Gestione della polypharmacy nel paziente HIV positivo:

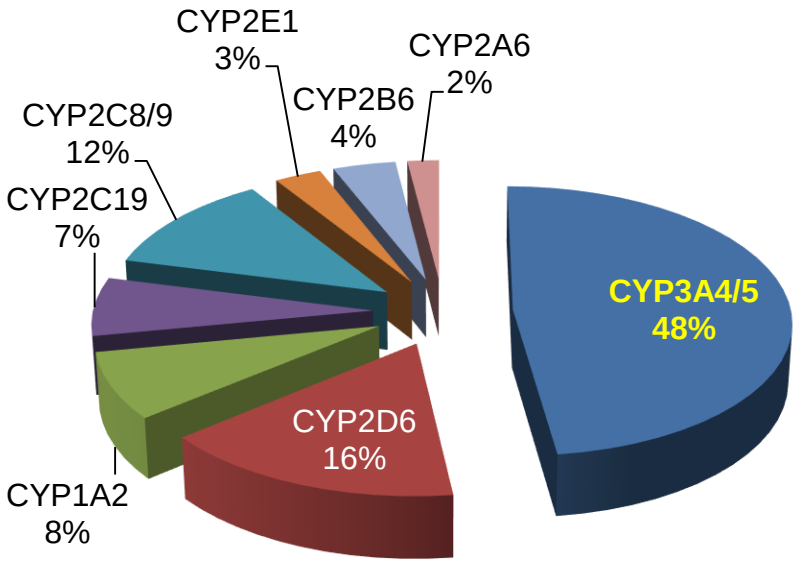
- Le basi teoriche vs. pratica clinica -

Dario Cattaneo, Cristina Gervasoni
Gestione Ambulatoriale Politerapie (GAP)
ASST Fatebenefratelli Sacco, Milano

Quali farmaci sono più a rischio di interazioni?

Farmaco	Metabolismo
Atazanavir	CYP3A (induttore UGT)
Darunavir	CYP3A
Fosamprenavir	CYP3A
Indinavir	CYP3A
Lopinavir	CYP3A
Ritonavir	CYP3A (inibitore CYP)
Saquinavir	CYP3A
Tipranavir	CYP3A
Efavirenz	CYP3A, CYP2B6 (induttore)
Etravirina	CYP3A, CYP2C9, CYP2C19
Nevirapina	CYP3A, CYP2B6
Rilpivirina	CYP3A (CYP2C19)
Abacavir	ADH, UGT
Didanosina	Xantina ossidasi
Zidovudina	UGT
Maraviroc	CYP3A
Enfuvirtide	Esterasi
Raltegravir	UGT
Elvitegravir	CYP3A
Dolutegravir	UGT/CYP3A

*Emtricitabina, Lamivudina, Stavudina, Tenofovir eliminati principalmente immodificati

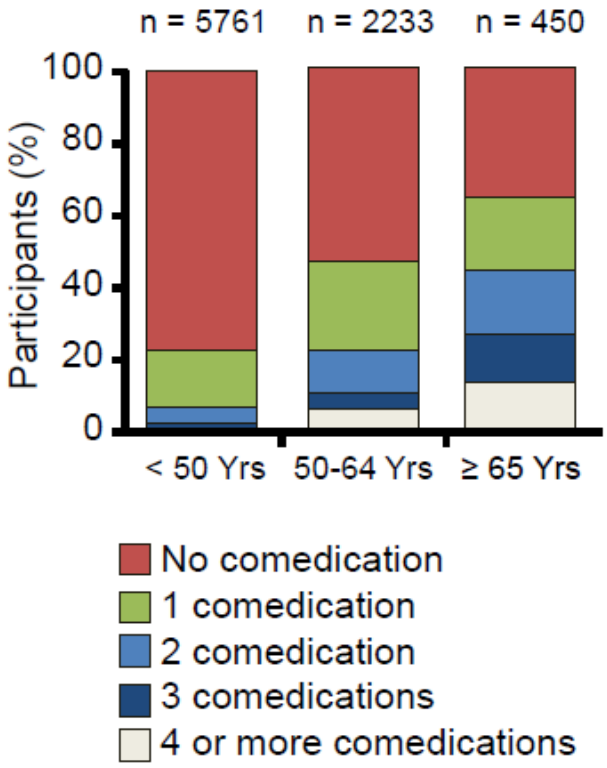


Il 50% di **tutti** i farmaci oggi in commercio (non solo ARVs) viene metabolizzato dal citocromo 3A (CYP3A4/5)…

