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

Multidisciplinary experience to manage polypharmacy in the clinical setting

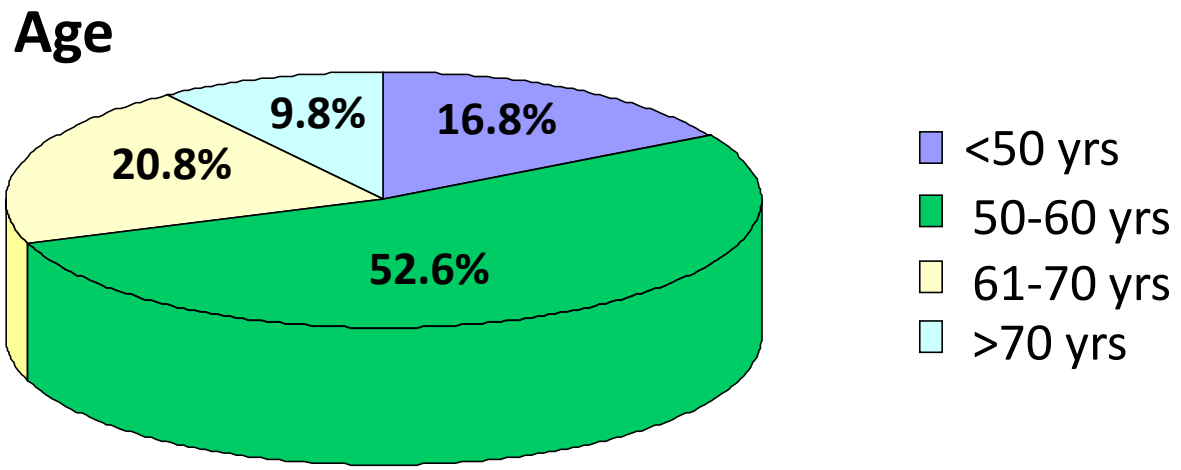
Dario Cattaneo, PhD

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*

- ✓ Cristina Gervasoni (Infectious Diseases physician)
- ✓ Dario Cattaneo (Pharmacologist)
- ✓ & Collaborators
- ✓ Kick-off : September 2016
- ✓ Nearly 1000 HIV patients included in the database



*Outpatient clinic for the management of polypharmacy in HIV

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
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- Gervasoni et al, AIDS Rev 2019 -

Informazioni Anagrafiche

Nuovo Paziente | Precedente | Successivo | Trova Paziente | Salva Paziente

ID Contatore)

Cognome Nome

Data nascita

Sesso

Domicilio

Comune di nascita

Prov

CF

Scolarità

Professione

Telefono

Etnia

Telefono 2

Data prima visita

Naive ☐

Data HIV primo riscontro

CD4<200 ☐

Data ultimo Follow up

Epidemiologia

Data inizio TARV

Coinfezione

Terapia Antiretrovirale

Altre Terapie

Anamnesi Fisiologica

Farmacocinetica Antiretrovirale

Farmacocinetica Altri Farmaci

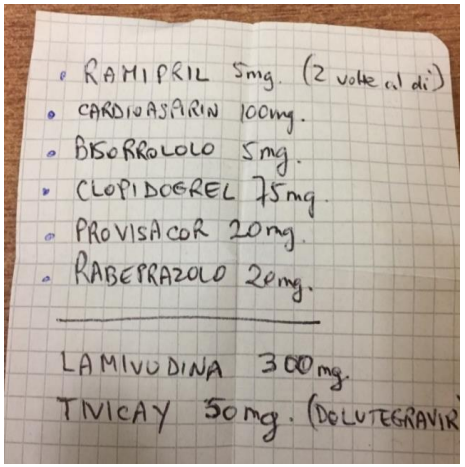
Farmacogenetica

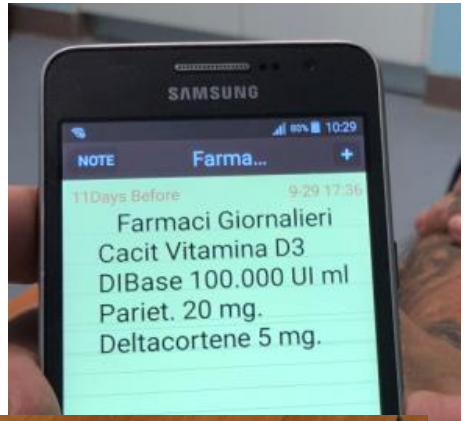
Esami Ematochimici

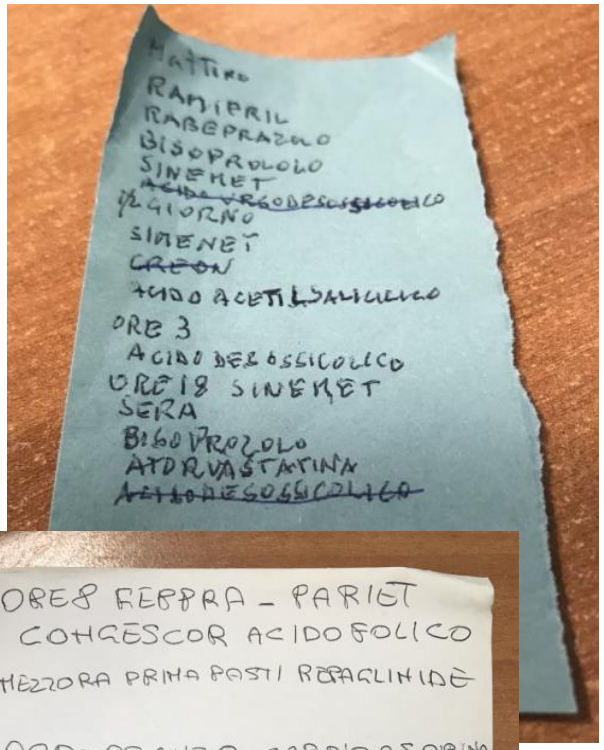
Altre Patologie

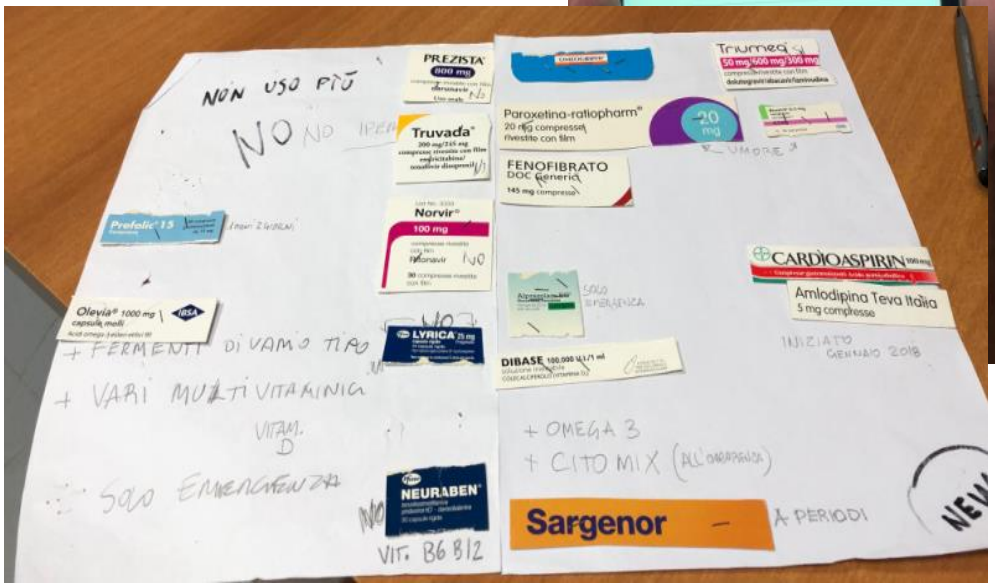
Consigli

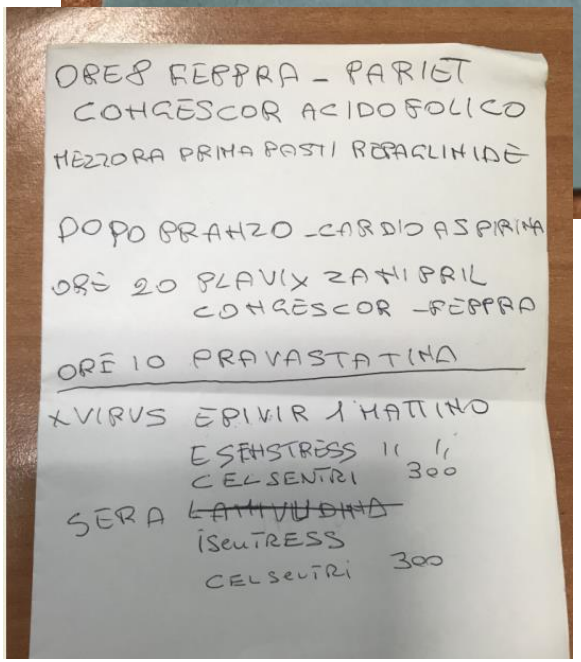
…The most difficult task is...











