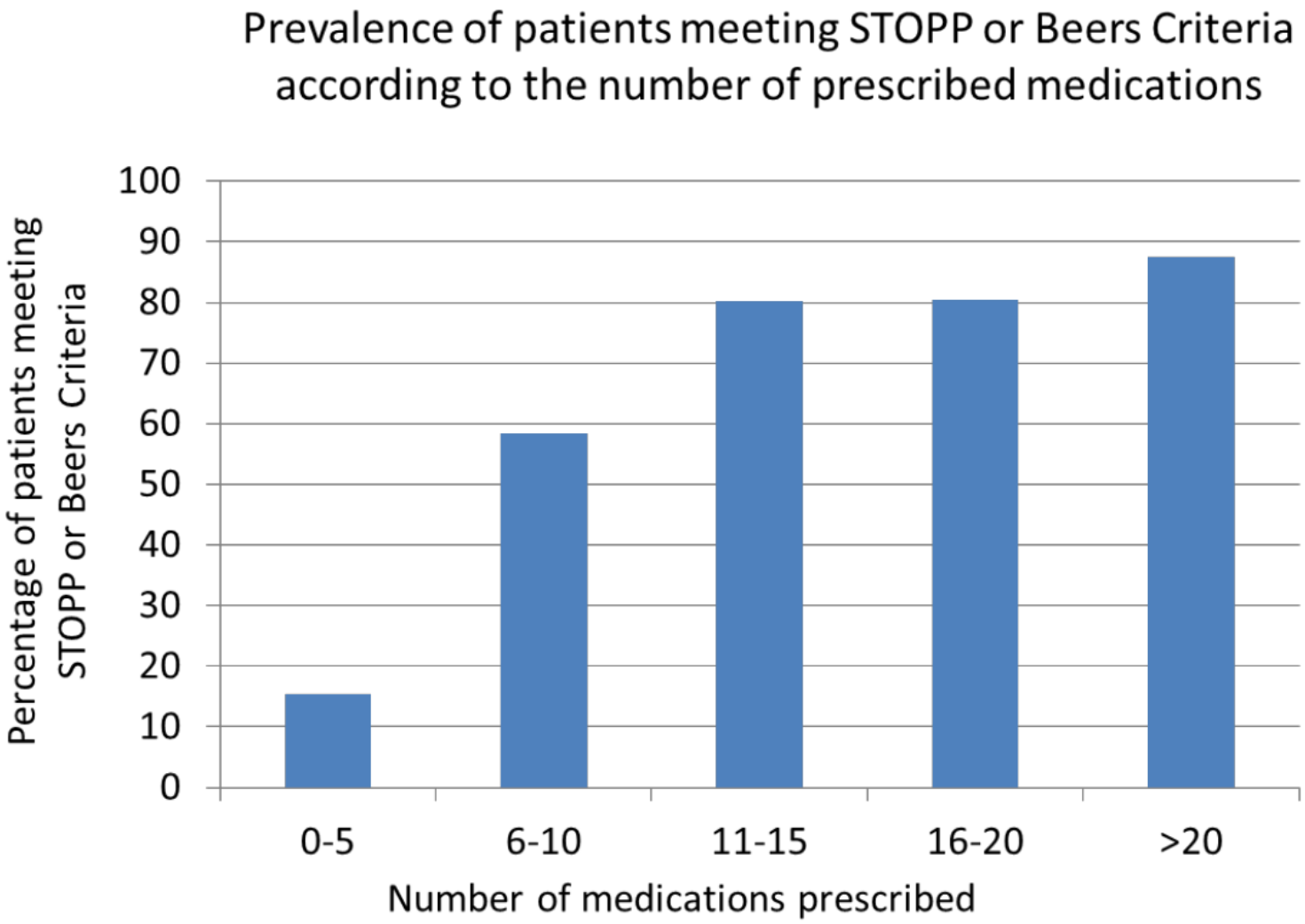
A Pharmacist-Led Program to Evaluate and Reduce Polypharmacy and Potentially Inappropriate Prescribing in Older, HIV-Positive Patients

I R McNicholl ✉, M Gandhi, C Bradley Hare, M Greene, E Pierluissi

Accepted manuscript online: 10 October 2017 Full publication history

- ✓ To assess potentially inappropriate prescribing (PIP) in older (>50 yrs) HIV-infected patients using both Beers and STOPP criteria in a large US urban clinic (approx. 2700 HIV-infected patients)

- McNicholl, Pharmacother 2017 -



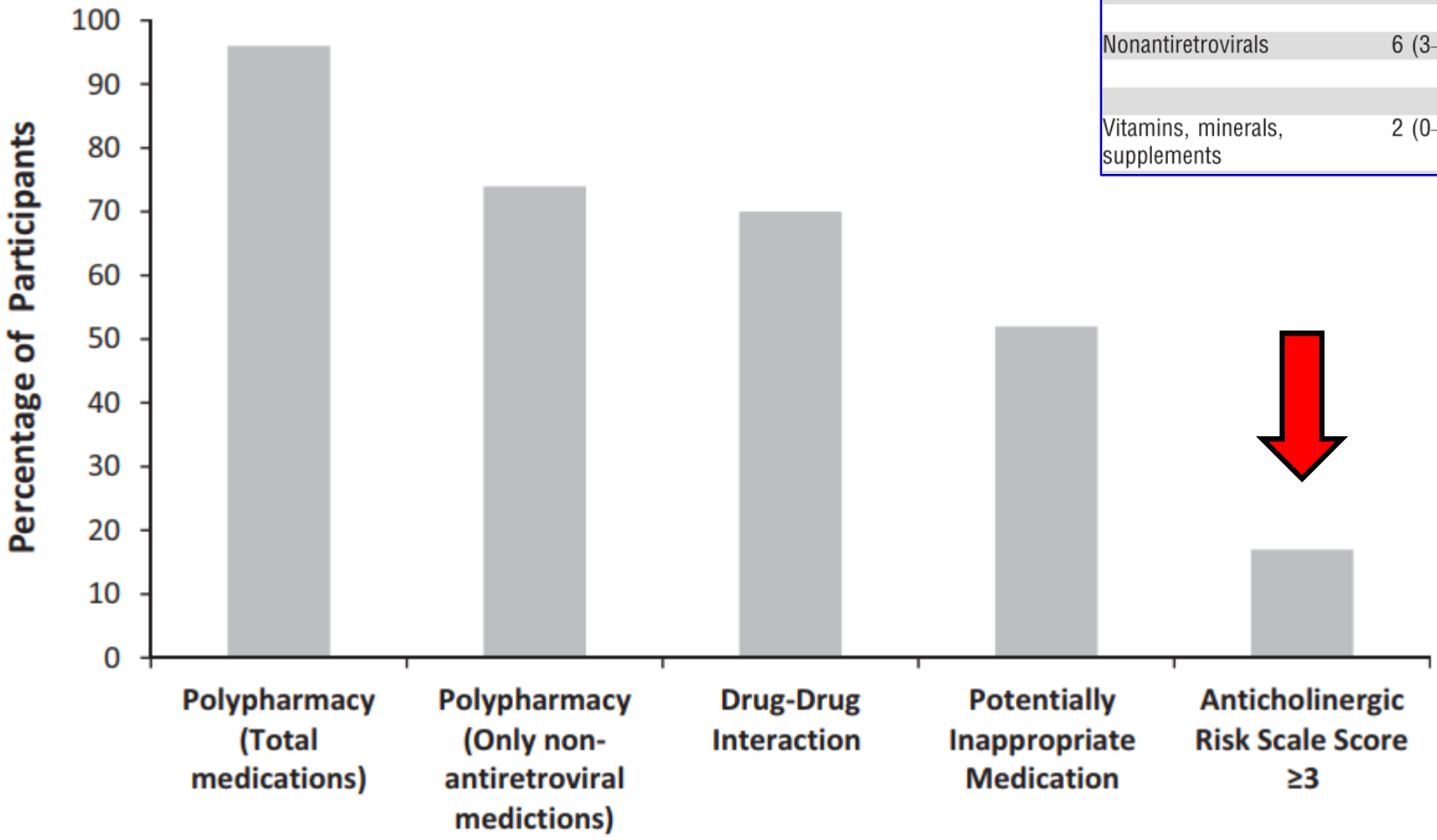
Potentially inappropriate prescribing was identified in 54% and 63% of patients using the STOPP and Beers criteria, respectively

- McNicholl, Pharmacother 2017 -

Polypharmacy, Drug–Drug Interactions, and Potentially Inappropriate Medications in Older Adults with Human Immunodeficiency Virus Infection

- ✓ 89 HIV-positive patients, median age of 64 (range 60-82)

Medication	Median (Interquartile Range)
Total	13 (9–17)[a]
Antiretrovirals	4 (3–5)
Nonantiretrovirals	6 (3–9)
Vitamins, minerals, supplements	2 (0–5)



