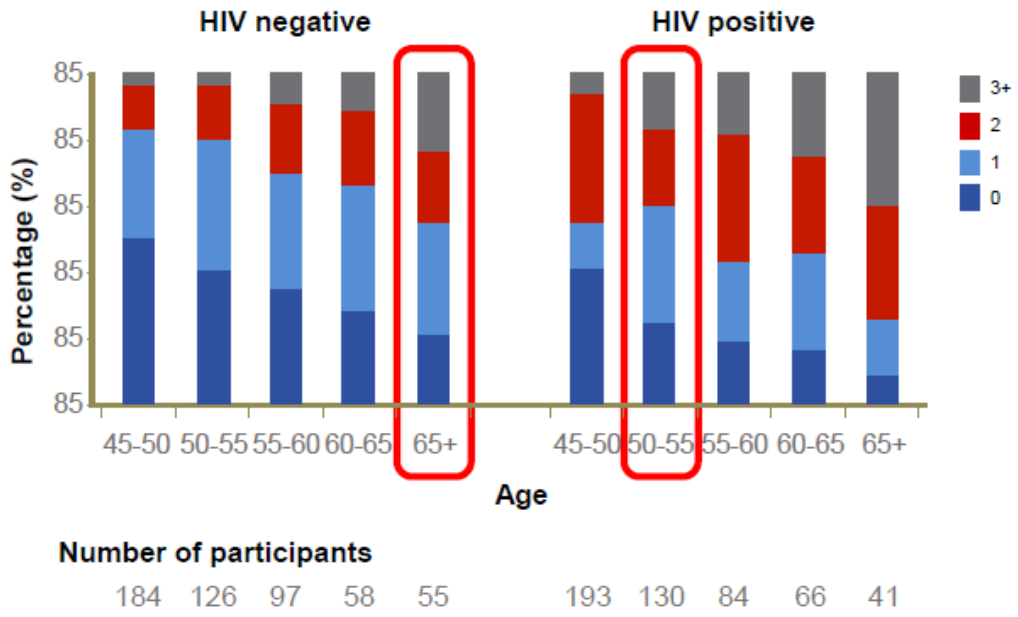
La polifarmacia

Cristina Gervasoni
ASST FBF SACCO

Ageing and multimorbidity

PLHIV are at increased risk of age-associated non-communicable comorbidities

HIV negative and HIV positive adults with comorbidities by age group, Netherlands: 2014

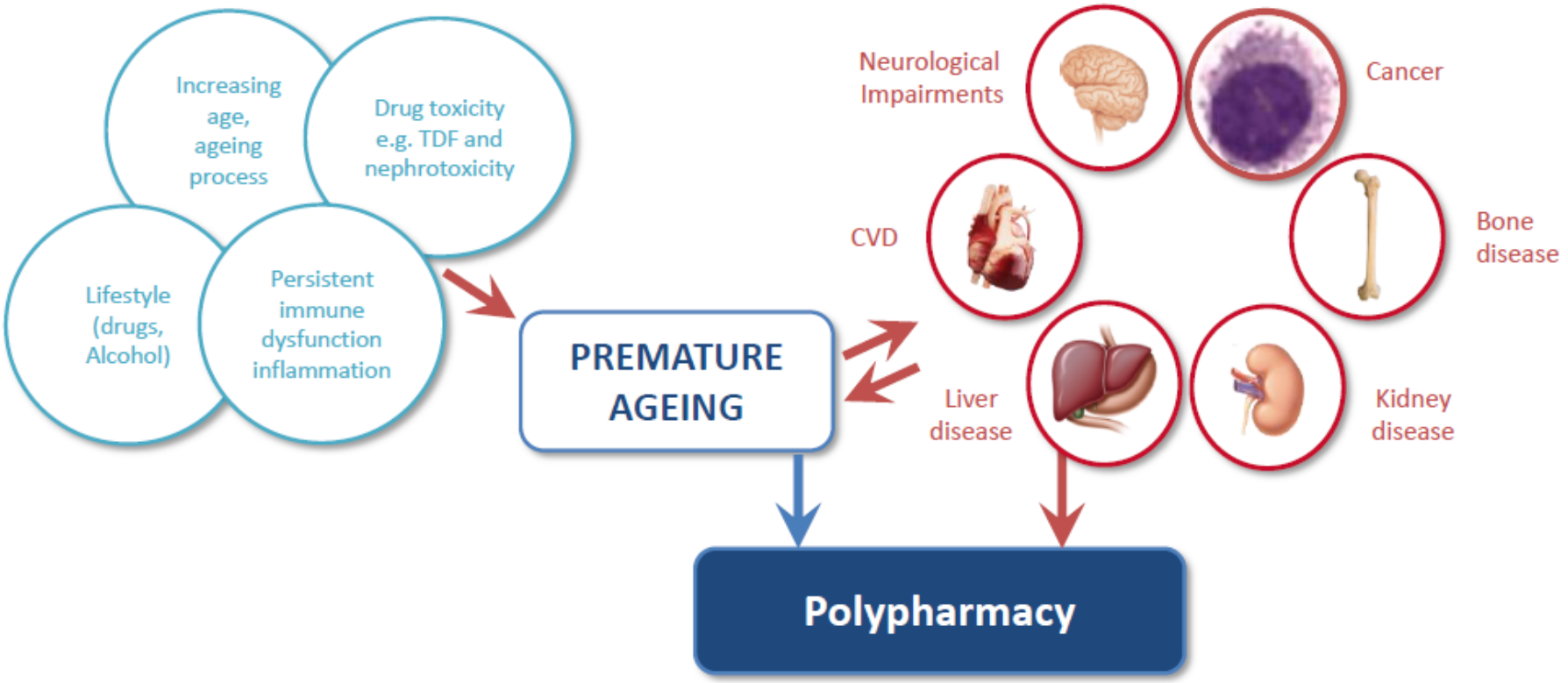


- N=524 HIV-negative and 540 HIV-positive persons

- Hypertension (45.4% vs 30.5%; p<0.001)
- MI (3.9% vs 1.5%; p=0.018)
- Impaired renal function 4.3% vs 2.1%; p=0.044
- Peripheral arterial disease 2.6% vs 0.6%; p=0.008

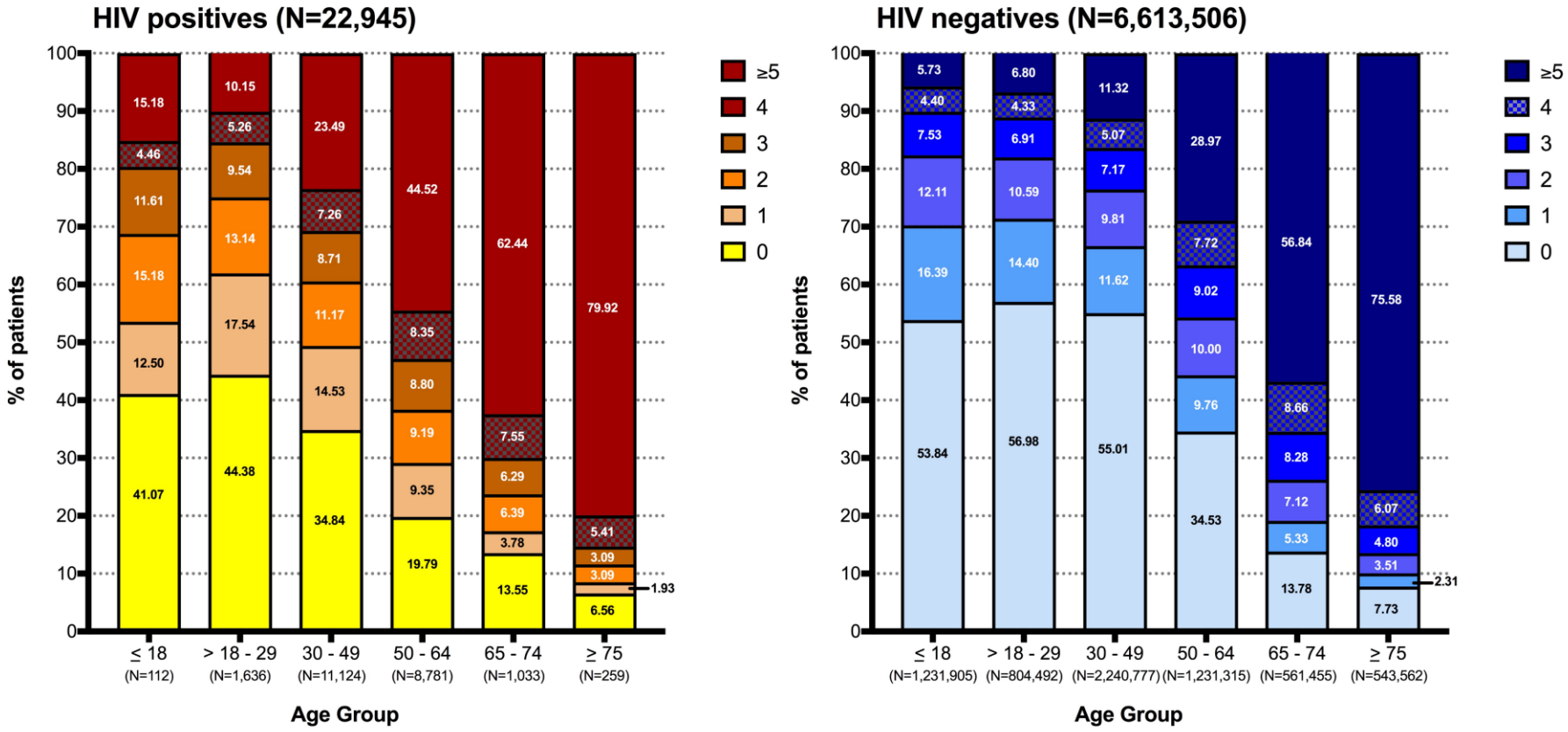
Schouten et al. Clinical Infectious Diseases 2014