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

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- Gervasoni et al, AIDS Rev 2019 -

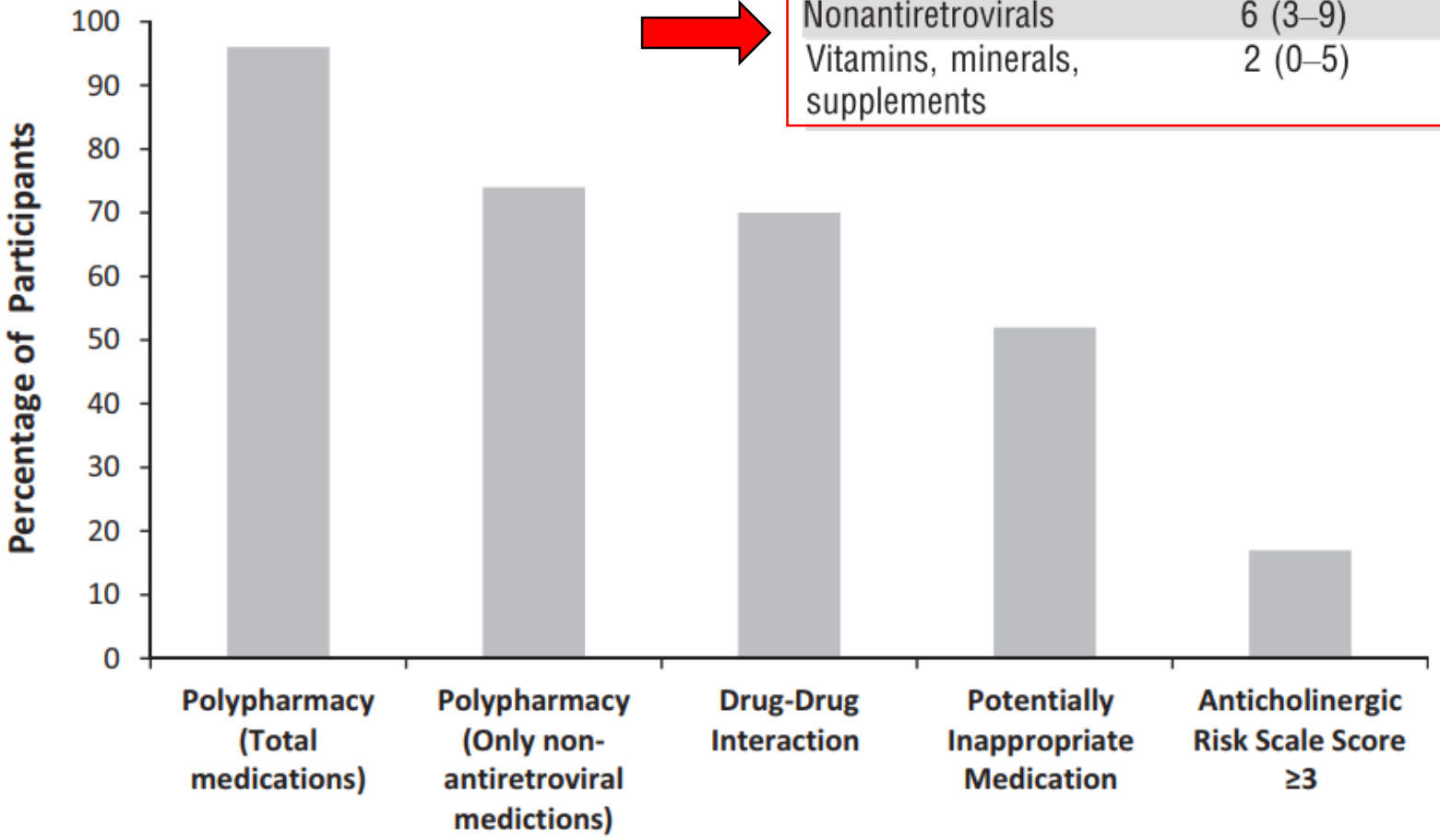
The golden standard tool for checking DDIs involving antiretroviral drugs…

https://www.hiv-druginteractions.org/

…but….

Polypharmacy, DDIs and PIMs in older adults with HIV

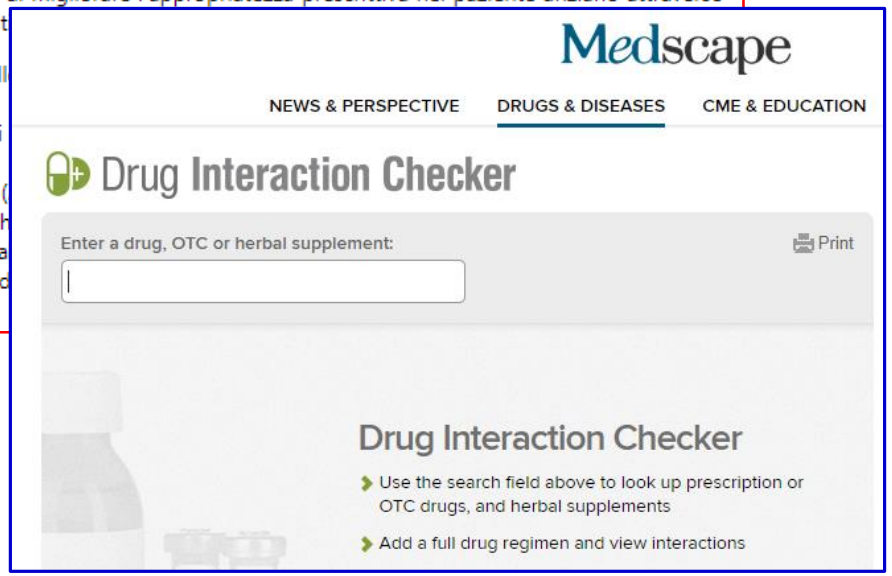
Medication	Median (Interquartile Range)
Total	13 (9–17)[a]
Antiretrovirals	4 (3–5)
Nonantiretrovirals	6 (3–9)
Vitamins, minerals, supplements	2 (0–5)



- Greene, J Am Geriatr Soc 2014 -

Rember to check potential DDIs between non-antiretroviral drugs…

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



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

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

▸ Cosa sono e quando usarli

ACB Score (Anticholinergic Cognitive Burden): **7**

ATTENZIONE: I farmaci con effetti anticolinergici possono indurre (soprattutto nel soggetto anziano) effetti indesiderati a carico del sistema nervoso centrale come deficit cognitivo e stato confusionale acuto. Un punteggio all'ACB Score ≥ 5 è associato a peggiori performance cognitive e riduzione dell'autonomia funzionale. I sintomi centrali sono reversibili ed evidenti già nelle prime settimane di trattamento.

Principio Attivo	ACB Score
Clorpromazina	3
Paroxetina	3
Paliperidone	1

Fonte: Boustani M et al. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health 2008;4(3):311-320

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- Gervasoni et al, AIDS Rev 2019 -

Complementary and Alternative Medicine (CAM)

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" [11]. It comprises herbs, dietary supplements, meditation, biofeedback, hypnosis, acupuncture, Ayurveda, homeopathy, naturopathy, Chinese medicine, chiropractic, massage, *tai chi*, yoga, electromagnetic therapy, kinesiology, *reiki*, and *qigong*.

- ✓ The global prevalence of CAM in the general population varies with cultures, countries, ranging from less than 10% up to 80%
- ✓ Up to 60% of patients with HIV report regular use of CAM…
- ✓ Nearly 80% of them have reported CAM usage at HIV diagnosis…

Bahall BMC 2017, Brooks Expert Opin Clin Pharmacol 2017

Bahall *BMC Complementary and Alternative Medicine* (2017) 17:422
DOI 10.1186/s12906-017-1928-4

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Prevalence, patterns, and perceived value of complementary and alternative medicine among HIV patients: a descriptive study