- Greene, J Am Geriatr Soc 2014 -

The issue of anticholinergic burdern…

Background

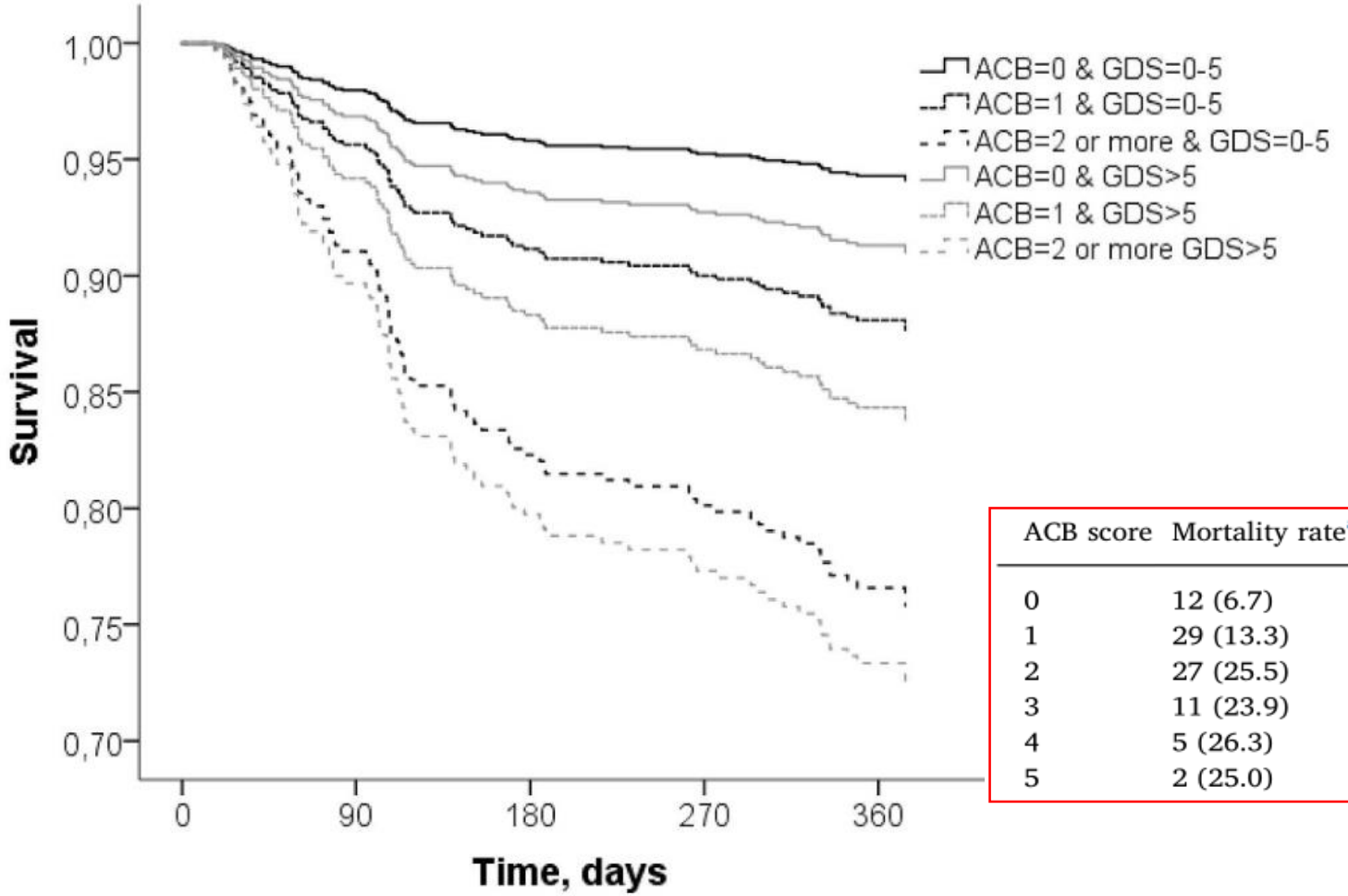
Medicines with anticholinergic properties are frequently prescribed in the older population for various medical conditions [1]. The cumulative effect of taking one or more medicines with anticholinergic properties is referred to as anticholinergic burden [2].

1. Roe CM, Anderson MJ, Spivack B. Use of anticholinergic medications by older adults with dementia. J Am Geriatr Soc. 2002;50(5):836–42.
2. Tune LE. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry. 2001;62 Suppl 21:11–4.

Drug class	Potential PD issues	Comments
Anticholinergic agents	↑ sensitivity (agitation, confusion, decompensation of glaucoma, dry mouth, constipation, urinary retention…) **Injurious falls**	avoid

Salahudeen *et al. BMC Geriatrics* (2015) 15:31

The excess mortality risk associated with anticholinergic burden among older patients discharged from acute care hospital with depressive symptoms



ACB score	Mortality rate[a]	HR (95%CI)
0	12 (6.7)	1.0
1	29 (13.3)	1.70 (0.86–3.63)
2	27 (25.5)	3.32 (1.67–6.60)
3	11 (23.9)	3.31 (1.45–7.56)
4	5 (26.3)	4.16 (1.46–11.5)
5	2 (25.0)	6.38 (1.41–28.9)

ACB: Anticholinergic Cognitive Burden score
GDS: Geriatric Depression Scale

- Corsonello, Eur J Intern Med, in press 2019 -

RESEARCH ARTICLE Open Access

Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review

Table 1 Overview of included anticholinergic rating scales

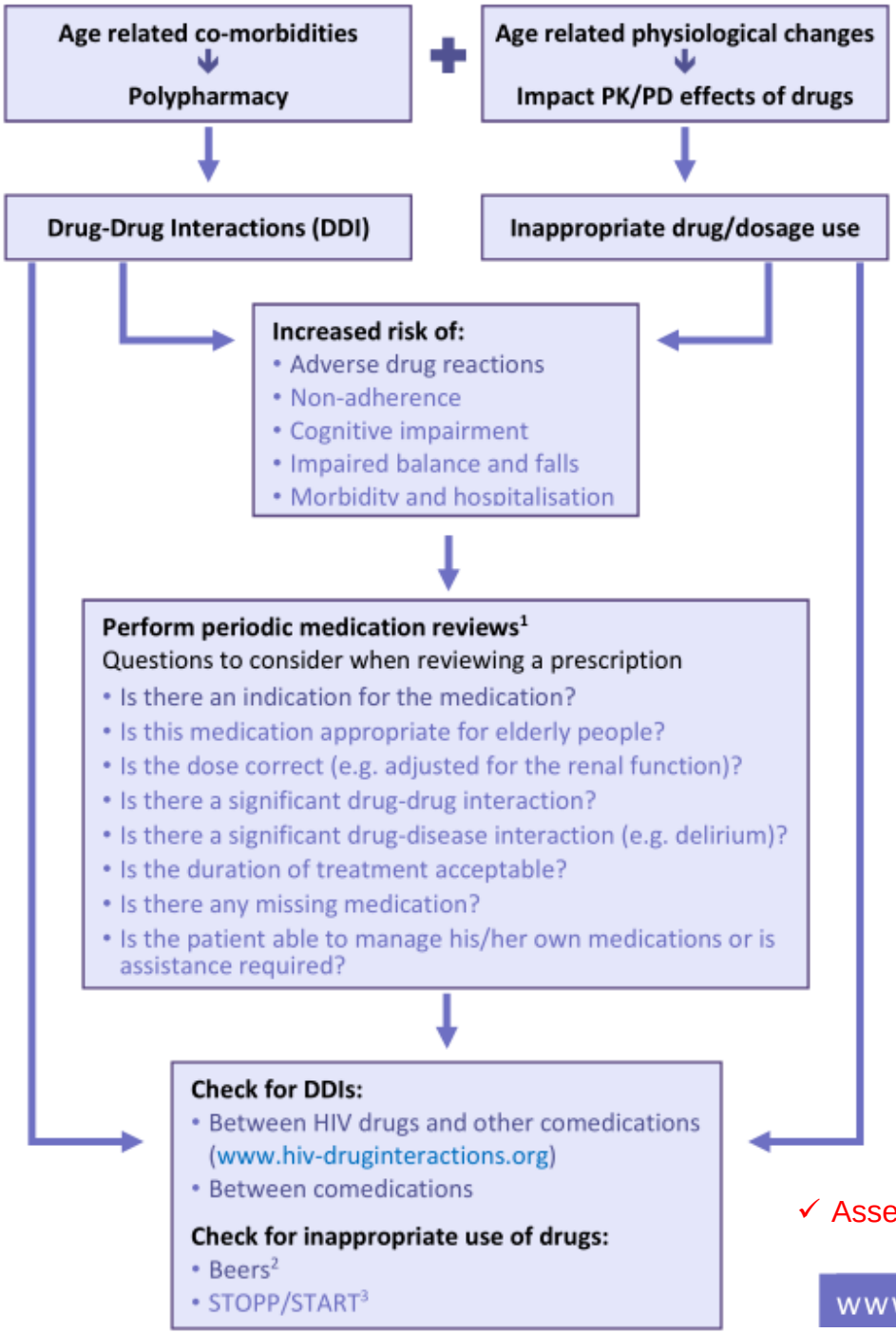
Expert opinion based rating scales	Description	Number of medicines
Carnahan USA, 2006 [9]	ADS is a four-point (0-3) scale that ranks anticholinergic drugs based on expert opinion	117
Ancelin France, 2006 [25]	ABC is a four-point scale (0-3) based on SAA and expert opinion	27
Han USA, 2008 [22]	CrAS is a four-point scale (0-3) based on pre-existing published anticholinergic scales and expert opinion	60
Rudolph USA, 2008 [19]	ARS is a four-point scale (0-3) based on extensive literature review and expert opinion	49
Boustani USA, 2008 [24]	ACB is a four-point (0-3) scale developed based on published data and expert opinion	88
Ehrt Norway, 2010 [26]	AAS is a five-point scale (0-4) based on existing evidence (Chew 2008 [38]) and expert opinion	99
Sittironnarit Australia, 2011 [23]	ACL is a four-point (0-3) scale based on pre-existing published anticholinergic scales and expert opinion	49

- Salahudeen, BMC Geriatrics 2015 -

Am J Geriatr Psychiatry. 2018 Mar;26(3):280-288. doi: 10.1016/j.jagp.2017.08.005. Epub 2017 Aug 14.

