Ospedale Luigi Sacco
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Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

GAP

Multidisciplinary experience to manage polypharmacy in the clinical setting

Dario Cattaneo, PharmD, PhD

Unit of Clinical Pharmacology
ASST Fatebenefratelli Sacco University Hospital, Milano, Italy

President-elect, International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

Gestione Ambulatoriale Politerapie*

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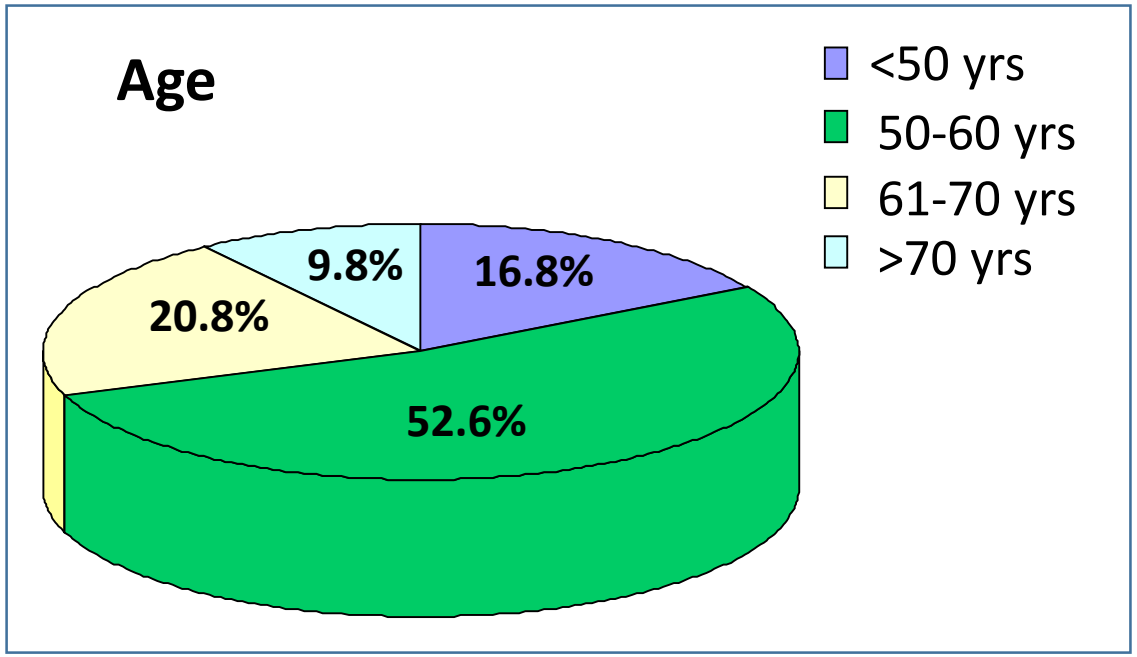
UNIVERSITÀ DEGLI STUDI DI MILANO

Cristina Gervasoni (*Infectious Diseases physician*)
Dario Cattaneo (*Clinical Pharmacologist*)
& Collaborators:

From the lab…
Sara Baldelli
Igor Bonini
Simone Castoldi†
Valeria Cozzi
Cristina Montrasio
Stefania Cheli
Marta Fusi
Emilio Clementi

…the clinics..
Noemi Astuti
Cecilia Bonazzetti
Lucia Bradanini
Giacomo Casalini
Federico Conti
Alice Covizzi
Tiziana Formenti
Bianca Ghisi
Andrea Giacomelli
Paola Meraviglia
Davide Minisci
Valentina Morena
Letizia Oreni
Gabriele Pagani
Laura Pezzati
Chiara Resnati
Annalisa Ridolfo
Agostino Riva
Marco Schiuma

…and beyond…
Stefano Bonora
Andrea Calcagno
Antonio D'Avolio
Gianni di Perri
Carlo Filice
Danijela Kocic
Debbie Marriott
Luca Pasina



- ✓ Kick-off : September 2016
- ✓ Nearly 1000 HIV patients

*Multidisciplinary outpatient clinic

Activities of the GAP outpatient clinic

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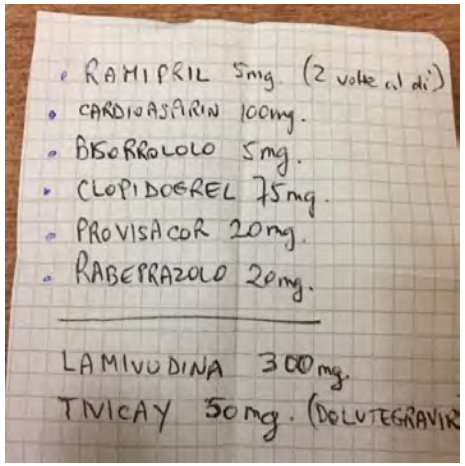
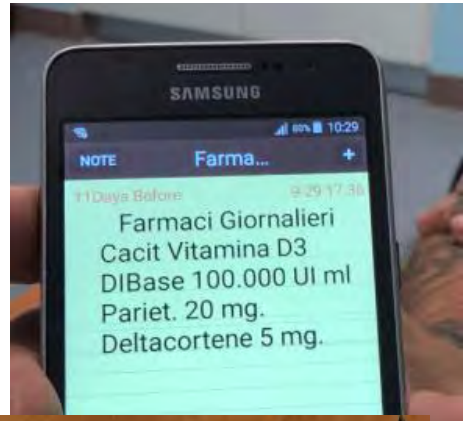
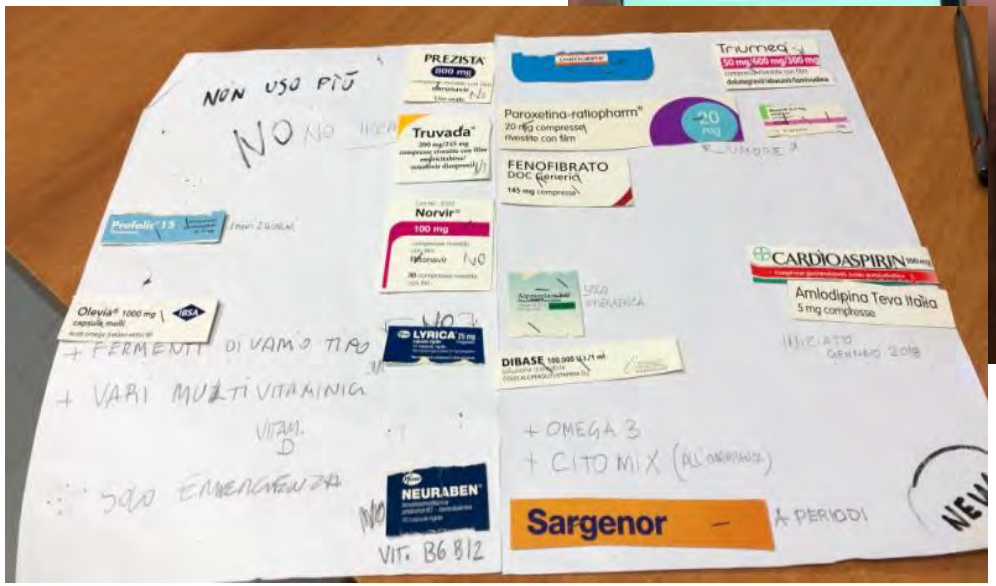
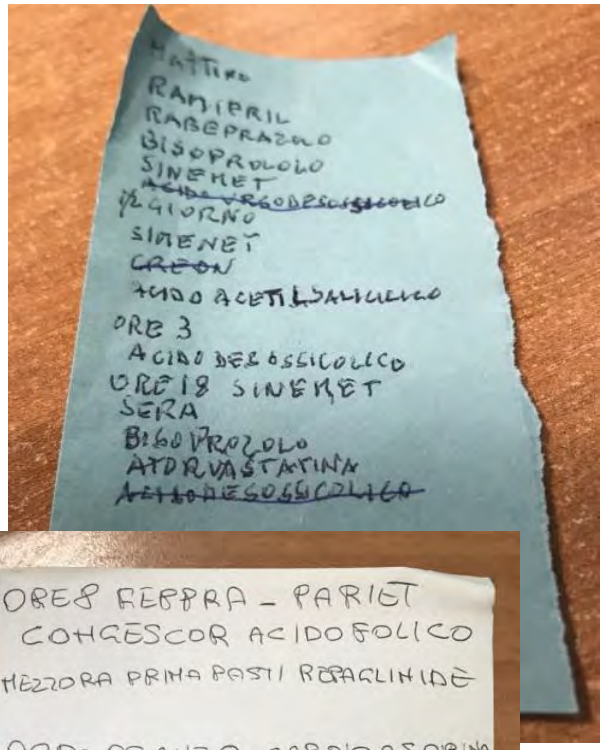
- Gervasoni et al, AIDS Rev 2019 -

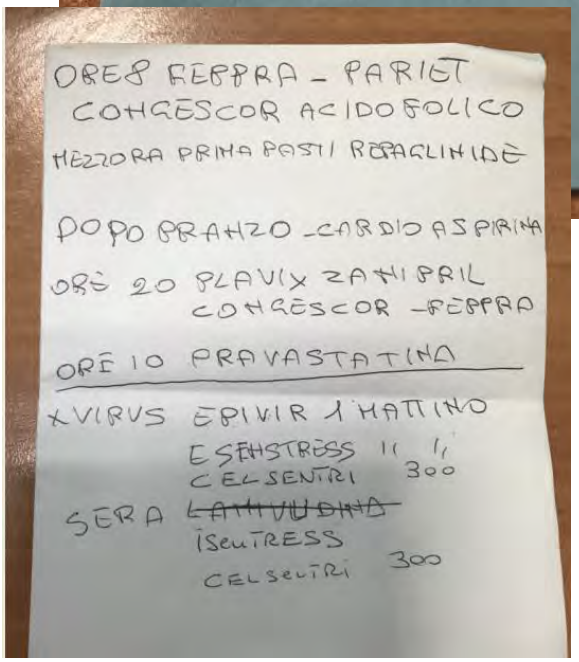
…The most difficult task is...











…to understand what the patient is taking…!!!

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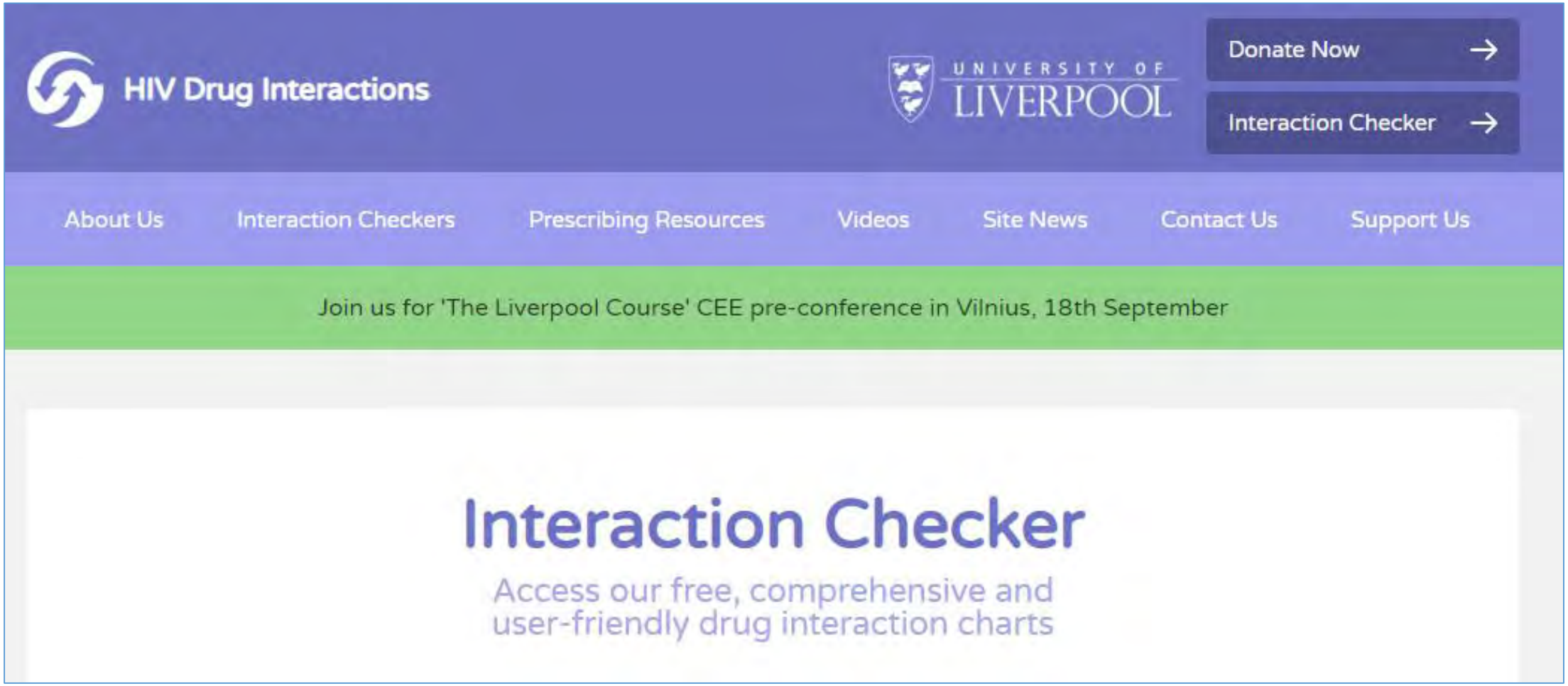
PIMs: potentially inappropriate medications

