Ospedale Luigi Sacco
POLO UNIVERSITARIO

Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

Multidisciplinary experience to manage polypharmacy in HIV-positive persons

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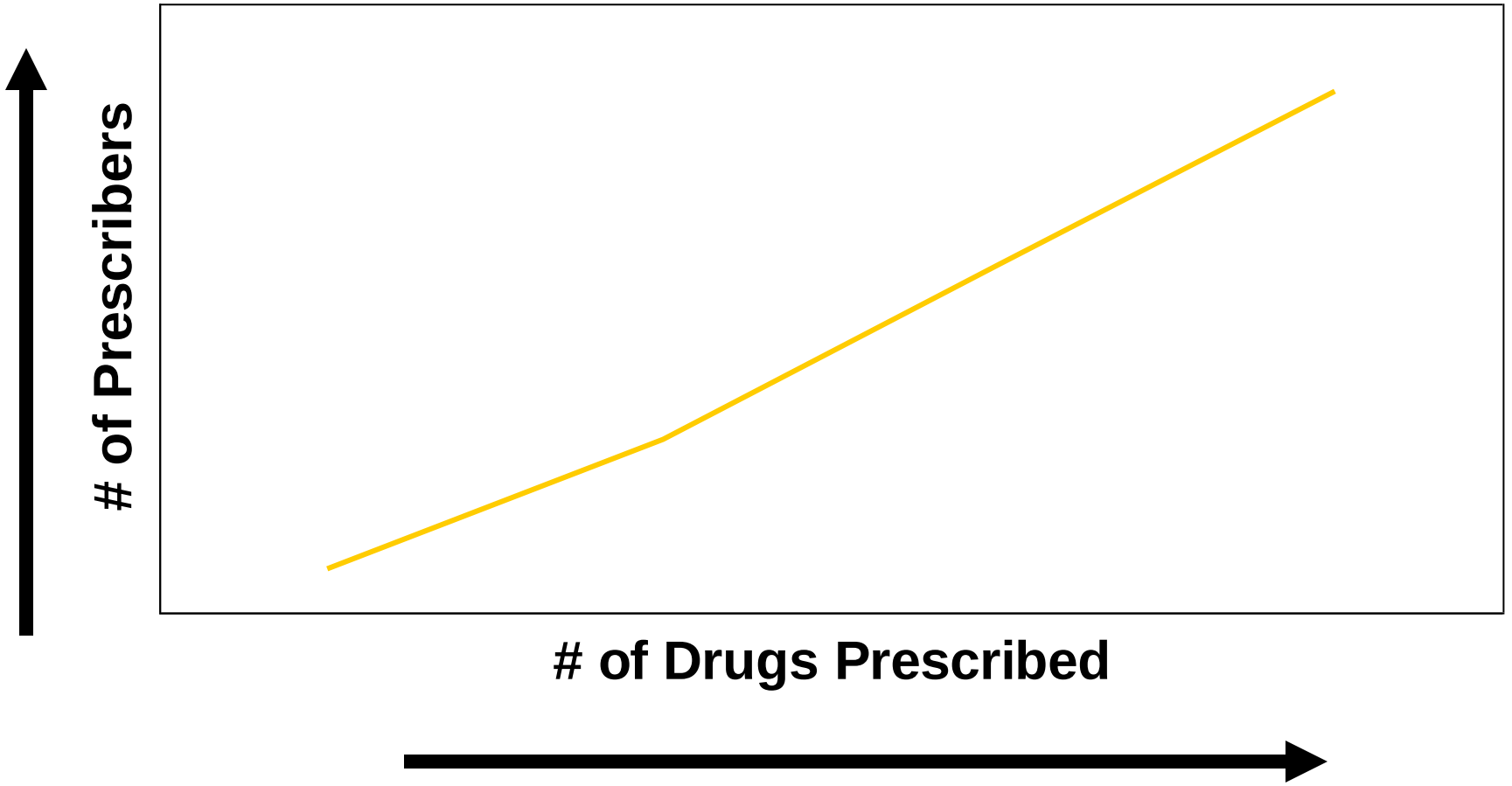
International Association of
Therapeutic Drug Monitoring and Clinical Toxicology
Fostering education, research and practice in TDM and CT

Prevalence of comorbidities in PLWH

	Population	Mean age, years	Diabetes, %	Dyslipidaemia, %	Hypertension, %	Renal disease, %	CVD disease, %	Bone disorder, %	Respiratory disorder, %	Cancer, %
Brazil [28]	451 PLWH	58	14.9	26.7				6.7		3.1
3 HIV centres										
Brazil [29]	208 PLWH	57	22.6		62.0	16.8	9.6	52.9		10.6
Brazilian cohort	*208 HIV neg*	*57*	*28.4*		*69.7*	*6.7*	*12.5*	*10.1*		*6.3*
USA [30]	2359 PLWH	71	25.9	35.7	47.9		20.9	20.3	31.3	
Medicare	*2 mio HIV neg*	*76*	*24.1*	*46.9*	*59.4*		*19.6*	*21.4*	*26.3*	
Portugal [31]	401 PLWH	59	13.5	60.8	39.7	8.0		5.7	9.0	8.0
7 HIV centres										
France [32]	16436 PLWH	56	9.1	58.3	21.0	4.5	10.8	6.4		12.3
Dat'AIDS cohort	572 PLWH	78	22.0	60.8	43.5	29.4	23.4	12.6		22.9
France [19]	10318 PLWH	56	9.3	23.6	21.0	9.6	9.0			14.6
11 HIV centres										
Europe [33]	3797	50 to 60	8.0	79.5	79.0	7.0	7.0			
EuroSIDA cohort[a]	PLWH	≥60	17.0	84.0	84.0	23.0	15.5			
	1837 PLWH									
Italy [34]	965 PLWH	65 to 74	27.5	70.0	60.8	17.1	16.9		6.6	
GEPPO cohort	*224 HIV neg*	*65 to 74*	*22.3*	*57.8*	*66.5*	*5.0*	*18.3*		*9.1*	
	293 PLWH	≥75	31.2	74.6	71.8	26.0	29.2		9.8	
	91 HIV neg	*≥75*	*15.4*	*50.0*	*67.0*	*10.0*	*30.8*		*18.9*	

- Back et al, J Int AIDS Soc 2020 -

More Comorbidities…more drug prescribers… more drugs prescribed!!!



Nolan L et al.. JAGS 1988

Prevalence of polypharmacy (≥5 non-HIV drugs) in PLWH aged 50 years and older

Reference	Country	N	Age	Polypharmacy
Livio F et al. Int Work Clin Pharm HIV 2018	Switzerland	111	≥ 75	60%
Courlet P et al. CROI 2019	Switzerland	131	≥ 65	46%
Guaraldi G et al. BMC Geriatr 2018	Italy	1258	≥ 65	37%
Justice A et al. AIDS 2018	USA	1311	≥ 65	43%
Halloran MO et al. Antivir Ther 2019	UK/Ireland	698	≥ 50	30%
Lopez-Centeno B et al. HIV Drug Ther 2018	Spain	10073	≥ 50	47%
Nunez-Nunez M et al. Farm Hosp 2018	Spain	242	≥ 50	48%
Ruzicka DJ et al. BMJ Open 2018	Japan	526	≥ 50	35%
Ssonko M et al. BMC Geriatr 2018	Uganda	411	≥ 50	15%
Krentz H et al. AIDS Pat Care STDS 2016	Canada	386	≥ 50	43%
Holtzman C et al. J Gen Intern Med 2013	USA	1312	≥ 50	54%

- Back et al, J Int AIDS Soc 2020 -

DDIs in PLWH (N=22,945) according to Co-meds

Co-meds (ATC Code)	Red-flag		Orange-flag		Yelow-flag		Green-flag	
	Nº	%	Nº	%	Nº	%	Nº	%
Nervous system drugs (N)	115	0.50	1,833	7.99	1,163	5.07	5,686	5.07
Cardiovascular drugs (C)	97	0.42	674	2.94	730	3.18	3,512	3.18
Musculoskeletal system (M)	1	0.00	575	2.51	16	0.07	3,208	0.07
Antiinfectives (J)	7	0.03	353	1.54	128	0.56	3,179	0.56
Respiratory system (R)	314	1.37	324	1.41	386	1.68	2,248	1.68
Blood drugs (B)	61	0.27	368	1.60	0	0.00	1,998	0.00
Gastrointestinal drugs (A)	62	0.27	273	1.19	9	0.04	1,841	0.04
Dermatological drugs (D)	117	0.51	394	1.72	90	0.39	953	0.39
Systemic Hormones (H)	5	0.02	466	2.03	0	0.00	905	0.00
Genitourinary drugs (G)	11	0.05	342	1.49	20	0.09	674	0.09
Antineoplastic drugs (L)	0	0.00	15	0.07	0	0.00	230	0.00
Sensory organs (S)	0	0.00	23	0.10	31	0.14	179	0.14
Antiparasitic drugs (P)	0	0.00	42	0.18	84	0.37	134	0.37
Various/Therapeutic drugs (V)	0	0.00	0	0.00	0	0.00	0	0.00

Red-flag = contraindicated.

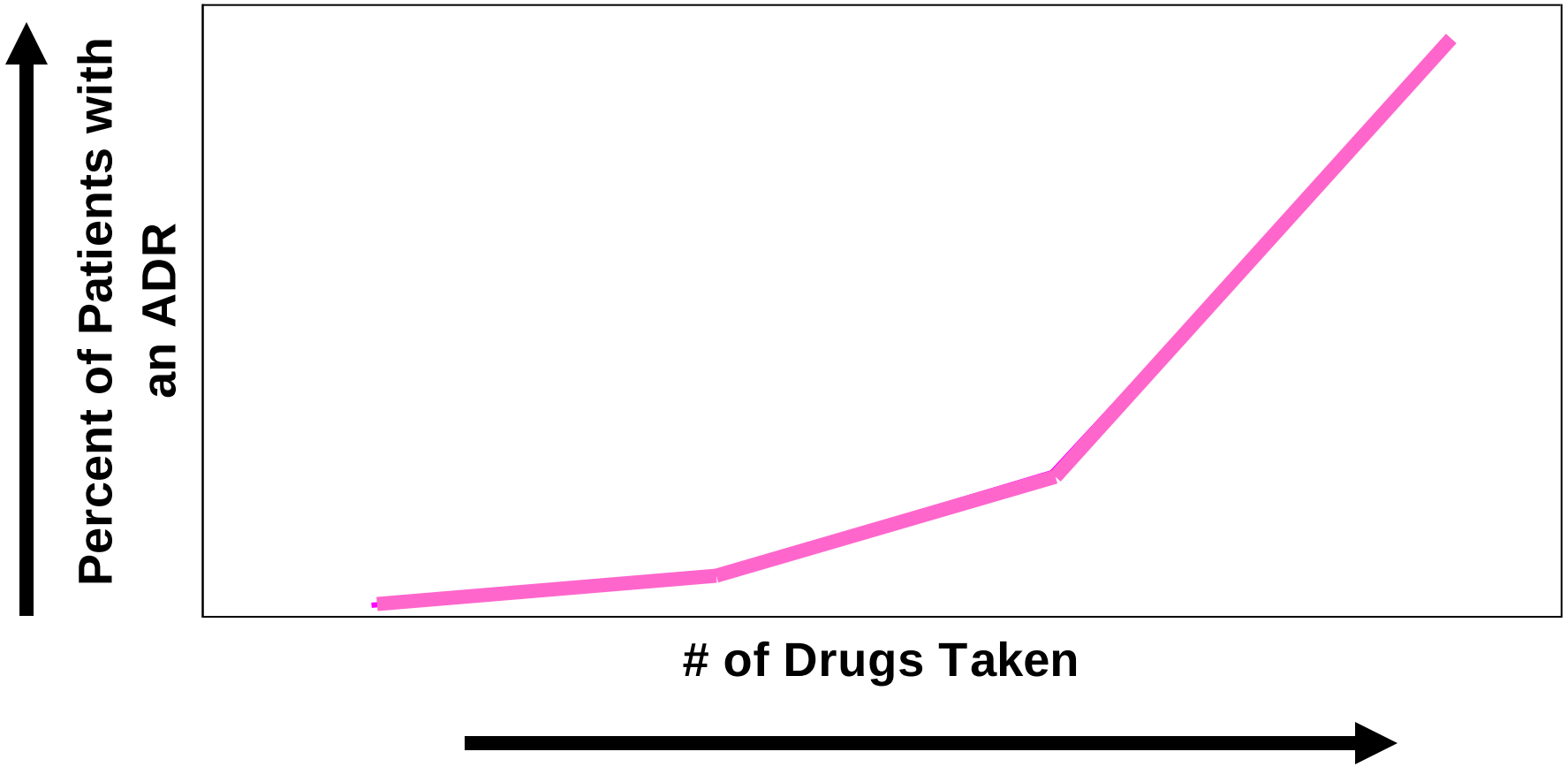
Orange-flag = potential interaction: require dosage modification or close monitoring.