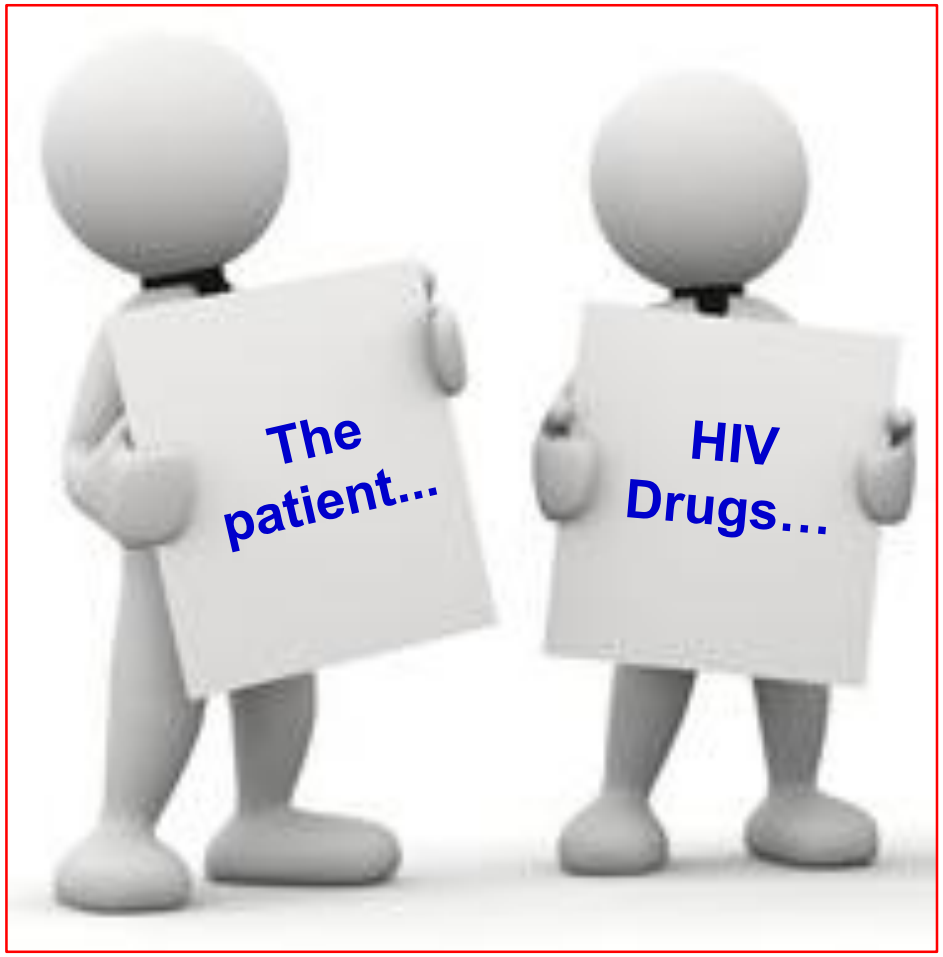
Reduction of the Anticholinergic Burden Makes It Possible to Decrease Behavioral and Psychological Symptoms of Dementia.

Jaïdi Y[1], Nonnonhou V[2], Kanagaratnam L[3], Bertholon LA[2], Badr S[2], Noël V[2], Novella JL[4], Mahmoudi R[4].

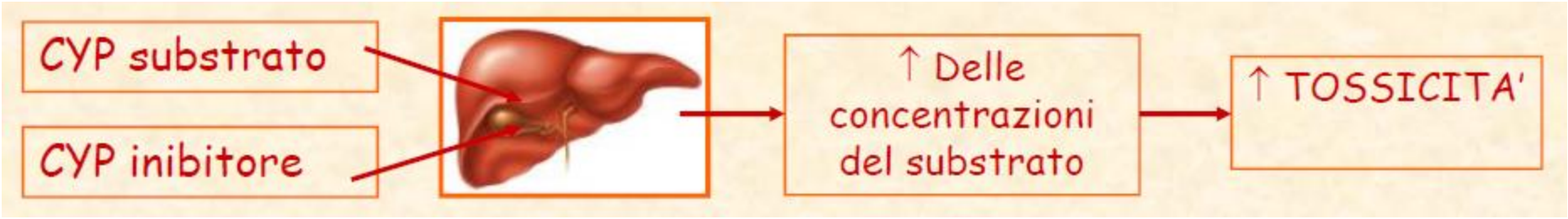


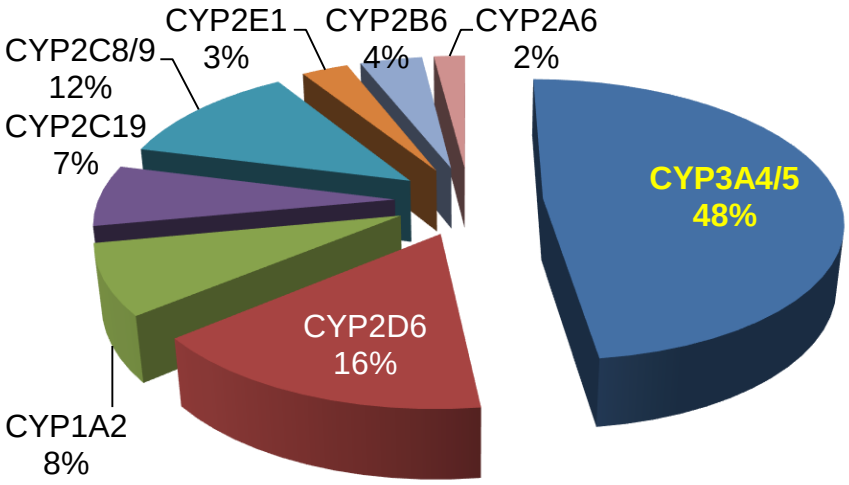
✓ Assess the anticholinergic burden

Beyond Liverpool site: pharmacological support for the management of polypharmacy in HIV-positive patients



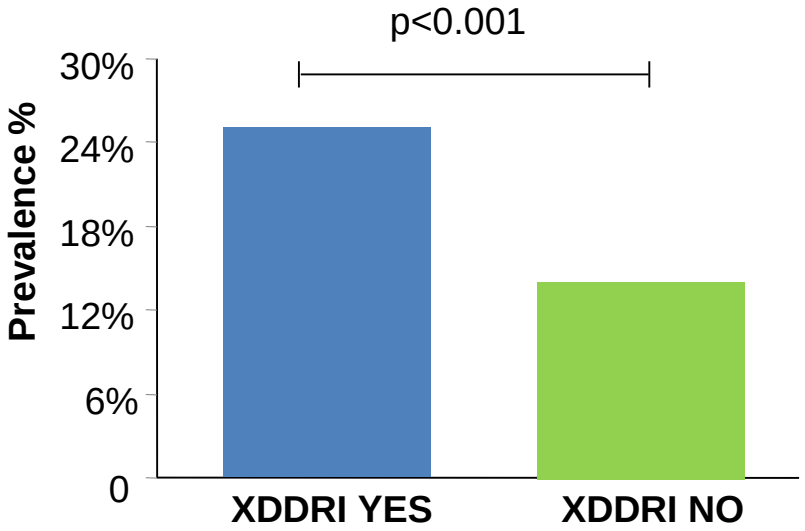
DDIs mainly involve alterations of the liver enzymes…





Nearly 40-50% of marketed drugs are metabolized by CYP3A isoforms (3A4 and 3A5)…

Prevalence of hospital admission in the HIV-veterans cohort: the role of the booster…



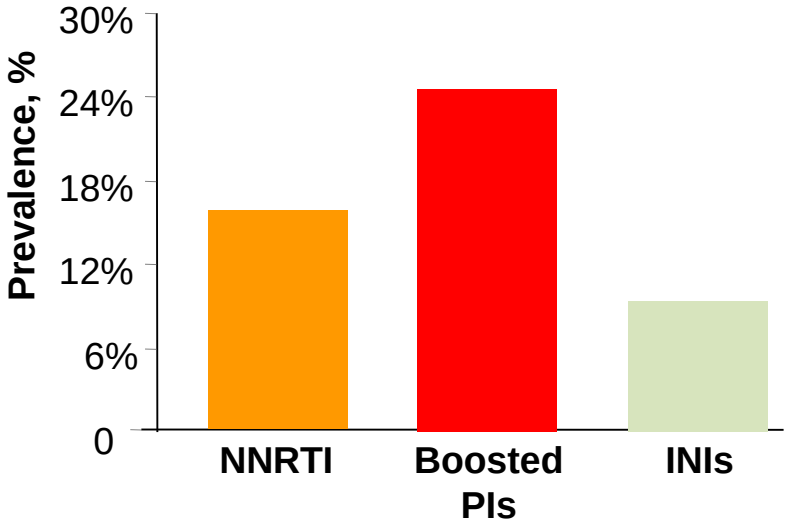


Table 1: Variables independently associated with hospitalization

Covariate	Odds Ratio	95% Confidence Interval	P-value
≥ 10 comorbidities*	1.78	1.19 – 2.68	0.005
XDDI	1.60	1.03 – 2.49	0.04
NNRTI-based regimen	1.43	0.92 – 2.23	0.11
PI-based regimen	1.93	1.23 – 3.02	0.004
ISTI-based regimen	REF	REF	REF