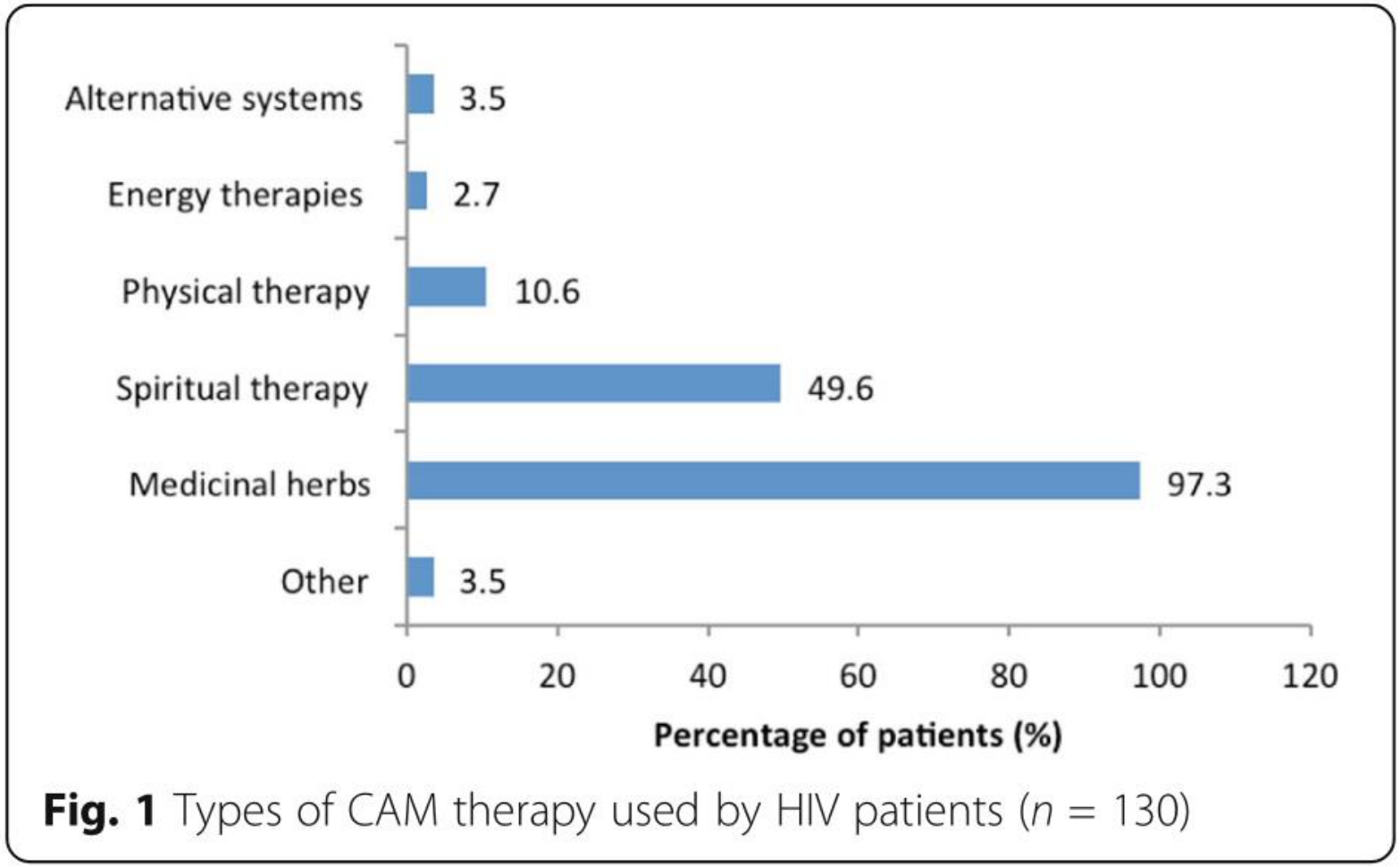
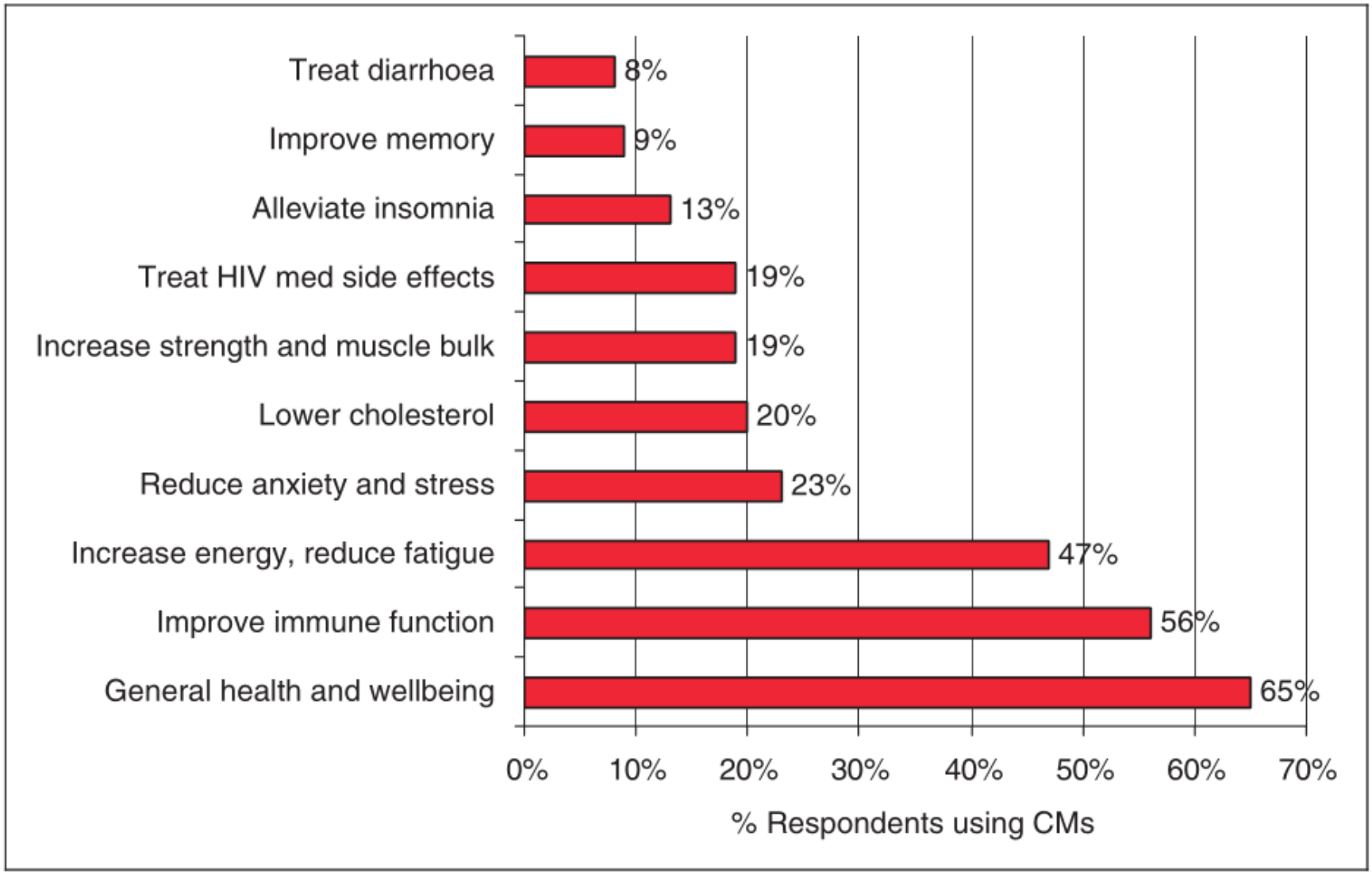


Fig. 1 Types of CAM therapy used by HIV patients ($n = 130$)

Top 10 reasons reported for using CAMs



…Which are the potential risks associated with the use of CAMs?

Reduced risk of adherence to ART…

Table III. Association between CAM use and antiretroviral non-adherence.

Type of CAM	OR*	95% CI	*p*-value
Individual CAM	3.04	1.54–6.00	.001
Vitamins	1.55	0.94–2.58	.088
Religious healing	0.89	0.51–1.57	.697
Bodywork	1.05	0.47–2.37	.903
Psychic healing	1.01	0.47–2.41	.999
Combined CAM			
Oral CAM	1.69	1.02–2.80	.041
Body/Healing CAM	1.20	0.7–2.060	.506

Note: *Adjusted for age, education, race, religion and income.

AIDS Care, May 2007; 19(5): 589–593

Unanticipated, clinically-relevant DDIs…

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	Gunabasic 7 g daily 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

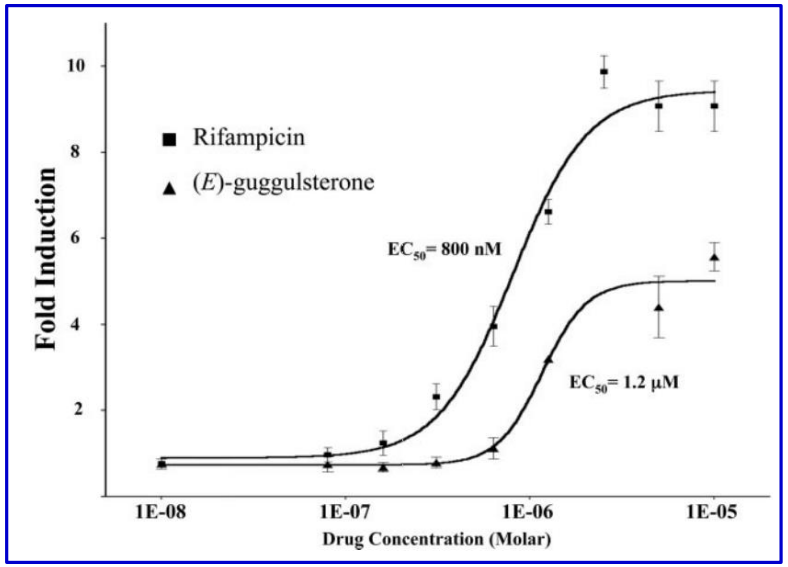
CUT 4 HIM + is a thermogenic complex aimed at the requirements of men who wish to lose weight and increase their muscle definition and energy