- Gervasoni et al, AIDS Rev 2019 -

The golden standard tool for checking DDIs involving antiretroviral drugs…



HIV Drug Interactions

Do Not Coadminister

Ritonavir (RTV)

Budesonide

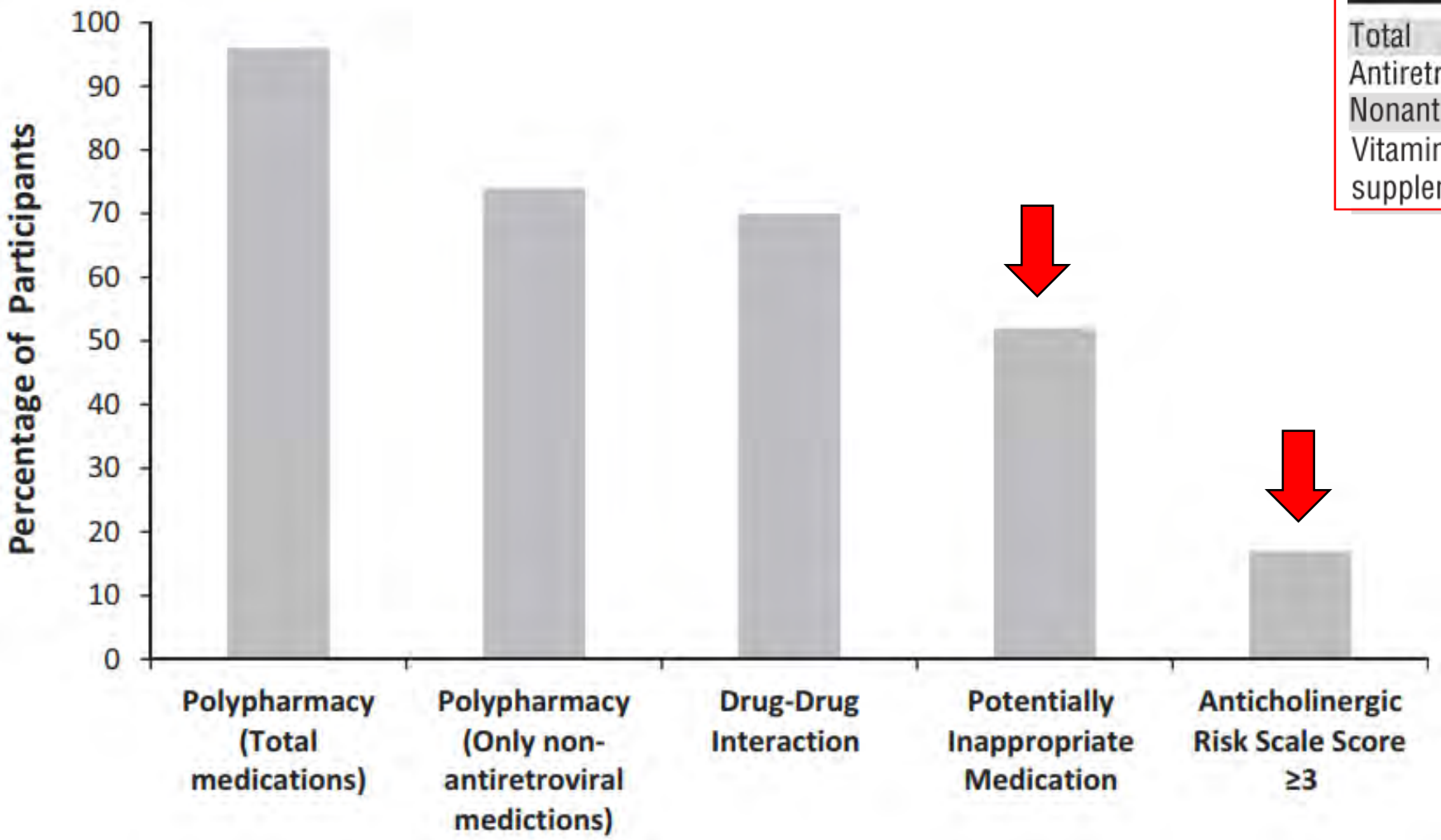
Ritonavir/cobicistat-induced Cushing syndrome in HIV patients treated with non-oral corticosteroids: a call for action?

Pt	Sex	Age	ARV	Corticosteroid (drug, route)	Indication of corticosteroid	DDI duration (months)	Clinical features	Cortisol ng/mL*	New ARV
1	M	38	TAF, FTC/ Elvitegravir/cobi	Betamethasone, topical	COPD	2	ICS, hair loss	5	TAF/FTC dolutegravir
2	M	52	TAF/FTC/ Darunavir/cobi	Budesonide, inhaled	COPD	36	ICS, osteoporosis, spine fractures	2	TAF/FTC Raltegravir
3	M	46	Lamivudine Atazanavir/rtv	Budesonide, inhaled	Plaque psoriasis	40	ICS	16	TAF/FTC rilpivirine
4	F	45	TAF/FTC Atazanavir/cobi	Triamcinolone intra-articular	Shoulder pain	Single dose	ICS, ankle edema, depression	11	TAF/FTC bictegravir

- Cattaneo et al, Am J Med Sci 2020 -

…..4 cases recorded in our hospital in the last year…

..but there is more we can do….



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

The term **anticholinergic (Ach) burden** refers to the cumulative effect of using multiple medications with ACh properties concomitantly.

- Greene, J Am Geriatr Soc 2014 -

Do not focus only on antiretroviral drugs…

Prevention of Inappropriate Prescribing in Hospitalized Older Patients Using a Computerized Prescription Support System (INTERcheck®)

Beers's criteria
STOPP/START criteria
ACB score

https://clinicalweb.marionegri.it/intercheckweb/

https://reference.medscape.com/drug-interactionchecker

A pharmacist-led program to evaluate and reduce polypharmacy and potentially inappropriate prescribing in HIV patients

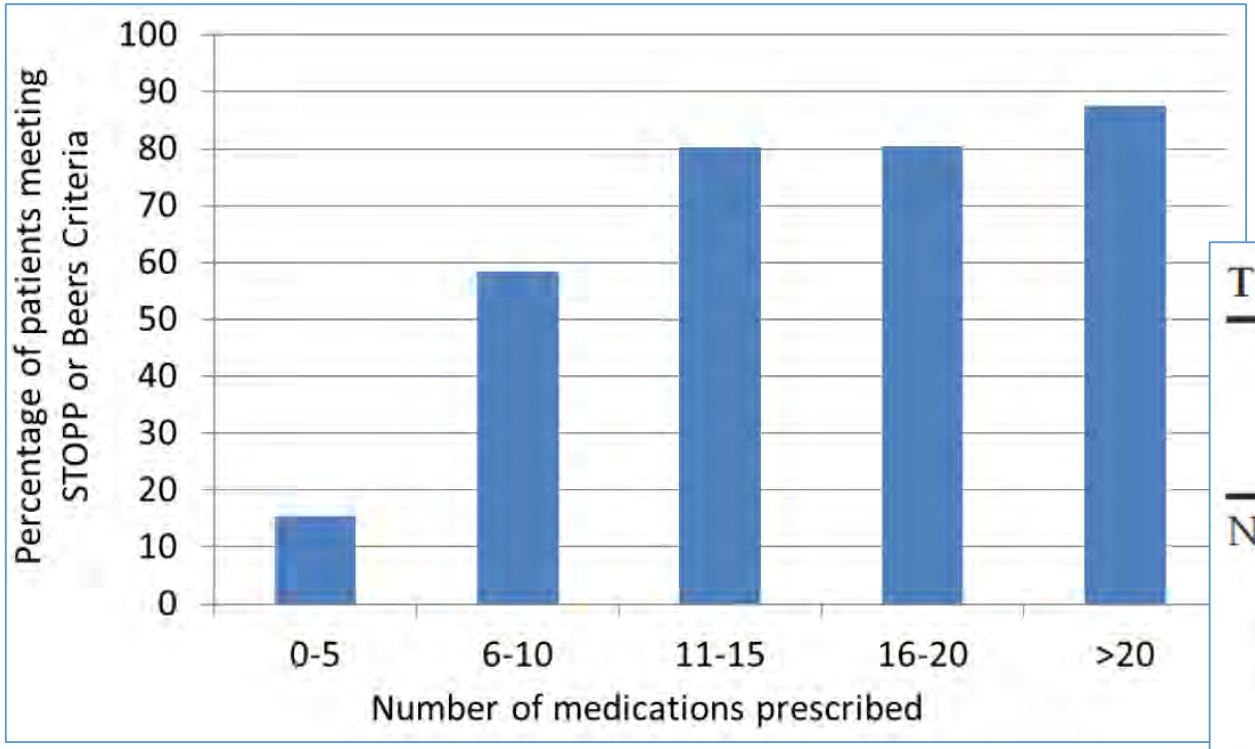


Table 4. Interventions Made after Medication Review

	Patients meeting criteria
No. of medications per patient discontinued, N (%)	
0	77 (31.1)
1	48 (19.4)
2	33 (13.3)
3	27 (10.9)
4	22 (8.9)
5	17 (6.9)
6–10	21 (8.5)
≥ 11	3 (1.2)
No. of medications per patient removed, mean (SD)	2.2 (2.5)

- McNicholl, Pharmacother 2017 -

TABLE: DRUGS WITH MODERATE TO STRONG ANTICHOLINERGIC EFFECTS

Tricyclic Antidepressants
Amitriptyline (Elavil)
Amoxapine (Asendin)
Clomipramine (Anafranil)
Desipramine (Norpramin)
Doxepin (Sinequan)
Imipramine (Tofranil)
Nortriptyline (Aventyl)
Protriptyline (Vivactil)
Trimipramine (Surmontil)

Antiemetics
Cyclizine (Marezine)
Dimenhydrinate (Dramamine)
Meclizine (Antivert)
Prochlorperazine (Compazine)
Scopolamine (Transderm Scop)

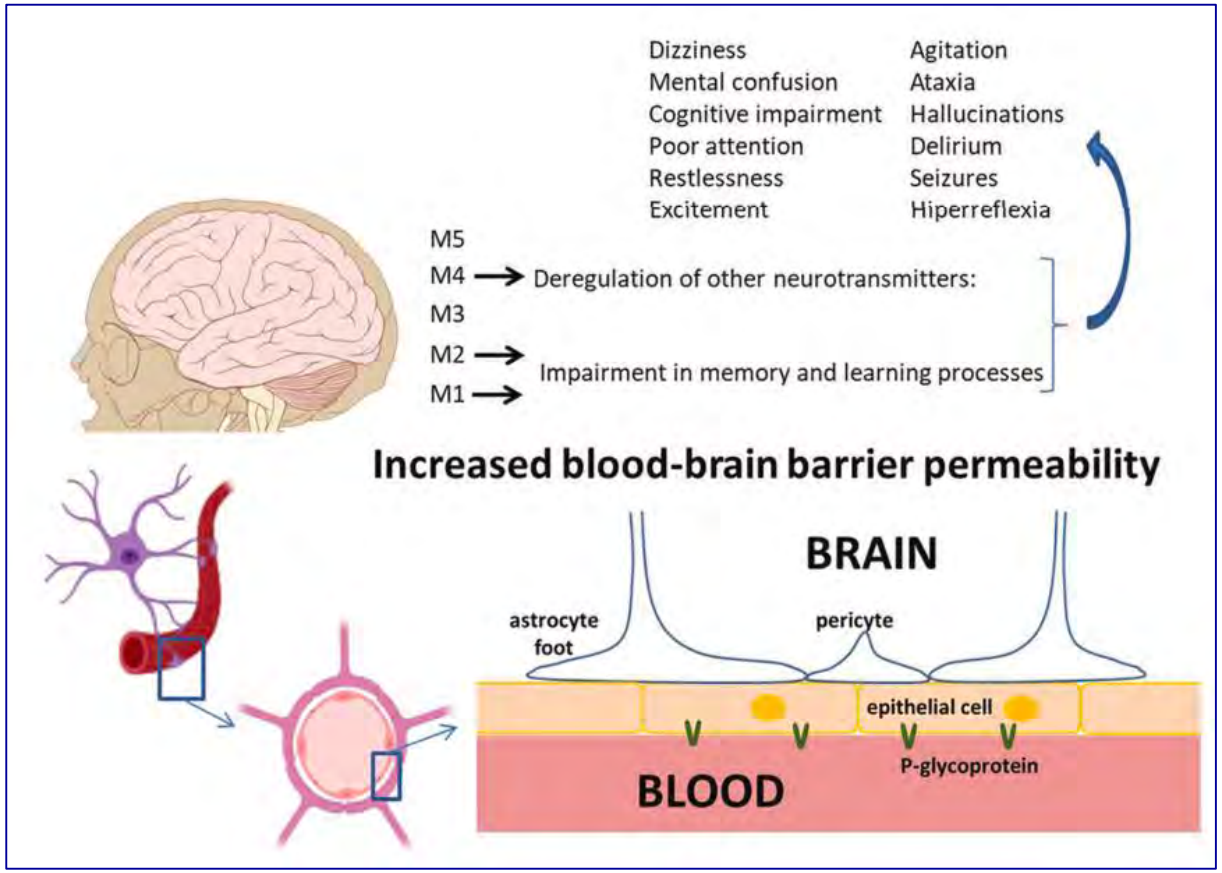
Antihistamines
Azatadine (Optimine)
Azelastine (Astelin)
Brompheniramine (Dimetapp)
Chlorpheniramine (Chlor-Trimeton)
Clemastine (Tavist)
Dexchlorpheniramine (Polaramine)
Hydroxyzine (Atarax)
Triprolidine (Actidil)