*CONTRAINDICATED DRUG-DRUG INTERACTIONS (XDDI)

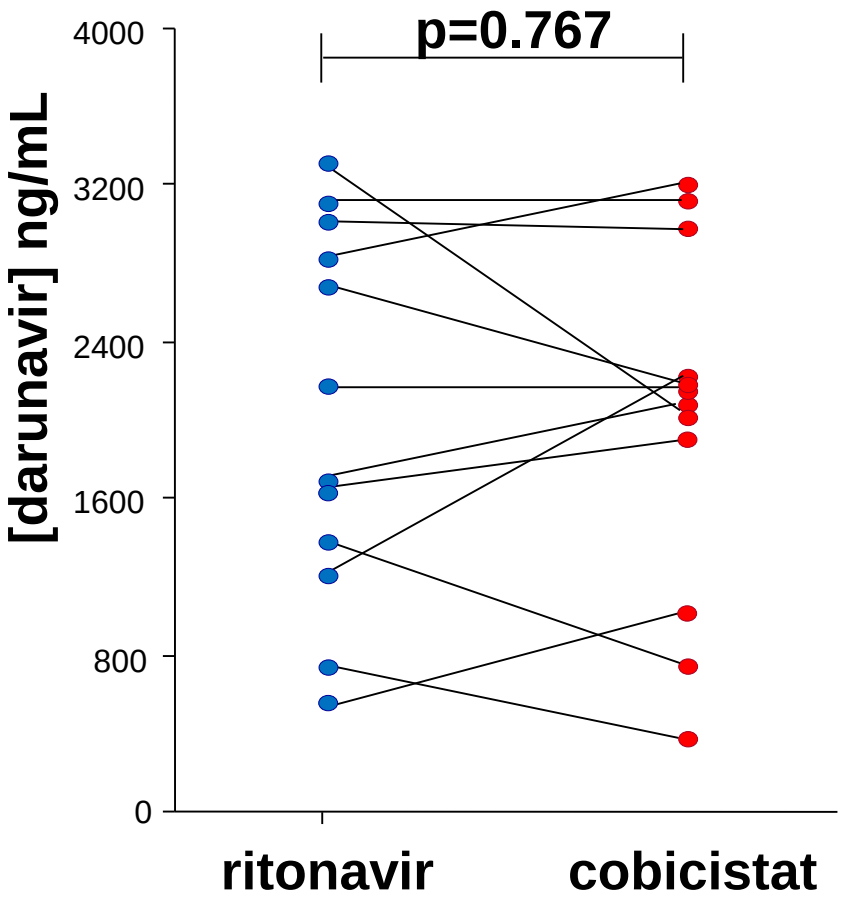
Jakeman B et al, ICAAC 2015, Abstract H-780

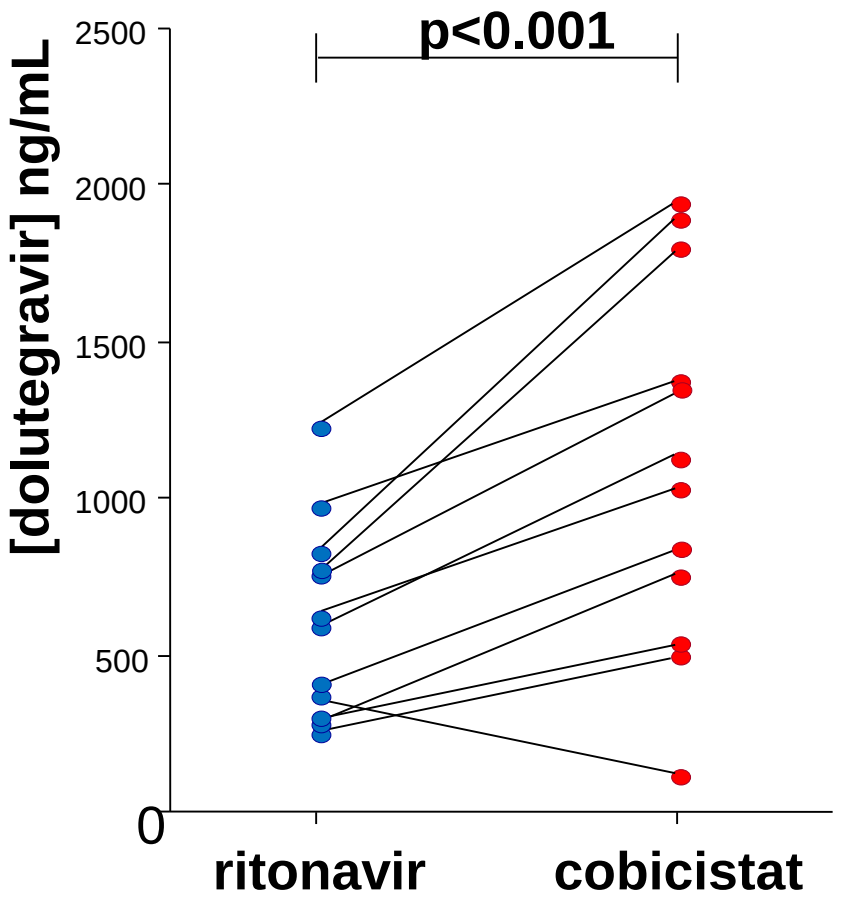
Are there differences between the boosters?

	IC_{50} (μM)	
	ritonavir	cobicistat
Cytochrome		
CYP1A2	>25	>25
CYP2B6	2.9	2.8
CYP2C8	2.8	>25
CYP2C9	4.4	>25
CYP2C19	>25	>25
CYP2D6	2.8	9.2
CYP3A4	0.11	0.15
Transporter		
P-gp	>20	36
BCRP	>20	59
OATP1B1	2.05	3.5
OATP1B3	1.83	1.88
MATE1	1.34	1.87
MATE2-K	>20	33.5
OAT1	>20	>100
OAT3	8.46	>100
OCT2	~20	14

- Marzolini, JAC 2016 -

The change in the booster may impact on the disposition of concomitant antiretroviral drugs: the case of dolutegravir…





Ritonavir induces UGT, whereas cobicistat does not…

- Gervasoni, JAC 2017 -

TDM has still a role in HIV!!!

Drug	Therapeutic ranges
Tenofovir from TDF	40-180 ng/mL
Efavirenz	1000-4000 ng/mL
Etravirine	>300 ng/mL
Nevirapine	3000-6000 ng/mL
Rilpivirine	>20 ng/mL
Amprenavir	>400 ng/mL
Atazanavir	150-800 ng/mL
Darunavir	>550 ng/mL
Indinavir	150-550 ng/mL
Lopinavir	1000-7000 ng/mL
Saquinavir	100-250 ng/mL
Tipranavir	>20500 ng/mL
Dolutegravir	>100 ng/mL
Elvitegravir	>45 ng/mL
Raltegravir	>40 ng/mL
Maraviroc	>50 ng/mL

The dolutegravir monograph suggests to double the drug dose (from 50 mg qd to 50 mg bid) in presence of drug inducers…

Comedications	Patients (n)	Dolutegravir* (ng/mL)
Abacavir/emtricitabine	12	1045 [856-1115]
Atazanavir (85% at 400 mg qd)	26	2399 [1929-4070]
Darunavir (800/100 mg qd)	26	756 [556-1048]
Efavirenz	2	**58, 40**
Etravirine	3	**25**, 182, 931
Rilpivirine	12	603 [432-1373]
Nevirapina	1	102
Rifampicin	1	**22**

***protein-adjusted IC_{90}: 64 ng/ mL (clinical cutoff: 300 ng/mL)**

- Cattaneo, D. Antiviral Therapy 2017 -

…eventually combined with pharmacogenetics…

	Patient 1	Patient 2
Clinical data	Male, 57 years, IVD, HIV therapy since 2000	Male, 53 yeas, HIV therapy since 1993
TARV	Drv/cobi 800/150 mg TAF/FTC 10/200 mg	Drv/r 600/10 mg bid TAF/FTC 10/200 mg
Other drugs	diazepam, rosuvastatin, cholecalciferol, acyclovir e carbamazepine	rosuvastatin
CD4, VL	828 cells/mL, <37 cp/mL	790 cells/mL, <37 cp/mL
$[drv]_{trough}$ pre-steroide	**2588 ± 742 ng/mL**	**2339 ± 1056 ng/mL**
Steroid, dose and duration	Prednisone 25 mg bid (2 weeks of therapy)	methylprednisolone 16mg, (progressively tapered)
Underlying disease	Trigeminal neuralgia	lumbar disc herniation
$[drv]_{trough}$ post-steroide	**220 ng/mL (-93%)**	**3127 ng/mL**

- Cattaneo, Eur J Clin Pharmacol 2019 -

Data from literature are unconclusive…

"In vitro studies have shown that glucocorticoids significantly modulate the expression of both phase I and phase II metabolic enzymes, thus potentially affecting the disposition of several drugs. However, clinical studies aimed at assessing the impact of glucocorticoids on drugs bioavailability provided conflicting results"

Matoulková P, et al. Cytochrome P450 enzyme regulation by glucocorticoids and consequences in terms of drug interaction. Expert Opin Drug Metab Toxicol. 2014; 10: 425-35.