Yellow-flag = weak potential interaction: no require additional monitoring or dosage adjustment.

Green-flag = non clinically significant interaction.

Lopez-Centeno B, et al. CID 2020

Polypharmacy/DDIs are exponentially related to adverse drug reactions



Nolan L et al.. JAGS 1988

Risk factors for potentially preventable hospital readmissions among persons living with human immunodeficiency virus infection

- ✓ Single center retrospective study from the University of New Mexico Hospitals. Of the 908 identified admissions for PLWH during 2010-2014, 7.8% were 30-day readmissions

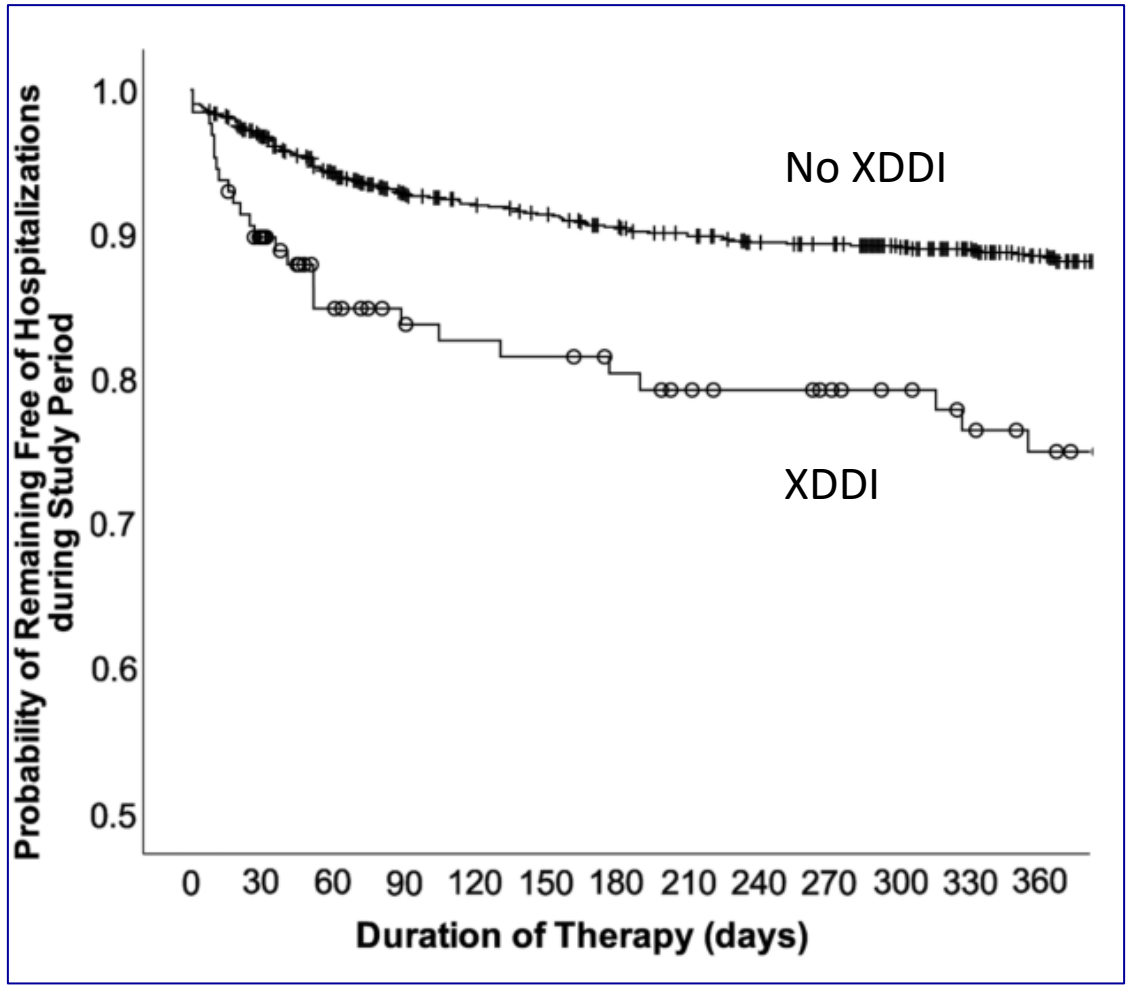
Table 2. Multivariate logistic regression analysis of characteristics of people living with HIV with 30-day readmissions and their association with PPR.

	Multivariate logistic regression analysis	
Covariate	Odds ratio (95% CI)	*p*-value
≥10 discharge medications	3.92 (1.181–13.043)	0.026*
Not on ART on index admission	5.59 (0.936–33.405)	0.059
Scheduled follow-up appointment documented at discharge	3.59 (1.057–12.212)	0.041*

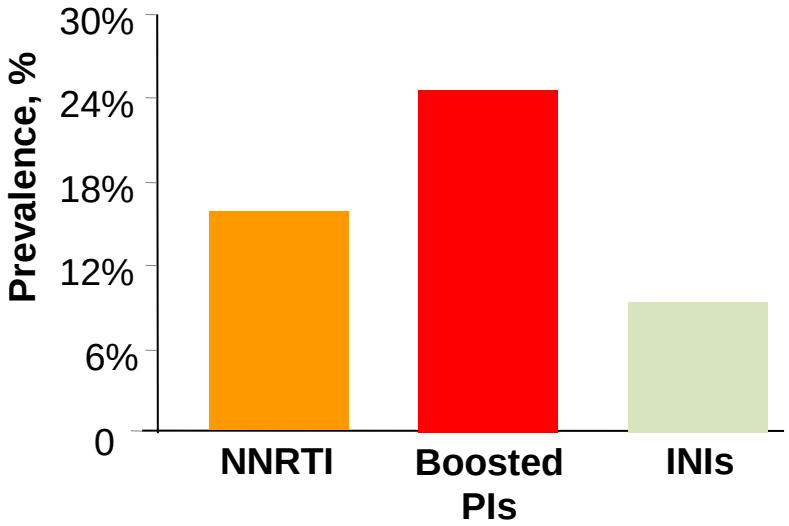
*Indicates statistical significance ($p < 0.05$).

- Hadlock et al, Aids Care 2021 -

Relationship Between Contraindicated Drug–Drug Interactions (XDDI) and Subsequent Hospitalizations Among PLWH Initiating Combination Antiretroviral Therapy



- ✓ Of the 1329 patients evaluated, 149 (11.2%) patients were hospitalized within 1 year of antiretroviral therapy initiation



- Sangiovanni et al, AIDS Res Hum Retroviruses 2019 -

HIV Drug Interactions

Do Not Coadminister
Ritonavir (RTV)
Budesonide

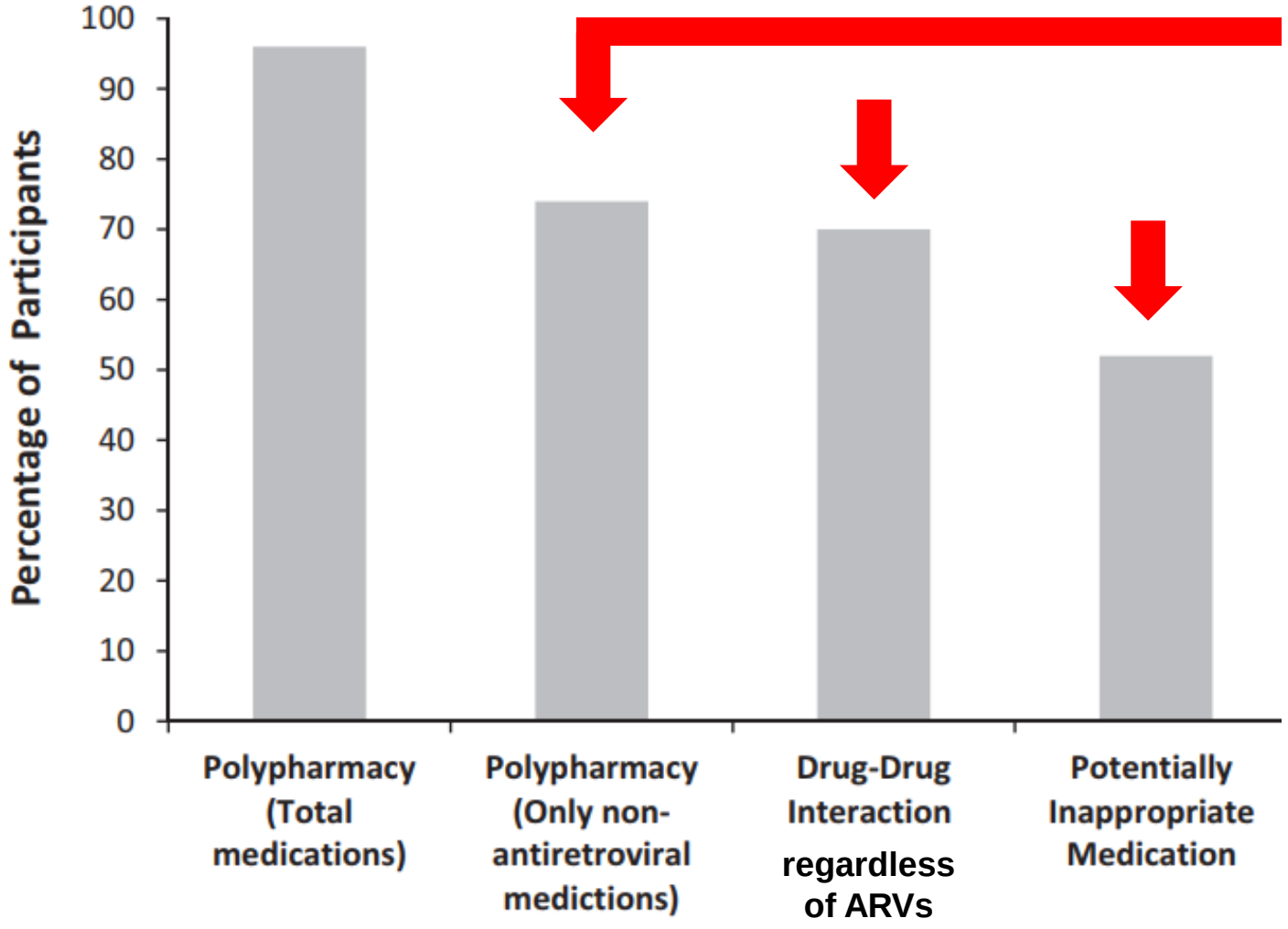
Do Not Coadminister
Atazanavir/cobicistat (ATV/c)
Triamcinolone