Anti-Parkinson Drugs
Benztropine (Cogentin)
Biperiden (Akineton)
Procyclidine (Kemadrin)
Trihexyphenidyl (Artane)

Antipsychotics
Chlorpromazine (Thorazine)
Clozapine(Clozaril)
Olanzapine (Zyprexa)
Quetiapine (Seroquel)
Thioridazine (Mellaril)
Trifluoperazine (Stelazine)

Antispasmodics
Atropine (Donnatal)
Dicyclomine (Bentyl)
Clidinium (Quarzan)
Darifenacin (Enablex)
Fesoterodine (Toviaz)
Flavoxate (Urizpas)
Glycopyrrolate (Robinul)
Hyoscyamine (Anaspaz)
Methscopolamine (Pamine)
Oxybutynin (Ditropan)
Propantheline (Pro-Banthine)
Solifenacin (Vesicare)
Tolterodine (Detrol)
Trospium (Sanctura)

Miscellaneous
Cyclobenzaprine (Flexaril)
Disopyramide (Norpace)
Methocarbamol (Robaxin)
Orphenadrine (Norflex)



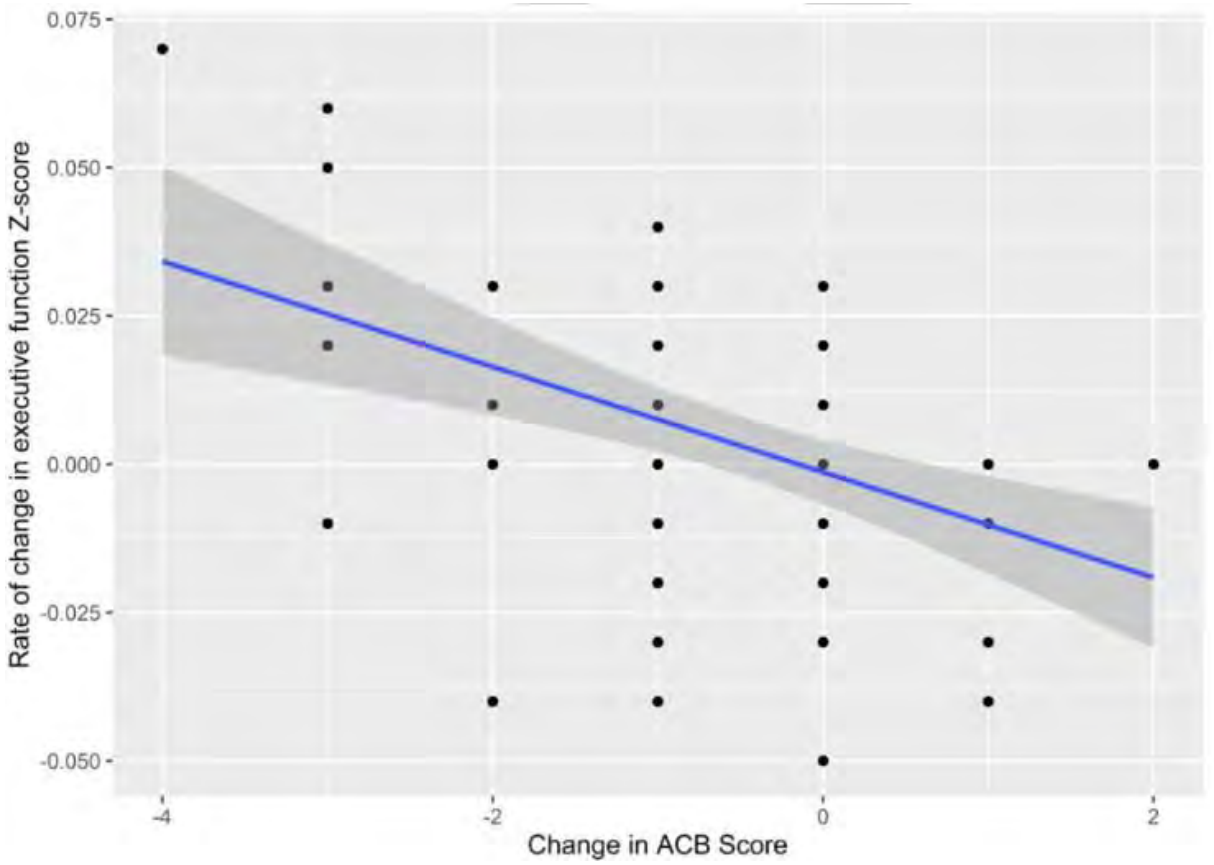
↑ sensitivity (agitation, confusion, decompensation of glaucoma, dry mouth, constipation, urinary retention...) Injurious falls, worst outcome

- Lavrador, Pharmacol Res, in press 2021-

Effects of anticholinergic medication use on brain integrity in persons living with HIV and persons without HIV

- ✓ Neuropsychological performance Z-scores (learning, retention, executive function, motor/psychomotor speed, language domains and global cognition), were analyzed in PLWH (n=209) and HIV- (n=95) grouped according to the ACB scale

Change in ACB score from the first study visit to the second study visit significantly correlated with the rate of change (per month of study visit interval) of the executive function Z-score.



- Cooley, AIDS, in press 2020 -

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- Check for the use of phytotherapeutic agents, supplements, complementary & alternative medicines (CAMs) and/or recreational drugs
- Prescription of the pharmacokinetic and pharmacogenetic tests offered by the hospital's Pharmacological Service (when deemed appropriate)
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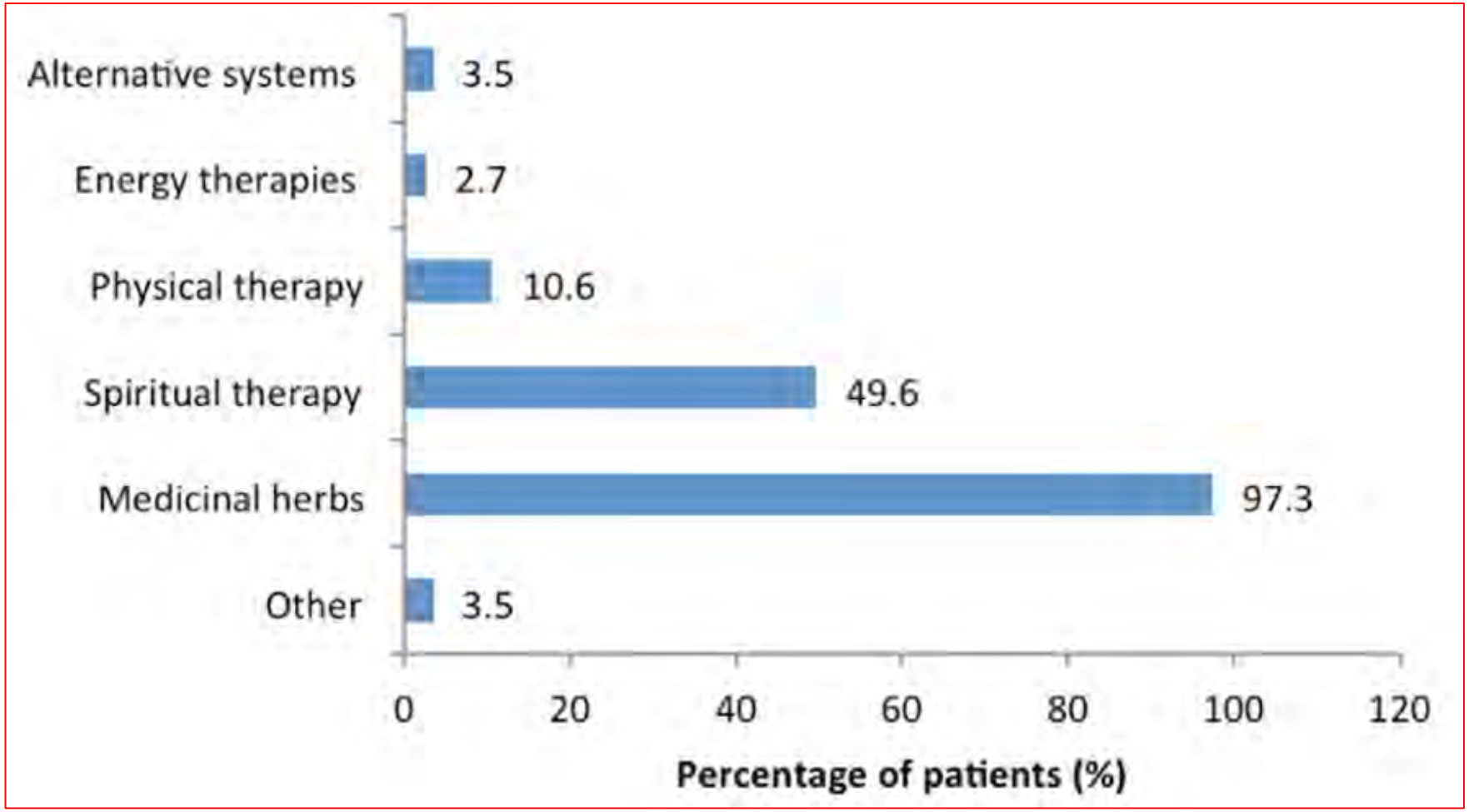
- Gervasoni et al, AIDS Rev 2019 -

CAM is defined as a group of diverse medical and health care systems, practices and products that are not generally considered part of conventional medicine



- Bahall BMC 2017 -

Table 1 Reported prevalence studies of complementary alternative medicines (CAMs) and use of antiretroviral drugs in HIV-positive

Study	Country	Sample size	CAM use (%)
Josephs *et al.* [4]	USA	914	16
Bica *et al.* [5]	USA	642	60
Hsiao *et al.* [6]	USA	2466	53
Furler *et al.* [7]	Canada	104	89
Wiwanitkit [8]	Thailand	160	95
De Visser *et al.* [9]	Australia	924	55
Colebunders *et al.* [10]	Europe	517	63*
Duggan J *et al.* [11]	USA	191	67
Barton *et al.* [12]	UK	190	38
Anderson *et al.* [13]	USA	184	40

Less than 10% of patients informed their healthcare providers of CAM usage

Bahall BMC 2017
Brooks Exp Opin Clin Pharmacol 2017
Ladenheim, HIV Med 2008

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

Patient	ARV	CAM	TDM 1	TDM 2	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	Lipidyum 6.5 g daily	*Not available*	*Not available*	*Not available*

Sinetrol contains mainly **naringin,** a flavanone-7-O-glycoside which inhibits the activity of carrier proteins 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

- Cattaneo et al, Obesity 2018 -

European Journal of Clinical Pharmacology (2019) 75:1177–1178
https://doi.org/10.1007/s00228-019-02677-2

LETTER TO THE EDITOR

Effects of guggulsterones-containing thermogenic complex on elvitegravir plasma concentrations: a case report

Dario Cattaneo[1,2] · Annalisa Ridolfo[3] · Sara Baldelli[2] · Cristina Gervasoni[1,3]