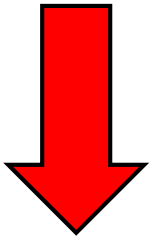
However…

Association between *CYP3A5* Genotypes in Graft Liver and Increase in Tacrolimus Biotransformation from Steroid Treatment in Living-donor Liver Transplant Patients

- Drug Metab Pharmacokinet 2014 -

Genotype of the two HIV-infected patients on maintenance darunavir therapy treated concomitantly with glucocorticosteroids

Genes	Genetic variant considered	Reference genotype	Genotype of Patient 1	Genotype of Patient 2
CYP3A4	rs35599367 C>T CYP3A4*22	CC	CC	CC
CYP3A5	rs776746 A>G CYP3A5*3	AA	GG	GG



Both patients were categorized as “intermediate metabolizers” on the basis of CYP3A4*22 and CYP3A5*3 combined genotypes

- Cattaneo, Eur J Clin Pharmacol 2019 -

Genotype of the two HIV-infected patients on maintenance darunavir therapy treated concomitantly with glucocorticosteroids

Genes	Genetic variant considered	Reference genotype	Genotype of Patient 1	Genotype of Patient 2
CAR	rs2307424 540G>A	GG	GA	GA
CYP3A4	rs35599367 C>T CYP3A4*22	CC	CC	CC
CYP3A5	rs776746 A>G CYP3A5*3	AA	GG	GG
POR	rs1057868 C>T POR*28	CC	CC	CT
PPARA	rs4253728 c.209-1003 G>A	GG	**AA**	GG
PXR	rs2472677 63396 C>T	CC	CT	**TT**

CAR: constitutive androstane receptor; CYP3A4: cytochrome P450 3A4; CYP3A5: cytochrome p450 3A5; POR: NADPH-cytochrome P450 oxidoreductase; PPARA: peroxisome proliferator-activated receptor alpha; PXR: pregnane X receptor

- Cattaneo, Eur J Clin Pharmacol 2019 -

Beyond Liverpool site: pharmacological support for the management of polypharmacy in HIV-positive patients

Rifampicin is not only an issue for dolutegravir….

Eur J Clin Pharmacol (2015) 71:643–644
DOI 10.1007/s00228-015-1833-z

LETTER TO THE EDITORS

Prolonged inductive effect of rifampicin on linezolid exposure

Cristina Gervasoni · Francesco R. Simonetti · Chiara Resnati · Nitin Charbe · Emilio Clementi · Dario Cattaneo

Glucocorticoids are not only an issue for boosted PIs….

Glucocorticoids interfere with mycophenolate mofetil bioavailability in kidney transplantation

Dario Cattaneo, Norberto Perico, Flavio Gaspari, Eliana Gotti, and Giuseppe Remuzzi

Kidney International, Vol. 62 (2002), pp. 1060–1067

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Regione Lombardia
ASST Fatebenefratelli Sacco

TDM service (beyond antiretrovirals)

Antiepileptics

- ❑ Lamotrigine
- ❑ Etosuccimide
- ❑ Zonisamide
- ❑ Rufinamide
- ❑ levetiracetam
- ❑ Topiramate
- ❑ Felbamate
- ❑ Oxcarbazepine
- ❑ Perampanel
- ❑ Lacosamide
- ❑ Valproate
- ❑ Carbamazepine
- ❑ Phenobarbital
- ❑ Phenytoin
- ❑ Primidone

Immunosuppressants

- ❑ Cyclosporine
- ❑ Tacrolimus
- ❑ Mycophenolate
- ❑ Sirolimus
- ❑ Everolimus

NOACs

- ❑ Dabigatran
- ❑ Rivaroxaban
- ❑ Apixaban

Others

- ❑ Chinidine
- ❑ Teophyllin
- ❑ Acetaminophen
- ❑ Ibuprofen
- ❑ Litium

Anti-infectives

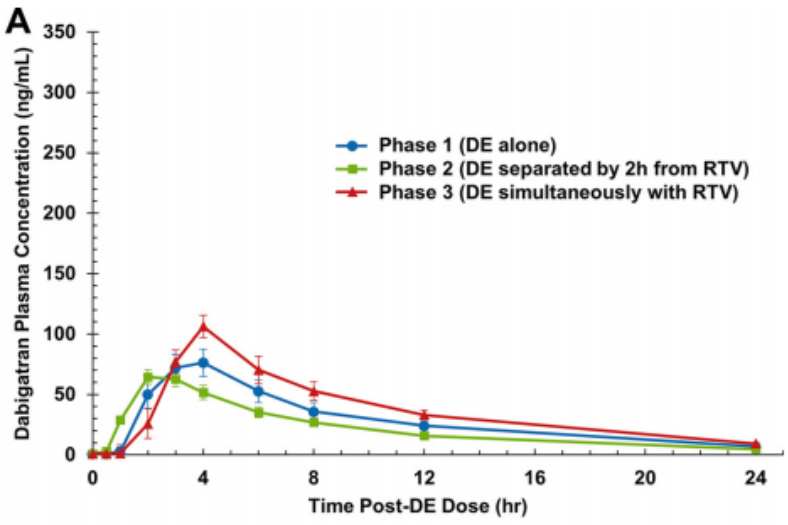
- ❑ Teicoplanin
- ❑ Levofloxacin
- ❑ Rifampicin
- ❑ Linezolid
- ❑ Cyprofloxacin
- ❑ Vancomycin
- ❑ Amikacin
- ❑ Gentamycin
- ❑ Trimethoprim
- ❑ Meropenem
- ❑ Piperacillin
- ❑ Voriconazole
- ❑ Posaconazole
- ❑ Isavuconazole
- ❑ Itraconazole
- ❑ Caspofungin

Psychotropics

- ❑ Citalopram
- ❑ Escitalopram
- ❑ Quetiapine
- ❑ Paroxetine
- ❑ Aripiprazole
- ❑ Olanzapine
- ❑ Risperidone
- ❑ Haloperidole
- ❑ Clozapine
- ❑ Paliperidone
- ❑ Fluoxetine
- ❑ Duloxetine
- ❑ Flufenazine
- ❑ Clomipramine
- ❑ Venlafaxine
- ❑ Ziprasidone
- ❑ Sertraline

To monitor the effects of ARVs on other drugs….

Differential Influence of Ritonavir and Cobicistat on Intestinal P-gP Transport and PK/PD Disposition of Dabigatran



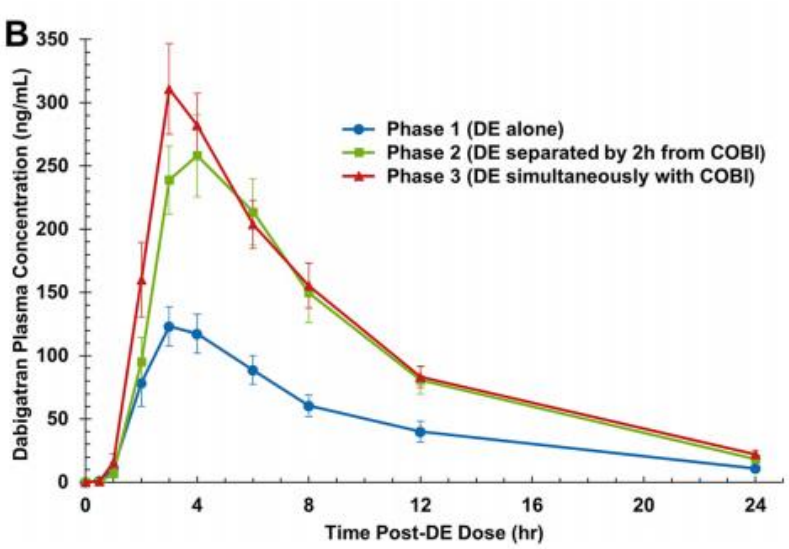


TABLE 4 Geometric mean TT anticoagulation parameters in arm B (COBI)[a]

Parameter	$AUEC_{0-24}$ (s · h)	Thrombin time (s)
Geometric mean value (% CV)		
Phase 1 (DE alone)	1,508 (16.9)	29.2 (25.4)
Phase 2 (DE + COBI separated)	1,964 (12.2)	42.5 (27.8)
Phase 3 (DE + COBI simultaneously)	2,038 (10.9)	45.4 (28.8)
GMR (90% CI) for comparison of phases		
Phase 2 vs phase 1	1.30 (1.21–1.39)[b]	1.46 (1.30–1.61)[b]
Phase 3 vs phase 1	1.33 (1.22–1.44)[b]	1.51 (1.24–1.78)[b]

- Kumar, AAC 2017 -

…or to monitor the exposure of non-ARV comedications in HIV-patients...