Polypharmacy



- Use of 5 or > drugs, common in older adults
- Associated with > rates of AEs and > DDI
- Clinicians need to be aware of important DDI/drug-disease interactions that are common and important
- Tools and approaches to reducing polypharmacy can enhance care outcomes of older adults

Co-meds categorized by HIV serostatus and age



Lopez-Centeno B, et al. HIV Drug Therapy, Glasgow 2018

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

Co-meds (ATC Code)	Red-flag		Orange-flag		Yelow-flag		Green-flag		Grey-flag	
	Nº	%	Nº	%	Nº	%	Nº	%	Nº	%
Nervous system drugs (N)	115	0.50	1,833	7.99	1,163	5.07	5,686	5.07	25	0.11
Cardiovascular drugs (C)	97	0.42	674	2.94	730	3.18	3,512	3.18	0	0.00
Musculoskeletal system (M)	1	0.00	575	2.51	16	0.07	3,208	0.07	0	0.00
Antiinfectives (J)	7	0.03	353	1.54	128	0.56	3,179	0.56	0	0.00
Respiratory system (R)	314	1.37	324	1.41	386	1.68	2,248	1.68	0	0.00
Blood drugs (B)	61	0.27	368	1.60	0	0.00	1,998	0.00	0	0.00
Gastrointestinal drugs (A)	62	0.27	273	1.19	9	0.04	1,841	0.04	1	0.00
Dermatological drugs (D)	117	0.51	394	1.72	90	0.39	953	0.39	0	0.00
Systemic Hormones (H)	5	0.02	466	2.03	0	0.00	905	0.00	0	0.00
Genitourinary drugs (G)	11	0.05	342	1.49	20	0.09	674	0.09	0	0.00
Antineoplastic drugs (L)	0	0.00	15	0.07	0	0.00	230	0.00	0	0.00
Sensory organs (S)	0	0.00	23	0.10	31	0.14	179	0.14	0	0.00
Antiparasitic drugs (P)	0	0.00	42	0.18	84	0.37	134	0.37	0	0.00
Various/Therapeutic drugs (V)	0	0.00	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.

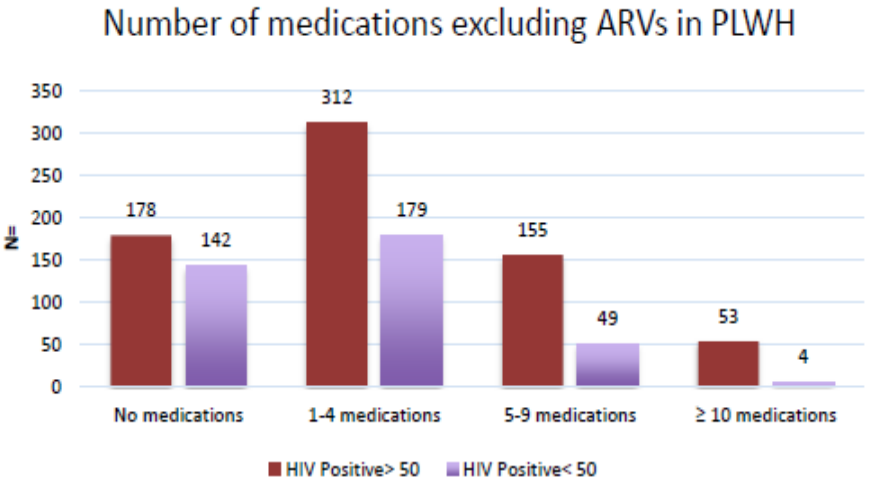
Green-flag = non clinically significant interaction.

Grey-flag = no data to indicate interaction.

Lopez-Centeno B, et al. HIV Drug Therapy, Glasgow 2018

Polypharmacy and potential DDI in HIV older and young people: the POPPY Study

	PLWH aged >50 years	PLWH aged <50 years	HIV-negative controls aged >50 years	P-value
Age (years) Median (range)	56 (50-82)	43 (20-49)	58 (50-87)	0.001
% MSM	78.8%	71.9%	47.4%	0.001
% Hetrosexual	21.2%	28.1%	52.6%	0.001
% Male	87.7%	80.8%	64.1%	0.001
% Black African	13.6%	20.1%	10.2%	0.001
Total number of medications Median (range)	6 (0-27)	4 (0-17)	1 (0-39)	0.001
N (%) with PP	459 (65.3%)	180 (48.1%)	40 (13.2%)	0.001
PDDI between non-ARV and non-ARV drugs N (%) ≥ 1	252 (36.1%)	76 (20.3%)	49 (16.1%)	0.001
Median (range)	0 (0-48)	0 (0-21)	0 (0-14)	0.001
% on ARVs	98.7%	95.2%	-	
PDDI between ARV and non-ARV drugs N (%) ≥1	398 (57.3%)	121 (32.4%)	-	0.001
Median (range)	1 (0-11)	0 (0-5)	-	0.001



- Older PLWH more likely to have polypharmacy than HIV-negative controls or younger PLWH, even when ARVs were excluded.
- Older people were more likely to be at risk of a PDDI involving non-ARV/ARV drugs compared to younger PLWH.
- Older PLWH were more likely to be at risk of a PDDI involving non-ARV drugs than HIV-negative controls or younger PLWH.
- These results highlight the need for increased awareness and additional research around polypharmacy and all PDDI.

Halloran et al. Antiviral Ther 2019

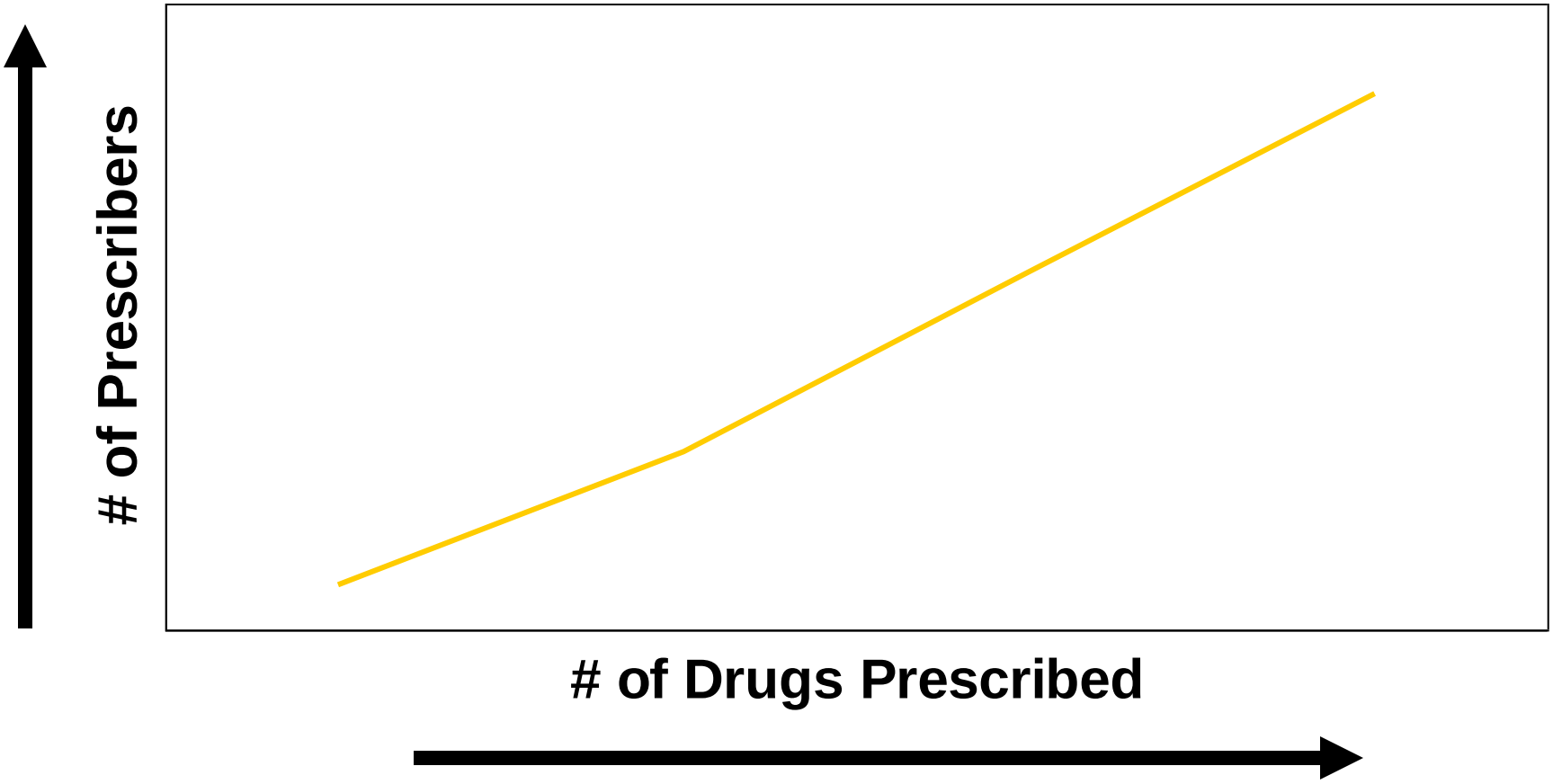
Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid Diseases