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 -

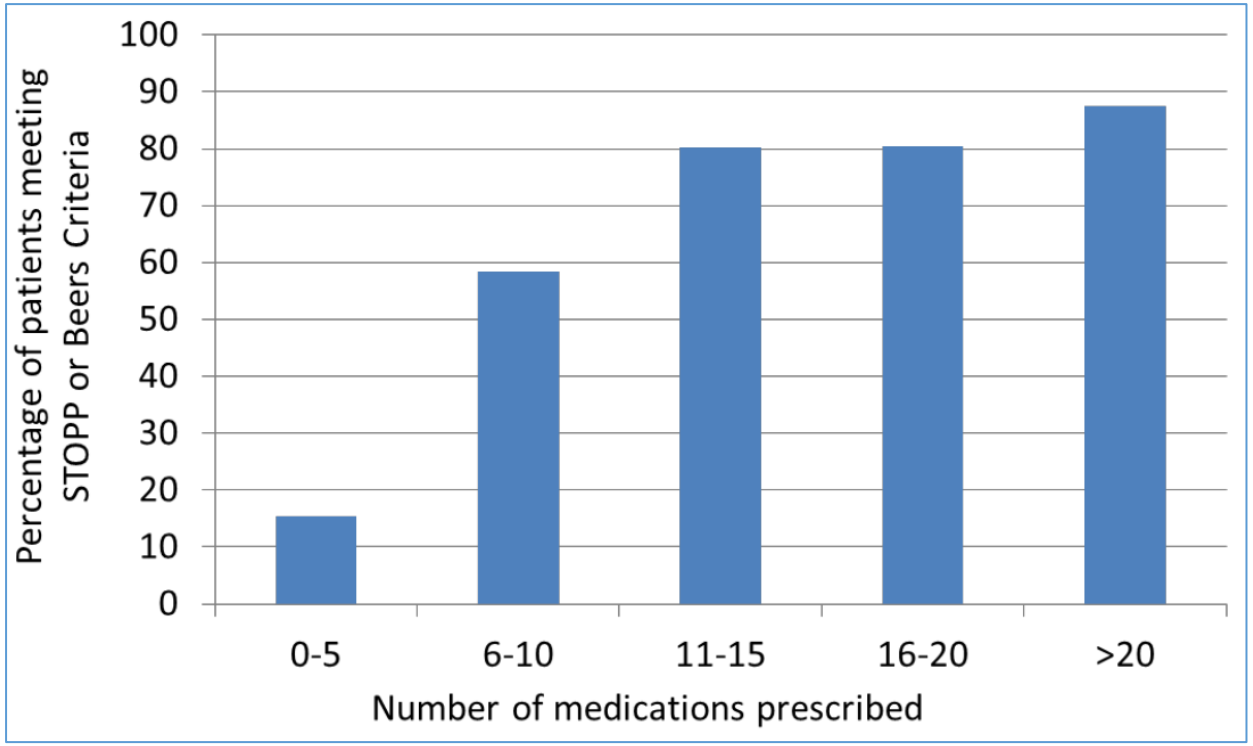
..There is more we can do than just check DDIs involving ARVs….



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

- Green et al, J Am Geriatr Soc 2014 -

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



Characteristics	Results
Age, years	57.8 ± 5.1
N° of drugs before intervention	14.2 ± 5.9
Antiretroviral pill burden	3.5 ± 2.0
N° of medication removed	2.2 ± 2.5
Contraindicated DDIs	25
N° of drugs after intervention	12.4 ± 5.3

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

- McNicholl et al, Pharmacother 2017 -

..There is more we can do than just check DDIs involving ARVs….

Medication	Median (Interquartile Range)
Total	13 (9–17)[a]
Antiretrovirals	4 (3–5)
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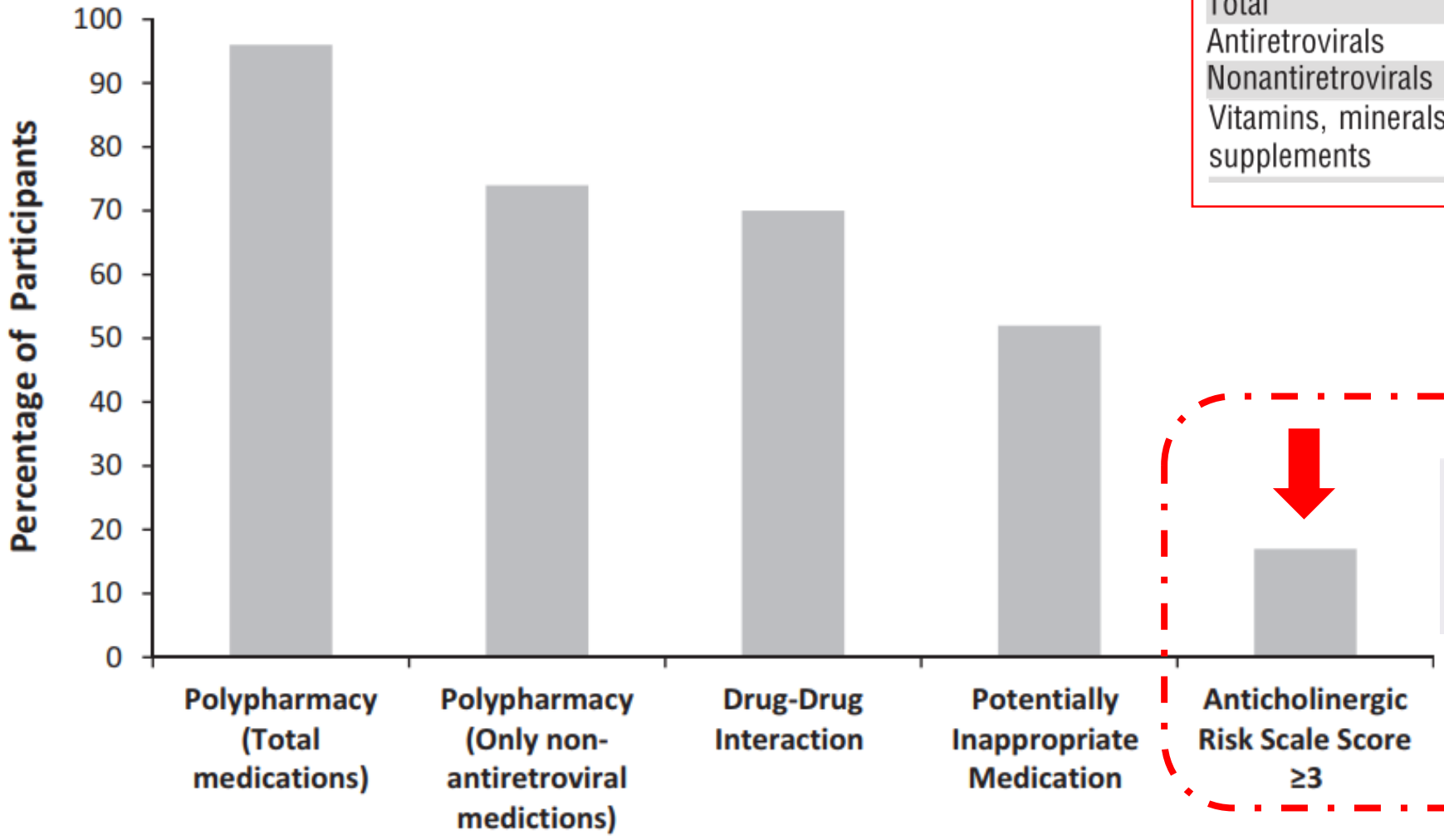
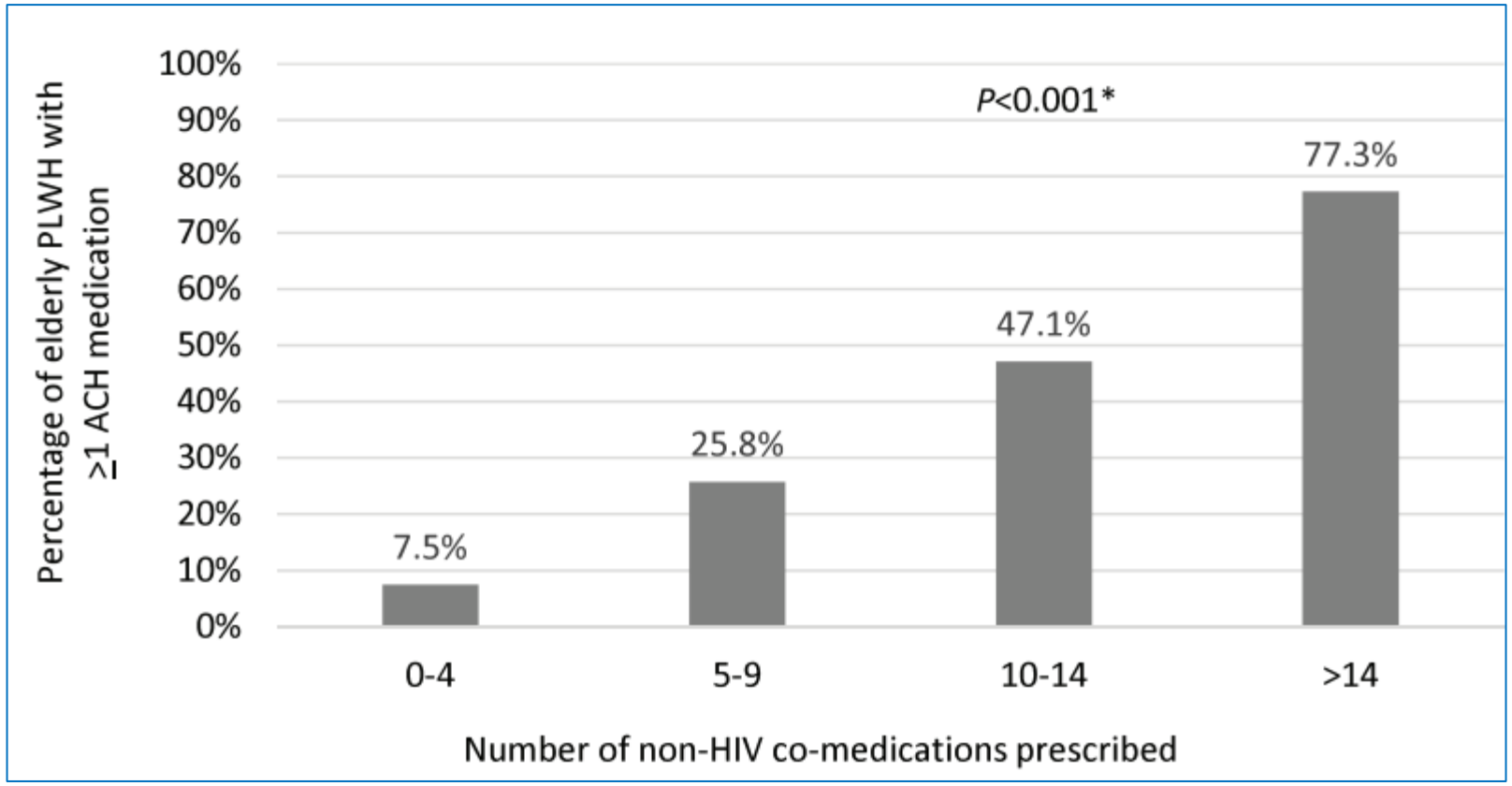


↑ sensitivity (agitation, confusion, decompensation of glaucoma, dry mouth, constipation, urinary retention…) **Injurious falls**

- Greene et al, J Am Geriatr Soc 2014 -

Anticholinergic medication use in elderly people living with HIV and self-reported neurocognitive impairment: a prospective cohort study