Journal
The World Journal of Biological Psychiatry ›

Evaluation of the concentrations of psychotropic drugs in HIV-infected versus HIV-negative patients: Potential implications for clinical practice

Dario Cattaneo, Sara Baldelli, Chiara Resnati, Andrea Giacomelli, Paola Meraviglia, Davide Minisci, ...show all

Received 03 Apr 2018, Accepted 09 Jul 2018, Accepted author version posted online: 30 Jul 2018, Published online: 20 Sep 2018

- ✓ In the present study we sought to evaluate the distribution of plasma trough concentrations of psychotropic drugs (antidepressants or antipsychotics) in HIV-infected patients during routine outpatient visits and compare them with those measured in HIV-negative patients

Consensus Guidelines for Therapeutic Drug Monitoring in Neuropsychopharmacology: Update 2017

Drugs and active metabolites	Therapeutic reference range	t1/2 (h)	Laboratory alert level	Level of recommenda-tion to use TDM
Antipsychotic drugs				
Amisulpride	100–320 ng/mL	12–20 h	640 ng/mL	1
Aripiprazole Aripiprazole plus dehydroaripiprazole	100–350 ng/mL 150–500 ng/mL	60–80 h	1 000 ng/mL	2
Asenapine	1–5 ng/mL	13–39 h	10 ng/mL	4
Benperidol	1–10 ng/mL	4–6 h	20 ng/mL	3
Brexpiprazole	40–140 ng/mL	91 h	280 ng/mL	3
Bromperidol	12–15 ng/mL	20–36 h	30 ng/mL	2
Cariprazine	10–20 ng/mL	48–120 h	40 ng/mL	3
Chlorpromazine	30–300 ng/mL	15–30 h	600 ng/mL	2
Chlorprothixene	20–300 ng/mL	8–12 h	400 ng/mL	3
Clozapine	350–600 ng/mL	12–16 h	1 000 ng/mL	1
Flupentixol	0.5–5 ng/mL (cis-isomer)	20–40 h	15 ng/mL	2
Fluphenazine	1–10 ng/mL	16 h	15 ng/mL	1
Fluspirilen	0.1–2.2 ng/mL	7–14 days	4.4 ng/mL	3
Haloperidol	1–10 ng/mL	12–36 h	15 ng/mL	1

1. Strongly recommended
2. Recommended
3. Useful
4. Potentially useful

Hiemke C et al. Consensus Guidelines for Therapeutic … Pharmacopsychiatry

Distribution of psychotropic drug trough concentrations in HIV-positive patients versus HIV-negative controls according to the AGNP guidelines

Drug	HIV-pos pts, n	Trough levels (ng/mL)	Sub-therapeutic samples, %	HIV-neg pts, n	Trough levels (ng/mL)	Sub-therapeutic samples, %
Citalopram	15	65±67	60%*	50	73±58	34%
Duloxetine	8	32±35	63%	19	68±41	32%
Fluoxetine	5	204±190	50%	14	250±160	21%
Paroxetine	13	22±20	54%	21	150±116	33%
Sertraline	10	20±12	20%*	85	47±43	6%
Haloperidol	7	1.4±0.5	57%^	41	4.1±2.6	5%
Olanzapine	8	16±16	88%*	37	47±66	46%
Quetiapine	12	266±225	46%	112	211±251	31%

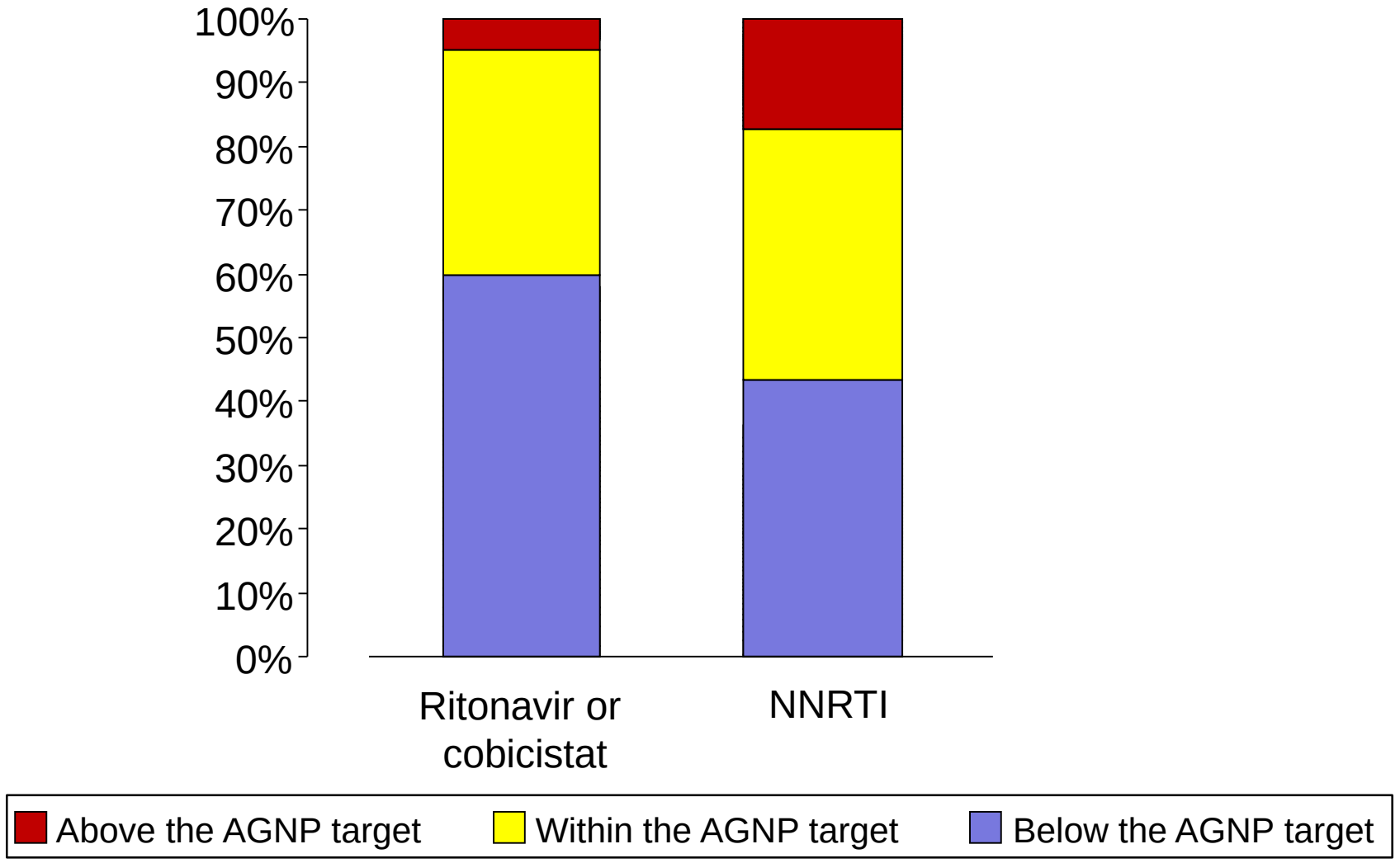
*p<0.05 or ^p<0.01 versus HIV-negative controls

- Cattaneo, World J Biol Psyc 2018 -

Can these results be eventually explained by drug-drug interactions between antiretrovirals and psychotropics?

- ✓ Boosting agents (rtv, cobi) inhibit cytochromial enzymes…
- ✓ NNRTIs induce cytochromial enzymes…

Distribution of psychotropic trough concentrations clustered according to ARV therapy (booster- vs. NNRTI versus INI-based regimens)



What about antiepileptic drugs?

Antiepileptic drug	No. of TDM	[drug], mg/L	Below the target, %	Within the target, %	Above the target, %
HIV-positive patients					
Carbamazepine	20	8.2 ± 3.6	0	95%	5%
Lamotrigine	9	4.0 ± 4.5	67%	33%	0
Levetiracetam	136	18.6 ± 12.3	29%	67%	4%
Oxcarbazepine	5	8.2 ± 3.6	20%	80%	0
Phenytoin	10	35.6 ± 12.0*	0	95%	5%
Phenobarbital	45	19.1 ± 7.2	11%	89%	0
Topiramate	10	6.6 ± 5.0	0	70%	30%
Valproate	75	47.9 ± 21.2^	57.0%	43%	0
HIV-negative patients					
Carbamazepine	381	7.3 ± 2.7	9%	87%	4%
Lamotrigine	400	5.9 ± 4.1	28%	68%	4%
Levetiracetam	1137	21.0 ± 14.3	22%	68%	10%
Oxcarbazepine	141	17.7 ± 8.8	22%	72%	6%
Phenytoin	121	11.2 ± 10.7	60%	23%	17%
Phenobarbital	290	19.1 ± 8.7	13%	85%	2%
Topiramate	159	7.3 ± 4.3	15%	61%	25%
Valproate	859	53.9 ± 21.6	46%	52%	2%

**p<0.01 and ^p<0.05 versus HIV-negative patients*

- Cattaneo, submitted 2019 -

Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid

VPA dose (mg) and route of administration	DTG C_{min} (µg/mL)	DTG C_{max} (µg/mL)	DTG AUC_{0-12} (µg·h/mL)	VPA dose (mg) and route of administration	DTG C_{min} (µg/mL)	DTG C_{max} (µg/mL)	DTG AUC_{0-24} (µg·h/mL)
VPA 1500 iv	0.79	1.29	13.28	–	–	–	–
VPA 1500 po	0.56	1.30	9.86	–	–	–	–
VPA 750 po	0.21	0.87	7.13	VPA 1500 po	0.14	0.79	10.72
DTG 50 mg q12h reference values	*2.12*	*4.15*	*75.1*	*DTG 50 mg q24h reference values*	*1.11*	*3.76*	*53.6*

Our small case series highlights a need to monitor a potential DDI between dolutegravir and valproic acid. Formal pharmacokinetic studies are needed in order to identify the magnitude and possible mechanisms of interaction. Meanwhile, we suggest careful clinical monitoring and performance of TDM in patients taking both dolutegravir and valproic acid who may be at a higher risk of failing on dolutegravir-containing regimens.