	Chronic Disease Addressed by Guideline				
	Diabetes Mellitus[19-32]	Hypertension[30]	Osteoarthritis[33-36]	Osteoporosis[40]	COPD[37,38]
Guideline addressed treatment for type of patient?	Older: yes Multiple comorbidities: yes Both: yes	Older: yes Multiple comorbidities: no Both: no	Older: yes Multiple comorbidities: yes Both: yes†	Older: no Multiple comorbidities: no Both: no	Older: no Multiple comorbidities: no Both: no
Quality of evidence discussed for type of patient?	Older: yes Multiple comorbidities: yes Quality of evidence poor, requires extrapolation for nutrition recommendations	Older: yes Multiple comorbidities: no Quality of evidence good for treating hypertension in older patients	Older: no Multiple comorbidities: no	Older: no Multiple comorbidities: no	Older: no Multiple comorbidities: no
Specific recommendations for patients with 1 comorbid condition?	Yes Diseases: hypercholesterolemia, hypertension, congestive heart failure, chronic kidney disease, cardiovascular disease, peripheral vascular disease, benign prostatic hypertrophy	Yes Diseases: coronary artery disease, diabetes mellitus, metabolic syndrome, sleep apnea, chronic kidney disease, gout, left ventricular hypertrophy, erectile dysfunction, peripheral	Yes Diseases/drugs: anticoagulants, glucocorticoids, peptic ulcer disease, chronic kidney disease, hypertension, congestive heart failure	No	No

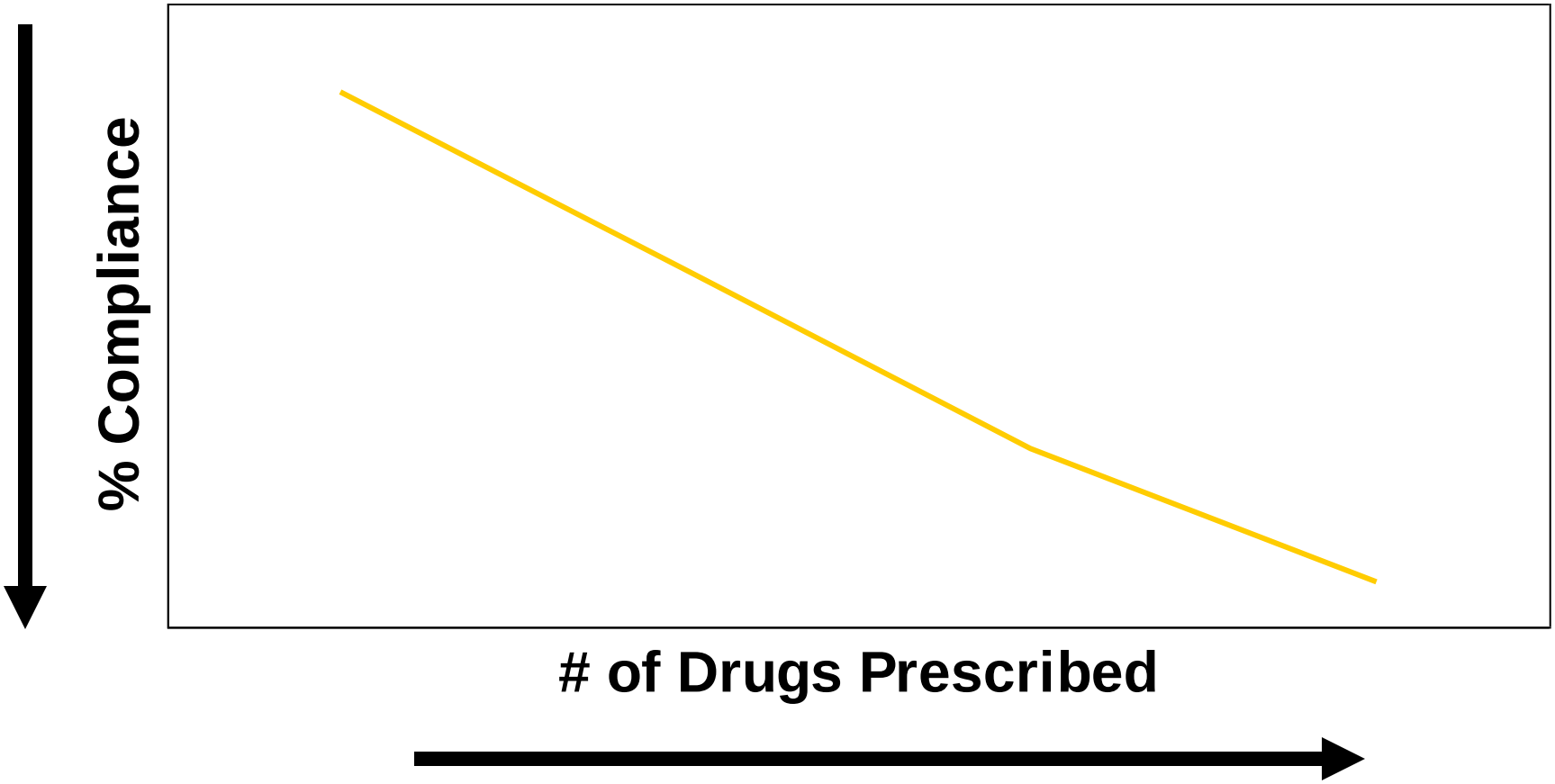
JAMA, August 10, 2005—Vol 294, No. 6

Hypothetical 79 yrs old HIV + woman
12 meds, 19 doses/day, 5 times/day

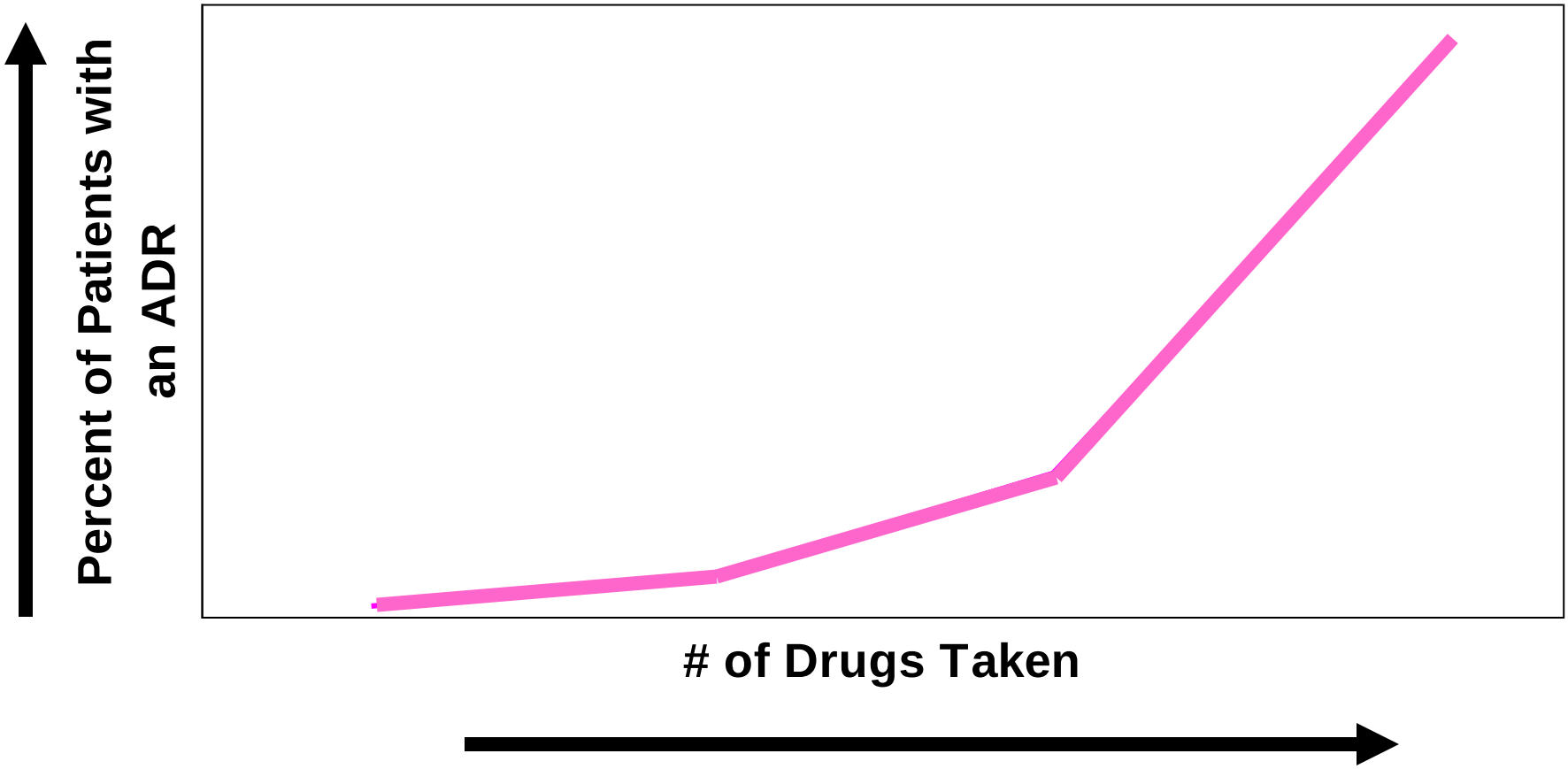
Relation between polypharmacy and number of prescribers