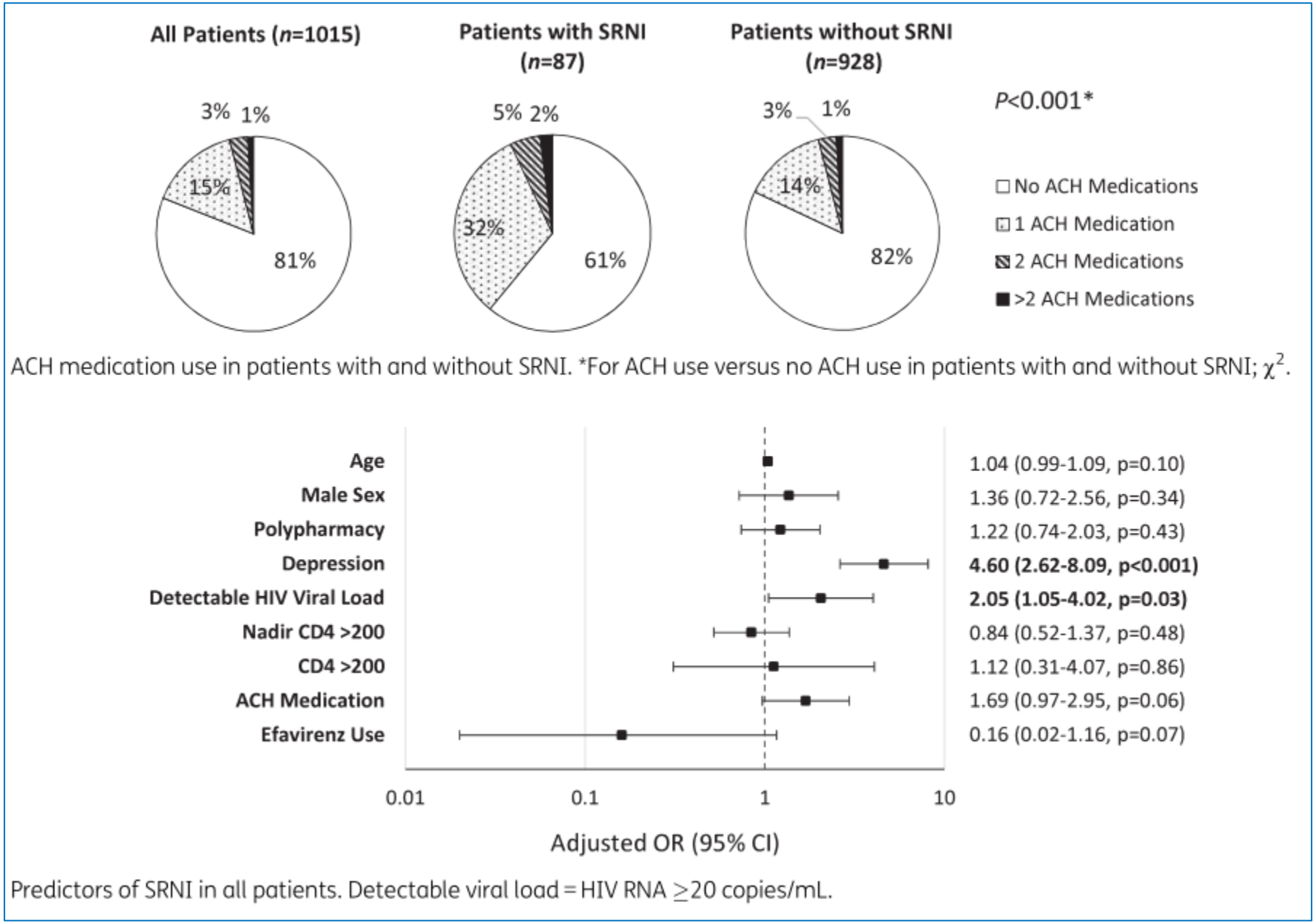
✓ 1019 PLWH (82% male) with a median age of 70 (IQR = 67–74) years were included



Most commonly prescribed medications with ACH activity

	n (%)
ACH score 1	
mirtazapine	25 (10)
citalopram	22 (9)
escitalopram	19 (7)
duloxetine	17 (7)
sertraline	14 (5)
glycopyrronium	9 (4)
ranitidine	7 (3)
fluoxetine	7 (3)
ACH score 2	
quetiapine	7 (3)
ACH score 3	
trimipramine	10 (4)
paroxetine	8 (3)

- Jakeman and Marzolini, JAC 2021 -



SRNI: self-reported neurocognitive impairment

- Jakeman and Marzolini, JAC 2021 -

Gestione Ambulatoriale Politerapie*

*Multidisciplinary outpatient clinic

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UNIVERSITÀ DEGLI STUDI DI MILANO

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

From the lab…
Sara Baldelli
Igor Bonini
Simone Castoldi†
Valeria Cozzi
Cristina Montrasio
Stefania Cheli
Marta Fusi
Chiara Resnati
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
Laura Pezzati
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

September 2016

13° CONGRESSO NAZIONALE
Italian Conference on AIDS and Antiviral Research
Riccione 21-23 Ottobre 2021

Promosso da SIMIT

n. P66

POSTER 4 YOU ICAR 2021

Management of polypharmacy in people living with HIV: A 5-year experience of a multidisciplinary outpatient clinic

- ✓ The GAP database (>1000 PLWH on active follow-up) was retrospectively investigated to search for patients with at least 2 recorded visits from September 2016 to June 2021

Characteristics	Data
Patients	556
Age, years	55±11
Females, n (%)	167 (30%)
HIV diagnosis, years	19 ± 11
Co-medications^	4.2 ± 2.7 (1-17)

Co-medications	Data
< 50 years of age	3.0 ± 2.2
50-64 years of age	4.1 ± 2.5**
> 65 years of age	6.3 ± 3.2**
Females	3.8±2.6
Males	4.3±2.8*

^excluding HAART

**P<0,01 vs. other groups; *p<0.05 vs. females

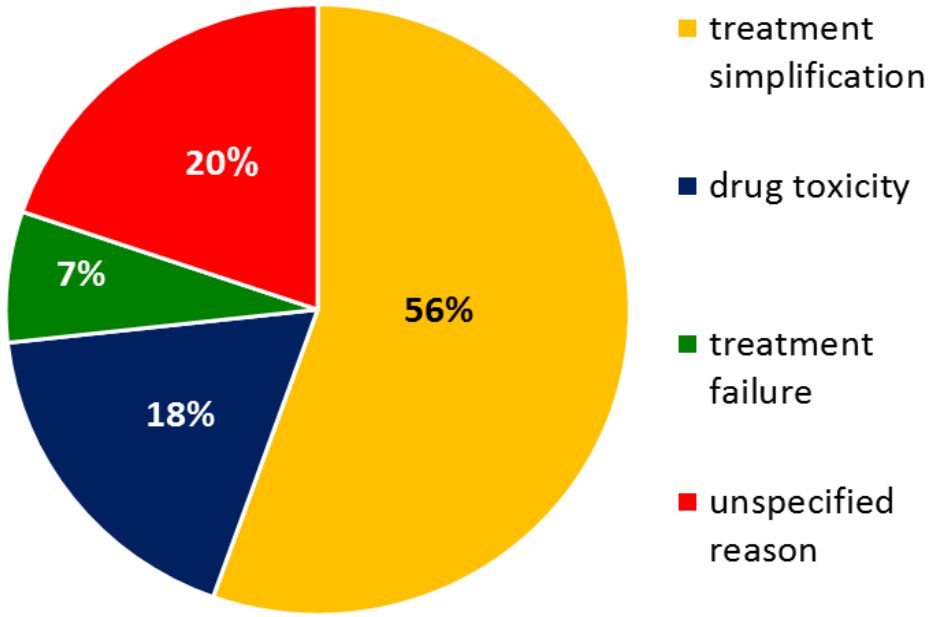
HAART	Data
Dual therapies, %	29%
3TC/DTG	22%
DTG/DRV/c	15%
DTG/RPV	14%
Other	49%
Triple therapies, %	71%
TAF/FTC/RPV	21%
ABC/3TC/DTG	17%
TAF/FTC/BIC	14%
Other	52%

	Dual	Triple
Age	58±9**	54±11
History of HIV	21±9*	18±11
Comedications	5.1±3.2**	3.8±2.5

*p<0,5; **p<0,01

Reasons for changing the ARV

- ✓ 39% of PLWH switched their antiretroviral therapies at the second GAP visit

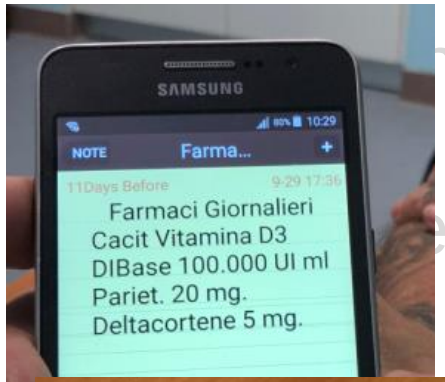


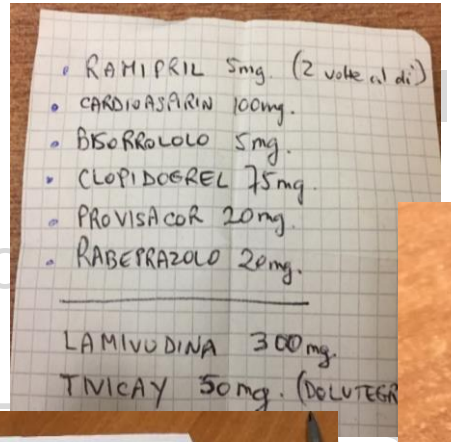
- ✓ 32% of the switches were from triple to dual therapies
- ✓ Booster-based ARVs decreased moving from the 1st to the 2nd GAP visit (53% vs. 23%; p<0,001)

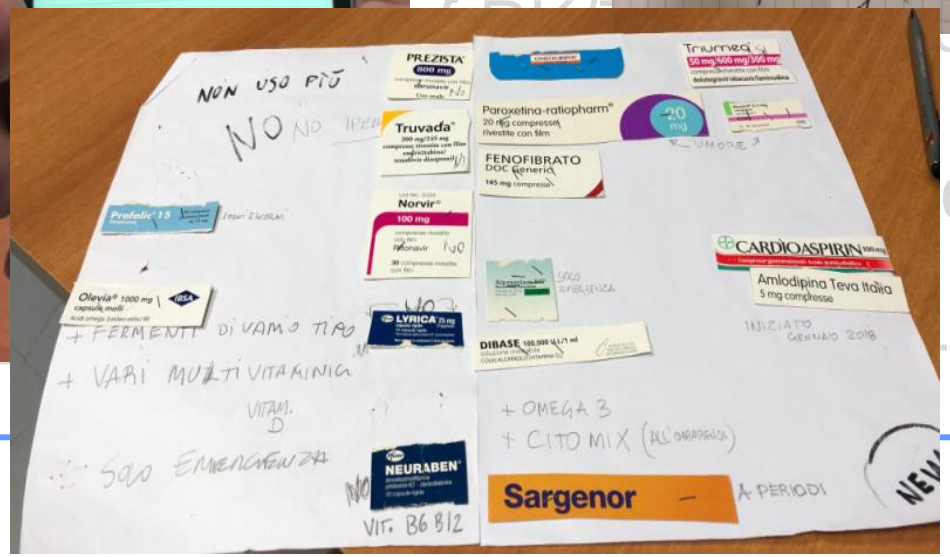
- Resnati et al, ICAR 2021 -

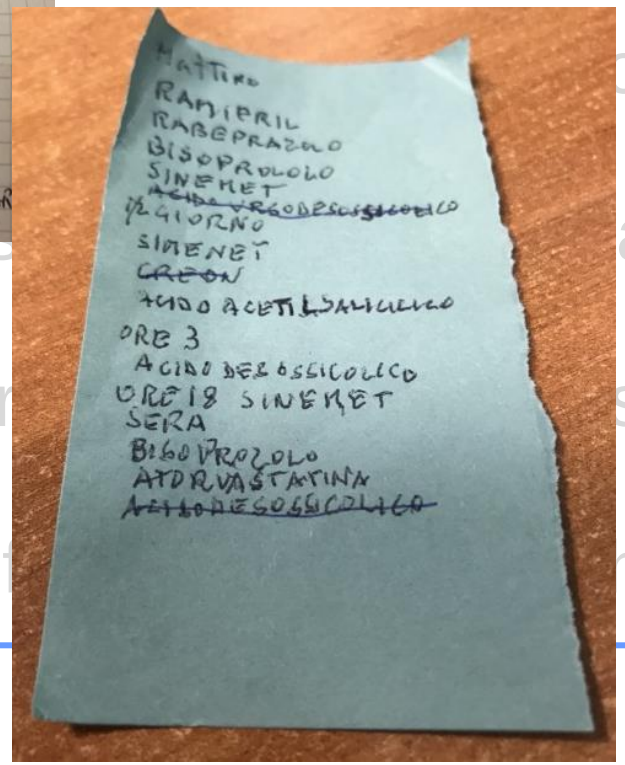
Activities of the GAP outpatient clinic

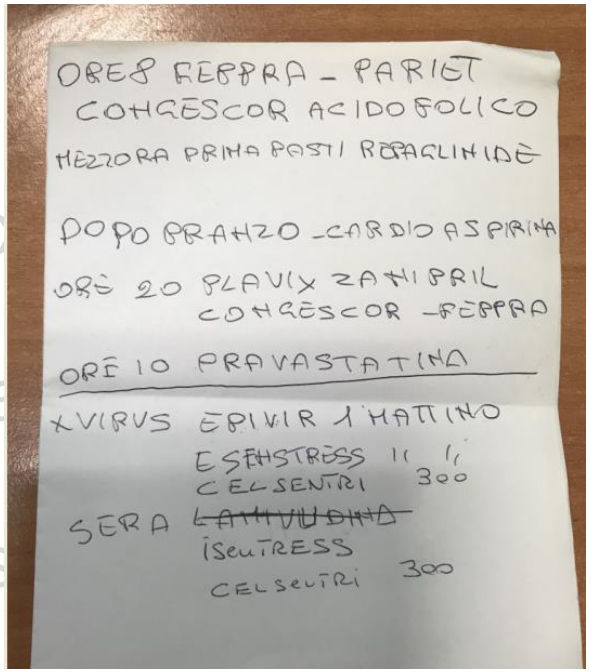
- Collection of anamnestic, clinical, therapeutic and laboratory data