- Palazzo et al, JAC 2018 -

Psychotropics versus antiepileptics…

- ✓ The large majority of our HIV-infected patients were treated with traditional antiepileptic drugs, such as carbamazepine, phenytoin, phenobarbital and levetiracetam, whose pharmacology has been well established, as well as their risk to be victims of DDIs…

- ✓ The TDM of antiepileptic drugs has been used for years, and still is, in most of the hospitals for the management of antiepileptic therapies, whereas its use for the optimization of antidepressant and/or antipsychotic treatments is still in its infancy, with controversial results…

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…ok, sounds good…but, What to do if there is no TDM service in my center..?!?

Free web databases tat can be used to verify possible DDIs

Link	Notes
https://clinicalweb.marionegri.it/intercheckweb	A database that evaluates prescriptive appropriateness in the elderly by considering various aspects of geriatric pharmacology (it requires individual registration)
https://reference.medscape.com/drug-interactionchecker	A "generalist" database that also includes over-the-counter products, some phytotherapeutic agents and supplements
https://www.hiv-druginteractions.org	A database verifying interactions between anti-retroviral agents (HIV), and between antiretroviral and non-antiretroviral agents
https://www.hep-druginteractions.org	A database verifying interactions between antiviral agents (HCV), and between antiviral and non-antiviral agents
http://www.drugs.com/drug_interactions.html	A "generalist" database
https://cancer-druginteractions.org/checker	A database verifying interactions between antitumoral agents, and between antitumoral and non-antitumoral agents
http://healthlibrary.uchospitals.edu	A "generalist" database
https://www.rxlist.com/drug-interaction-checker.htm	A "generalist" database
https://stahlonline.cambridge.org/drug_interaction.jsf?	A "generalist" database that particularly focuses on drugs acting on the central nervous system

- Gervasoni, AIDS Rev in press 2019 -

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http://www.drugs.com/drug_interactions.html	A "generalist" database
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Check always for potential DDIs between non-ARVs comedications!!!

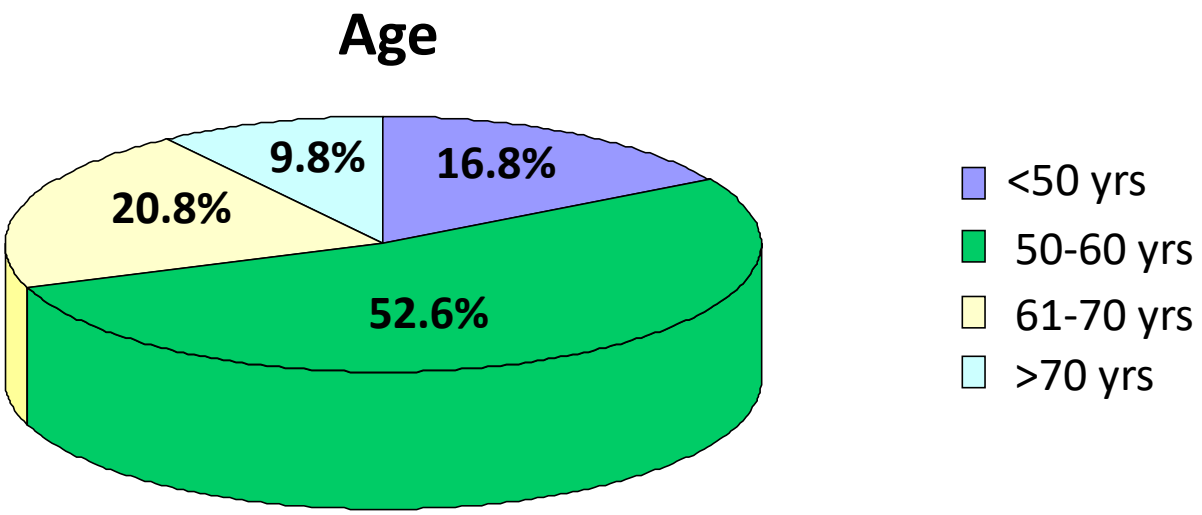
- Gervasoni, AIDS Rev in press 2019 -

Beyond Liverpool site: pharmacological support for the management of polypharmacy in HIV-positive patients

Gestione Ambulatoriale Politerapie

Dott.ssa Cristina Gervasoni
Dott. Dario Cattaneo
& collaboratori

- ✓Kick-off : August 2016
- ✓to date, more than 900 HIV patients included in the DB

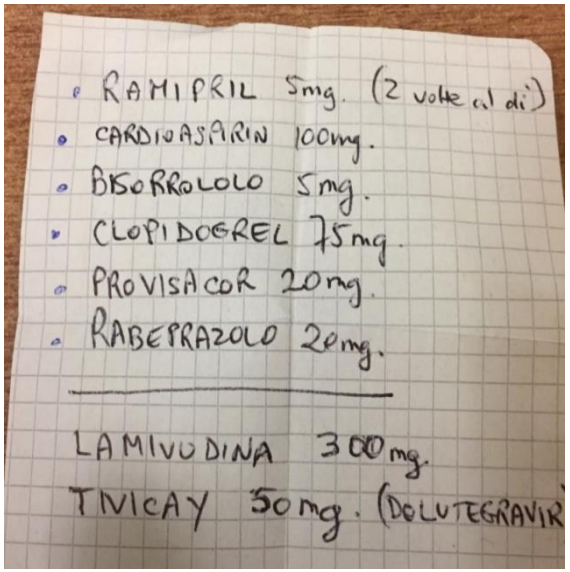


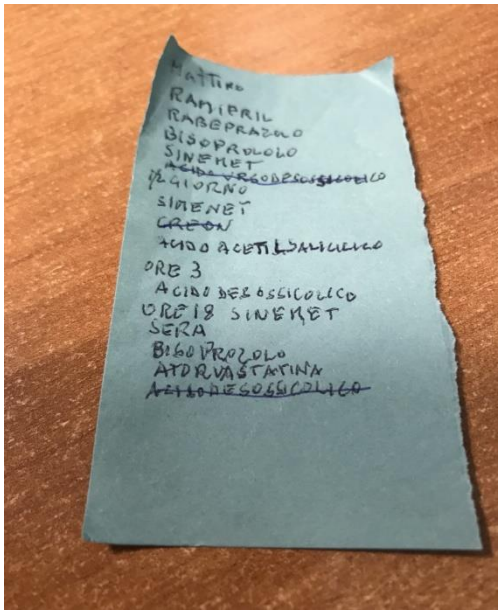
Activities of the GAP outpatient clinic

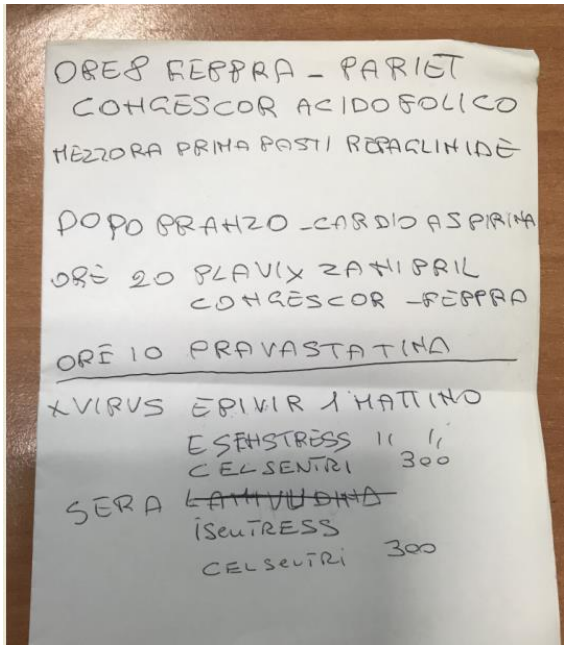
- ✓ The detailed collection of anamnestic, clinical, therapeutic and *ad hoc* laboratory data relating to individual patients taking antiretroviral and other drugs (OTC, supplements, etc.) in order to verify whether there are potential DDIs
- ✓ When appropriate, prescription of the TDM/PG tests offered by the hospital's Pharmacological Service in order to quantify any identified interactions
- ✓ Verification of known/potential interactions on the basis of drug metabolism and scientific evidence
- ✓ Verification of the real clinical relevance of the interactions by carefully evaluating the current and previous clinical conditions of each patient, and the possible risks/benefits of his/her current treatments
- ✓ Written report to the attending specialist in infectious diseases concerning any required change in the current treatments

- Gervasoni, AIDS Rev in press 2019 -

…the most difficult task...