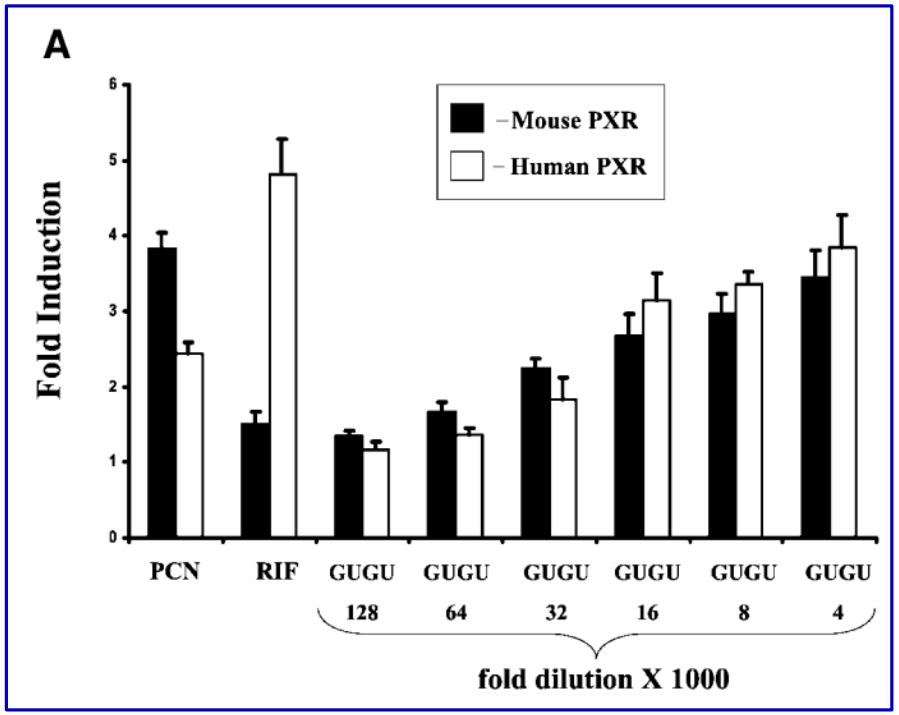
06/12/2018 Elvitegravir trough concentrations: **56 ng/mL (-93%!!)**

0022-3565/04/3102-528–535$20.00
THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 310, No. 2
64329/1158202
Printed in U.S.A.

JPET 310:528–535, 2004

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





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

Development of toxicity in selected patients…

Letter to the Editor

Liver Injury After Occasional Energy Drink Use in a Patient Living With HIV and Diabetes

Table 1. Ingredients of the Energy Drink Taken by the Patient.

Ingredients	Amount Per Serving (9 g)
Vitamin B6 (as pyridoxal-5-phosphate)	35 µg
Vitamin B12 (as methylcobalamin)	35 µg
Calcium (as calcium silicate)	17 µg
Magnesium (as magnesium chloride)	12 µg
Sodium (as sodium citrate)	60 µg
Potassium (as dipotassium phosphate)	20 µg
Performance blend: micronized creatine monohydrate, CarnoSyn β-alanine, arginine, α-ketoglutarate, sodium citrate, magnesium chloride, dipotassium phosphate	4.9 g
Energy blend: taurine, caffeine anhydrous (135 mg), pyridoxal-5-phosphate, methylcobalamin	1.135 g

- Cattaneo et al, Annals Pharmacother 2019 -

OPEN ACCESS Freely available online

PLOS ONE

Traditional Herbal Medicine Use Associated with Liver Fibrosis in Rural Rakai, Uganda

Herb used
Asteraceae Family
Vernonia amygdalina
Vernonia, species unknown
Microglossa densiflora
Aspilia Africana
Fabaceae Family
Pseudarthria hookeri
Indigofera congesta
Lamaceae Family
Ocimum gratissimum
Hoslundia opposita

Table 6. Association of herbs with significant liver fibrosis in HIV-infected participants.

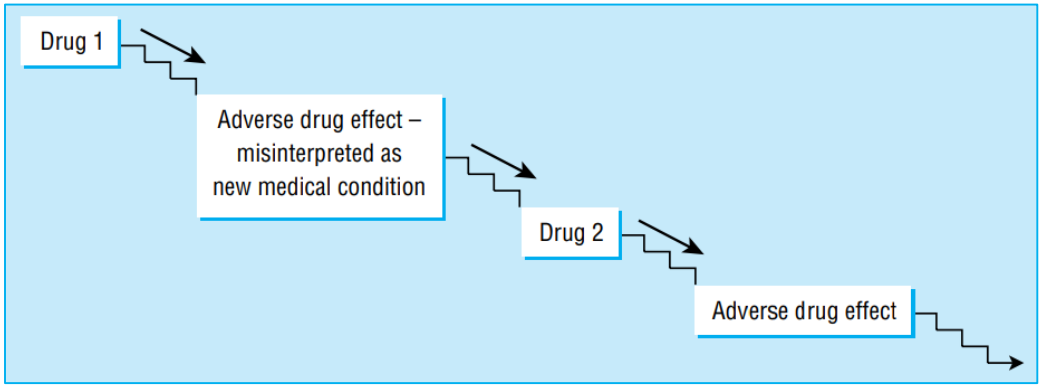
	Univariate			Multivariate		
Herb (n taking)	**PRR**	**95% CI**	**P value**	**adjPRR**	**95% CI**	**P value**
Any current herb use (8)	3.0	1.4–6.2	0.003	2.3	1.0–5.0	0.044
Asteraceae (2)	6.0	4.9–7.3	<0.001	5.0	1.7–14.7	0.004
Unknown herb (5)	1.2	0.20–6.8	0.87	1.0	0.15–6.7	0.998

Multivariate model for HIV-infected participants adjusts for: age, occupational fishing, positive Hepatitis B surface antigen, gender, heavy liquor use (≥1.25 L/week), ART, and CD4 nadir. Only participants with a valid TE scan (468/500) were included in the model. CI (Confidence Interval).

Conclusions

Traditional herbal medicine use was independently associated with a substantial increase in significan liver fibrosis in both HIV-infected and HIV-uninfected study participants

Novel 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

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

- 34-year-old MSM
- ELV/c/TAF/FTC for 24 months
- BIC/TAF/FTC for a month
- HIV-RNA < 37 copies/mL
- CD4+ cell count 590 cells/mmc

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

- Cattaneo et al, submitted -

Diagnosis of HIV

Start TAF/FTC/ELV/cobi

Good immunovirologic outcome, well being

Start GHB as recreational drug

New medical condition: depression

Start daily GHB as antidepressant

New medical condition: Cushing's syndrome

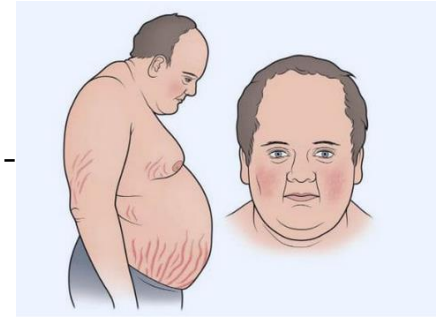
New medical condition: muscle weakness and fatigue

Start anabolic hormones injections

New medical condition: hypothalamic-pituitary-adrenal axis block

New medical condition: worsening of plaque psoriasis

Topical corticosteroids abuse



- Cattaneo et al, submitted -

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- Gervasoni et al, AIDS Rev 2019 -

TDM of ARVs 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

Ask to David…

17:30

Plasma measurement of antivirals in the clinical setting: which role in 2020

David Burger

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A few examples from our hospital…

…to check for DDIs in individual patients…

Comedications	Dolutegravir trough (ng/mL)
ABC/3TC	1045 [856-1115]
Atazanavir	2399 [1929-4070]
Darunavir	756 [556-1048]
Rilpivirine	603 [432-1373]
Efavirenz*	58, 40
Etravirine*	25, 182, 931
Nevirapine*	102
Rifampicin*	576, 585, 240, 251, 94, 22, <20

*the dolutegravir dose should be doubled according to the USP

- Modified from Cattaneo, D, Antiviral Therapy 2017 -

…when there are no information available….

www.hiv-druginteractions.org

HIV Drugs	Co-medications	Drug Interactions
rilpivirine	ursodeoxycholic acid	Check HIV/ HIV drug interactions
A-Z Class Trade	A-Z Class Trade	Drug Interactions will be displayed here
Nevirapine (NVP)	Selected Co-medications will be displayed here.	
Dolutegravir/Rilpivirine (DTG/RPV)		
Rilpivirine/ Emtricitabine/Tenofovir alafenamide (RPV/FTC/TAF)		
Rilpivirine (RPV)		