- Gervasoni et al, AIDS Rev 2019 -

Activities of the GAP outpatient clinic

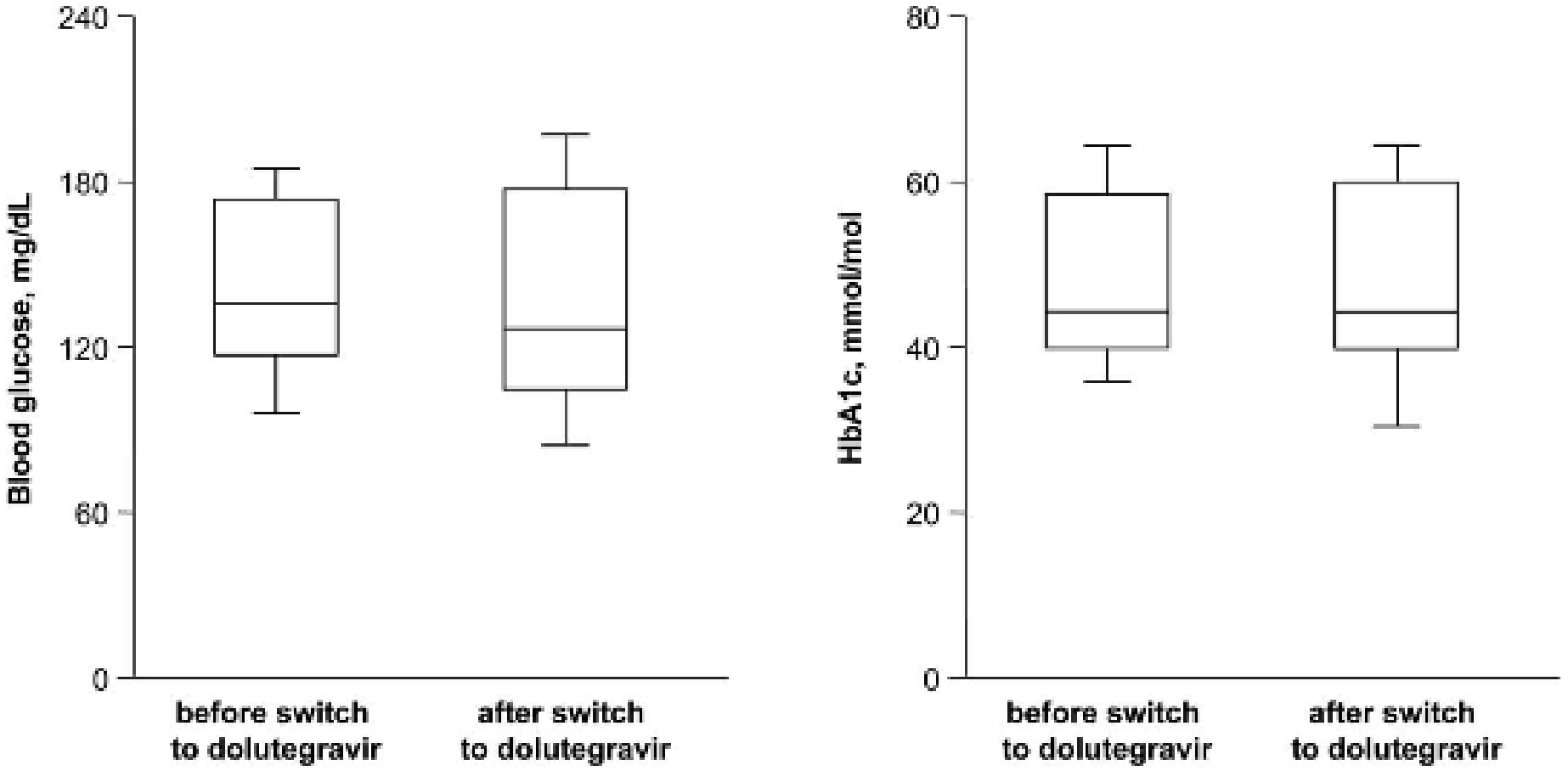
- Collection of anamnestic, clinical, therapeutic and laboratory data
- Check for clinically relevant DDIs and PIMs
- Check for the use
- Prescription of PK
- Evaluation of the
- Preparation of a v

- Gervasoni et al, AIDS Rev 2019 -

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

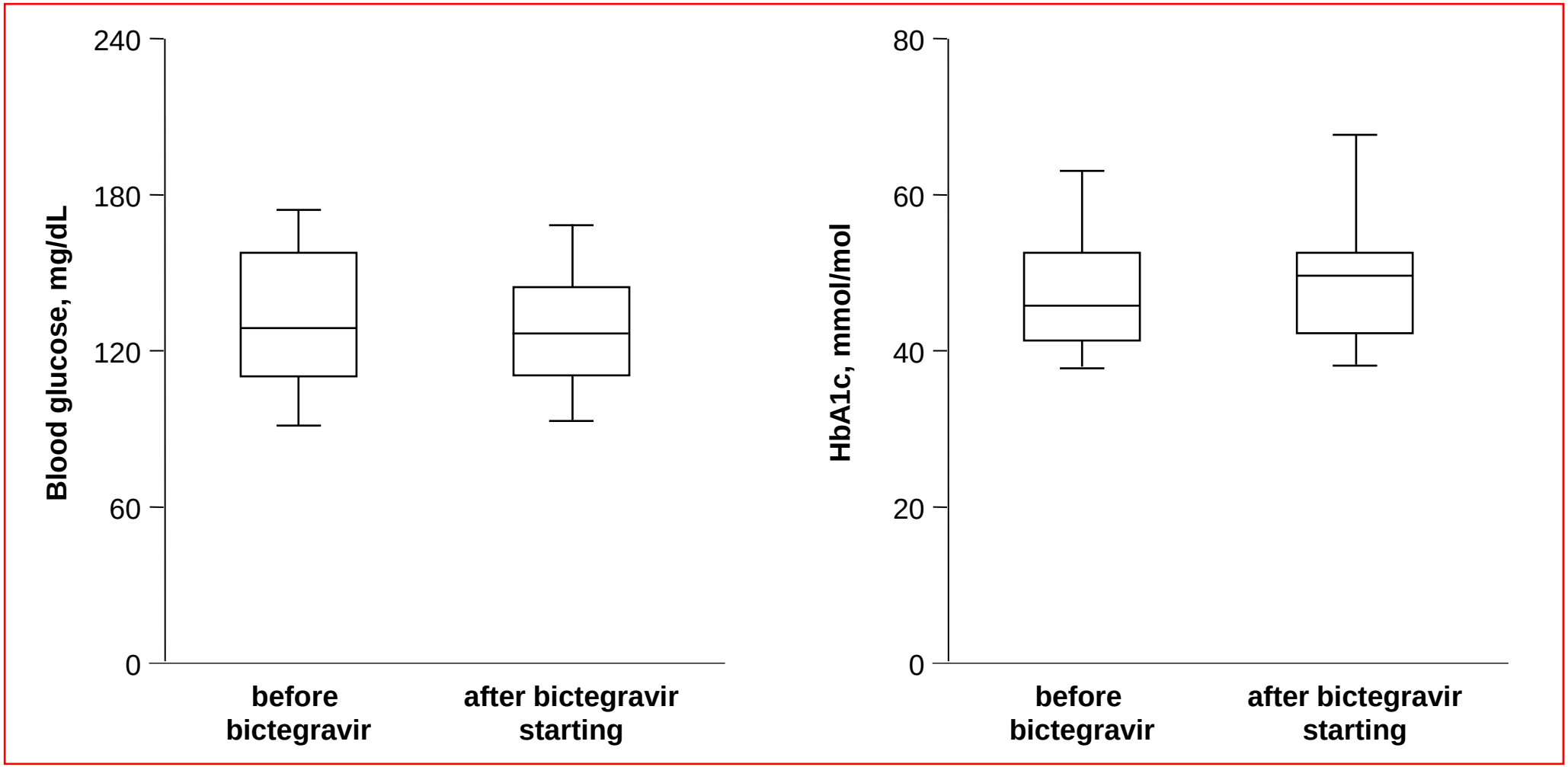
How Relevant is the Interaction Between Dolutegravir and Metformin in Real Life?

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

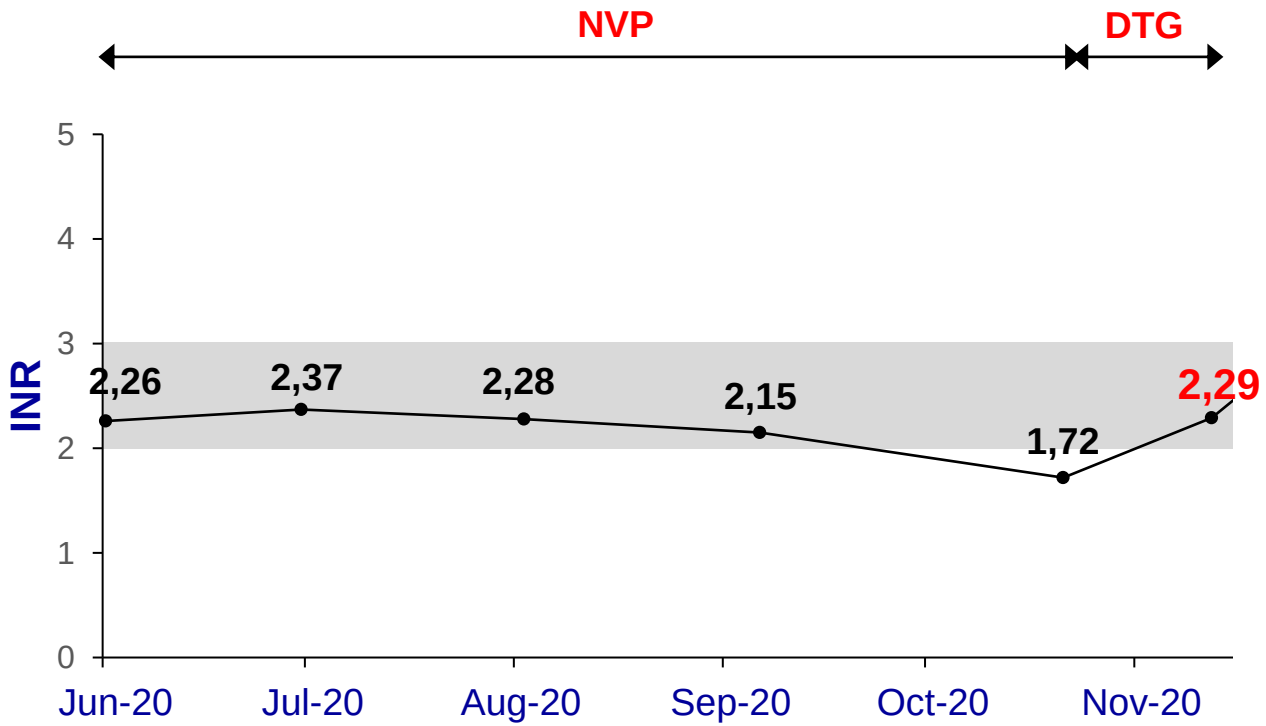


- Cattaneo et al, JAC 2021 -

“When the absence of a DDI can become clinically relevant…”