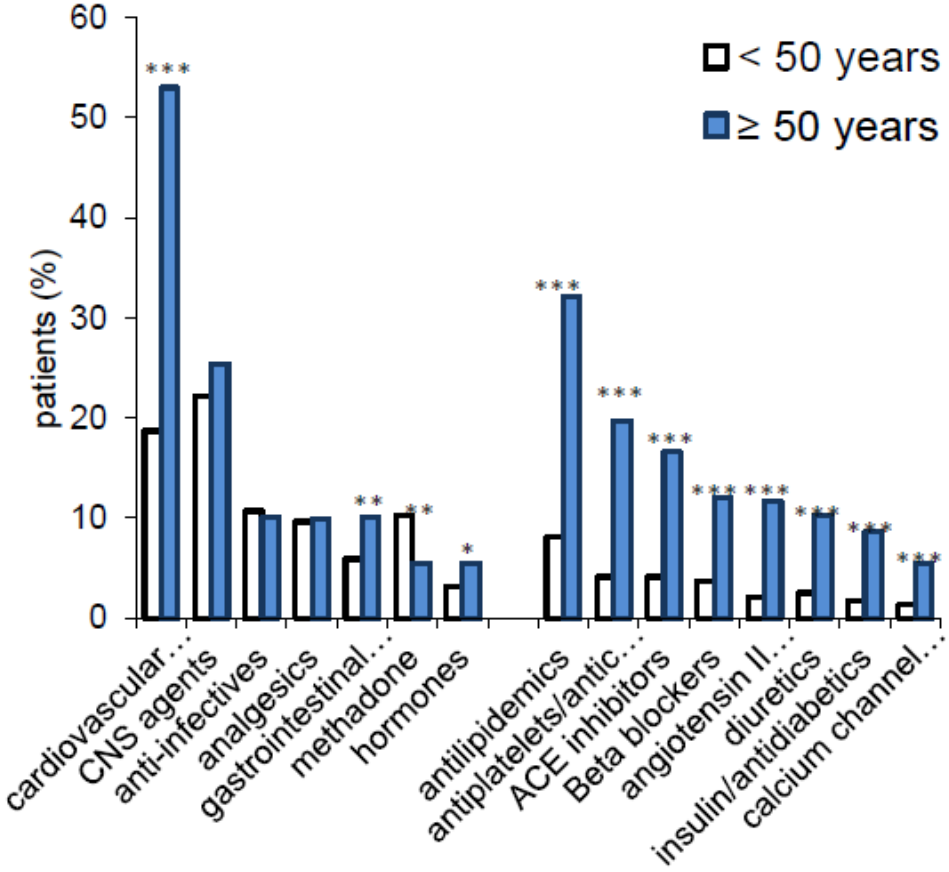
Quali pazienti sono più a rischio di interazioni?