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 -

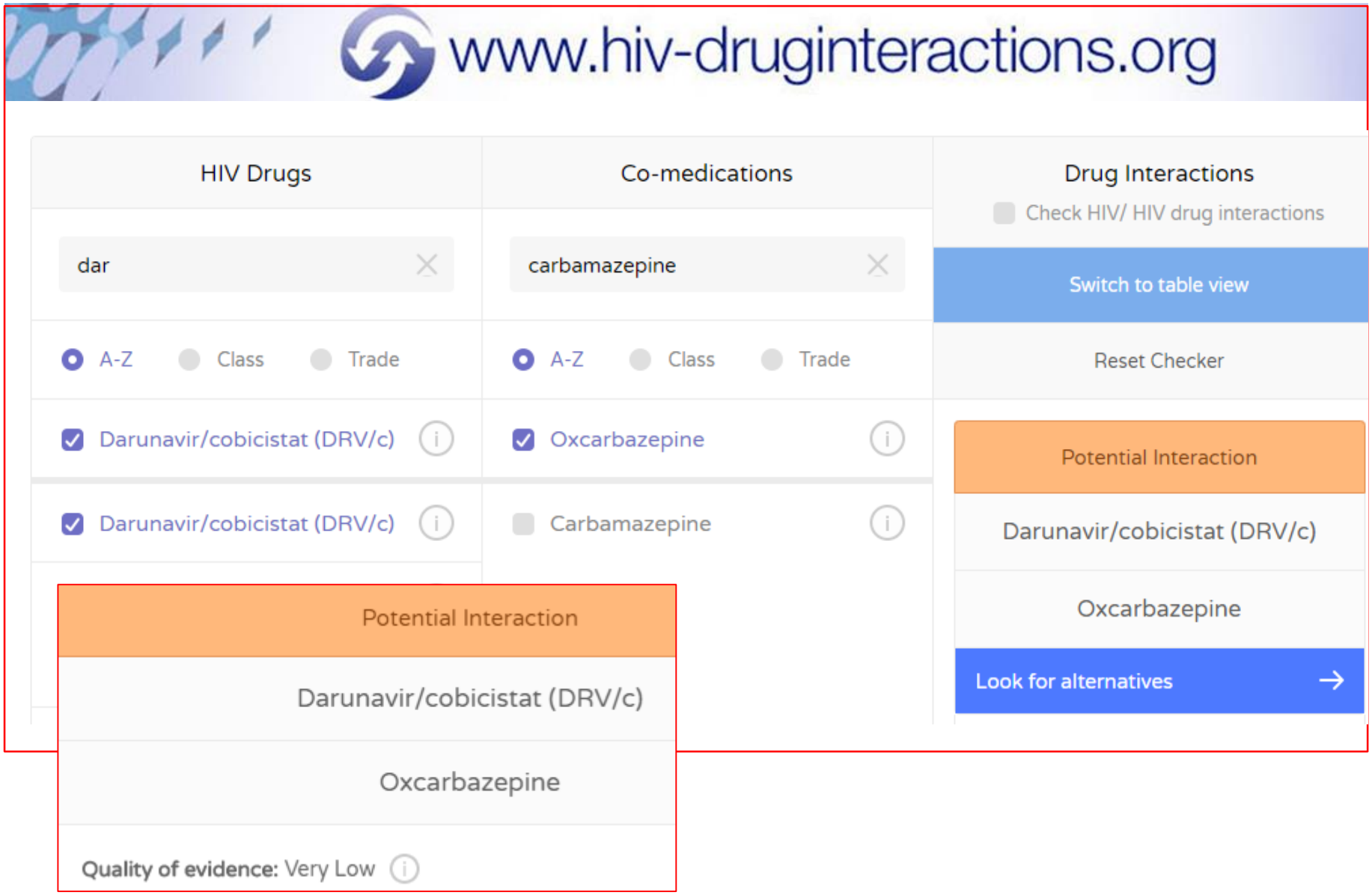
Proposed mechanisms for this DDI

- ✓ Significant effects of UDCA on the disposition of anion exchange resins, aluminum hydroxide, cyclosporine and ciprofloxacin have been described. Accordingly, it has been proposed that UDCA, through competition with endogenous biliary acids, can reduce the solubility of some drugs ultimately resulting in impaired drug absorption

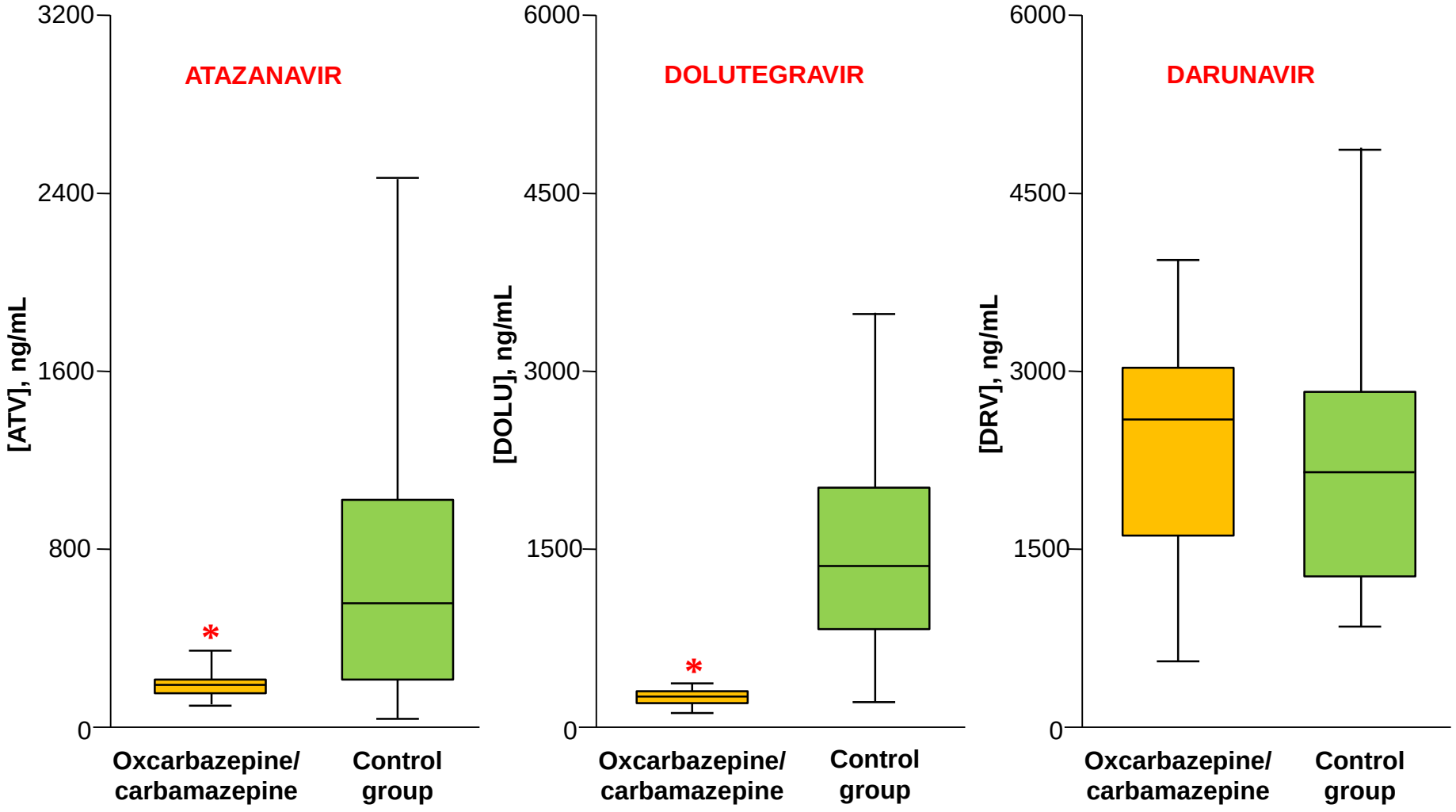
- ✓ Studies in human hepatocytes have shown that lithocolic acid – the active metabolite of UDCA produced by intestinal bacteria – activates the nuclear pregnane X receptor, a known transcriptional inducer of CYP3A expression. Indeed, significant reduction in the concentrations of CYP3A substrates, such as nitrendipine, digoxin and dapsone have been reported in human studies

- ❑ Schuetz EG, et al. Disrupted bile acid homeostasis reveals an unexpected interaction among nuclear hormone receptors, transporters, and cytochrome P450. J Biol Chem 2001; 276: 39411–39418.
- ❑ Staudinger JL, et al.The nuclear receptor PXR is a lithocholic acid sensor that protects against liver toxicity. Proc Natl Acad Sci USA 2001; 98: 3369–3374.
- ❑ Sasaki M, et al. Effect of bile acids on absorption of nitrendipine in healthy subjects. Br J Clin Pharmacol 2001; 52: 699–701.
- ❑ Becquemont L, et al. Effects of ursodeoxycholic acid on P-glycoprotein and cytochrome P450 3A4-dependent pharmacokinetics in humans. Clin Pharmacol Ther 2006; 79: 449-460.
- ❑ Stroubou E, Dawn G, Forsyth A. Ursodeoxycholic acid causing exacerbation of dermatitis herpetiformis. J Am Acad Dermatol 2001; 45: 319–320.