A 50-year-old woman living with HIV

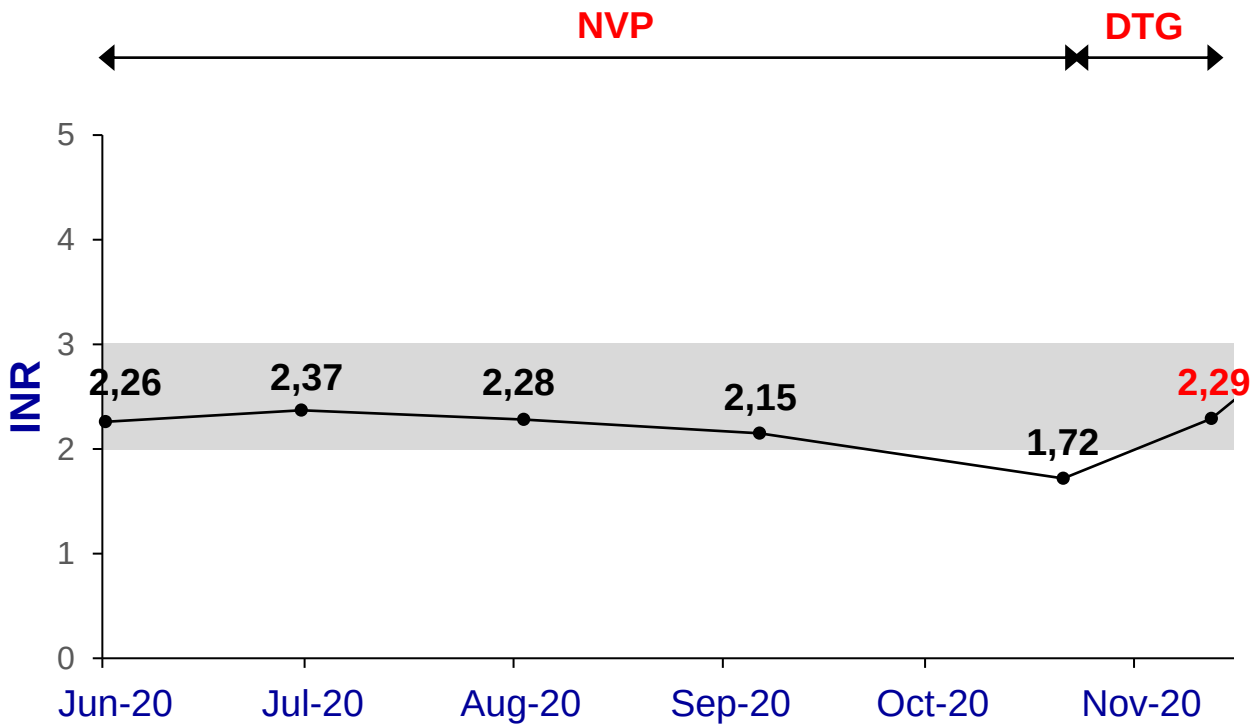
- On warfarin for deep venous thrombosis since 2007
- On NVP/3TC/ABC since 2015
- November 2020: ARV switched to DOLU/3TC (treatment simplification)



Warfarin given at 8,75 mg/daily from Monday to Saturday and at 7,5 mg/daily on Sunday

- Cattaneo et al, AIDS 2021 -

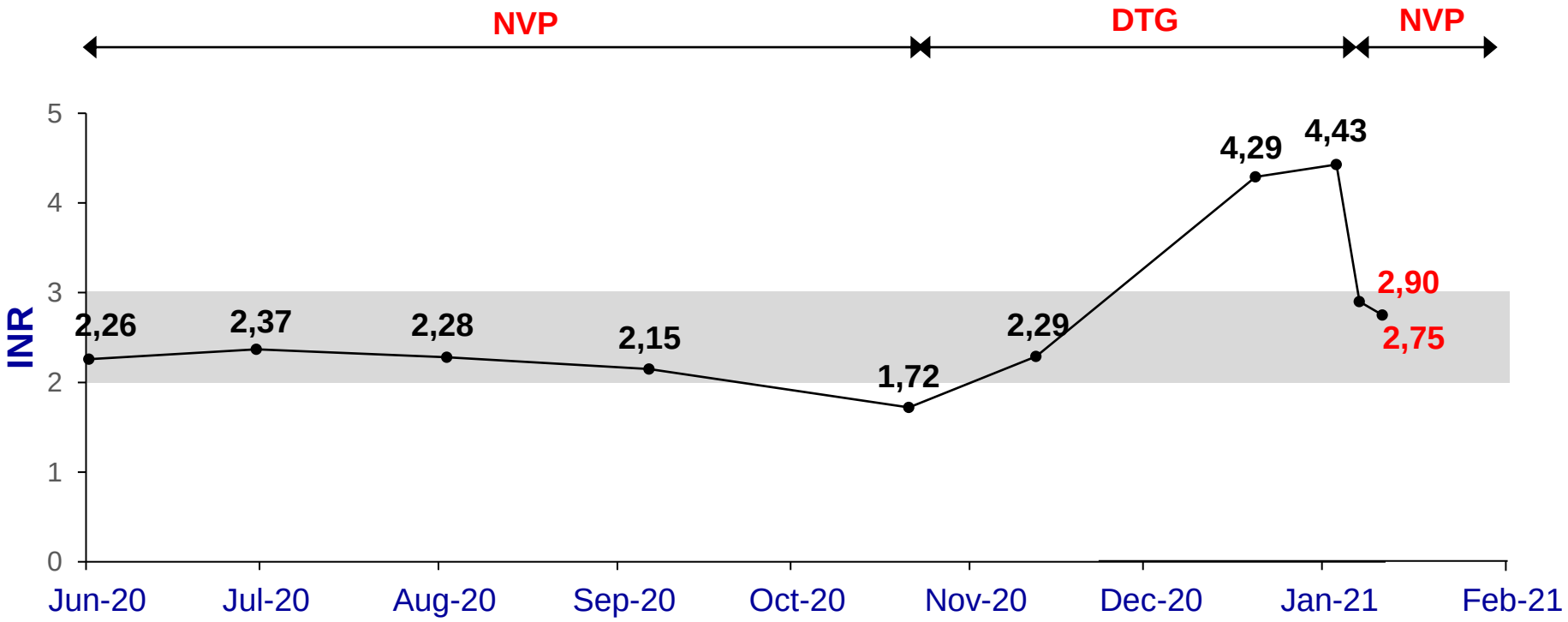
- December 2020: gum bleeding while brushing her teeth.
- INR was not measured because in Italy we were experiencing the peak of the second COVID-19 pandemic wave



Warfarin was voluntarily reduced by the patient to 7,5 mg/daily

- Cattaneo et al, AIDS 2021 -

- December 29: INR, measured for the persistence of gingival bleeding, revealed over-anticoagulation
- The antiretroviral therapy was switched back to previous regimen



- Cattaneo et al, AIDS 2021 -

HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

No Interaction Expected

Dolutegravir/Lamivudine (DTG/3TC)

Warfarin

Quality of evidence: Very Low

Summary:
Coadministration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely. Warfarin is a mixture of enantiomers which are metabolized by different cytochromes. R-warfarin is primarily metabolized by CYP1A2 and 3A4. S-warfarin (more potent) is metabolized by CYP2C9. Dolutegravir is not expected to inhibit or induce CYP450 enzymes at clinically relevant concentrations. No interaction is expected with lamivudine.

- ✓ We excluded that the increase of the INR resulting in bleeding was related to a DDI between dolutegravir and warfarin…

- Cattaneo et al, AIDS 2021 -

Potential Interaction

Nevirapine (NVP)

Warfarin

Quality of evidence: Moderate

Summary:
Coadministration may alter warfarin concentrations. The nature and magnitude of any effect may change with time. Frequent monitoring of INR recommended.

Description:
The interaction between nevirapine and the antithrombotic agent warfarin is complex, with the potential for both increases and decreases in coagulation time when used concomitantly. Close monitoring of anticoagulation levels is warranted.

In case studies of three Italian patients all taking antiretroviral therapy including nevirapine plus warfarin, all experienced increased Quick times. In the first case 5 mg of warfarin per day was able to stabilise anticoagulant activity. In the second case 12 mg of warfarin was required and in the third case only after stopping nevirapine was 7.5 mg of warfarin enough to achieve the therapeutic range needed.
Need for increased dose of warfarin in HIV patients taking nevirapine. Dionisio D, Mininni S, Bartolozzi D et al. AIDS, 2001,15:277–78.

- ✓ We assumed that a DDI had taken place between warfarin and nevirapine (NVP)
- ✓ In our patient this DDI had been well managed over the years by adjusting warfarin dosing based on INR results
- ✓ The switch to dolutegravir removed the effect of NVP on warfarin that was not immediately captured by INR because of the long drug half-life (2 weeks are needed to completely remove NVP from the body)
- ✓ The COVID-19 pandemic has created the “perfect scenario” hampering the proper INR assessments during ART switch

- Cattaneo et al, AIDS 2021 -

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

Milano, 26/11/2021

In data odierna è pervenuta al Nostro servizio una richiesta di verifica delle possibili interazioni farmacologiche nella Sig.ra [redacted] (UOC Oncologia).

La paziente è attualmente in terapia con:

- dolutegravir
- lamivudina
- abacavir
- amlodipina
- clopidogrel
- metoprololo
- pantoprazolo
- ramipril

Il quesito diagnostico riguarda le possibili interazioni farmacologiche tra la terapia in corso e la chemioterapia, modificata di recente, costituita da:

- bleomicina
- dacarbazina
- doxorubicina
- vinblastina

Potential Interaction

Dolutegravir (DTG)