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

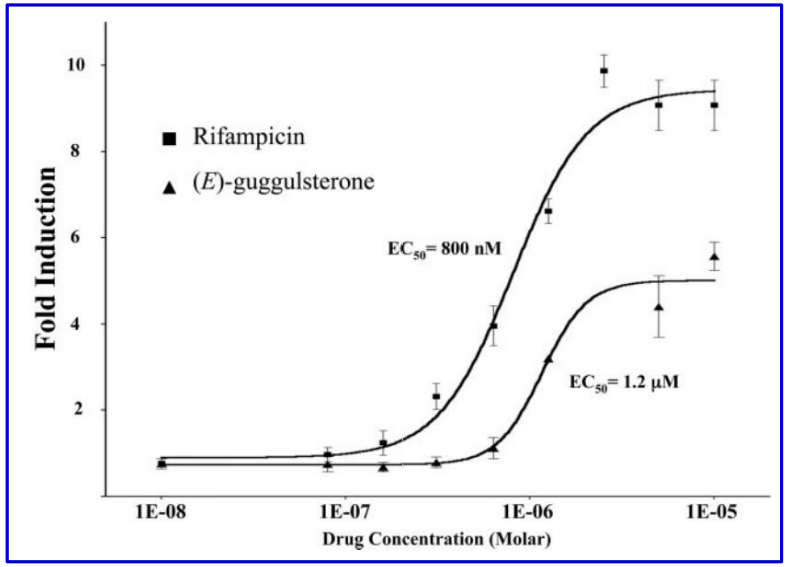
24/09/2018

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

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

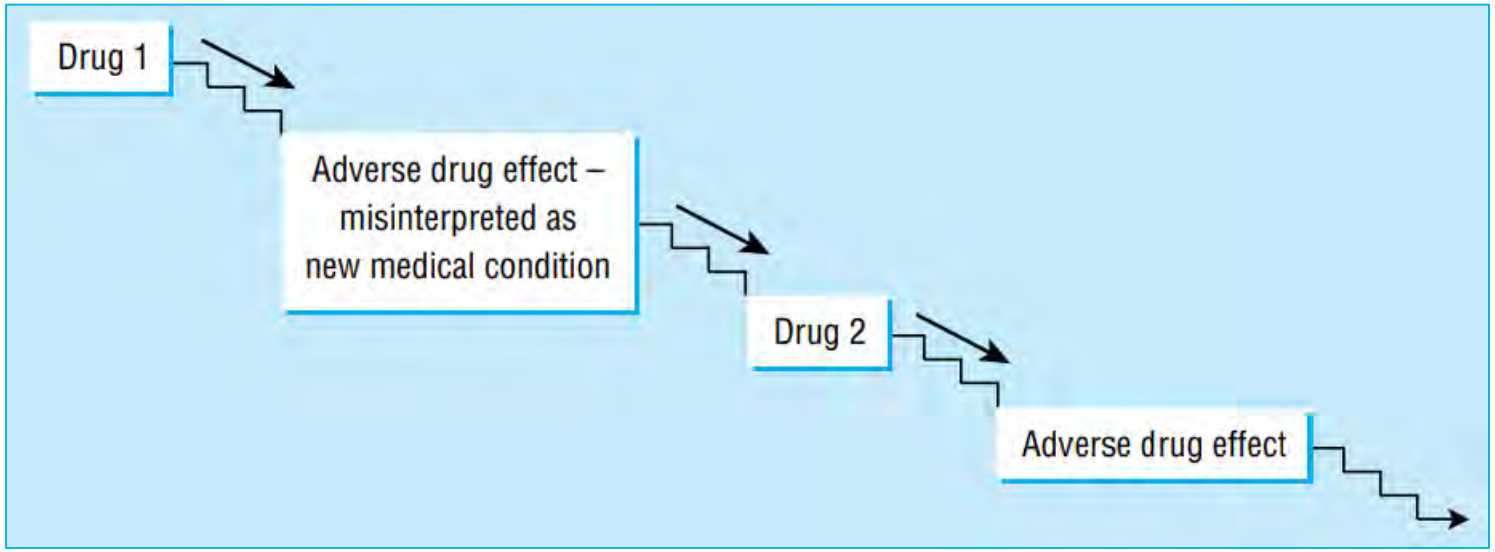
0022-3565/04/3102-528–535$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Copyright © 2004 by The American Society for Pharmacology and Experimental Therapeutics
JPET 310:528–535, 2004
Vol. 310, No. 2
64329/1158202
Printed in U.S.A.

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



Guggul (+) PXR (+) CYP3A (+) elvitegravir metabolism

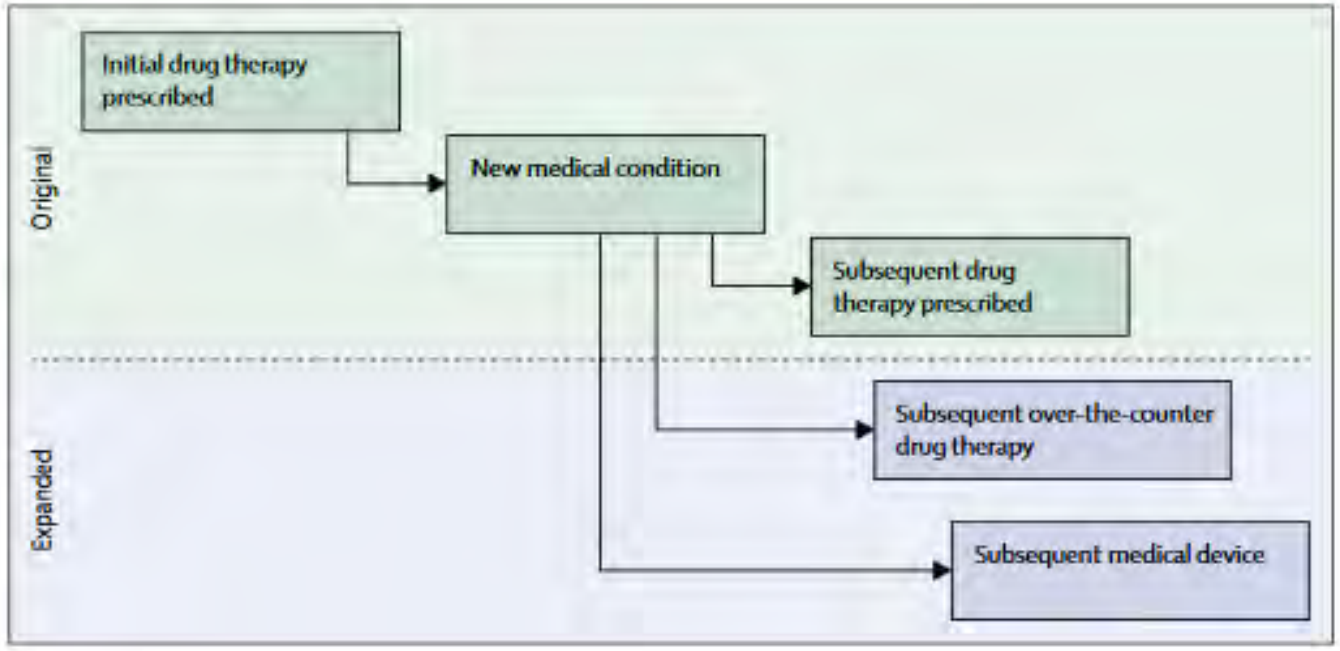
Pay attention to prescription cascades…



The "prescribing cascade" cascade begins when an adverse drug reaction is misinterpreted as a new medical condition

Another drug is then prescribed, and the patient is placed at risk of developing additional adverse effects relating to this potentially unnecessary treatment

To prevent the prescribing cascade, doctors should always consider any new signs and symptoms as a possible consequence of current drug treatment

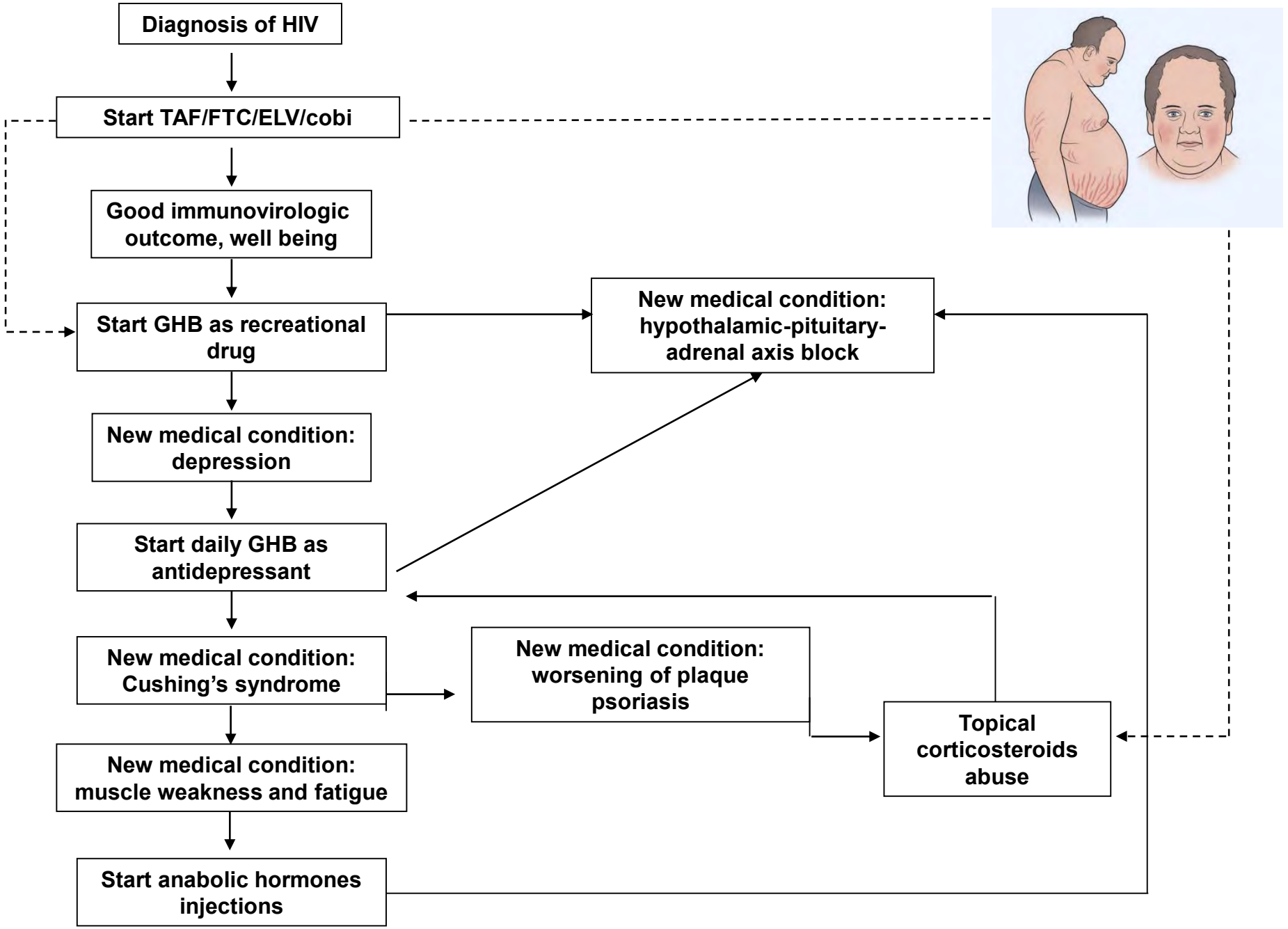


Prescribing cascades may involve:

- Conventional medicines
- Over-the-counter products
- And…

The prescribing cascade 3.0: a case for recreational drugs in HIV

- Prominent cheeks
- Dorsocervical fat pads
- Ankle oedema
- Skin fragility
- Hair loss
- Decreased libido
- Fatigue
- Depression
- High blood pressure



- Cattaneo et al, AIDS 2020 -

Hair testing to assess both known and unknown use of drugs amongst ecstasy users in the electronic dance music scene

Joseph J. Palamar[a,b,*], Alberto Salomone[c], Enrico Gerace[c], Daniele Di Corcia[c], Marco Vincenti[c,d], Charles M. Cleland[b,e]

- ✓ 74.4% tested positive for MDMA, 33.3% tested positive for an NPS, and 27.8% tested positive specifically for one or more synthetic cathinones (e.g., butylone, ethylone, pentylone, methylone)
- ✓ 51.1% of participants tested positive for a drug not self-reported, with most testing positive for synthetic cathinones (72.0%), methamphetamine (69.0%), other NPS stimulants (66.7%), or new dissociatives (e.g., methoxetamine, diphenidine; 60.0%)
- ✓ Attending parties every other week or more often, reporting higher-frequency ecstasy pill use and having found out one's ecstasy was adulterated, were risk factors for testing positive for NPS

International Journal of Drug Policy 48 (2017) 91–98

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- Gervasoni et al, AIDS Rev 2019 -

TDM has still a role in HIV!!!

16:00

Plasma measurement of antivirals in the clinical setting: which role in 2021?