Relation between polypharmacy and compliance

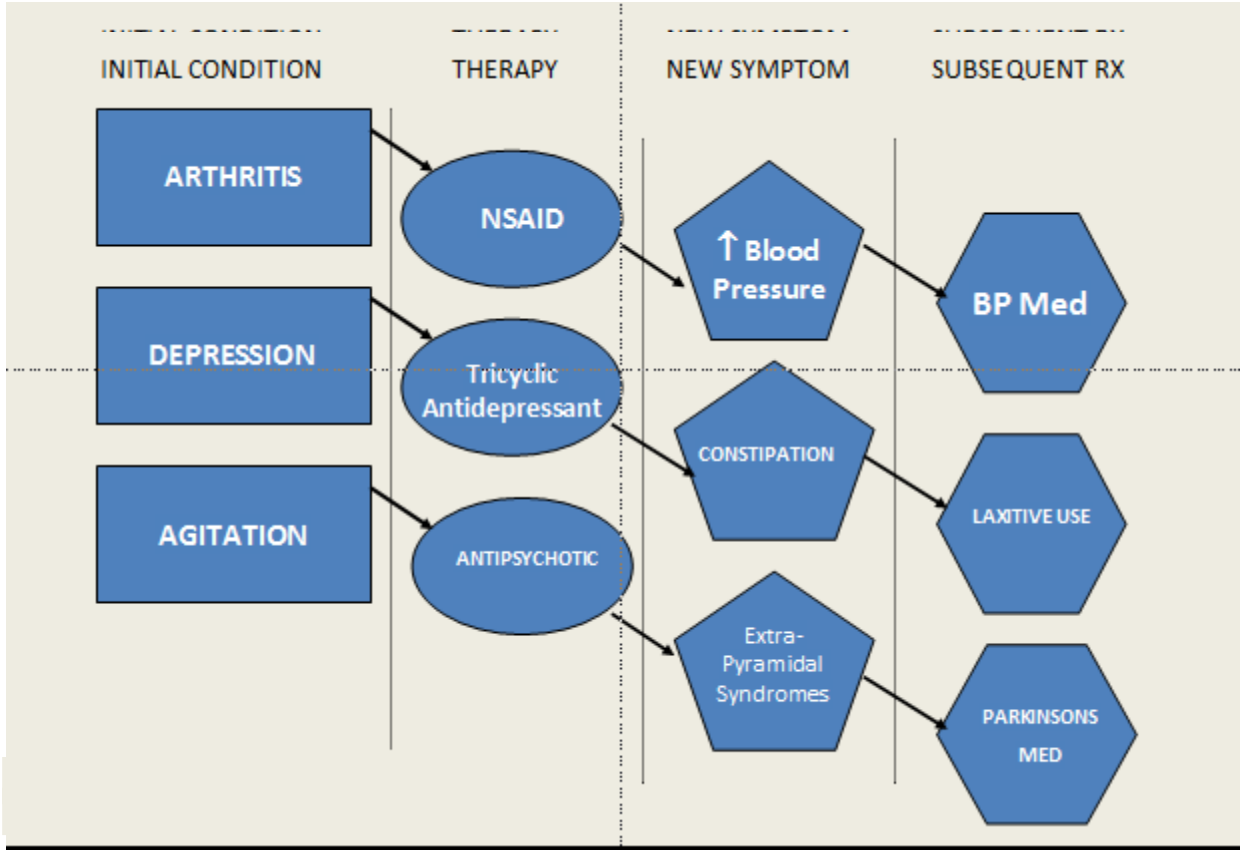


Exponential relation between polypharmacy and ADRS



Nolan L et al.. JAGS 1988

The prescribing cascade



Gurwitz JH et al. Pharmacology & Therapeutics 1997

MORE PATIENTS ON ARVs

Ageing

Different prescribers

Polypharmacy

MORE PATIENTS ON ARVs

Ageing

Different prescribers

Polypharmacy

Online access drugs

MORE PATIENTS ON ARVs

Ageing

Different prescribers

Online access drugs

Polypharmacy

MORE PATIENTS
ON ARVs

Ageing

Different
prescribers

Online access drugs

Polypharmacy

In an HIV patient with comorbidities, polypharmacy, or other….. the management

1. Is based on your experience and knowledge of the drugs
2. Is with the input of a multi-disciplinary team
3. Is passed to a colleague
4. Is straightforward since DDI are rarely a problem

MORE PATIENTS
ON ARVs

Ageing

GAP

Different
prescribers

Online access drugs

Polypharmacy

.3

GESTIONE AMBULATORIALE POLITERAPIA

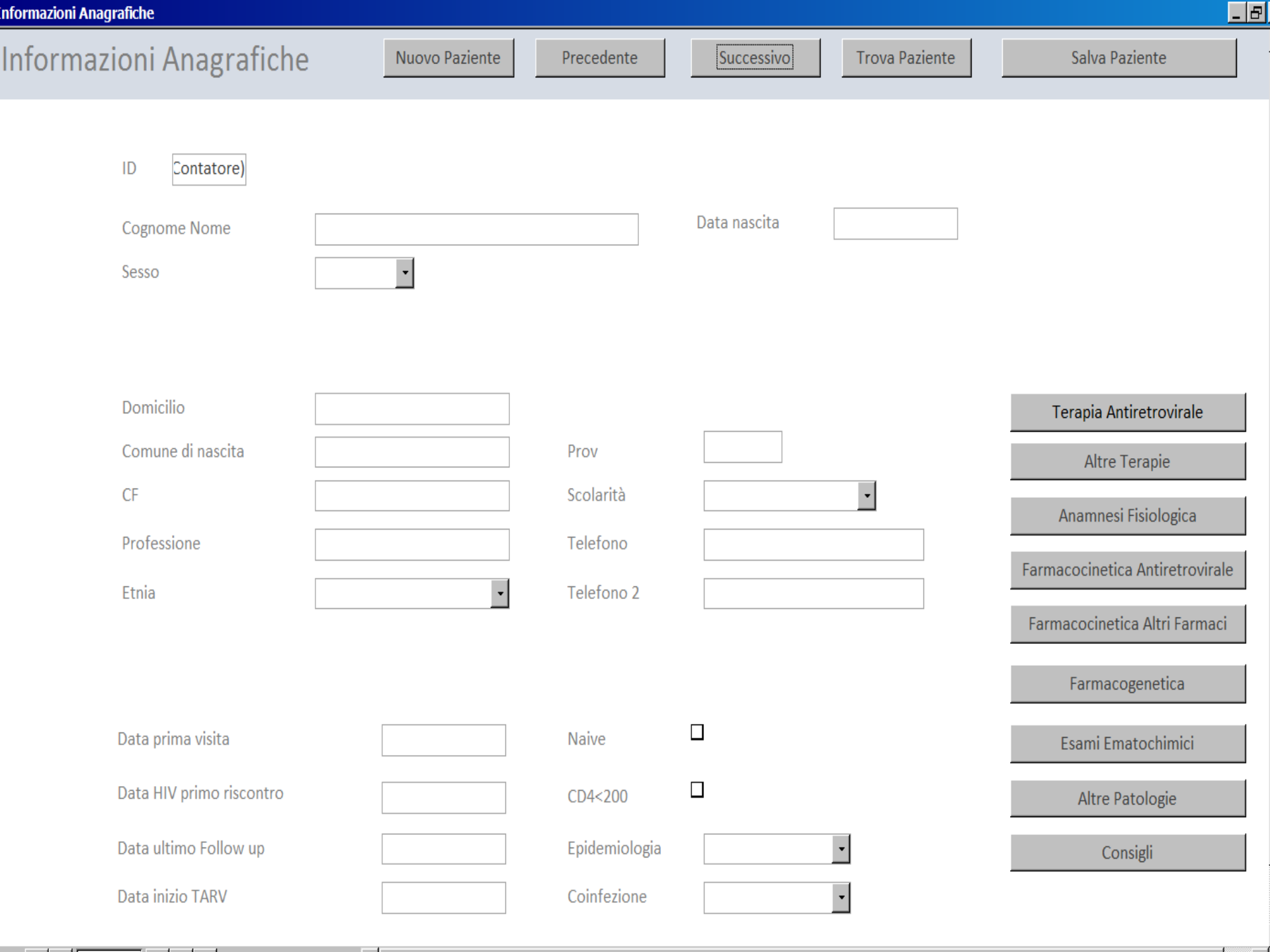
N: > 900 pazienti

Visita multidisciplinare - Cod. 61E103

Farmacologo: D. Cattaneo

Infettivologo: C. Gervasoni

Collaboratori


Informazioni Anagrafiche
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
Terapia Antiretrovirale
Altre Terapie
Anamnesi Fisiologica
Farmacocinetica Antiretrovirale
Farmacocinetica Altri Farmaci
Farmacogenetica
Esami Ematochimici
Altre Patologie
Consigli
Data prima visita
Naive
Data HIV primo riscontro
CD4<200
Data ultimo Follow up
Epidemiologia
Data inizio TARV
Coinfezione