… when the quality of evidence is low….



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[1] · Agostino Riva[1]

Manuscript ID: JAC-2019-1840.R1 (in press 2020)
Title: PHARMACOKINETIC PROFILE OF DOLUTEGRAVIR AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PLACEMENT
Author(s): Fabbiani, Massimiliano; Cattaneo, Dario; Lombardi, Andrea; Colaneri, Marta; Sambo, Margherita; Novati, Stefano; Fusi, Marta; Bruno, Raffaele

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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

Anti-infectives

- ❑ Teicoplanin
- ❑ Levofloxacin
- ❑ Rifampicin
- ❑ Linezolid
- ❑ Cyprofloxacin
- ❑ Vancomycin
- ❑ Amikacin
- ❑ Gentamycin
- ❑ Trimethoprim
- ❑ Meropenem
- ❑ Piperac/tazob
- ❑ Ceftaz/avib
- ❑ Cefepime
- ❑ ampicilline
- ❑ Voriconazole
- ❑ Posaconazole
- ❑ Isavuconazole
- ❑ Itraconazole
- ❑ Caspofungin

Psychotropics

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

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 -

Antiepileptic drug	No. of TDM	[drug], mg/L	AGNP targets, mg/L	Below the target, %	Within the target, %	Above the target, %
HIV-positive patients						
Carbamazepine	20	8.2 ± 3.6	4 – 12	0	95%	5%
Lamotrigine	9	4.0 ± 4.5	3 – 15	67%	33%	0
Levetiracetam	136	18.6 ± 12.3	10 – 40	29%	67%	4%
Oxcarbazepine	5	8.2 ± 3.6	10 – 35	20%	80%	0
Phenytoin	10	35.6 ± 12.0*	10 – 20	0	95%	5%
Phenobarbital	45	19.1 ± 7.2	10 – 40	11%	89%	0
Topiramate	10	6.6 ± 5.0	2 – 10	0	70%	30%
Valproate	75	47.9 ± 21.2^	50 – 100	57.0%	43%	0
HIV-negative patients						
Carbamazepine	381	7.3 ± 2.7	4 – 12	9%	87%	4%
Lamotrigine	400	5.9 ± 4.1	3 – 15	28%	68%	4%
Levetiracetam	1137	21.0 ± 14.3	10 – 40	22%	68%	10%
Oxcarbazepine	141	17.7 ± 8.8	10 – 35	22%	72%	6%
Phenytoin	121	11.2 ± 10.7	10 – 20	60%	23%	17%
Phenobarbital	290	19.1 ± 8.7	10 – 40	13%	85%	2%
Topiramate	159	7.3 ± 4.3	2 – 10	15%	61%	25%
Valproate	859	53.9 ± 21.6	50 – 100	46%	52%	2%

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

- Cattaneo, Clin Pharmacokinet 2019 -

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. Therefore, it is likely that antiepileptic therapies and dosages are easier to handle in the clinical practice

Hp: the fear for potential DDIs….

Another example on the fear of DDIs: the use of direct oral anticoagulants (DOACs) in people living with HIV

- ✓ DOACs have been developed to overcome the challenges posed by vitamin K inhibitors. More than 70% of HIV-negative patients requiring anticoagulant therapy are actually treated with these drugs

- ✓ Experiences on the use of DOACs in people living with HIV are limited to case reports, small case series and analyses of theoretically anticipated drug-drug interactions (DDIs) with antiretrovirals. Here, we sought to assess the use of DOACs in HIV-infected patients from our Clinics.

- ✓ The database of our Infective Diseases Clinics (with nearly 2300 HIV-infected patients on active follow-up) was retrospectively investigated in search for patients starting antithrombotic therapy after January 2012 or starting therapy on any date but suspending it after 2012. The risk of DDIs was scored using the University of Liverpool HIV Drug Interactions checker

- Cattaneo et al, submitted -

Characteristics	Current situation	Hypothetical DOACs-based scenario
Patients, n	50	
Age, years	66 ± 13	
Body weight, Kg	77 ± 12	
CD4 cell count, cells/microliter	629 ± 256	
Patients with HIV RNA >50 copies/mL	1	
Antiretroviral therapy	- 30% abacavir-based - 36% tenofovir-based - 10% lamivudine-based - 24% NRTI free - 38% boosted PI-based* - 30% NNRTI-based* - 64% INI-based*	
Days of antiretroviral therapy	3923 ± 2015	
Antithrombotic therapy	**- 82% vitamin K inhibitors** **- 14% DOACs** **- 4% others^**	**- 22% vitamin K inhibitors** **- 78% DOACs**
Causes for antithrombotic therapy	- 52% atrial fibrillation - 24% DVP - 10% PE - 10% DVP + PE - 4% valve replacement	
Days of antithrombotic therapy	2624 ± 2328	
Liverpool score for potential DDIs	**- 0% red flag** **- 58% orange flag** **- 42% green flag**	**- 0% red flag** **- 20% orange flag** **- 80% green flag**

- Cattaneo et al, submitted -

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 -

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

UNIVERSITÀ DEGLI STUDI DI MILANO

CODICE A BARRE DEL PRELIEVO

COGNOME_____NOME_____

☐M ☐F Data di nascita____/_____/_____

Reparto:_____ Data del prelievo:_____

Medico Richiedente_____

SETTORE DI FARMACOGENETICA

(M FACL G-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
Anamnestic data	Male, 57yrs, ART since 2000
ART	DRV/cobi 800/150 mg TAF/FTC 10/200 mg
Other drugs	diazepam, rosuvastatine, colecalciferol, acyclovir, carbamazepine
CD4, VL	828 cell/mL, <37 cp/ml
$[DRV]_{trough}$ pre-steroid	2588 ± 742 ng/mL
Steroid, dose and duration	Prednisone 25 mg bid (therapy started from 6 weeks)
Reason for steroid use	Trigeminal neuralgia
$[DRV]_{trough}$ post-steroid	220 ng/mL

NCBI Resources

PubMed.gov
US National Library of Medicine
National Institutes of Health

Regulation of **CYP3A** genes by **glucocorticoids** in human lung cells.

Roberts JK, Moore CD, Romero EG, Ward RM, Yost GS, Reilly CA.

Version 2. F1000Res. 2013 Aug 13 [revised 2013 Jan 1];2:173. doi: 10.12688/f1000research.2-173.v2. eCollection 2013.

PMID: 24555085 **Free PMC Article**

Similar articles

Cytochrome P450 enzyme regulation by **glucocorticoids** and consequences in terms of drug interaction.

Matoulková P, Pávek P, Malý J, Vlček J.

Expert Opin Drug Metab Toxicol. 2014 Mar;10(3):425-35. doi: 10.1517/17425255.2014.878703. Epub 2014 Jan 23. Review.

PMID: 24451000

Similar articles

Mechanisms of **CYP3A** induction by **glucocorticoids** in human fetal liver cells.

Matsunaga T, Maruyama M, Matsubara T, Nagata K, Yamazoe Y, Ohmori S.

Drug Metab Pharmacokinet. 2012;27(6):653-7. Epub 2012 May 22.

PMID: 22673009 **Free Article**

Similar articles

Regulation of drug-metabolizing **cytochrome** P450 enzymes by **glucocorticoids**.

Dvorak Z, Pavek P.

Drug Metab Rev. 2010 Nov;42(4):621-35. doi: 10.3109/03602532.2010.484462. Review.