David Burger

Drug	Therapeutic ranges
Tenofovir from TDF	40-180 ng/mL
Tenofovir from TAF	5-30 ng/mL
Efavirenz	1000-4000 ng/mL
Etravirine	>300 ng/mL
Nevirapine	3000-6000 ng/mL
Rilpivirine	>20 ng/mL
Atazanavir	150-800 ng/mL
Darunavir	>550 ng/mL
Lopinavir	1000-7000 ng/mL
Dolutegravir	>100 ng/mL
Elvitegravir	>45 ng/mL
Raltegravir	>40 ng/mL
Maraviroc	>50 ng/mL
Doravirine	Available soon
Bictegravir	Available soon

Just a couple of examples from our hospital…

Dosing of Dolutegravir in TB/HIV Coinfected Patients on Rifampicin: Twice Is (Always) Better Than Once

Dario Cattaneo, PharmD, PhD[a,b]
Agostino Riva, MD[c]
Paola Columpsi, MD[d]
Giuseppe Lapadula, MD[d]
Carlo Filice, MD[e]
Cristina Gervasoni, MD[a,c]

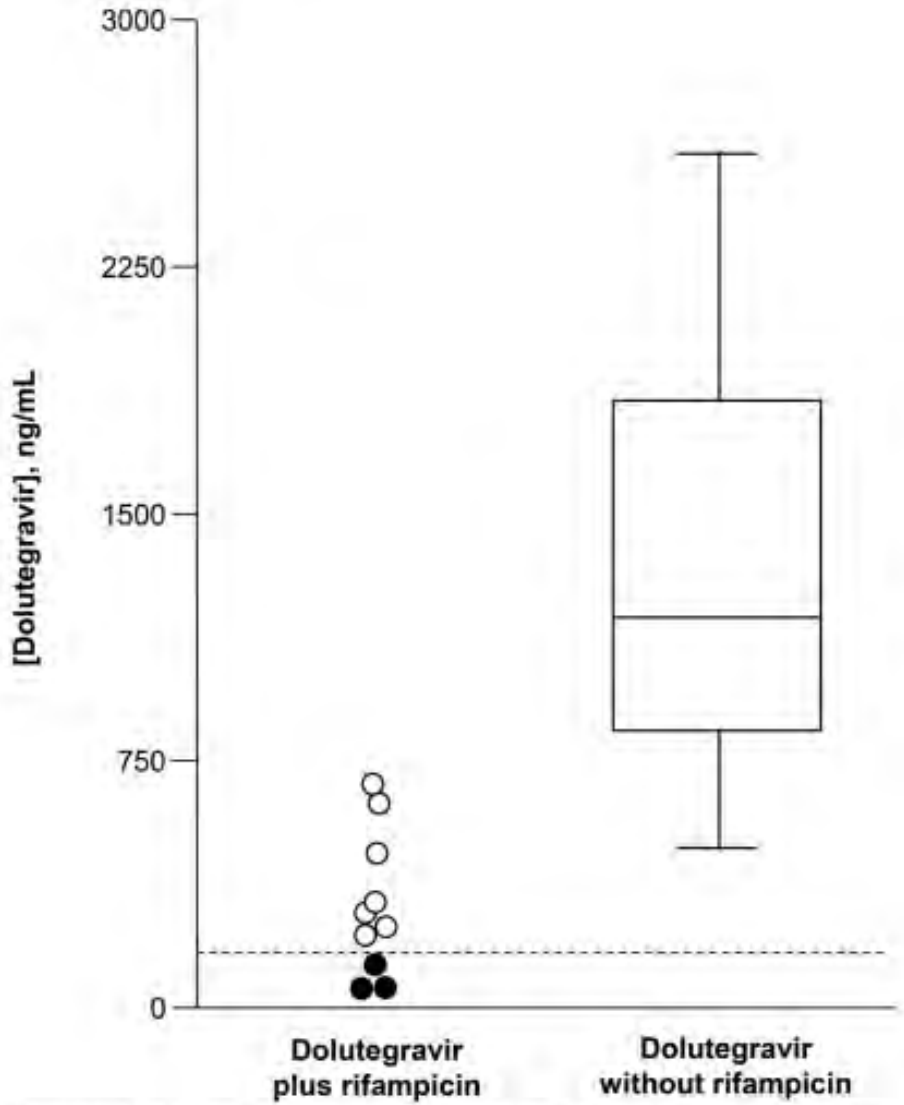


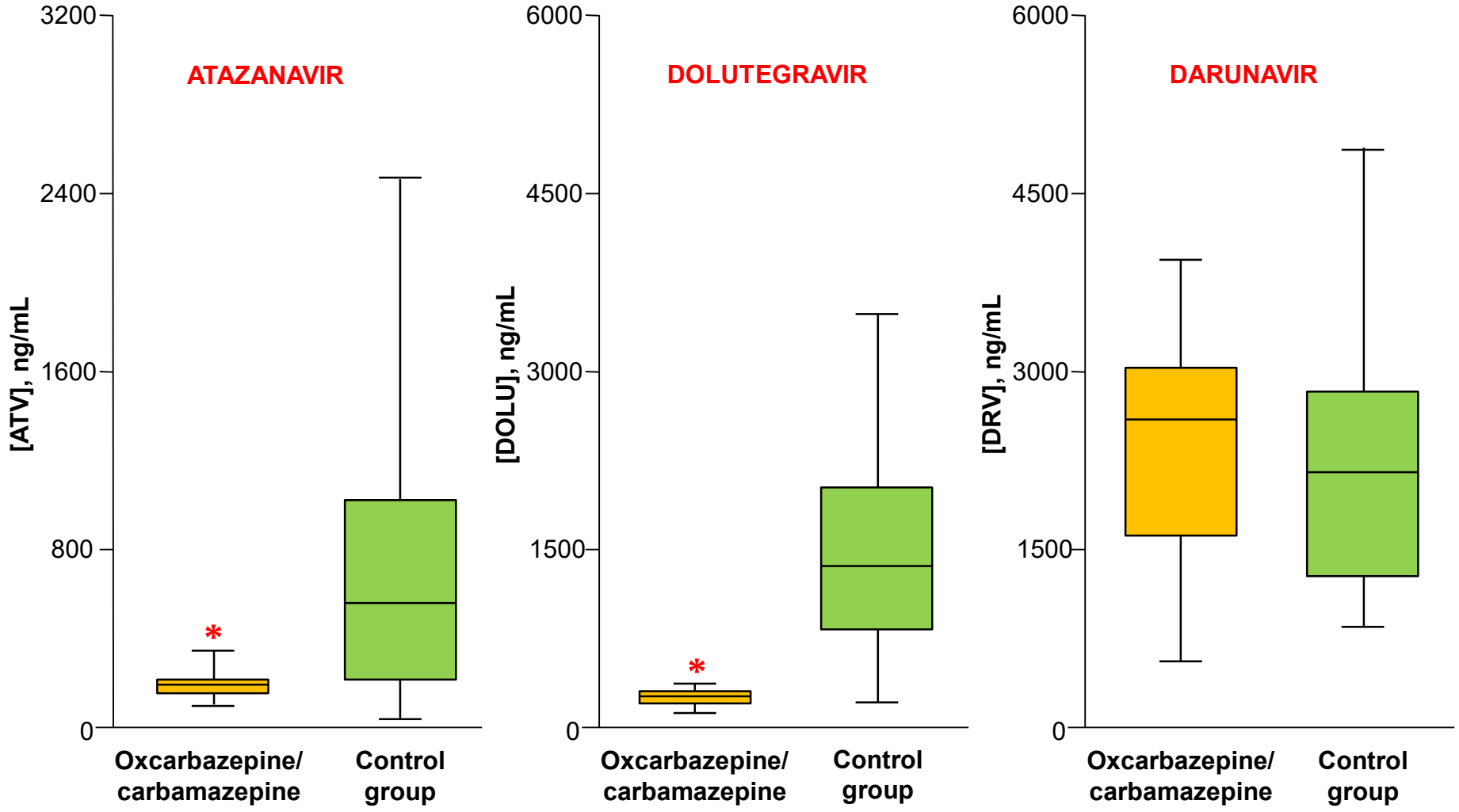
FIGURE 1. Box-plot of dolutegravir trough concentrations measured in HIV-infected patients given the drug with (n = 10) or without rifampicin (n = 200). Full and empty circles represent, respectively, patients given dolutegravir at 50 mg once daily and 50 mg twice daily. Dashed line represents the minimum effective drug concentration set at 100 ng/mL.

Effects of ursodeoxycholic acid on rilpivirine plasma trough concentrations: a case report

- ✓ A 52-year-old HIV-infected man on stable antiretroviral therapy with RPV plus TAF coformulation (last trough concentrations 89 and 8,5 ng/mL, respectively) since 15 months with optimal virologic control (HIV RNA always < 37 copies/mL)
- ✓ UDCA,300 mg bid was prescribed by general practitioner for the management of symptomatic intrahaepatic stones
- ✓ RPV and TDF trough measured 1 months after starting UDCA: <20 ng/mL and 9,7 ng/mL. Repeated after one week: <20 and 6,7 ng/mL
- ✓ To allow the patient to continue UDCA treatment, RPV was replaced with darunavir/ cobicistat (the patient had a history of poor tolerability to HIV integrase inhibitors). Darunavir trough concentrations measured at the two following visits, while the patient was still taking UDCA, were 2132 and 1851 ng/mL

- Cattaneo et al, Eur J Clin Pharmacol 2020 -

DDIs Between ARVs and Carbamazepine/Oxcarbazepine: A Real-Life Investigation



- Cattaneo et al, Ther Drug Monit 2020 -

..or in selected clinical conditions…

Eur J Clin Pharmacol (2017) 73:789–790
DOI 10.1007/s00228-017-2231-5

LETTER TO THE EDITOR

The impact of gastrectomy on the pharmacokinetics of atazanavir and tenofovir

Cristina Gervasoni[1] · Dario Cattaneo[2] · Chiara Resnati[1] · Diletta Pezzani Agostino Riva[1]

J Antimicrob Chemother 2020; **75**: 1354–1356
doi:10.1093/jac/dkz572
Advance Access publication 24 January 2020

Pharmacokinetic profile of dolutegravir after transjugular intrahepatic portosystemic shunt placement

Massimiliano Fabbiani[1,2]*, Dario Cattaneo[3], Andrea Lombardi[1], Marta Colaneri[1], Margherita Sambo[1], Stefano Novati[1], Marta Fusi[3] and Raffaele Bruno[2]

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POLO UNIVERSITARIO
Sistema Socio Sanitario
Regione Lombardia
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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

Antibiotics

- ❑ Teicoplanin
- ❑ Levofloxacin
- ❑ Rifampicin
- ❑ Linezolid
- ❑ Cyprofloxacin
- ❑ Vancomycin
- ❑ Amikacin
- ❑ Gentamycin
- ❑ Trimethoprim
- ❑ Meropenem
- ❑ Piperac/tazob
- ❑ Ceftaz/avib
- ❑ Cefepime
- ❑ Ampicilline
- ❑ Fosfomycin
- ❑ Dalbavancin*

Antifungals

- ❑ Voriconazole
- ❑ Posaconazole
- ❑ Isavuconazole
- ❑ Itraconazole
- ❑ Caspofungin

Biologics

- ❑ Infliximab
- ❑ Anti-infliximab ab
- ❑ Adalimumab
- ❑ Anti-adalimumab ab

Psychotropics

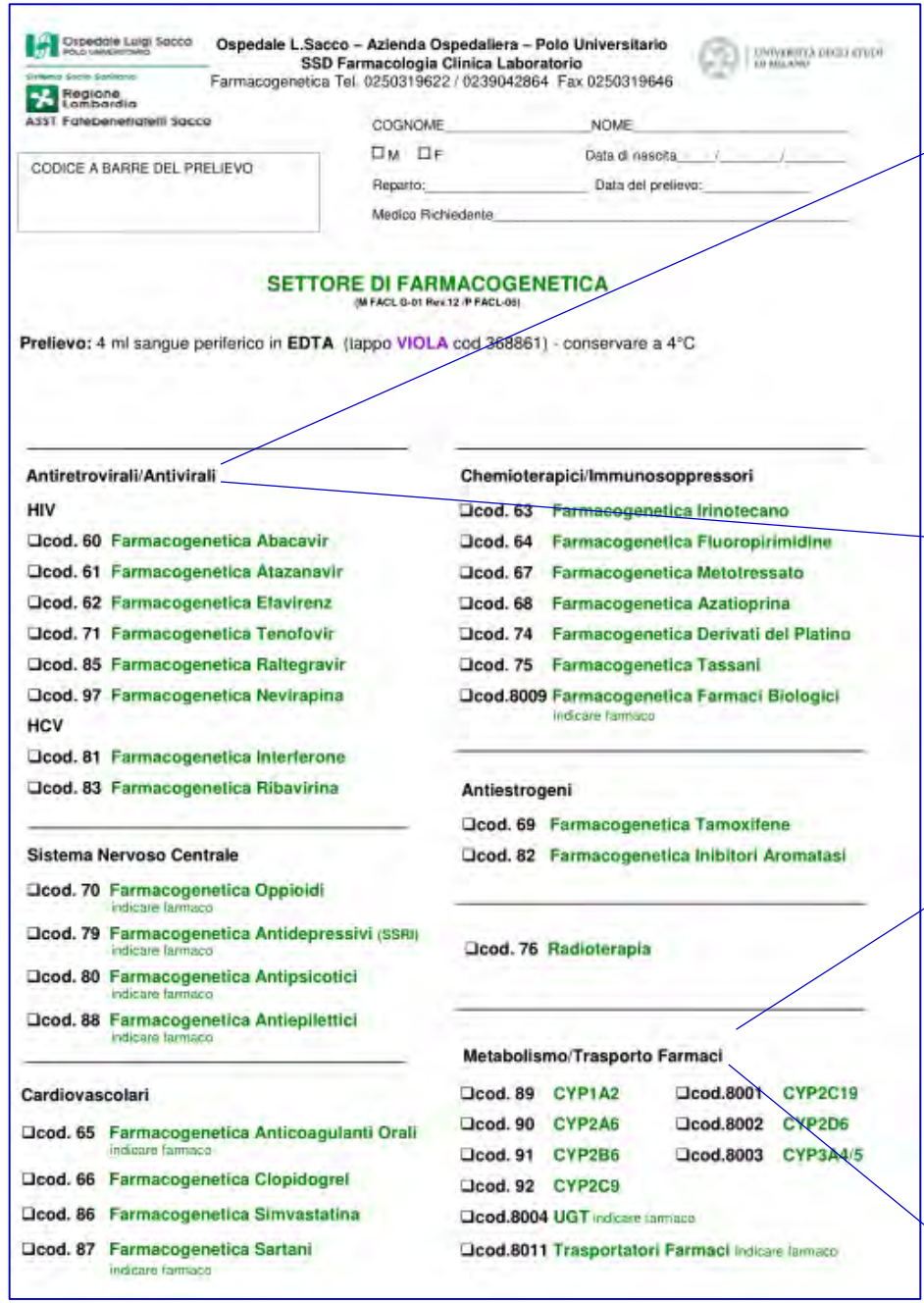
- ❑ Citalopram
- ❑ Escitalopram
- ❑ Quetiapine
- ❑ Paroxetine
- ❑ Aripiprazole
- ❑ Olanzapine
- ❑ Risperidone
- ❑ Haloperidole
- ❑ Clozapine
- ❑ Paliperidone
- ❑ Fluoxetine
- ❑ Fluvoxamine
- ❑ Duloxetine
- ❑ Flufenazine
- ❑ Clomipramine
- ❑ Venlafaxine
- ❑ Ziprasidone
- ❑ Sertraline