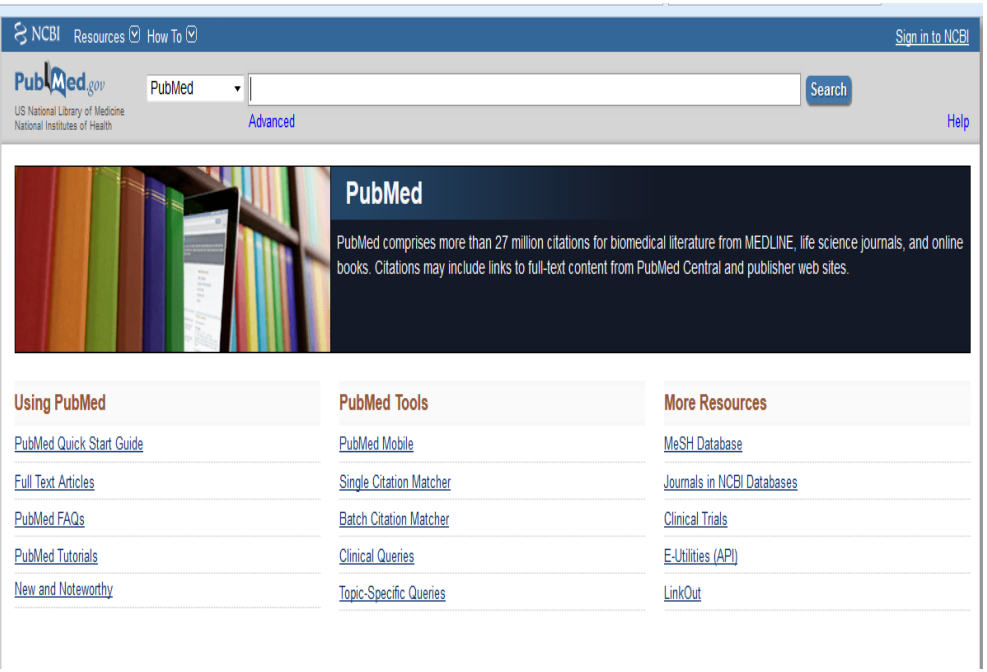
Activities of the GAP outpatient clinic

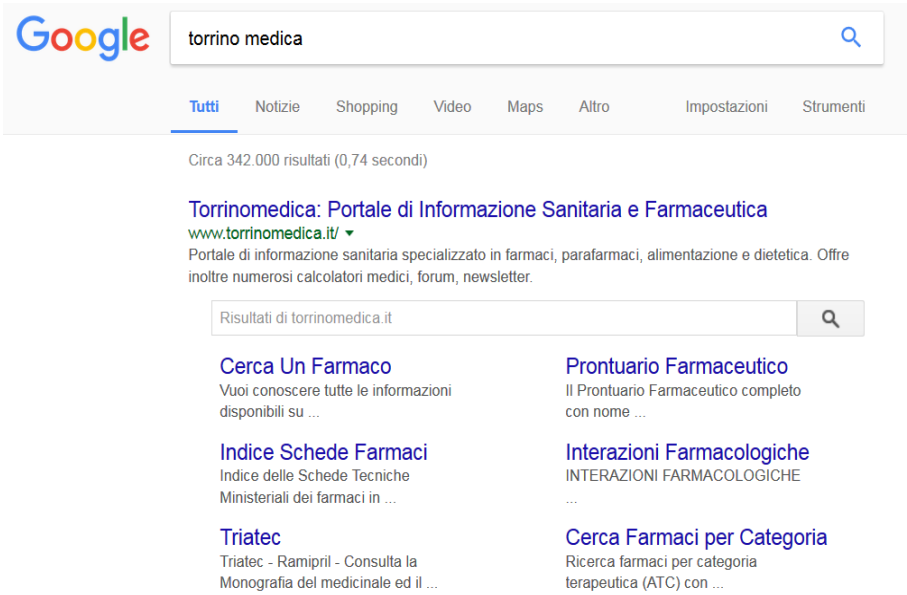
- The detailed collection of anamnestic, clinical, therapeutic and *ad hoc* laboratory data relating to individual patients taking antiretroviral and other drugs, phytotherapeutic agents, supplements, etc.
- When appropriate, prescription of the pharmacokinetic tests offered by the hospital's Pharmacological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

Some of the free web databases that can be used to verify possible drug interactions

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

...però questi siti non possono prevedere tutto....


NCBI Resources How To
Sign in to NCBI
PubMed.gov
US National Library of Medicine
National Institutes of Health
PubMed
Search
Advanced
Help
PubMed
PubMed comprises more than 27 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.
Using PubMed
PubMed Quick Start Guide
Full Text Articles
PubMed FAQs
PubMed Tutorials
New and Noteworthy
PubMed Tools
PubMed Mobile
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Topic-Specific Queries
More Resources
MeSH Database
Journals in NCBI Databases
Clinical Trials
E-Utilities (API)
LinkOut


Google
torrino medica
Tutti
Notizie
Shopping
Video
Maps
Altro
Impostazioni
Strumenti
Circa 342.000 risultati (0,74 secondi)
Torrinomedica: Portale di Informazione Sanitaria e Farmaceutica
www.torrinomedica.it/
Portale di informazione sanitaria specializzato in farmaci, parafarmaci, alimentazione e dietetica. Offre inoltre numerosi calcolatori medici, forum, newsletter.
Risultati di torrinomedica.it
Cerca Un Farmaco
Vuoi conoscere tutte le informazioni disponibili su ...
Prontuario Farmaceutico
Il Prontuario Farmaceutico completo con nome ...
Indice Schede Farmaci
Indice delle Schede Tecniche Ministeriali dei farmaci in ...
Interazioni Farmacologiche
INTERAZIONI FARMACOLOGICHE ...
Triatec
Triatec - Ramipril - Consulta la Monografia del medicinale ed il ...
Cerca Farmaci per Categoria
Ricerca farmaci per categoria terapeutica (ATC) con ...

DARIO

Ospedale Luigi Sacco
POLO UNIVERSITARIO
Sistema Socio Sanitario
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UNIVERSITÀ DEGLI STUDI DI MILANO

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Milano, 23-11- 2018

In data 21/11/2018 è pervenuta al Nostro servizio una richiesta di consulenza da parte del Prof Massimo Puoti (Ospedale Niguarda) per la verifica delle possibili interazioni farmacologiche nella paziente **Graziella** [redacted] (05/09/1942), attualmente in terapia con:

- voriconazolo
- omeprazolo
- valsartan
- lercanidipina
- canrenone
- levotiroxina
- ticlopidina
- simvastatina
- salmeterolo/fluticasone

Nello specifico, il quesito diagnostico/farmacologico riguarda la possibile presenza di interazioni farmacologiche tra i regimi attualmente assunti alla luce della recente introduzione di voriconazolo per il trattamento di aspergillosi polmonare, terapia che la paziente dovrà assumere per diversi mesi.

INTERAZIONI FARMACOLOGICHE IPOTIZZABILI SU BASE TEORICA

Co-somministrazione controindicata (considerare regimi alternativi)

Voriconazolo e simvastatina: l'effetto inibitorio di voriconazolo sugli enzimi metabolizzanti può determinare un aumento significativo dell'esposizione alla simvastatina e del rischio di miopatia o rabdomiolisi. A sua volta la statina, competendo a livello degli enzimi metabolizzanti epatici può causare un aumento delle concentrazioni ematiche di voriconazolo e del rischio di epatotossicità.

Co-somministrazioni che richiedono un attento monitoraggio

Voriconazolo e fluticasone: l'effetto inibitorio di voriconazolo sugli enzimi metabolizzanti può determinare un aumento della biodisponibilità del corticosteroide con rischio di effetti avversi (disturbi neuropsichici, alterazioni elettroliche, metaboliche, Cushing ecc).

Voriconazolo e salmeterolo: la co-somministrazione di questi due farmaci può avere un effetto additivo sul prolungamento dell'intervallo QT con aumento del rischio di cardiotossicità.

Voriconazolo e omeprazolo: l'effetto inibitorio di voriconazolo sugli enzimi metabolizzanti può aumentare le concentrazioni e gli effetti di omeprazolo. A sua volta omeprazolo può aumentare l'esposizione a voriconazolo.

Valsartan, canrenone, omeprazolo, fluticasone e salmeterolo: l'inibizione di angiotensina II mediata da valsartan causa una diminuzione della secrezione di aldosterone (già inibita da canrenone), che a sua volta può provocare la ritenzione di potassio. Per contro il salmeterolo e fluticasone possono ridurre i livelli di potassio (monitorare la potassiemia). Il quadro può essere peggiorato dalla concomitante presenza di inibitore di pompa protonica, con rischio di tossicità cardiaca dovuta ad effetti diretti sull'intervallo QT e/o ad alterazioni elettrolitiche.

Interazioni di minore rilevanza clinica

Voriconazolo e lercanidipina: l'effetto inibitorio di voriconazolo sugli enzimi metabolizzanti può determinare un aumento dell'esposizione sistemica e degli effetti avversi del calcioantagonista.

Levotiroxina e omeprazolo: gli inibitori di pompa protonica possono ridurre l'assorbimento di levotiroxina.

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Voriconazolo e ticlopidina: la ticlopidina può causare un modesto aumento delle concentrazioni di voriconazolo

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.

Commento finale

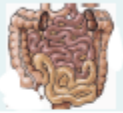
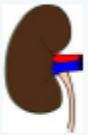
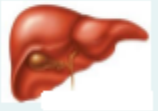
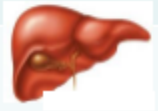
Si consiglia il monitoraggio periodico delle concentrazioni ematiche basali di voriconazolo (inizialmente ogni 2 settimane, poi eventualmente ridotto ad una volta al mese fino a termine della terapia). Alla luce della possibile interazione con voriconazolo si consiglia la sostituzione di simvastatina con atorvastatina a basso dosaggio oppure con pravastatina (senza limitazioni nella dose). Considerato sia il possibile effetto negativo di una terapia con steroide in pazienti con infezione fungina che l'interazione attesa tra voriconazolo e fluticasone/salmeterolo, si suggerisce la sospensione della coformulazione in aerosol.

Sarebbe infine auspicabile la sospensione di omeprazolo o, se non fattibile, di sostituirlo con pantoprazolo.

Selected DDI for boosted regimens

Drug class	Comment
Corticosteroids	Risk of Cushing syndrome. **Avoid** PI/r, PI/c, EVG/c. Risk not just oral but inhaled, eye drops, injection, topical. Triamcinolone, budesonide, fluticasone, mometasone ***contra-indicated***.
Antidepressants	Avoid tricyclics - can cause anticholinergic effects, sedation, orthostatic hypotension.
Benzodiazepines	Caution - increased sensitivity in elderly with risk of cognitive impairment, falls etc. AEs increased by inhibition of CYP metabolism. Use lowest dose for short duration. Midazolam, triazolam ***contraindicated***.
Chemotherapy drugs	Many chemotherapy drugs metabolised by CYP. Increased risk of chemo related toxicities.
Anticoagulants; Vit K antagonists	Monitor INR and adjust dose accordingly. Dose adjustment may be required if switching from ritonavir to cobicistat.
Direct acting anticoagulant *(DOAC)*	Significant effect expected (limited data). Effect not routinely measured. Recommended - avoid with boosted regimens
Calcium channel blockers	Increased exposure and potential hypotensive effect. Start with lowest dose and titrate based on response
Statins	Increased exposure of **some** statins. Simva-, lovastatin ***contraindicated.*** Pitavastatin can be used. Others – start with low dose and titrate.