PMID: 20482443

Similar articles

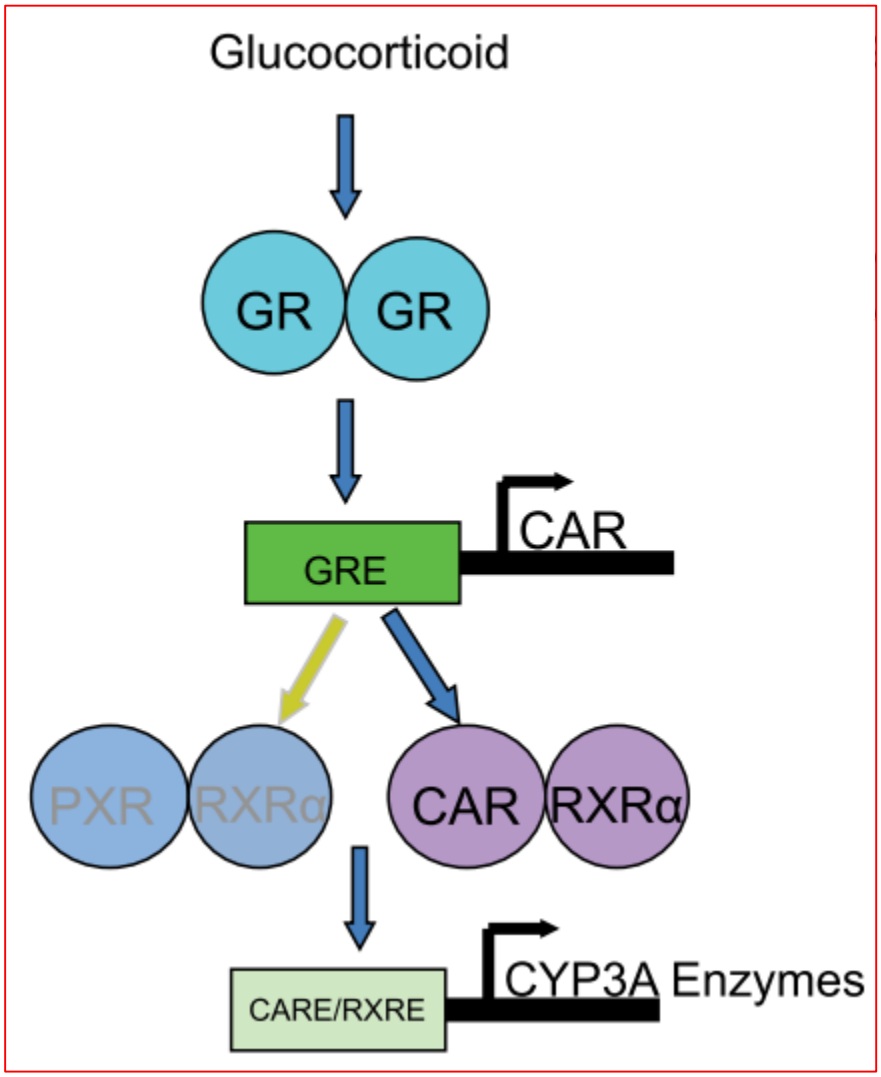
Regulation of **CYP3A5** by **glucocorticoids** and cigarette smoke in human lung-derived cells.

Hukkanen J, Väisänen T, Lassila A, Piipari R, Anttila S, Pelkonen O, Raunio H, Hakkola J.

J Pharmacol Exp Ther. 2003 Feb;304(2):745-52.

PMID: 12538830

Similar articles



Possible mechanisms for the induction of CYP3A genes

Active glucocorticoid will bind to the glucocorticoid receptor (GR), which forms a homodimer and translocates to the nucleus. The homodimer binds to its response element (GRE) and induces the expression of either the pregnane X receptor (PXR) or the constitutive androstane receptor (CAR). CAR or PXR forms a heterodimer with the retinoic X receptor alpha (RXRα) which in turn induces the expression of the CYP3A enzymes via binding of the respective response-elements (CARE and/or PXRE)

	Patient 1
Anamnestic data	Male, 57yrs, ART since 2000
ART	DRV/cobi 800/150 mg TAF/FTC 10/200 mg
Other drugs	diazepam, rosuvastatin, colecalciferol, acyclovir, carbamazepine
CD4, VL	828 cell/mL, <37 cp/ml
$[DRV]_{trough}$ pre-steroid	2588 ± 742 ng/mL
Steroid, dose and duration	Prednisone 25 mg bid (from 6 weeks)
Reason for steroid use	Trigeminal neuralgia
$[DRV]_{trough}$ post-steroid	220 ng/mL

Reduction of DRV concentrations related to steroid-induced increased CYP3A-mediated metabolism

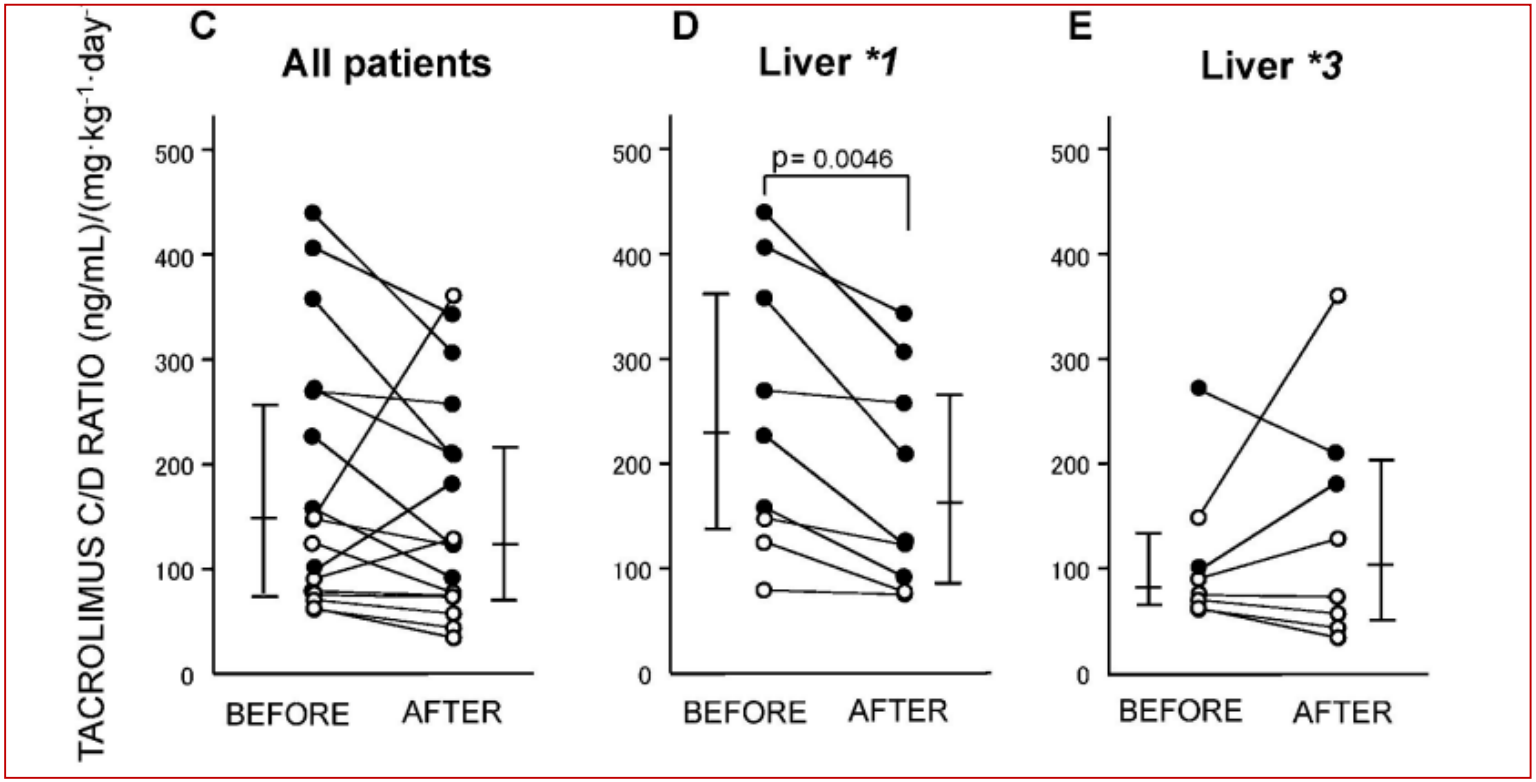
…two months later….

	Patient 1	Patient 2
Anamnestic data	Male, 57yrs, ART since 2000	Male, 53yrs, ART since 1993
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, rosuvastatin, colecalciferol, acyclovir, 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

…different clinical conditions….

	Patient 1	Patient 2
Anamnestic data	Male, 57yrs, ART since 2000	Male, 53yrs, ART since 1993
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, rosuvastatin, colecalciferol, acyclovir, 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

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



Blood concentrations of tacrolimus before versus after bolus of steroids in liver transplant recipients stratified according to CYP3A5 genotypes

- Hosohata, DMP 2014 -

Genotype 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
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- 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)
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- Preparation of a written report for the general practitioner, attending physician and other specialists

- Gervasoni et al, AIDS Rev 2019 -

The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects

Table 1. Statistical comparison of metformin PK parameters with and without dolutegravir

Plasma Metformin PK Parameter	GLS mean Metformin Alone (Period 1)	Metformin + DTG (Period 2)	GLS mean ratio (90% CI) Metformin + DTG vs. Metformin Alone
Cohort 1 (DTG 50 mg QD)	n = 15	n = 14	
Cmax (μg/mL)	0.932	1.55	1.66 (1.53, 1.81)
AUC(0-τ) (hr*μg/mL)	6.83	12.2	1.79 (1.65, 1.93)
Cohort 2 (DTG 50 mg BID)	n = 15	n = 14	
Cmax (μg/mL)	0.845	1.878	2.11 (1.91, 2.33)
AUC(0-τ) (hr*μg/mL)	6.49	15.9	2.45 (2.25, 2.66)

Zong J et al. *Journal of the International AIDS Society* 2014, **17(Suppl 3)**:19584