Distribution of psychotropic drug trough concentrations in HIV-positive patients versus HIV-negative controls

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 -



Ospedale Luigi Sacco
Ospedale L.Sacco – Azienda Ospedaliera – Polo Universitario
SSD Farmacologia Clinica Laboratorio
Farmacogenetica Tel. 0250319622 / 0239042864 Fax 0250319646
Regione Lombardia
ASST Fatebenefratelli Sacco

COGNOME_____NOME_____
☐M ☐F Data di nascita__/__/____
Reparto:_____ Data del prelievo:_____
Medico Richiedente_____

CODICE A BARRE DEL PRELIEVO

SETTORE DI FARMACOGENETICA
(M FACL 0-01 Rev.12 /P FACL-05)

Prelievo: 4 ml sangue periferico in **EDTA** (tappo VIOLA cod 368861) - conservare a 4°C

Antiretrovirali/Antivirali

HIV
- ❑cod. 60 Farmacogenetica Abacavir
- ❑cod. 61 Farmacogenetica Atazanavir
- ❑cod. 62 Farmacogenetica Efavirenz
- ❑cod. 71 Farmacogenetica Tenofovir
- ❑cod. 85 Farmacogenetica Raltegravir
- ❑cod. 97 Farmacogenetica Nevirapina

HCV
- ❑cod. 81 Farmacogenetica Interferone
- ❑cod. 83 Farmacogenetica Ribavirina

Sistema Nervoso Centrale
- ❑cod. 70 Farmacogenetica Oppioidi indicare farmaco
- ❑cod. 79 Farmacogenetica Antidepressivi (SSRI) indicare farmaco
- ❑cod. 80 Farmacogenetica Antipsicotici indicare farmaco
- ❑cod. 88 Farmacogenetica Antiepilettici indicare farmaco

Cardiovascolari
- ❑cod. 65 Farmacogenetica Anticoagulanti Orali indicare farmaco
- ❑cod. 66 Farmacogenetica Clopidogrel
- ❑cod. 86 Farmacogenetica Simvastatina
- ❑cod. 87 Farmacogenetica Sartani indicare farmaco

Chemioterapici/Immunosoppressori
- ❑cod. 63 Farmacogenetica Irinotecano
- ❑cod. 64 Farmacogenetica Fluoropirimidine
- ❑cod. 67 Farmacogenetica Metotressato
- ❑cod. 68 Farmacogenetica Azatioprina
- ❑cod. 74 Farmacogenetica Derivati del Platino
- ❑cod. 75 Farmacogenetica Tassani
- ❑cod.8009 Farmacogenetica Farmaci Biologici indicare farmaco

Antiestrogeni
- ❑cod. 69 Farmacogenetica Tamoxifene
- ❑cod. 82 Farmacogenetica Inibitori Aromatasi

- ❑cod. 76 Radioterapia

Metabolismo/Trasporto Farmaci
- ❑cod. 89 CYP1A2
- ❑cod. 90 CYP2A6
- ❑cod. 91 CYP2B6
- ❑cod. 92 CYP2C9
- ❑cod.8001 CYP2C19
- ❑cod.8002 CYP2D6
- ❑cod.8003 CYP3A4/5
- ❑cod.8004 UGT indicare farmaco
- ❑cod.8011 Trasportatori Farmaci Indicare farmaco

❑cod. 60 Farmacogenetica Abacavir
❑cod. 61 Farmacogenetica Atazanavir
❑cod. 62 Farmacogenetica Efavirenz
❑cod. 71 Farmacogenetica Tenofovir
❑cod. 85 Farmacogenetica Raltegravir
❑cod. 97 Farmacogenetica Nevirapina

Metabolismo/Trasporto Farmaci

❑cod. 89 CYP1A2
❑cod. 90 CYP2A6
❑cod. 91 CYP2B6
❑cod. 92 CYP2C9
❑cod.8001 CYP2C19
❑cod.8002 CYP2D6
❑cod.8003 CYP3A4/5
❑cod.8004 UGT indicare farmaco
❑cod.8011 Trasportatori Farmaci Indicare farmaco

	Patient 1	Patient 2
Anamnestic data	Male, 57yrs,	Male, 53yrs,
ART	DRV/cobi 800/150 mg TAF/FTC 10/200 mg	DRV/r 600/100 mg bid TAF/FTC 10/200 mg
Other drugs	diazepam, acyclovir, rosuvastatin, colecalciferol, Carbamazepine	rosuvastatin
CD4, VL	828 cell/mL, <37 cp/ml	790 cell/mL, <37 cp/ml
$[DRV]_{trough}$ pre-steroid	2588 ± 742 ng/mL	2339 ± 1056 ng/mL
Steroid, dose and duration	Prednisone 25 mg bid (6 weeks)	Metilprednisolone 16mg (10 days)
Reason for steroid use	Trigeminal neuralgia	Lumbar disc erniation
$[DRV]_{trough}$ post-steroid	220 ng/mL	3127 ng/mL

- Cattaneo, Eur J Clin Pharmacol 2019 -

Genotypes of the two HIV-infected patients on maintenance darunavir therapy treated concomitantly with glucocorticoids

Genes	Genetic variant considered	Reference genotype[a]	Genotype of Patient 1	Genotype of Patient 2
CAR	rs2307424	CC	CT	CT
CYP3A4	rs35599367 CYP3A4*22	CC	CC	CC
CYP3A5	rs776746 CYP3A5*3	AA	GG	GG
POR	rs1057868 POR*28	CC	CC	CT
PPARA	rs4253728	GG	AA	GG
PXR	rs2472677	CC	CT	TT

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

[a] Retrieved from Ensembl genome database (www.ensembl.org)

- Cattaneo, Eur J Clin Pharmacol 2019 -

Activities of the GAP outpatient clinic

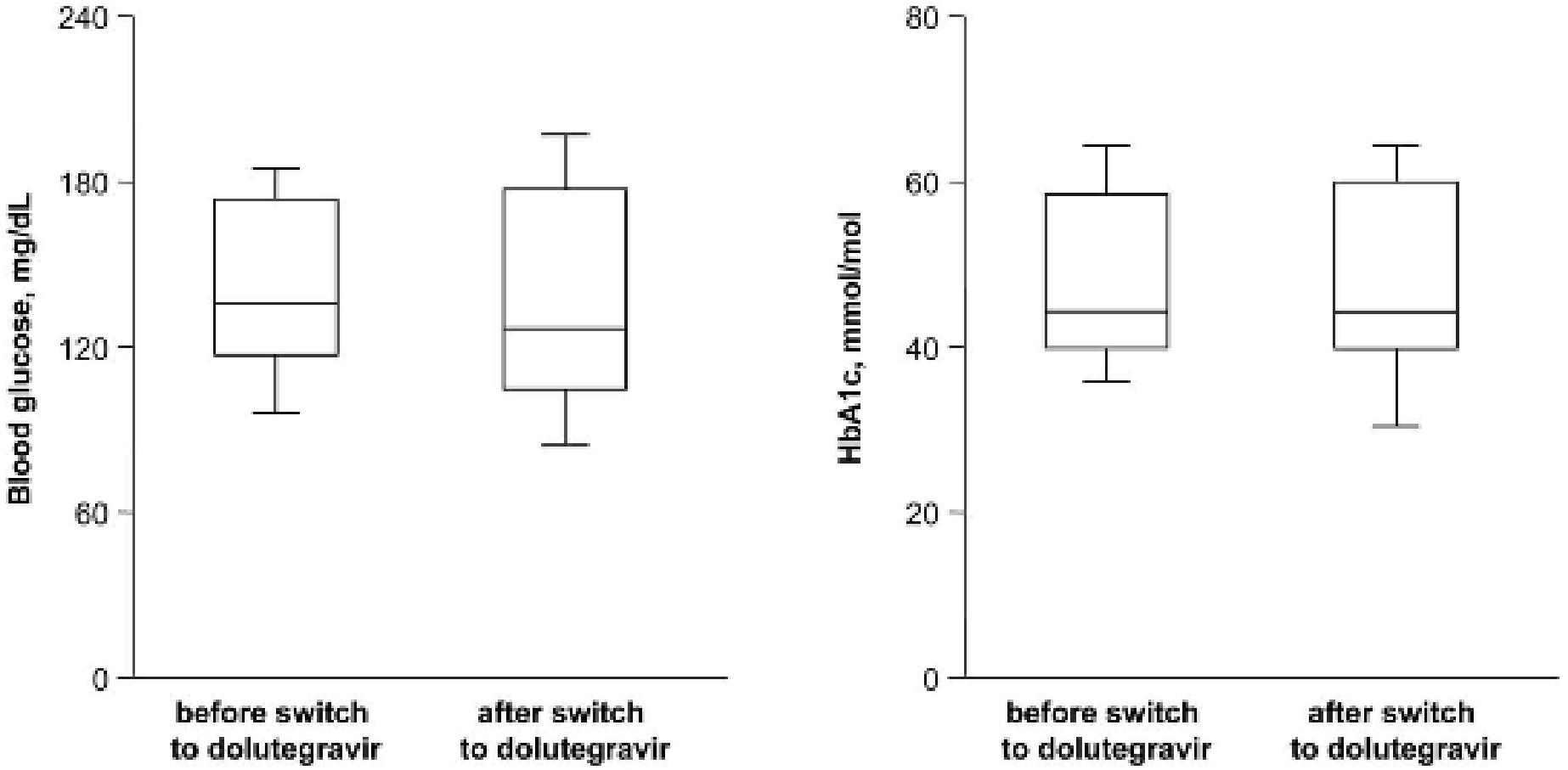
- Collection of detailed anamnestic, clinical, therapeutic (ARVs and comedications) and ad hoc laboratory data
- Verification of known/potential DDIs and PIMs on the basis of drug pharmacology and scientific evidence
- Check for the use of phytotherapeutic agents, supplements, complementary & alternative medicines and/or recreational drugs
- Prescription of the pharmacokinetic and pharmacogenetic tests offered by the hospital's Pharmacological Service (when deemed appropriate)
- Assessment of the clinical relevance of the DDIs by carefully evaluating the current and previous clinical conditions of each patient, and balancing the risks/benefits ratios
- Preparation of a written report for the general practitioner, attending physician and other specialists

- Gervasoni et al, AIDS Rev 2019 -

J Acquir Immune Defic Syndr. 2017 May 1;75(1):e24-e26. doi: 10.1097/QAI.0000000000001292.