Selected DDI for integrase inhibitors

Drug Class	Comment
Antacids Calcium, Mineral supplements	Integrase inhibitors form complex with divalent cations in the g.i.tract which limits absorption. Potential risk of treatment failure. 
Metformin	DTG **increases** metformin exposure (inhibits OCT2 in kidney). EVG/c **probably increases** metformin exposure. RAL has ***no effect***. BIC **increases** metformin exposure - but less than DTG. Note: No DDIs with most other antidiabetic drugs. 
Rifampicin	DTG – Rifampicin **decreases** DTG exposure. RAL – Rifampicin **decreases** RAL exposure EVG/c – Rifampicin **decreases** EVG exposure BIC – Rifampicin **decreases** BIC exposure 
Rifabutin	DTG and RAL – no clinically significant change in exposure EVG/c – Rifabutin **decreases** EVG exposure BIC – Rifabutin **decreases** BIC exposure 

Interazioni tra farmaci antiretrovirali, medicina complementare e alternativa e OTC

Tabella 2 **Caratteristiche cliniche dei 5 pazienti della coorte GAP in fallimento virologico o con risposta terapeutica inadeguata per interazioni farmacologiche con CAM**

Pazienti	Terapia antiretrovirale	Farmaci interagenti	TDM 1	TDM 2	Range terapeutico
Femmina, 43 anni	ATV/r 300/100 mg TDF/FTC 245/200 mg	Orlistat 60 mg x 3	ATV: 50 ng/mL	ATV: 195 ng/mL	150-800 ng/mL
Femmina, 39 anni	EFV 600 mg TDF/FTC 245/200 mg	Orlistat 60 mg x 3	EFV <150 ng/mL	EFV: 3795 ng/mL	1000-4000 ng/mL
Femmina, 40 anni	ATV/r 300/100 mg TDF/FTC 245/200 mg	Sinetrol 450 mg x 2	ATV: 85 ng/mL	ATV: 719 ng/mL	150-800 ng/mL
Maschio, 44 anni	TAF/FTC 10/200 mg DRV/cobi 800/150 mg	Gunabasic 7 g/die Lipidyum 6.5 g/die	Non disponibile	Non disponibile	Non disponibile
Maschio, 45 anni	EVG/cobi/TAF/FTC 150/150/10/200 mg	CUT4 HIM plus 4 gr x 4	EVG: 56 ng/mL	653 ng/mL	>45 ng/mL

TDF: tenofovir diproxil fumarato; FTC: emtricitabina; TAF: tenofovir alafenamide; ATV: atazanavir; r: ritonavir; EFV: efavirenz; DRV: darunavir; cobi: cobicistat; EVG: elvitegravir; TDM 1: monitoraggio terapeutico del farmaco effettuato durante l'assunzione del farmaco interagente; TDM 2: monitoraggio terapeutico del farmaco effettuato prima dell'assunzione (paziente 5) o dopo la sospensione del farmaco interagente.

J Antimicrob Chemother. 2016, Obesity (Silver Spring). 2018, Eur J Clin Pharmacol. 2019

After psychotropic drugs .....what about antiepileptic drugs....

Anticonvulsants	Atazanavir	Cobicistat (with ATV or DRV)	Darunavir	Efavirenz	Nevirapine	Ritonavir
Carbamazepine	■	●	■	■	■	■
Clonazepam	■	■	■	■	■	■
Ethosuximide	■	■	■	■	■	■
Gabapentin	◆	◆	◆	◆	◆	◆
Lacosamide	▲	◆	◆	■	■	◆
Lamotrigine	■	◆	■	■	◆	■
Levetiracetam	◆	◆	◆	◆	◆	◆
Oxcarbazepine	■	■	■	◆	▲	■
Phenobarbital (	■	●	●	■	■	■
Phenytoin	■	●	●	■	■	■
Pregabalin	◆	◆	◆	◆	◆	◆
Topiramate	◆	◆	◆	◆	◆	◆
Valproate	■	◆	■	◆	◆	■
Vigabatrin	◆	◆	◆	◆	◆	◆
Zonisamide	◆	◆	◆	■	■	◆

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

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%	95%	0
Phenytoin	10	35.6 ± 12.0*	10 – 20	0	89%	5%
Phenobarbital	45	19.1 ± 7.2	10 – 40	11%	88%	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						

Clinical Pharmacokinetics, 2019

Clinical outcome

- 33 out of the 97 HIV patients had seizures (34%). 16 of them were categorized as “poorly compliant” to antiepileptic therapies based on data from Pharmacy Dept, and confirmed by significant fluctuations in the antiepileptic drug concentrations between 2 consecutive visits

- 8 out of the 16 poorly compliant patients had an history of IV drug abuse or were on methadone-based therapy. Of the remaining (n=17), 7 and 6 patients had, respectively, antiepileptic drug concentrations within and below each specific therapeutic range

- 2 patients had drug-resistant epilepsy (failure to respond at different antiepileptic drugs despite adequate drug exposure)

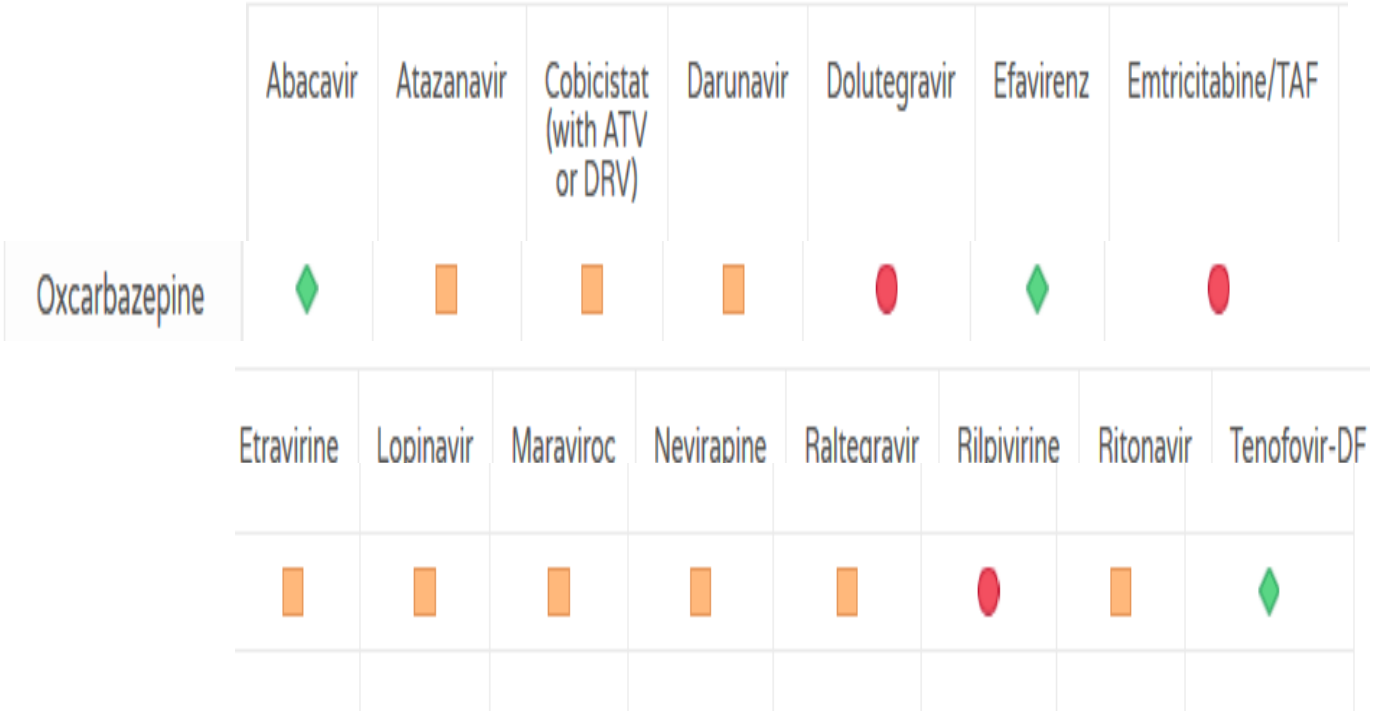
- One patient experienced an episode of nystagmus. At three consecutive assessments done close to the episode, phenytoin concentrations resulted 47.6±0.3 mg/L (therapeutic range: 10-20 mg/L). Such event resolved after phenytoin dose reduction

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

DDIs between oxcarbamazepine and antiretrovirals



DDIs between ARVs and carbamazepine or oxcarbazepine in real life settings

Drug	Drug TDM (n)	Drug concentrations	Therapeutic range
Oxcarbazepine, mg/L	10	19.5 ± 4.3	10 – 35
Carbamazepine, mg/L	21	7.4 ± 1.8	4 – 12
Tenofovir (TDF), ng/mL	10	49 ± 13	40 – 180
Tenofovir (TAF), ng/mL	12	11.4 ± 3.5	Not established
Atazanavir, ng/mL	8	190 ± 91	150 – 800
Darunavir, ng/mL	8	2329 ± 1274	>500
Dolutegravir, ng/mL	7	191 ± 78	>100
Raltegravir, ng/mL	6	472 ± 698	>40
Rilpivirine, ng/mL	2	<20, 35	>25
Elvitegravir, ng/mL	2	<25, 160	>45

TDF: tenofovir diproxil fumarate; TAF: tenofovir alafenamide; TDM: therapeutic drug monitoring

only one out of this ten patients experienced virologic failure with resistance mutations to raltegravir