Vinblastine

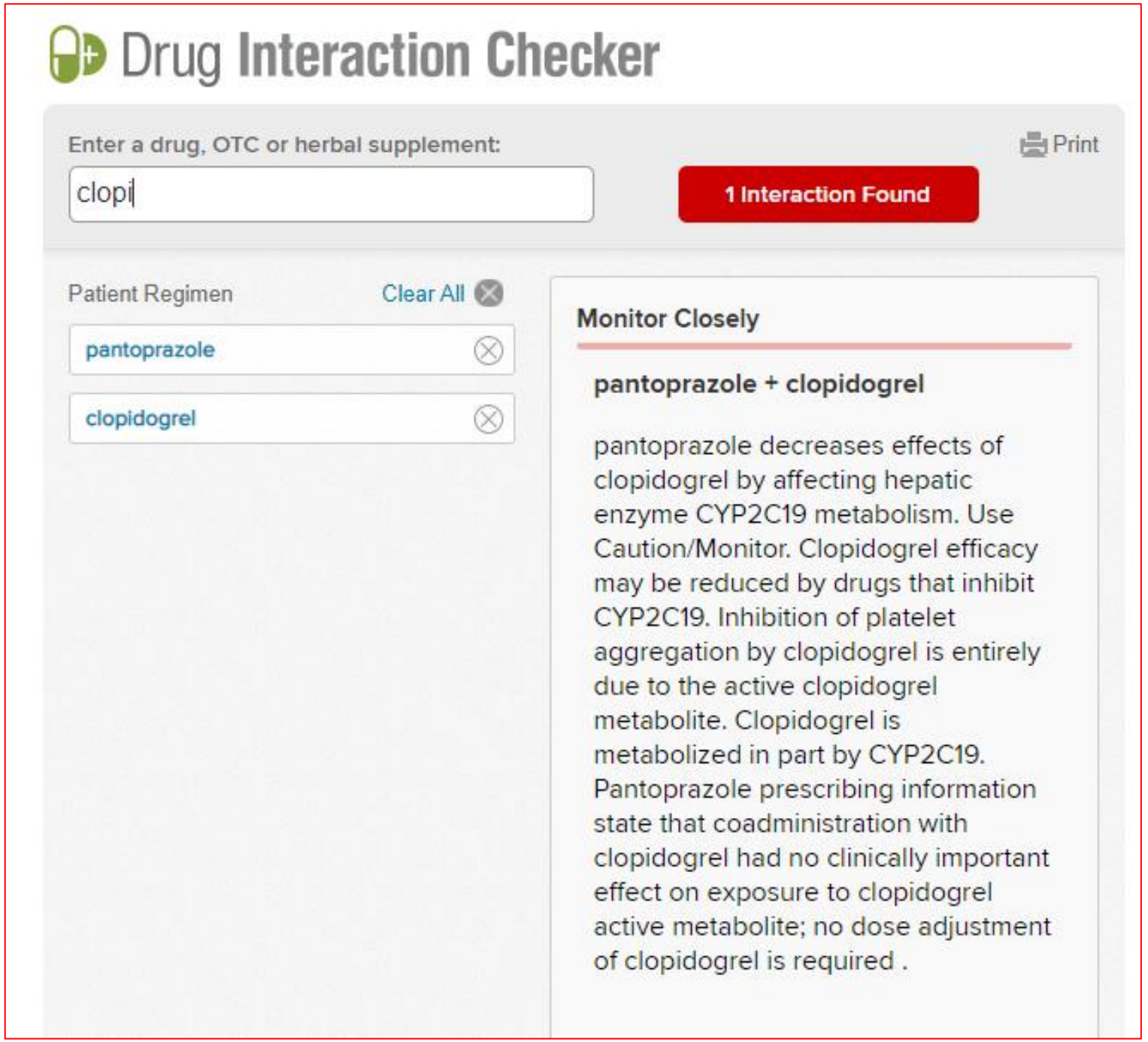
Quality of evidence: Very Low

Summary:

Coadministration has not been studied. Vinblastine is metabolized by CYP3A4, but dolutegravir is not expected to inhibit or induce CYP450 enzymes at clinically relevant concentrations. In vitro data suggest that vinblastine activates PXR and therefore could potentially decrease dolutegravir concentrations via induction of UGT1A1. Monitor response to antiretroviral therapy.

But…

In this HIV patient the most important DDI involve 2 non-antiretrovirals…



Activities of the GAP outpatient clinic

- Collection of anamnestic, clinical, therapeutic and laboratory data
- Check for clinically relevant DDIs and PIMs
- Check for the use of supplements, CAMs and recreational drugs
- Prescri tests opriate)
- Evalua drug
- Prepar ort fo ian

- Gervasoni et al, AIDS Rev 2019 -

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

The large majority of patients did not inform their healthcare providers of CAM usage

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

…The issues of CAMs, OTC and supplements…

Sex	Age	Antiretroviral therapy	Supplements, CAMs or OTC	Claimed indication	Clinical implications
Female	43	TDF/FTC/ATV/r	Orilistat	Weight loss	4-fold reduction of ATV trough and HIV virologic failure
Female	39	TDF/FTC/EFV	Orlistat	Weight loss	20-fold reduction of EFV trough and HIV virologic failure
Female	40	TDF/FTC/ATV/r	Sinetrol	Weight loss	9-fold reduction of ATV trough and HIV virologic failure
Male	44	TAF/FTC/DRV/c	Gunabasic, lipidum	Weight loss	HIV virologic failure
Male	45	TAF/FTC/ELV/c	CUT4HIM+	Weight loss	9-fold reduction of ELV trough and HIV virologic failure
Male	47	TAF/FTC/DRV/c	Ariix Slenderiiz Day & Night	Weight loss	6-fold increments of transaminases
Male	38	TAF/FTC/ELV/c	C4 Sport	Improve athletic performance	8-fold increments of transaminases
Male	42	TAF/FTC/RAL	Silymarin,	Improve athletic performance	6-fold increments of transaminases
Female	49	ETV/DRV/c	Green tea	Antioxidant	8-fold increments of transaminases

Cattaneo et al, Obesity 2018

Cattaneo et al, Eur J Clin Pharmacol. 2019

Cattaneo et al, Ann Pharmacother.2020

Cattaneo et al,. Clin Gastroenterol Hepatol. 2021

Chems4EU: chemsex use and its impacts across four European countries in HIV-positive men who have sex with men attending HIV services

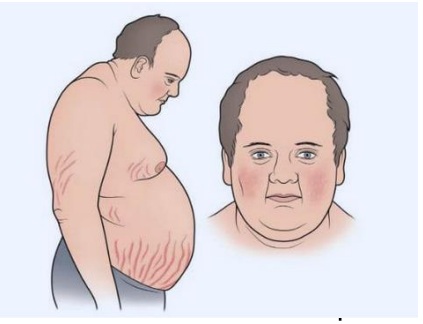
- ✓ In the previous 12 months, 45% had used recreational drugs, 24% reported chemsex and 6.5% reported injection of chemsex-associated drugs ('slamsex'). 41% reported unwanted side effects as a result of chemsex and 21% as a result of withdrawal from chemsex.

	All	UK	Spain	Greece	Italy
(a) Self-reported recreational drug use ($N = 709$)					
Total	709	271	223	160	55
Cannabis	399 (56.3)	126 (46.5)	116 (52.0)	119 (74.4)	38 (69.1)
Cocaine	301 (42.5)	134 (49.4)	92 (41.3)	105 (65.6)	20 (36.4)
GHB/GBL	247 (34.8)	116 (42.8)	71 (31.8)	48 (30.0)	12 (21.8)
Crystal methamphetamine	238 (33.6)	134 (49.4)	48 (21.5)	53 (33.1)	3 (5.5)
Ecstasy	198 (27.9)	91 (33.6)	71 (31.8)	35 (21.9)	1 (1.8)
Mephedrone	136 (19.2)	70 (25.8)	30 (13.5)	33 (20.6)	3 (5.5)
Ketamine	123 (17.3)	63 (23.2)	37 (16.6)	20 (12.5)	3 (5.5)
Amphetamine	80 (11.3)	36 (13.3)	26 (11.7)	15 (9.4)	3 (5.5)

- Whitlock et al, HIV Med 2021 -

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



Diagnosis of HIV

Start TAF/FTC/ELV/cobi

Good immunovirologic outcome, well being

Start GHB as recreational drug

New medical condition: hypothalamic-pituitary-adrenal axis block

New medical condition: depression

Start daily GHB as antidepressant

New medical condition: Cushing's syndrome

New medical condition: worsening of plaque psoriasis

Topical corticosteroids abuse

New medical condition: muscle weakness and fatigue

Start anabolic hormones injections

- Cattaneo et al, AIDS 2020 -

Activities of the GAP outpatient clinic

- ❑ Collection of anamnestic, clinical, therapeutic and laboratory data
- ❑ Check for clinically relevant DDIs and PIMs
- ❑ Check for the use of supplements, CAMs and recreational drugs
- ❑ Prescription of PK/TDM/PG tests (when deemed appropriate)
- ❑ Evaluation of the use of new drugs in HIV patients
- ❑ Preparation of a written report for the attending physician

- Gervasoni et al, AIDS Rev 2019 -

The case of enzalutamide…

(androgen receptor antagonist used for the treatment of prostatic cancer)

- ✓ A 63-year old male living with HIV was referred to our outpatient clinic with a diagnosis of prostate cancer Gleason score 9 (4+5), stage IV (bone metastasis)
- ✓ He was on maintenance antiretroviral therapy with ELV/cobi/TAF/FTC achieving full virological suppression and immunological recovery
- ✓ A hormonal therapy with degarelix was started and the patient underwent radiation therapy on the spinal column with a good clinical response
- ✓ In July 2021 a biochemical progression (increase of prostate-specific antigen levels) was observed and the oncologist prescribed him enzalutamide for the treatment of prostatic cancer in addition to degarelix
- ✓ It was decided to switch the antiretroviral therapy from ELV/cobi to dolutegravir (combined with TAF/FTC) to minimize the risk of potential DDIs…

- Londero et al, submitted 2022 -

HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

Potential Interaction

Dolutegravir (DTG)

Enzalutamide

Quality of evidence: Very Low

Summary:

Coadministration has not been studied. Enzalutamide is primarily metabolized by CYP2C8 and is a strong inducer of CYP3A4. Enzalutamide can induce UGT1A1. Dolutegravir is metabolized by UGT1A1 and to a lesser extent by CYP3A4. Dolutegravir has no inducing effects on CYPs. Coadministration is expected to decrease dolutegravir concentrations, thus dolutegravir should be administered at 50 mg twice daily in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided. Enzalutamide has a long half-life (5.8 days), therefore the dolutegravir dose should be kept at 50 mg twice daily for a minimum of 2 weeks (but preferably 4 weeks) following cessation of enzalutamide due to the persisting inducing effect upon discontinuation of a strong inducer.

Increase dolutegravir dose to 50 mg bid

Potential Weak Interaction

Emtricitabine/Tenofovir alafenamide (FTC/TAF, PrEP)

Enzalutamide

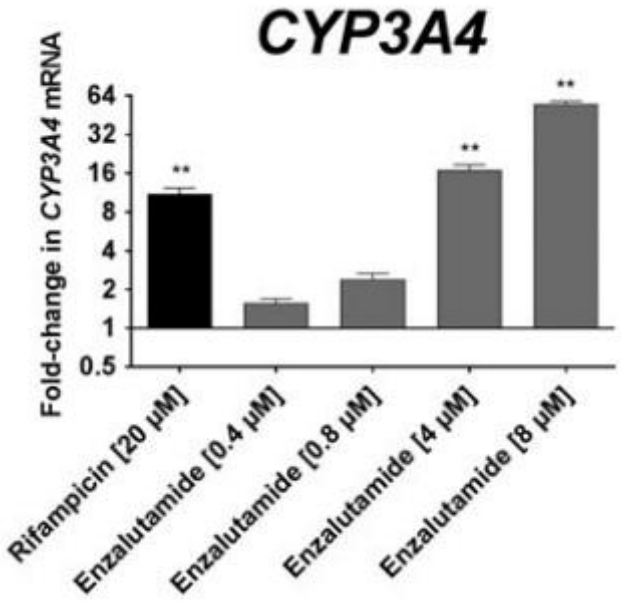
Quality of evidence: Very Low

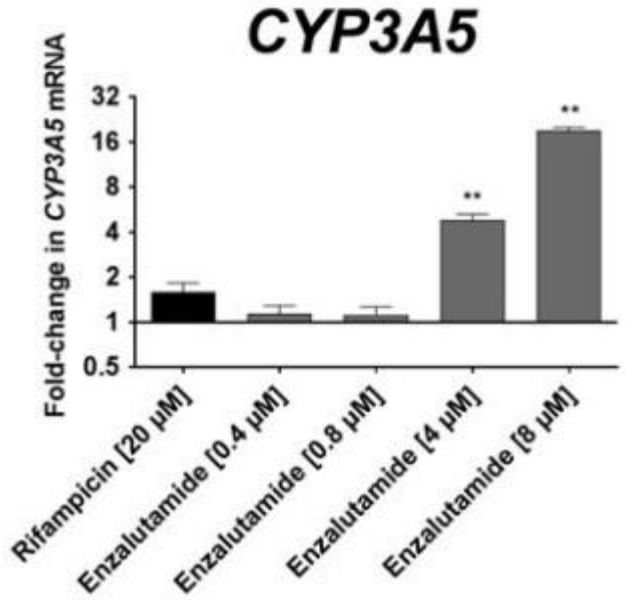
Summary:

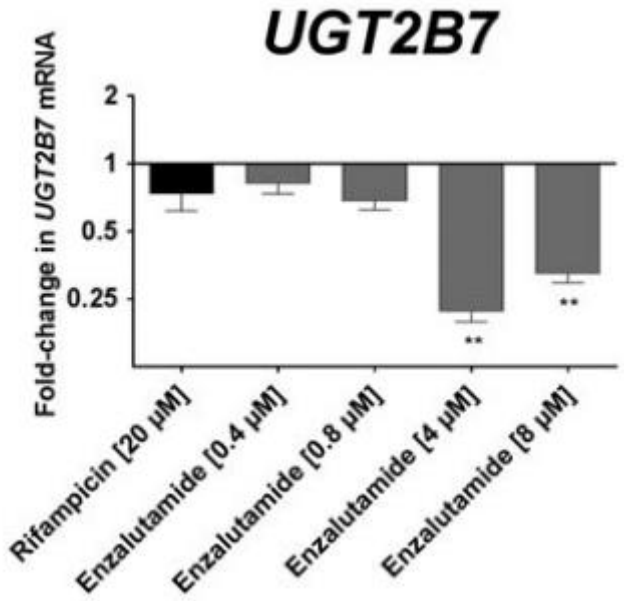
Coadministration has not been studied. Enzalutamide is primarily metabolized by CYP2C8 and may induce P-gp resulting in decreased absorption of tenofovir alafenamide. However, intracellular tenofovir-DP concentrations are still expected to be higher than those achieved by standard dose tenofovir-DF alone. If coadministration is required, use tenofovir alafenamide 25 mg once daily. Enzalutamide does not interact with emtricitabine.

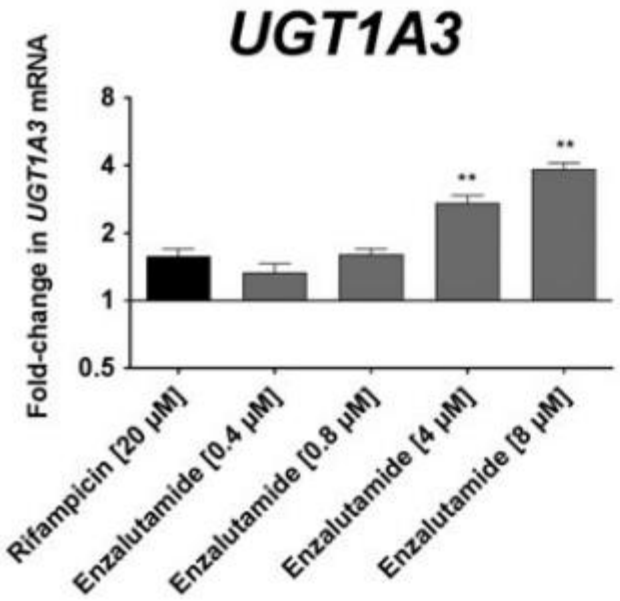
Use TAF at 25 mg once daily

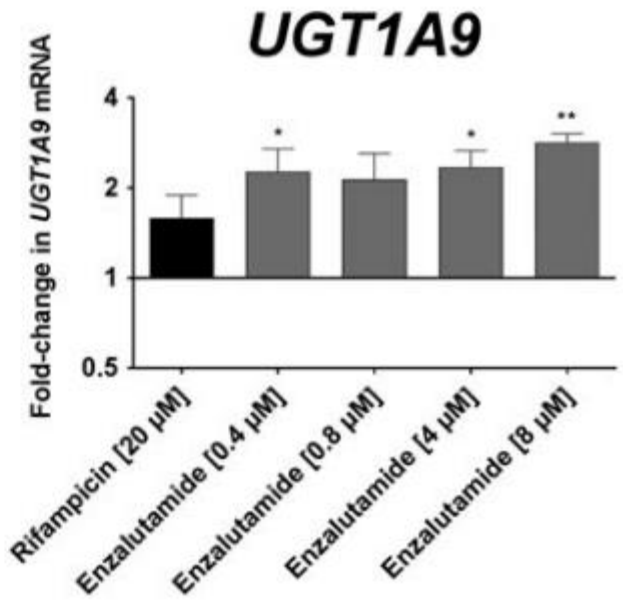
Impact of enzalutamide on drug metabolizing enzymes











Given the mixed effects on UGT isoforms, and the limited role played by CYP3A on dolutegravir metabolism we decided not to double the dose of dolutegravir and to monitor the drug pK

- Weiss et al, Biopharm Drug Disp 2017 -

Main dolutegravir and tenofovir pk parameters before and during concomitant enzalutamide administration

PK Parameters	Baseline evaluation	+ Enzalutamide 120 mg (15 days)	+ Enzalutamide 120 mg (30 days)	+ Enzalutamide 160 mg (15 days)	Historical Reference
Dolutegravir					
C_{min}, ng/mL	214	1106	371	1303	398 – 1262
C_{max}, ng/mL	2006	3094	2621	3788	2271 – 4409
AUC_{0-4h}, ng/mL*h	5902	9893	8941	12885	n.a.
AUC_{0-24h}, ng/mL*h	24828	50580	35440	54431	30380 – 56420
Tenofovir					
C_{min}, ng/mL	13	12	19	20	5 – 24
C_{max}, ng/mL	24	26	36	35	28 – 46
AUC_{0-4h}, ng/mL*hrs	79	82	106	122	74 – 154
AUC_{0-24h}, ng/mL*hrs	377	389	493	603	288 – 745

- Londero et al, submitted 2022 -

Ospedale Luigi Sacco
POLO UNIVERSITARIO
Sistema Socio Sanitario
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

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 et al, World J Biol Psyc 2018 -

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- Gervasoni et al, AIDS Rev 2019 -

The use of direct oral anticoagulants (DOACs) in PLHW (n=50)

Characteristics	Current situation	Hypothetical scenario
Antiretroviral therapy	30% abacavir-based 36% tenofovir-based 38% boosted PI-based 30% NNRTI-based 64% INI-based	
Antithrombotic therapy	82% vit. K antagonists 14% DOACs 4% others^	100% DOACs
Liverpool score for DDIs	0% red flag 58% orange flag 42% green flag	0% red flag 42% orange flag 58% green flag

- Cattaneo et al, Semin Thromb Haemost 2020 -

Management of diabetes mellitus in PLHW (n=200)

Characteristics	Data
Age, years	64 ± 9
Female patients, %	18%
Patients with VL >50 copies/mL, %	6%
CD4 count, cells/mm^3	720 ± 361
Serum glucose, mg/dL	143 ± 50
Patients with glucose >130 mg/dL, %	51%
HbA1c, mmol/mol	51 ± 16
Patients with HbA1c >53 mmol/mol, %	30%
Total cholesterol, mg/dL	173 ± 44
Triglycerides, mg/dL	178 ± 135
HDL-cholesterol, mg/dL	44 ± 12
LDL-cholesterol, mg/dL	95 ± 38
Patients with LDL>100 mg/dL, %	37%
Patients with LDL>70 mg/dL, %	75%

- Cattaneo et al, submitted -

Management of diabetes mellitus in PLHW (n=200)

Characteristics	PLWH and DM	HIV-negative pts with DM
- Metformin, %	53.8%**	37.7%
- Insulins, %	20.9%	23.6%
- Glifozins plus metformin, %	7.1%*	2.0%
- Insulin plus others, %	5.5%**	0.5%
- GLP-1 receptor agonists, %	4.4%	3.9%
- Sulfonylureas, %	3.3%**	13.2%
- Glinides, %	2.7%	3.5%
- DPP4 inhibitors, %	1.7%**	9.6%
- Glitazones, %	0.6%	2.7%
- Glifozins monotherapy, %	0%	2.0%
- Other	0%	1.3%

- Cattaneo et al, submitted -

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- Gervasoni et al, AIDS Rev 2019 -

Co-somministrazioni controindicate (considerare regimi alternativi)

Nessuna

Co-somministrazioni che richiedono un attento monitoraggio

Nessuna

Co-somministrazioni di dubbia rilevanza clinica

Equisetum e bictegravir: Equisetum contiene flavonoidi e fenoli, composti che potrebbero indurre CYP450, enzima che è coinvolto al 50% nel metabolismo di bictegravir. Nessuno studio ha però valutato il loro ruolo come potenziali induttori di CYP450. Al contrario, uno studio ha evidenziato un ruolo come potenziali inibitori di CYP1A2 e CYP2D6, senza però influenzare significativamente CYP3A4. Inoltre, per le sue proprietà diuretiche, Equisetum può aumentare l'escrezione renale di farmaci con escrezione prevalentemente renale (tra cui tenofovir e emtricitabina).

Uva Ursina e bictegravir: Uva ursina contiene gallotannini, composti che *in vitro* hanno evidenziato attività inibitoria su UGT1A1, enzima coinvolto al 50% nel metabolismo di bictegravir.

Valutazione dell'Anticholinergic Cognitive Burden (ABC) Score

ABC score: 0*

* 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.

Monitoraggio terapeutico della terapia assunta

Non eseguito

Commento finale

Non si possono escludere interazioni tra la terapia antiretrovirale in corso e i componenti della tisana consigliata, con effetti potenzialmente opposti e difficilmente prevedibili. Si sconsiglia l'assunzione della tisana.

Co-somministrazioni controindicate (considerare regimi alternativi)

Nessuna

Co-somministrazioni che richiedono un attento monitoraggio

Darunavir/cobicistat e warfarin: La concomitante somministrazione di cobicistat potrebbe aumentare l'esposizione e la possibile tossicità di warfarin per inibizione del metabolismo.

Darunavir/cobicistat e DOACs: La concomitante somministrazione di cobicistat potrebbe aumentare l'esposizione e la possibile tossicità di tutti i DOACs per inibizione del metabolismo e/o del trasporto mediato dalla glicoproteina P.

Interazioni di minore rilevanza clinica

Nessuna

Valutazione dell'Anticholinergic Cognitive Burden (ABC) Score

ABC score: 0*

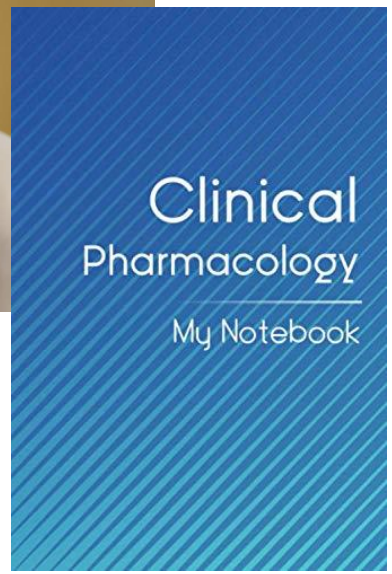
* I farmaci con effetti anticolinergici possono indurre (soprattutto nel soggetto anziano) effetti indesiderati a carico del sistema nervoso centrale come deficit cognitivo e stato confusionale acuto. Un punteggio all'ACB Score ≥ 5 è associato a peggiori performance cognitive e riduzione dell'autonomia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

Monitoraggio terapeutico della terapia assunta

Non eseguito

Commento finale

Sono attese interazioni tra la terapia antiretrovirale in corso ed ogni DOACs. Tali interazioni sono confrontabili a quella ipotizzabile tra darunavir/cobicistat e warfarin. Valutare la possibilità di modificare la terapia antiretrovirale in corso (sostituzione di darunavir/cobicistat con doravirina che non è associata ad interazioni con warfarin o con DOACs).



Very special thank to “Prof. Cristina” for the ongoing training as clinical pharmacologist!!!

Save the date

The 20th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology will be held from Sunday 18th to Wednesday 21st September 2022 in Prague, Czech Republic. The theme of the conference is ***Bridging the Troubled Waters***

International Association of
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Fostering education, research and practice in TDM and CT