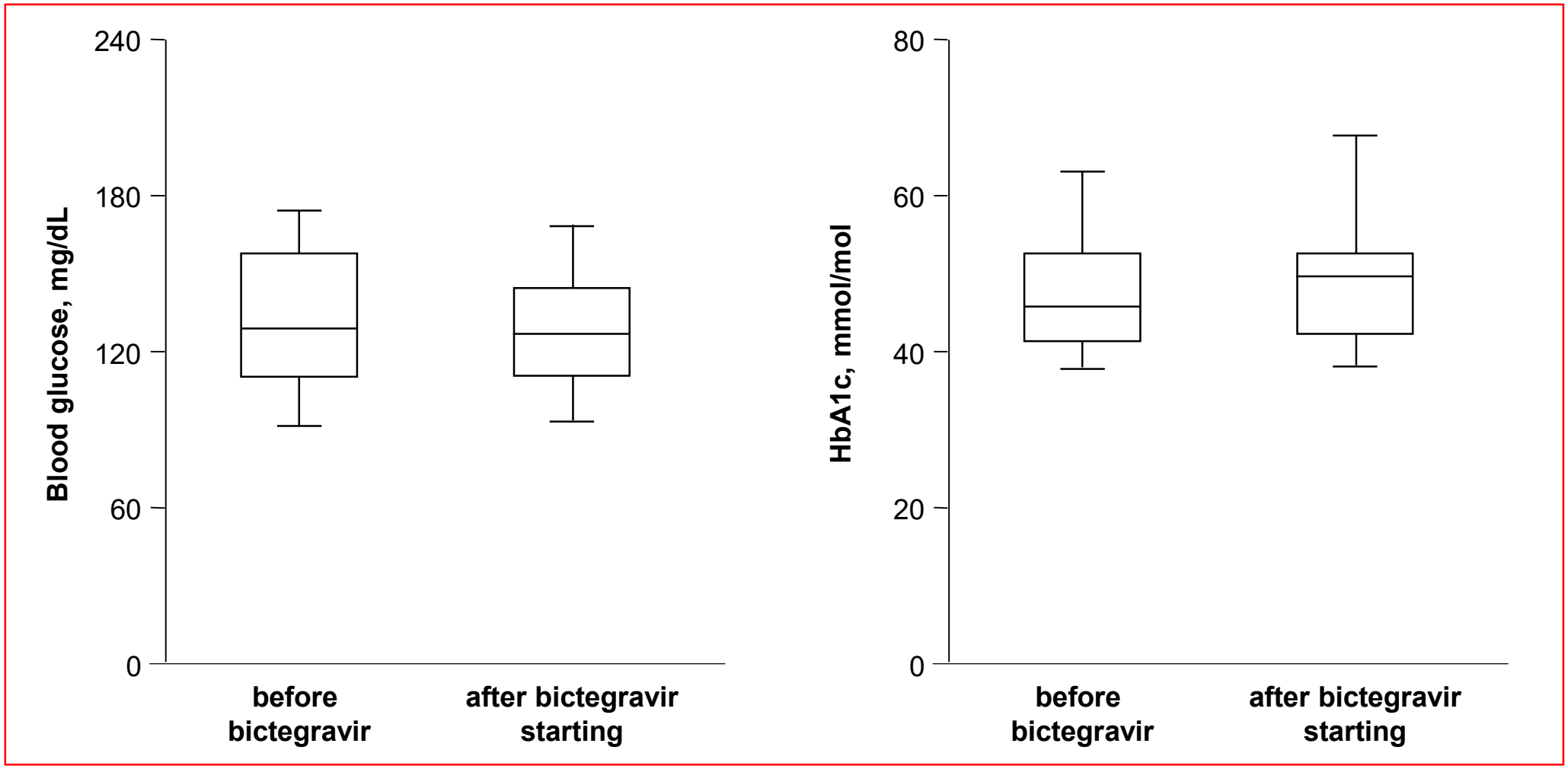
How Relevant is the Interaction Between Dolutegravir and Metformin in Real Life?

Gervasoni C[1], Minisci D, Clementi E, Rizzardini G, Cattaneo D.



…the same goes for bictegravir…

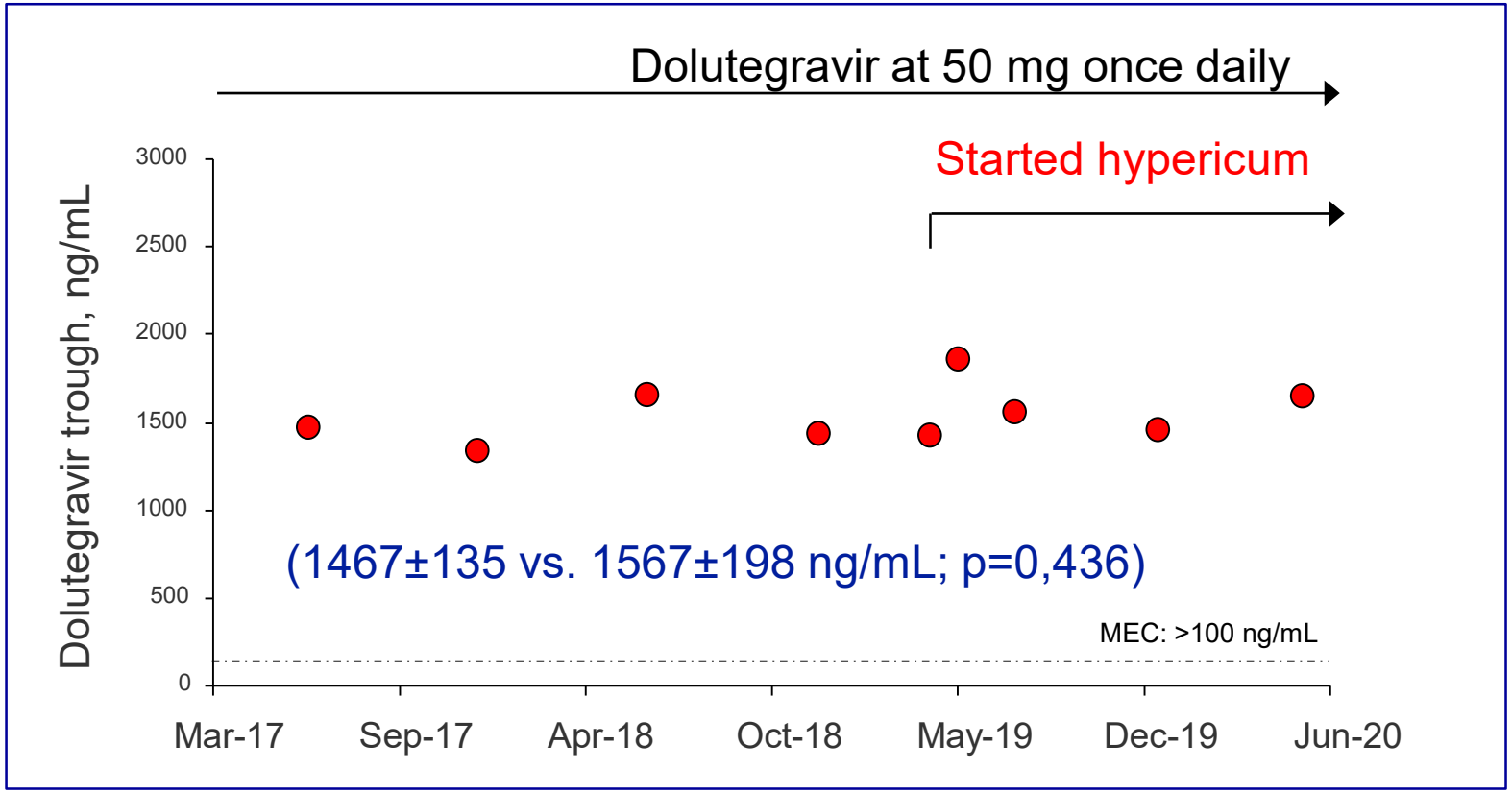
- ✓ 20 HIV infected diabetic patients treated with metformin up to 3 grams daily



- Cattaneo, submitted 2021 -

Should the dose of dolutegravir be changed during concomitant *Hypericum perforatum* treatment?

St. John's wort	Dolutegravir ↓ (Not studied, decrease expected due to induction of UGT1A1 and CYP3A enzymes, a similar reduction in exposure as observed with carbamazepine is	The recommended adult dose of dolutegravir is 50 mg twice daily when co-administered with St. John's wort. In paediatric patients the weight-based once daily dose should be administered twice daily. Alternative combinations that do not include St. John's wort should be used where possible in INI-resistant patients.



- Cattaneo, EJCP 2020 -

Activities of the GAP outpatient clinic

- Collection of detailed anamnestic, clinical, therapeutic (ARVs and comedications) and ad hoc laboratory data
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- Preparation of a written report for the general practitioner, attending physician and other specialists

- Gervasoni et al, AIDS Rev 2019 -

…What about the GAP outpatient clinics at the time of COVID-19?

Drugs & Aging
https://doi.org/10.1007/s40266-020-00812-8

ORIGINAL RESEARCH ARTICLE

Drug–Drug Interactions and Prescription Appropriateness in Patients with COVID-19: A Retrospective Analysis from a Reference Hospital in Northern Italy

Dario Cattaneo[1,2] · Luca Pasina[3] · Aldo Pietro Maggioni[4,5] · Andrea Giacomelli[6] · Letizia Oreni[6] · Alice Covizzi[6] · Lucia Bradanini[6] · Marco Schiuma[6] · Spinello Antinori[6] · Annalisa Ridolfo[6] · Cristina Gervasoni[1,6]

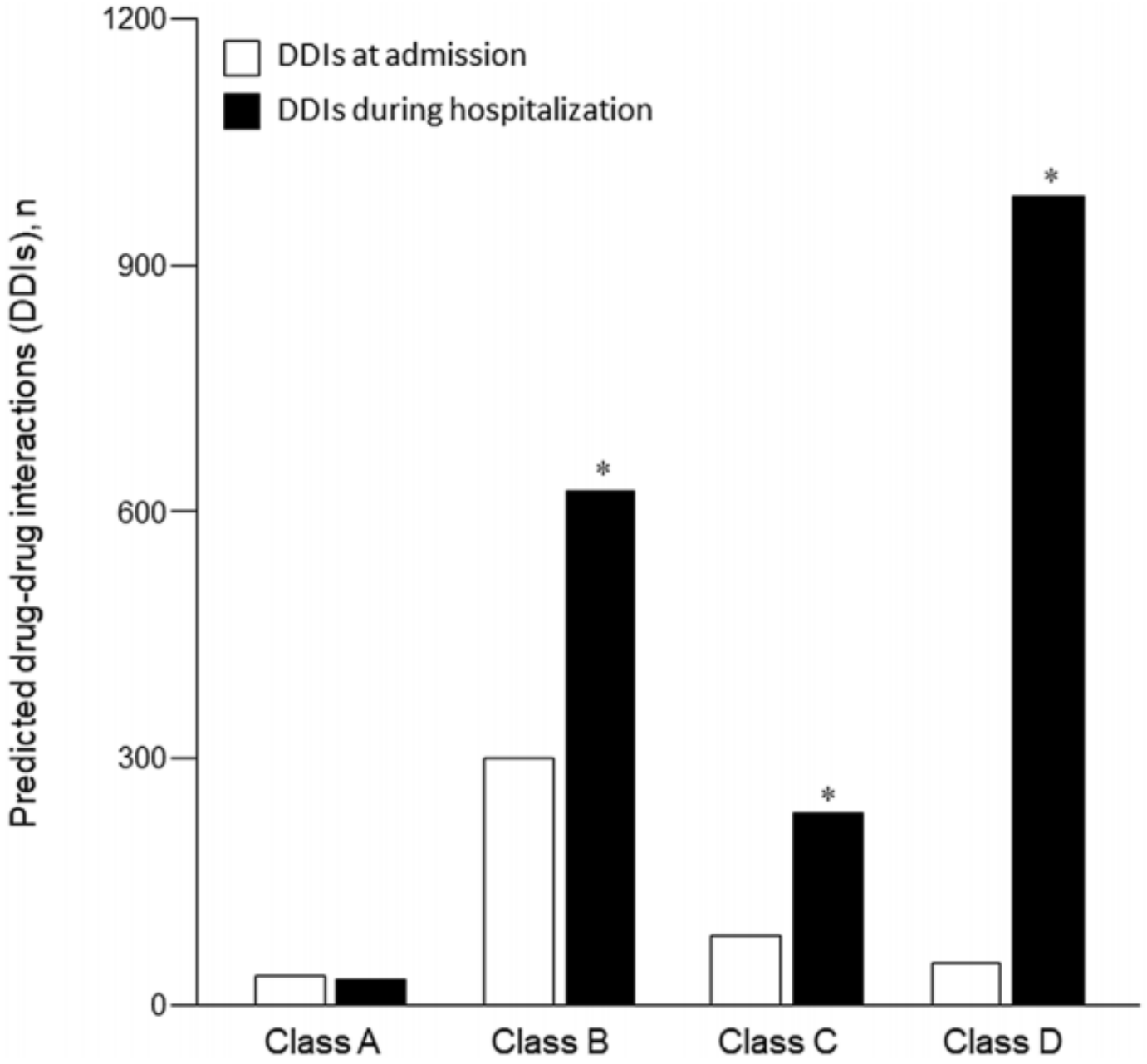
- ✓ We searched for patients with a proven diagnosis of SARS-CoV-2 infection hospitalised between 21 February and 30 April 2020 and treated with at least two drugs. All drugs were considered regardless of COVID-19 treatments
- ✓ The appropriateness of drug prescriptions was assessed in patients >65 years using INTERcheck® considering the potentially inappropriate medications (PIMs) by Beers' criteria and anticholinergic burden
- ✓ The potential DDIs were classified according to their clinical relevance

- Cattaneo et al, Drugs & Aging 2020 -

Clinical features	Upon admission	During hospitalisation
Patients treated with at least two drugs	285	367
Age, years	66 ± 14	62 ± 15
Women	101 (35)	111 (30)
Number of drugs	3.6 ± 2.6	7.3 ± 4.3
Total DDIs[a]	478	2160*
Severe DDIs[a]	134	1257*
Patients with at least one DDI	131 (46)	312 (85)*
Patients with at least one potentially severe DDI	62 (22)	294 (80)*
Patients aged > 65 years	155 (54)	155 (42)
Patients with at least one PIM[a]	147 (95)	137 (88)
ACB score	1.8 ± 1.2	1.8 ± 1.2
Patients aged > 65 years with an ABC score of ≥ 3	19 (12)	21 (14)
Patients aged > 65 years with an ABC score of ≥ 5	2 (1.3)	3 (1.9)

PIMs: potentially inappropriate medications; ACB: anti-cholinergic burden

- Cattaneo et al, Drugs & Aging 2020 -



Class A: minor (clinically irrelevant)
Class B: moderate (associated with an uncertain or variable event)
Class C: major (associated with a serious event that can me managed)
Class D: contraindicated or very severe