Association of HIV infection with epilepsy and other comorbid conditions

Comorbidities	Overall (n=97)	≤50 years (n=43)	>50 years (n=54)
Arterial hypertension, %	26%	4%	39%*
Dyslipidemia, %	12%	7%	17%°
Other infections, %	12%	16%	9%
Non infective liver diseases, %	9%	2%	15%°
Thyroid disorders, %	8%	7%	9%
Type 2 diabetes, %	4%	2%	6%
Other comorbidities	22%	19%	26%°
Other neurologic diseases, %	6%	5%	7%
Psychiatric disorders, %	36%	35%	37%

*°p<0.05 and *p<0.01 versus patients ≤50 years*

AIDS Behav. 2019

2 pazienti HIV, entrambi in terapia con DRV, hanno iniziato uno steroide…

	Paziente 1	Paziente 2
Dati clinici anamnestici	Maschio, 57 anni, terapia ARV dal 2000	Maschio, 53 anni, terapia ARV dal 1993 (vari fallimenti)
TARV	DRV/cobi 800/150 mg TAF/FTC 10/200 mg	DRV/r 600/100 mg bid TAF/FTC 10/200 mg
Altri farmaci	diazepam, rosuvastatina, colecalciferolo, acyclovir, carbamazepina	rosuvastatina
CD4, VL	828 cell/mL, <37 cp/ml	790 cell/mL, <37 cp/ml
$[DRV]_{trough}$ pre-steroide	**2588 ± 742 ng/mL**	**2339 ± 1056 ng/mL**
Steroide, dose e durata	Prednisone 25 mg bid (in terapia da 6 settimane)	Metilprednisolone 16mg, scalato e sospeso in 10 gg
Patologia	Nevralgia del trigemino	Ernia lombare
$[DRV]_{trough}$ post-steroide	**220 ng/mL (-93%)**	**3127 ng/mL**
Complicanze	Incremento delle transaminasi	ndp

Eur J Clin Pharmacol. 2019

welcome to the www.hiv-druginteractions.org website

UNIVERSITY OF LIVERPOOL

Cosa dice Liverpool?

Quality of evidence: very low

Coadministration could potentially increase prednisone concentrations thus increasing the risk of steroid related side effects. Monitor for corticosteroid side effects

Questo può spiegare l'incremento delle transaminasi osservato nel paziente 1

Cosa dice la letteratura?

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

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

Sicuramente ci sono delle differenze "cliniche" tra i 2 pazienti…

	Paziente 1	Paziente 2
TARV	DRV/cobi 800/150 mg TAF/FTC 10/200 mg	DRV/r 600/100 mg bid TAF/FTC 10/200 mg
Altri farmaci	diazepam, rosuvastatin, cholecalciferol, acyclovir e carbamazepine	rosuvastatin
Steroide, dose e durata	Prednisone 25 mg bid (in terapia da 6 settimane)	metilprednisolone 16mg, scalato e sospeso in 10 gg

- Diverso tipo di steroide utilizzato
- Diversa la durata della terapia
- Diversa la dose di steroide
- Diversa la terapia concomitante
- Diverso booster (ritonavir vs. cobi)

Ma c'è anche chi ha ipotizzato che l'effetto induttivo dei glucocorticoidi possa risentire del background genetico…

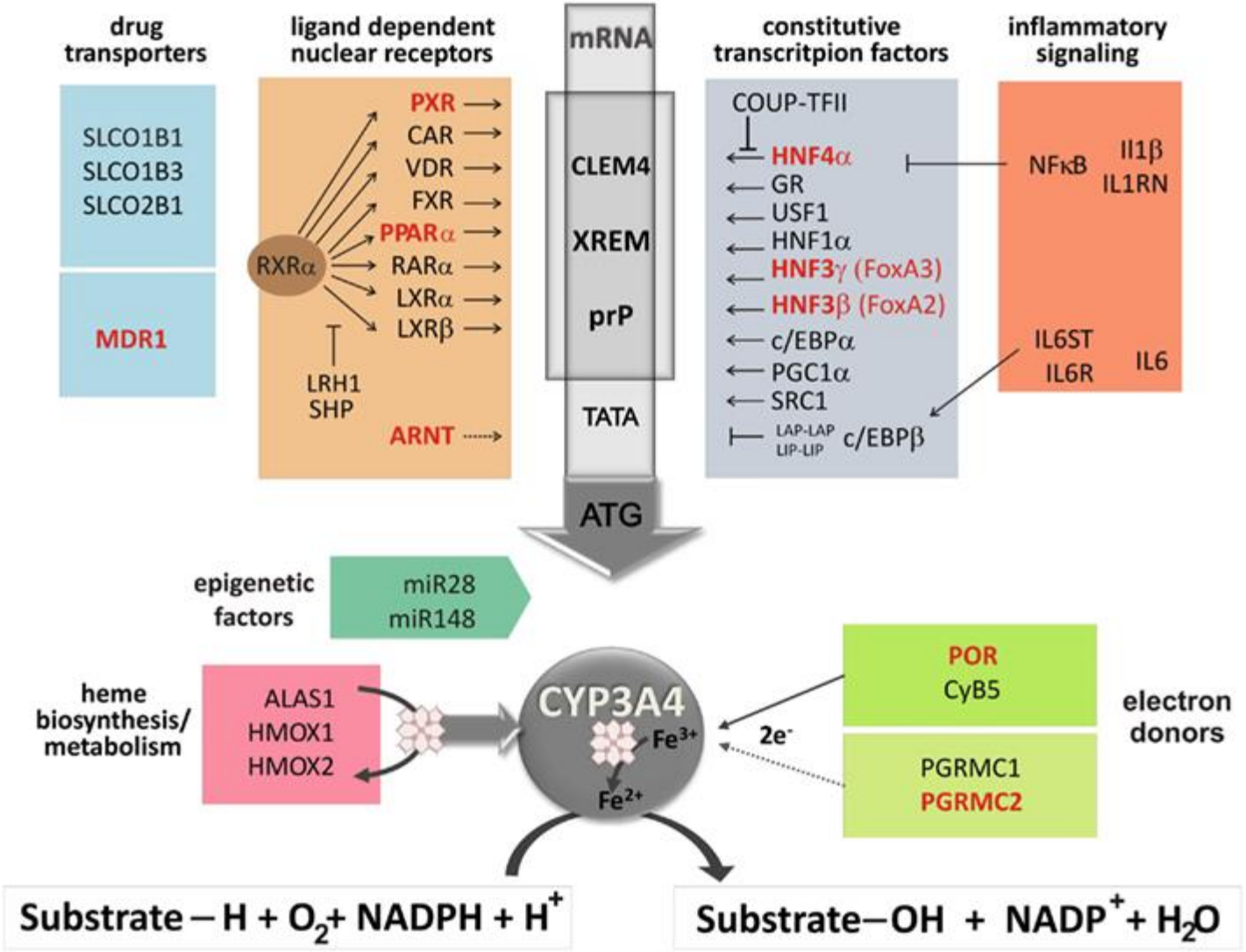
ANALISI GENOTIPICA CYP3A

Geni	Varianti alleliche considerate	Genotipo di riferimento	Genotipo del paziente 1	Genotipo del paziente 2
CYP3A4	rs35599367 C>T (CYP3A4*22)	CC	CC	CC
CYP3A5	Rs776746 A>G (CYP3A5*3)	AA	GG	GG
CYP3A4: cytochrome 3A4; CYP3A5: cytochrome 3A5				

METABOLISMO INTERMEDIO (74% Caucasici)

CM

Tuttavia è stato recentemente dimostrato che l'attività dei citocromi non dipende solo dalla presenza di polimorfismi nei geni codificanti ma soprattutto dall'attività di proteine che ne regolano a monte l'espressione (POR, PXR, PPARA)....



Profilo genotipico/fenotipico di metabolismo

Geni	Varianti alleliche considerate	Genotipo di riferimento (wild-type)	Genotipo del Paziente 1	Genotipo del paziente 2
CAR	rs2307424	GG	GA	GA
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

Le nostre conclusioni...

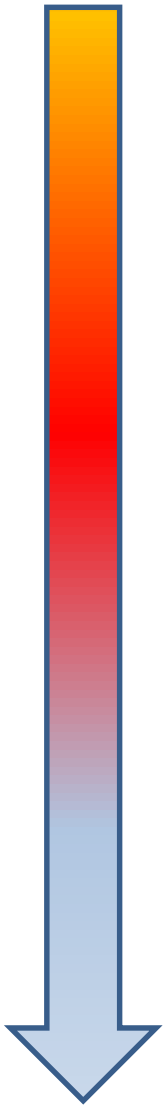
With these two case reports, we have added new pieces to the puzzle by proposing that the inductive effects of glucocorticoids (or the lack of) on the metabolism of CYP3A substrates, including darunavir, might be related to the patients' metabolic genotypes

Dolutegravir-based antiretroviral regimens for HIV liver transplant patients in real life

The database of our Infective Diseases Clinics (with 2300 HIV infected patients on active follow-up) was investigated in search for HIV, liver transplant recipients on:

- Calcineurin inhibitor-based immunosuppression;
- Treated with dolutegravir for at least one month;
- At least one year of follow-up after dolutegravir introduction/withdrawal;
- Available data on therapeutic drug monitoring of immunosuppressive trough concentrations

Time-course of ARV therapy



Time 0: **Liver Tx (n=9)**

-TDF/FTC/raltegravir (n=5)
-TDF/FTC/dolutegravir (n=1)
-TDF/FTC/fosamprenavir (n=1)
-ABC/3TC/raltegravir (n=1)
-Raltegravir/darunavir/r (n=1)

Simplification: **4.6 ± 3.5 years**

-TAF/FTC/dolutegravir (n=6)
-TDF/FTC/dolutegravir (n=1)
-Darunavir/cobi/dolutegravir (n=1)
-ABC/3TC/dolutegravir (n=1)