Potential Interaction
Dolutegravir
Metformin

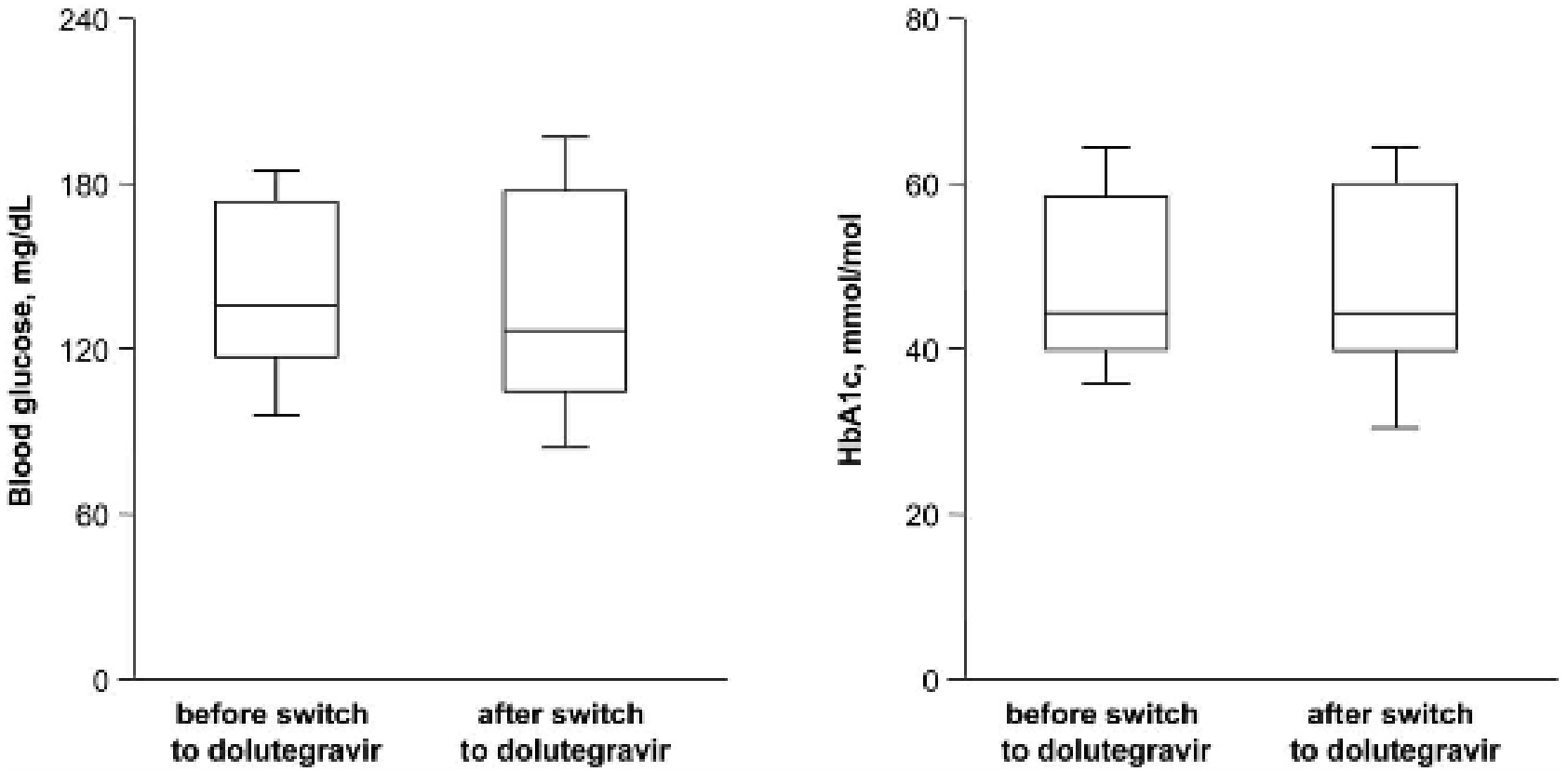
The US Prescribing Information suggests limiting the total daily dose of metformin to 1000 mg when starting metformin or dolutegravir. As metformin is eliminated renally, patients with moderate renal impairment may be at increased risk for lactic acidosis due to increased metformin concentrations.

(dolutegravir is an inhibitor of OCT2)

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.



How relevant are the drug–drug interactions between antiretroviral boosted-based regimens and calcium channel blockers in real life?

Dario Cattaneo[1,2], Tiziana Formenti[3], Noemi Astuti[3], Paola Meraviglia[3], Annalisa Ridolfo[3] and Cristina Gervasoni[1,3]*

The relevance of drug–drug interactions in clinical practice: the case of concomitant boosted protease inhibitors plus alpha-1 blocker administration

Cristina Gervasoni[1,2], Chiara Resnati[1], Tiziana Formenti[1], Alessandro Fossati[3], Davide Minisci[1], Paola Meraviglia[1], Dario Cattaneo[2,4]*

CCB and alpha-1 blockers are metabolized mainly by CYP3A

plus ritonavir or cobicistat (CYP3A4/5 inhibitors)

increased alpha1-blockers or CCB exposure and development of severe hypotension

Cattaneo, J Antimicrob Chemother 2018
Gervasoni Antiviral Ther 2018

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-019-02714-0

LETTER TO THE EDITOR

No effects of *Hypericum*-containing complex on dolutegravir plasma trough concentrations: a case report

Dario Cattaneo[1,2] · Marta Fusi[2] · Cristina Gervasoni[1,3]

Received: 7 June 2019 / Accepted: 25 June 2019

The stringent application of the suggestion to double dolutegravir dose in patients taking *Hypericum*, beside the problems of increased costs, might in fact potentially result in an unjustified overexposure to dolutegravir, which has been recently associated with the development of drug-related neurological adverse events [10]. Indeed, a more reasonable approach to handle this potential DDI would be using therapeutic drug monitoring and/or viral load to assess any effect that may be caused by co-administration.

Activities of the GAP outpatient clinic

- Collection of detailed anamnestic, clinical, therapeutic (ARVs and comedications) and ad hoc laboratory data
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- Prescription of the pharmacokinetic and pharmacogenetic tests offered by the hospital's Pharmacological Service (when deemed appropriate)
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- Preparation of a written report for the general practitioner, attending physician and other specialists

- Gervasoni et al, AIDS Rev 2019 -

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Ambulatorio GAP (Gestione Ambulatoriale Politerapie)
Infettivologo: Dott.ssa Cristina Gervasoni
Farmacologo: Dott. Dario Cattaneo
tel. 02/3904.2092 o .2858
cristina.gervasoni@unimi.it
dario.cattaneo@asst-fbf-sacco.it

Il paziente è attualmente in terapia antiretrovirale con:

-

Oltre alla terapia antiretrovirale il paziente sta assumendo:

-

INTERAZIONI FARMACOLOGICHE IPOTIZZABILI SU BASE TEORICA

Co-somministrazione controindicata (considerare regimi alternativi)

Co-somministrazioni che richiedono un attento monitoraggio

Interazioni di minore rilevanza clinica

Valutazione dell'Anticholinergic Cognitive Burden (ABC) Score

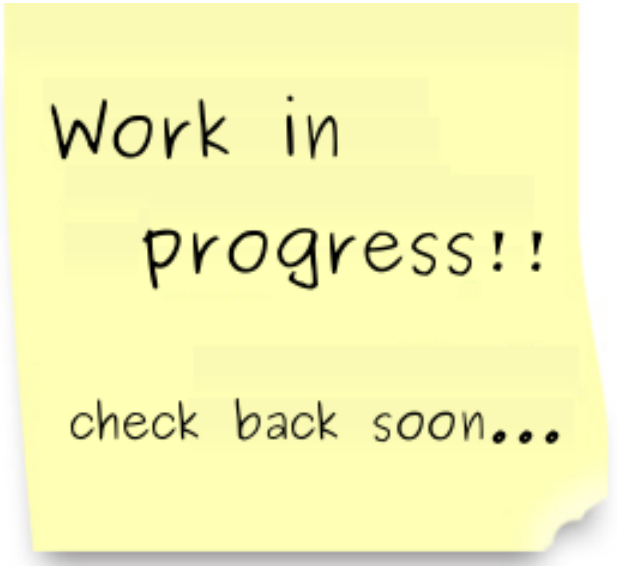
ABC score:

Monitoraggio terapeutico della terapia assunta

Commento finale

The future of GAP….

- ✓ Routine application of STOPP/START & Beers criteria in all HIV-infected patients with >50 (or>65?) yrs…
- ✓ Follow-up analysis of all patients enrolled in GAP…
- ✓ Open the GAP service also to HIV-negative patients with polypharmacy…



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UNIVERSITÀ DEGLI STUDI DI MILANO

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
Isabella Bronzino
Tiziana Formenti
Bianca Ghisi
Andrea Giacomelli
Paola Meraviglia
Davide Minisci
Chiara Resnati
Giuliano Rizzardini
Massimo Galli

Grazie Cristina…

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