- Cattaneo et al, Drugs & Aging 2020 -

Table 3 Class D drug–drug interactions[a] and potential adverse events upon hospital admission

Main DDIs	Potential adverse event	*n* (%)
Furosemide-induced DDI (*n* = 16) Amiodarone-induced DDI (*n* = 7) Quetiapine-induced DDI (*n* = 7) Formoterol-induced DDI (*n* = 5) Salmeterol-induced DDI (*n* = 5)	Increased risk of cardiotoxicity (QT prolongation)	40 (87)
Proton pump inhibitors + clopidogrel (*n* = 4)	Altered effect of antithrombotic therapy	4 (9)
Statin + vitamin K inhibitor (*n* = 1)	Increased risk of myopathy (rhabdomyolysis)	1 (2)
Proton pump inhibitor + methotrexate (*n* = 1)	Increased toxicity of methotrexate	1 (2)

[a]Contraindicated or very serious interaction associated with a serious event for which it is appropriate to avoid co-administration or establish careful monitoring

- Cattaneo et al, Drugs & Aging 2020 -

Table 4 Class D drug–drug interactions and potential adverse events during hospitalisation of patients with COVID-19

Main DDIs	Potential adverse event	*n* (%)
Lopinavir/ritonavir + hydroxychloroquine (*n* = 247) Lopinavir/ritonavir + azithromycin (*n* = 78) Lopinavir/ritonavir +piperacillin (*n* = 73) Other lopinavir/ritonavir-induced DDIs (*n* = 82) Hydroxychloroquine + piperacillin (*n* = 78) Hydroxychloroquine + azithromycin (*n* = 61) Other hydroxychloroquine-induced DDIs (*n* = 90) Other azithromycin-induced DDIs (*n* = 40) Other piperacillin-induced DDIs (*n* = 29)	Increased risk of cardiotoxicity (QT prolongation, Torsade de Pointes or life-threatening arrhythmias)	895 (88)
Lopinavir/ritonavir + statin (*n* = 38)	Increased risk of myopathy (rhabdomyolysis)	39 (3.8)
Lopinavir/ritonavir + benzodiazepine (*n* = 14) Lopinavir/ritonavir + benzodiazepine (*n* = 7)	Depression of central nervous system respiratory functions	22 (2.2)
Lopinavir/ritonavir + DOACs (*n* = 14) Proton pump inhibitors + clopidogrel (*n* = 4)	Altered effect of anti-thrombotic therapy	20 (2.0)
Lopinavir/ritonavir + fluticasone (*n* = 10) Lopinavir/ritonavir + budesonide (*n* = 4)	Increased systemic toxicity of corticosteroids (Cushing syndrome)	16 (1.6)
Lopinavir/ritonavir + alfuzosin (*n* = 5)	Altered blood pressure control	11 (1.1)
Lopinavir/ritonavir-induced DDI (*n* = 9)	Various	16 (1.6)

- Cattaneo et al, Drugs & Aging 2020 -

…And what happens at discharge?

Clinical features	Admission	Discharge
Patients, n	201	198
Age, years	63 ± 13	63 ± 13
Women, n (%)	73 (36%)	73 (37%)
Mean number of drugs (%)	3.5 ± 2.8	4.0 ± 3.0
- ACE inhibitors/angiotensin receptor blockers	79 (39%)	73 (37%)
- proton pump inhibitors	**48 (24%)**	**66 (33%)***
- beta-blockers	47 (23%)	47 (24%)
- diuretics	45 (22%)	43 (22%)
- hypoglycemic agents	42 (21%)	52 (26%)
Patients with at least one DDI, n (%)	87 (43%)	92 (46%)
Patients with at least 1 potentially severe DDI, n (%)	40 (20%)	49 (25%)
Heparin-induced potentially severe DDI, n (%)	**1 (0.5%)**	**11 (6%)****
Patients with at least 1 PIM, n (%)	103 (51%)	115 (58%)
Patients with ACB score ≥3, n (%)	13 (6%)	14 (7%)

- Cattaneo et al, submitted -

Fighting on two fronts: drug-drug interactions (DDIs) in PLWH infected with SARS-CoV-2: the facts…

- ✓ The majority of PLWH have other multimorbidities and polypharmacy
- ✓ Antiretroviral drugs can be substrates, inhibitors and or inducers of cytochromial enzymes as well as modulators of drug transporters
- ✓ Some of the drugs tested for SARS-CoV-2 are substrates, inhibitors and or inducers of cytochromial enzymes as well as modulators of drug transporters
- ✓ SARS-CoV-2 infection has been associated with increased inflammatory states significantly inhibit the activity of cytochromial enzymes as well of drug transporters
- ✓ Some of the drugs tested as potential treatments for SARS-CoV-2 act decreasing the inflammatory states, potentially reversing the inhibition of the activity of cytochrome P450 enzymes as well of drug transporters

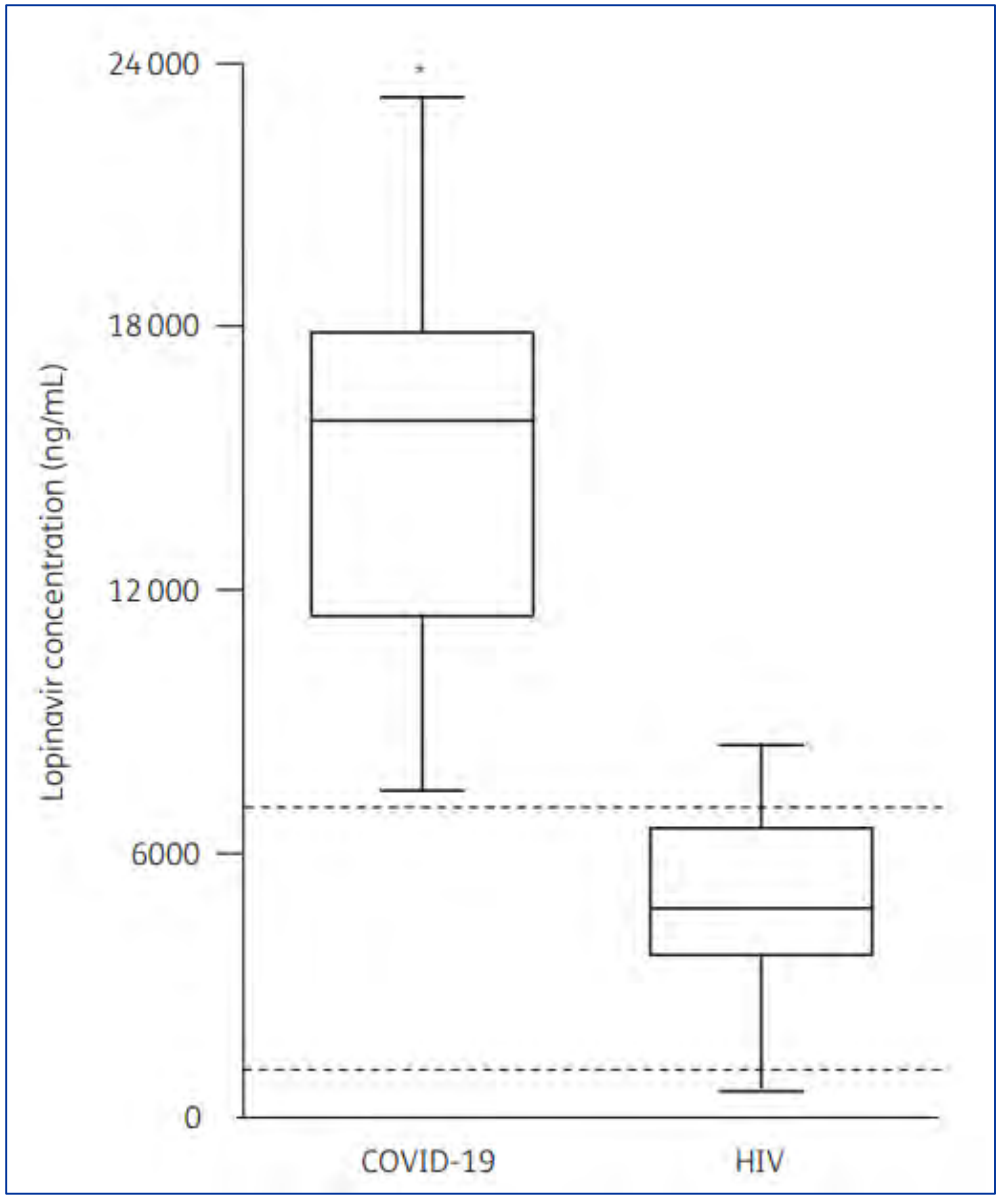
- Bahap et al, Eur J Hosp Pharm 2020 -

Frequent episodes of severe diarrhoea have been reported in patients with COVID-19 treated with lopinavir/ritonavir 400/100 mg bid

Lopinavir/ritonavir trough concentrations were measured in 21 COVID-19 patients and were compared with PK data from HIV patients

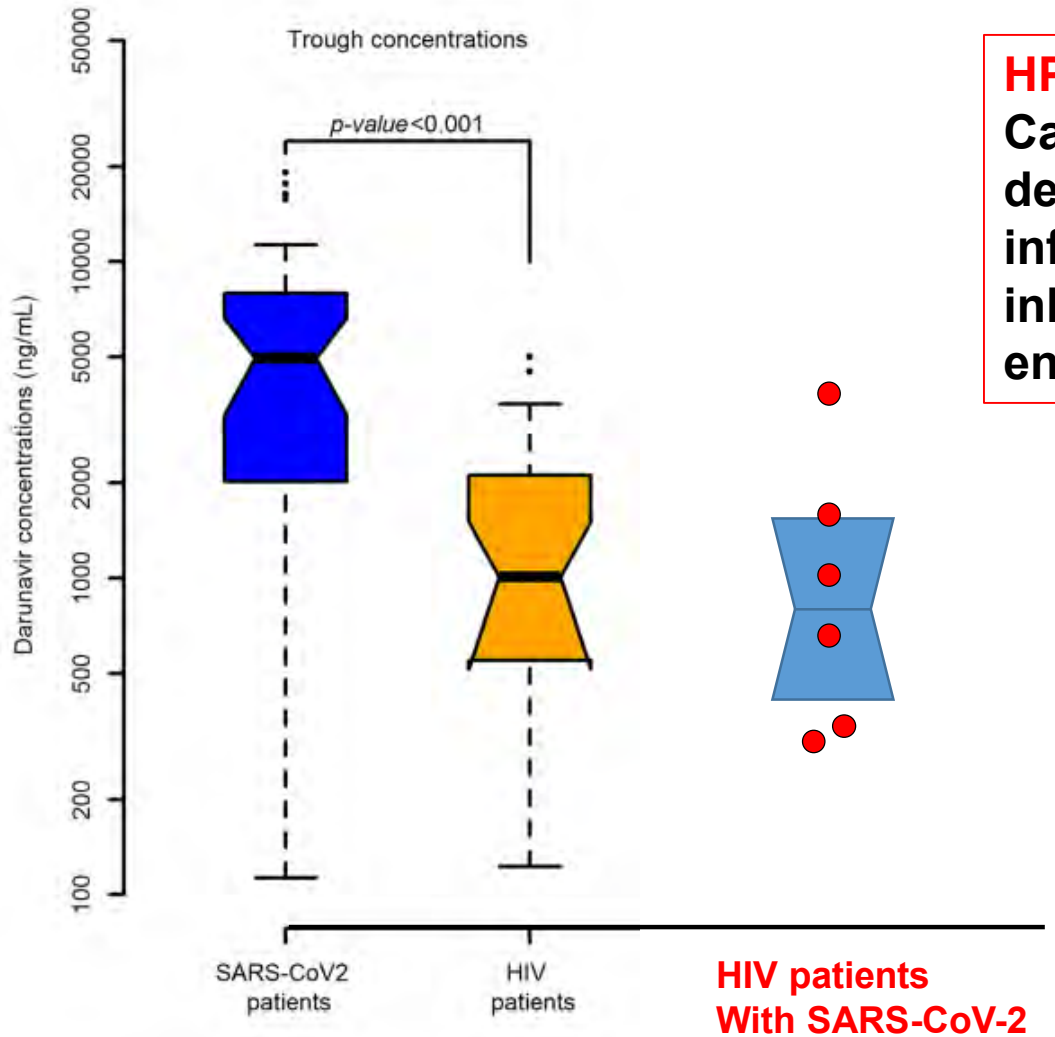
	COVID-19^	HIV
Lopinavir, ng/mL	15235 ± 5905**	4882 ± 2347
Ritonavir, ng/mL	772 ± 563**	214 ± 165

^6 out of the 21 patients reported GI side effects
**p<0,001 vs HIV



- Baldelli et al, JAC 2020 -

Comparative Population Pharmacokinetics of Darunavir in SARS-CoV-2 Patients vs. HIV Patients: The Role of Interleukin-6



HP:
Can HIV in some ways limit the development of SARS-CoV-2 inflammation reverting the inhibiting effect on metabolic enzymes?

Cojutti, Clin Pharmacokinet 2020
Cattaneo, Clin Pharmacokinet 2020

Save the date: first time in Italy!!!

International Association of
Therapeutic Drug Monitoring and Clinical Toxicology
Fostering education, research and practice in TDM and CT