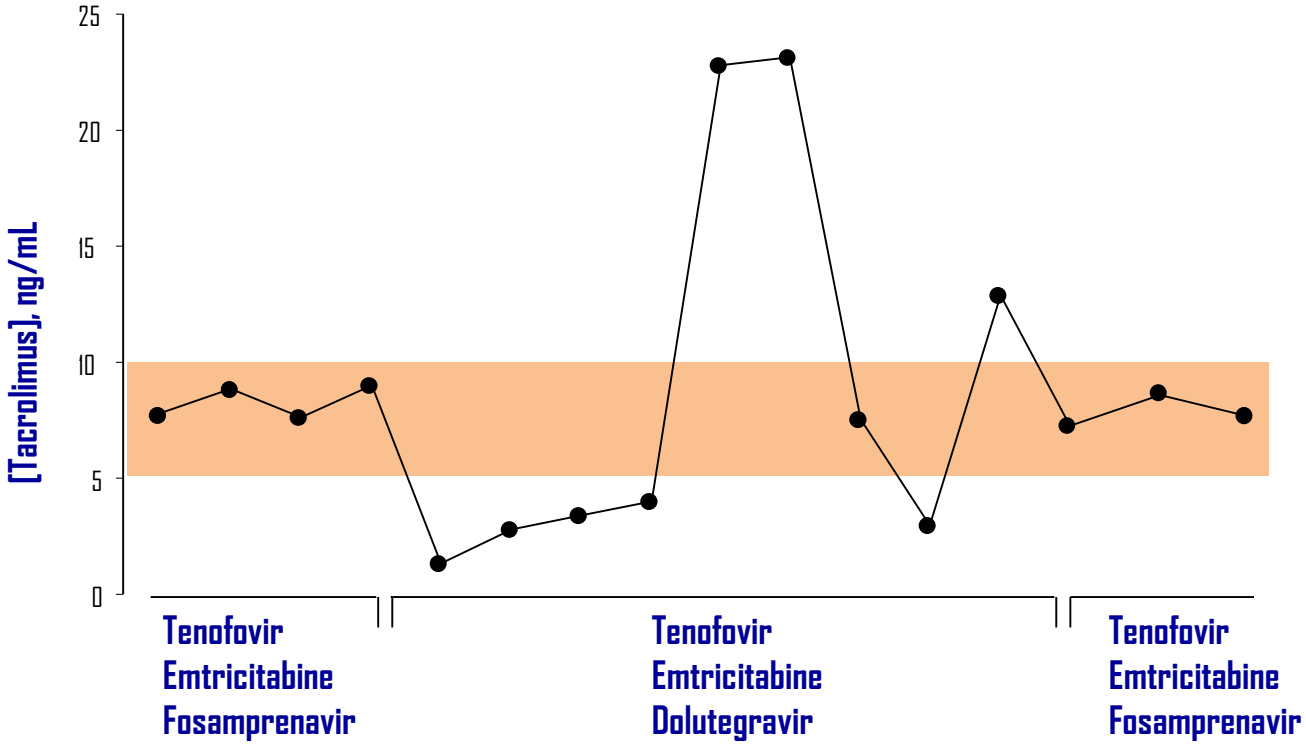
Last follow-up: **5.8 ± 3.2 years**

-TAF/FTC/dolutegravir (n=5)
-TDF/FTC/fosamprenavir (n=1)
-TAF/FTC/raltegravir (n=2)
-ABC/3TC/raltegravir (n=1)

4 out of the 9 patients returned to previous ART

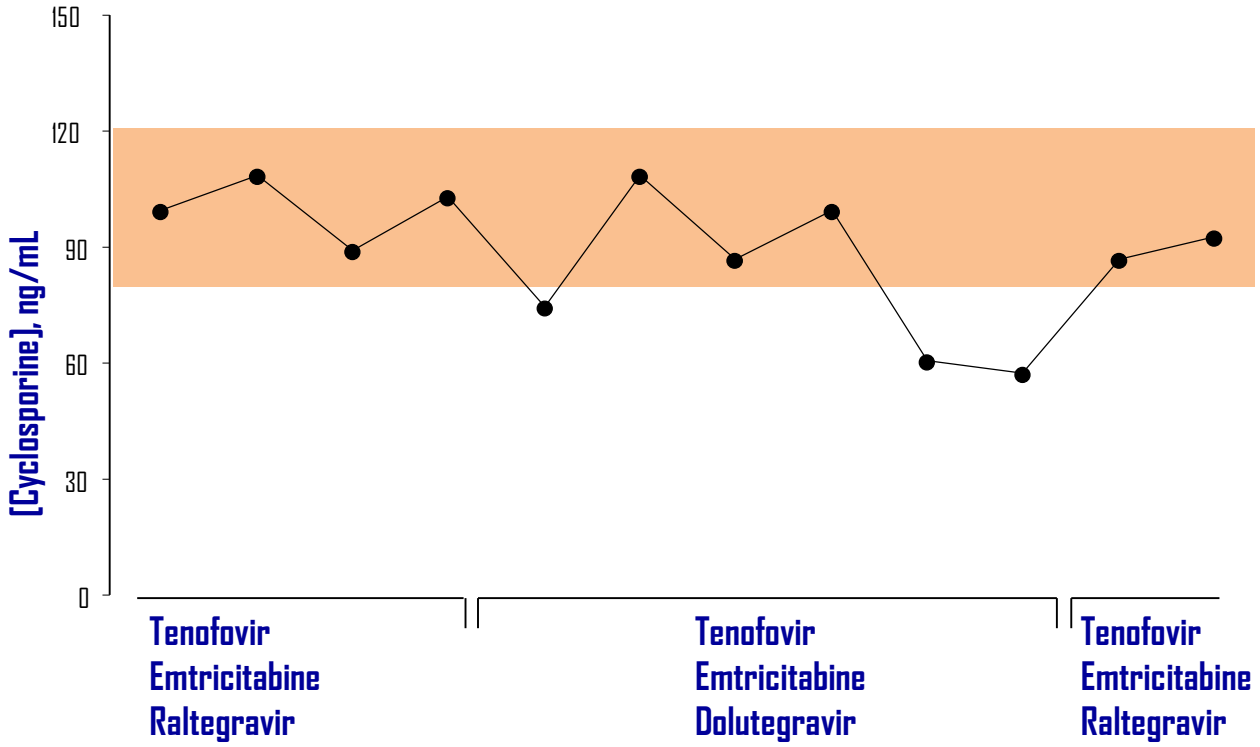
Patient 1

	Before switch to dolutegravir	During the switch to dolutegravir
Serum AST (IU/L)	38	78 (+105%)
Serum ALT (IU/L)	19	100 (+426%)



Patient 2

	Before switch to dolutegravir	During the switch to dolutegravir
S. creatinine (mg/dL)	0.8	1.8 (+125%)



Patient 3

	Before switch to dolutegravir	During the switch to dolutegravir
S. creatinine (mg/dL)	1.1	1.7 (+55%)

Patient 4

	Before switch to dolutegravir	During the switch to dolutegravir
S. creatinine (mg/dL)	1.3	1.6 (+23%)
GI disturbances**	none	Nausea/vomiting

** episodes of nausea/vomiting can be ascribed either to dolutegravir, cobicistat or calcineurin inhibitors…

Mercoledi 13 Marzo 2019

- ✓ Paziente maschio (Vo.Si. 26/03/1961)
- ✓ Trapianto di fegato per cirrosi: 2014
- ✓ TARV al trapianto: raltegravir + atazanavir/r
- ✓ Semplificazione: introdotto dolutegravir, tolto ritonavir
- ✓ Aumento creatinina sierica….
- ✓ Modificato dosaggio ciclosporina……..

Conclusions

- ✓ We have shown here that half of the LTx patients were switched back from dolutegravir-based to their previous antiretroviral regimens. However, not all safety concerns can be univocally ascribed to dolutegravir
- ✓ Significant fluctuation in the tacrolimus and cyclosporine concentrations were observed in some patients immediately after the switch to dolutegravir related to unknown mechanisms
- ✓ The management of HIV-infected liver transplant recipients in clinical practice is still a complex task...

Il futuro di GAP

..... Stiamo preparando card che ogni paziente dovrebbe conservare nel portafoglio...

Questa carta contiene informazioni importanti su un farmaco che riceve. Vi consigliamo di mostrare questa carta agli altri specialisti che vede.

Ricevete: **Evotaz®, Invirase®, Genvoya®, Kaletra®, Norvir®, Prezista®, Reyataz®, Rezolsta®, Stribild®, Symtuza® o Tybost®**

Questi farmaci interagiscono con i corticosteroidi somministrati per via orale, cutanea, nasale, oculare, polmonare, intraarticolare o per via intramuscolare e possono causare la sindrome di Cushing.

Se vi viene prescritto un corticosteroide, vi consigliamo di controllare che il farmaco non contenga alcuna delle seguenti sostanze (l'elenco dei preparati non è esaustivo :

Betamethasone: contenuto nel Betesil®, Betnesol®, Betnovate®
Budenoside: Budenid®, Budenoside®, Pulmicort®
Clobetasol: Dermovate®
Dexamethasone: Dexamethasone®, Fortecortin®, Maxitrol®
Fluticasone: Axotide®, Nasofan®, Seretide®
Mometasone: Elocom®, Mometason®, Nasonex®
Triamcinolone: Kenacort®, Nasacort®, Triamcort®

Avviso importante: altre classi di farmaci possono interagire con il trattamento. Si prega di consultare il vostro medico curante prima di prendere qualsiasi nuovo farmaco.

THANK YOU !

Dario Cattaneo

Tutti i colleghi che inviano pazienti

...e i pazienti...che chiedono informazioni!!!