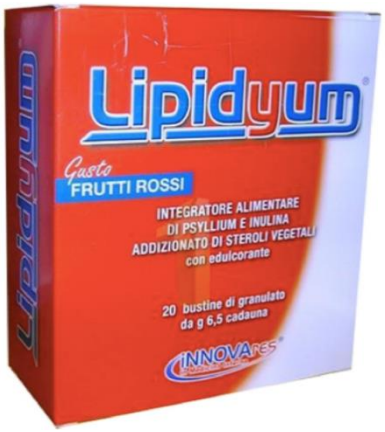


…be able to understand exactly what the patient is taking…!!!

For the patients these are not drugs…

Orlistat is a lipase inhibitor reported to inhibit the intestinal absorption of dietary fats and of highly lipophilic drugs

Sinetrol contains mainly naringin, a flavanone-7-O-glycoside which inhibits the activity of carrier proteins (p-glycoprotein and organic anion transporting polypeptide), ultimately resulting in impaired drug absorption



Lipidyum is a dietatry supplement of phytosterols (mainly psyllium). Psyllium, a soluble fiber from the husks of *Plantago ovata* able to increase stool weight, promote laxation and was reported to decrease the absorption of some molecules

Obesity

Loss of Control of HIV Viremia with OTC Weight-Loss Drugs: A Call for Caution?

Patient	Antiretroviral therapy	Weight- loss agent	TDM 1	TDM 2	Ther. range
Female, 43 years	ATV/r 300/100 TDF 245 mg FTC 200 mg	**Orlistat 60 mg thrice daily**	ATV: 50 ng/mL	ATV: 195 ng/mL	150-800 ng/mL
Female, 39 years	EFV 600 mg TDF245 mg FTC 200 mg	**Orlistat 60 mg thrice daily**	EFV <150 ng/mL	EFV: 3795 ng/mL	1000-4000 ng/mL
Female, 40 years	ATV/r 300/100 TDF 245 mg FTC 200 mg	**Sinetrol 450 mg twice daily**	ATV: 85 ng/mL	ATV: 719 ng/mL	150-800 ng/mL
Male, 44 years	DRV/cobi 800/150 TAF 10 mg FTC 200 mg	**Gunabasic 7 g daily** **Lipidyum 6.5 g daily**	*Not available*	*Not available*	*Not available*

TDM 1: performed during concomitant administration with the weight-loss agent; TDM 2: TDM performed after weight-loss agent discontinuation

- Cattaneo et al, Obesity 2018 -

…an additional patient not yet failing antiretroviral therapy was recently identified...

26/08/2018 Elvitegravir trough concentrations: **809 ng/mL**

24/09/2018

CUT 4 HIM + is a thermogenic complex aimed at the requirements of men who wish to lose weight and increase their muscle definition and energy.

CUT4HIM+ consists of carnitine, caffeine, the exclusive Olivo Plus formula, Guggul and Chilli…

06/12/2018 Elvitegravir trough concentrations: **56 ng/mL (-93%!!)**

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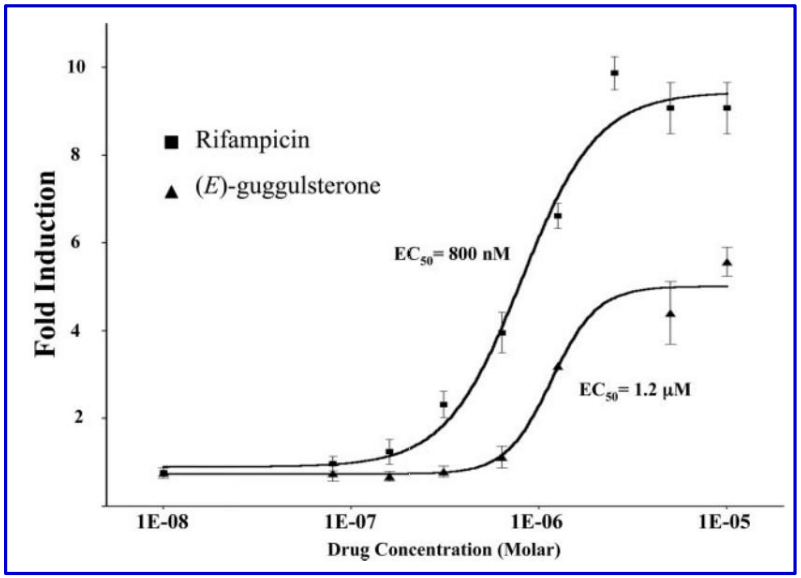
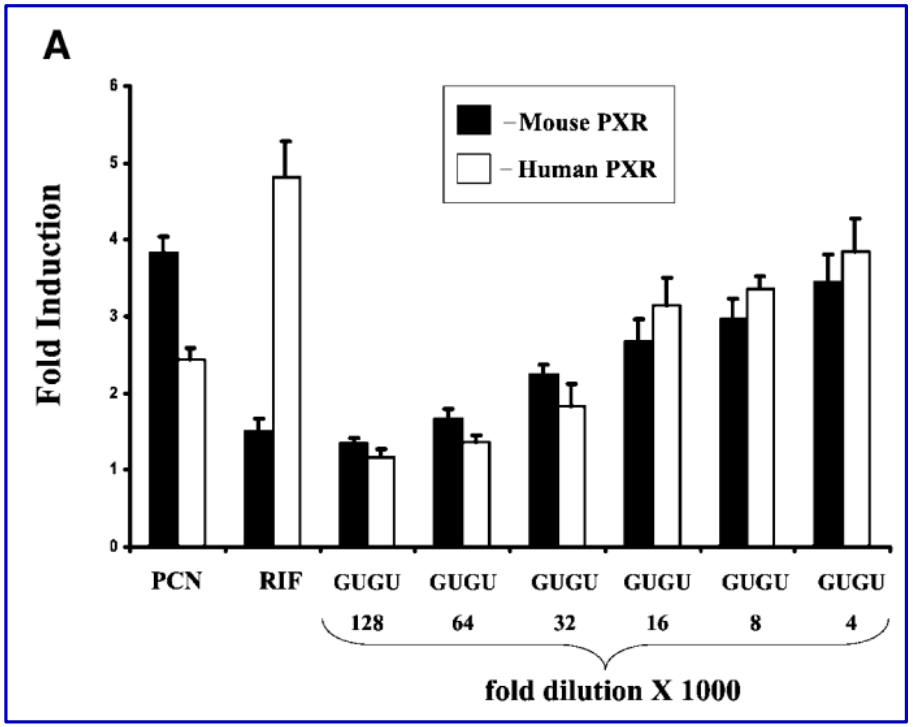
Guggulsterone Activates Multiple Nuclear Receptors and Induces CYP3A Gene Expression through the Pregnane X





Guggul (+) PXR

PXR (+) CYP3A

CYP3A (+) elvitegravir metabolism

…what GAP found...

Expected and unexpected clinically relevant DDIs

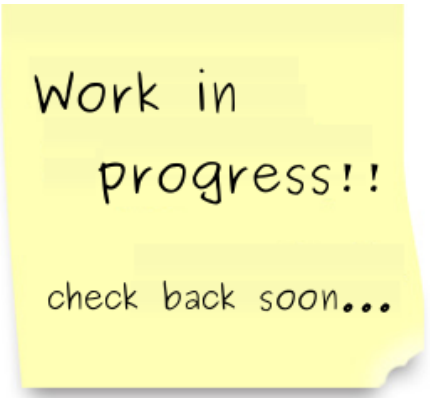
- ✓ Cattaneo D, et al. Loss of Control of HIV Viremia With OTC Weight-Loss Drugs: A Call for Caution? Obesity. 2018;26:1251-1252.

Expected but not clinically relevant DDIs

- ✓ Cattaneo D, et al. How relevant are the drug-drug interactions between antiretroviral boosted-based regimens and calcium channel blockers in real life? J Antimicrob Chemother. 2018;73:2271-2273.
- ✓ Cattaneo D, et al. Dolutegravir and metformin: a clinically relevant or just a pharmacokinetic interaction? AIDS. 2018;32:532-533.
- ✓ Gervasoni C, et al. How Relevant is the Interaction Between Dolutegravir and Metformin in Real Life? J Acquir Immune Defic Syndr. 2017 May 1;75(1):e24-e26
- ✓ Gervasoni C, et al. The relevance of drug-drug interactions in clinical practice: the case of concomitant boosted protease inhibitors plus alpha-1 blocker administration. Antivir Ther. 2018;23:467-469.

The fear of interactions (misinterpreted DDIs)

- ✓ Cattaneo D, et al. Evaluation of the concentrations of psychotropic drugs in HIV-infected versus HIV-negative patients: Potential implications for clinical practice. World J Biol Psychiatry. 2018;20:1-7.



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People from the lab…

Sara Baldelli
Igor Bonini
Simone Castoldi
Valeria Cozzi
Cristina Montrasio
Stefania Cheli
Marta Fusi
Emilio Clementi

…and those from GAP

Cristina Gervasoni
Noemi Astuti
Tiziana Formenti
Bianca Ghisi
Andrea Giacomelli
Paola Meraviglia
Davide Minisci
Chiara Resnati

Thank you all, guys!