Older HIV patients and risk of drug-drug interactions

Number of non-HIV co-medications stratified by age

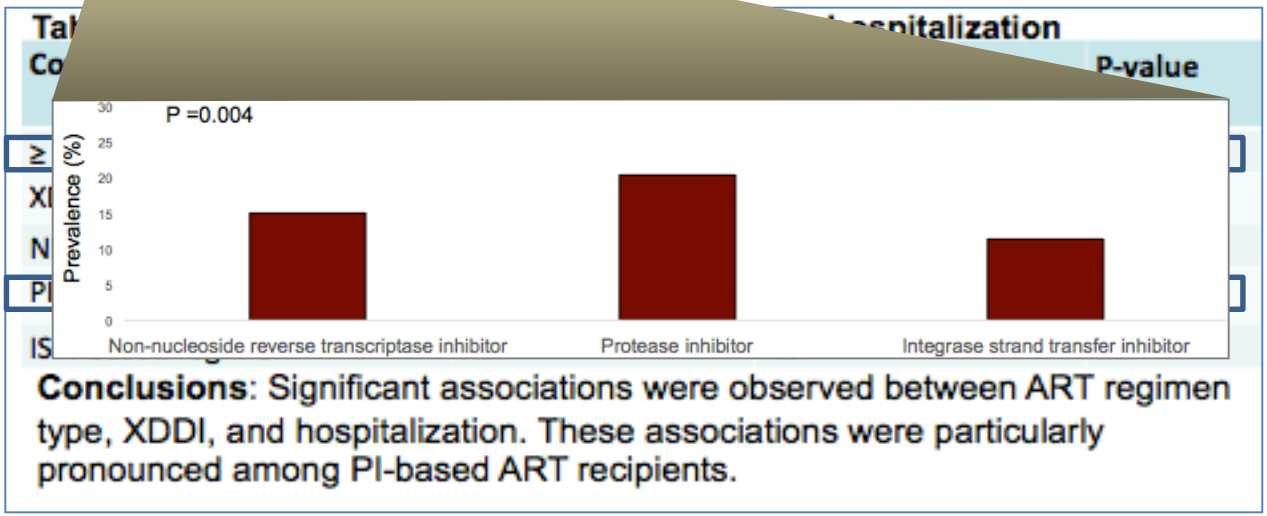


Prescribed therapeutic classes



Quali rischi in presenza di interazioni?

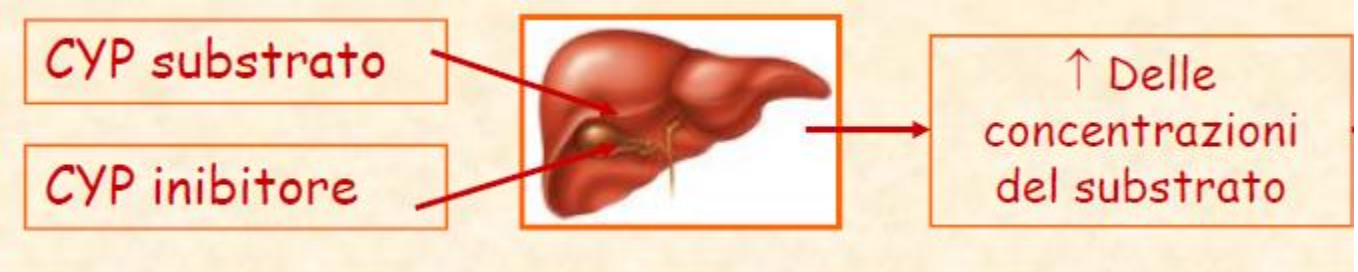
Veterans with an XDDI* (9,6%) had a significantly higher hospital admission rate in the first year of ART than veterans without an XDDI.



*CONTRAINDICATED DRUG-DRUG INTERACTIONS (XDDI)

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

L'elevato rischio di interazioni con PIs e elvitegravir è legato alla presenza del booster…ma perchè serve il booster?!?



Il booster aumenta la biodisponibilità del PI bloccandone il metabolismo mediato dagli enzimi metabolizzanti di fase I (isoforme citocromo 3A4/3A5). L'utilizzo del booster si rende necessario quando:

- La biodisponibilità orale di un farmaco è bassa;
- Le concentrazioni sistemiche del farmaco sono insufficienti se confrontate con le MEC (minimum efficacy concentration)

…l'esempio di atazanavir…(MEC = 150 ng/mL)

	Overall (n=85)	300/100 qd (n=31)	300 qd (n=54)
ATV conc. (ng/mL)	219 (79-632)	711 (394-914)	121 (52-209)

Median (interquartile range)

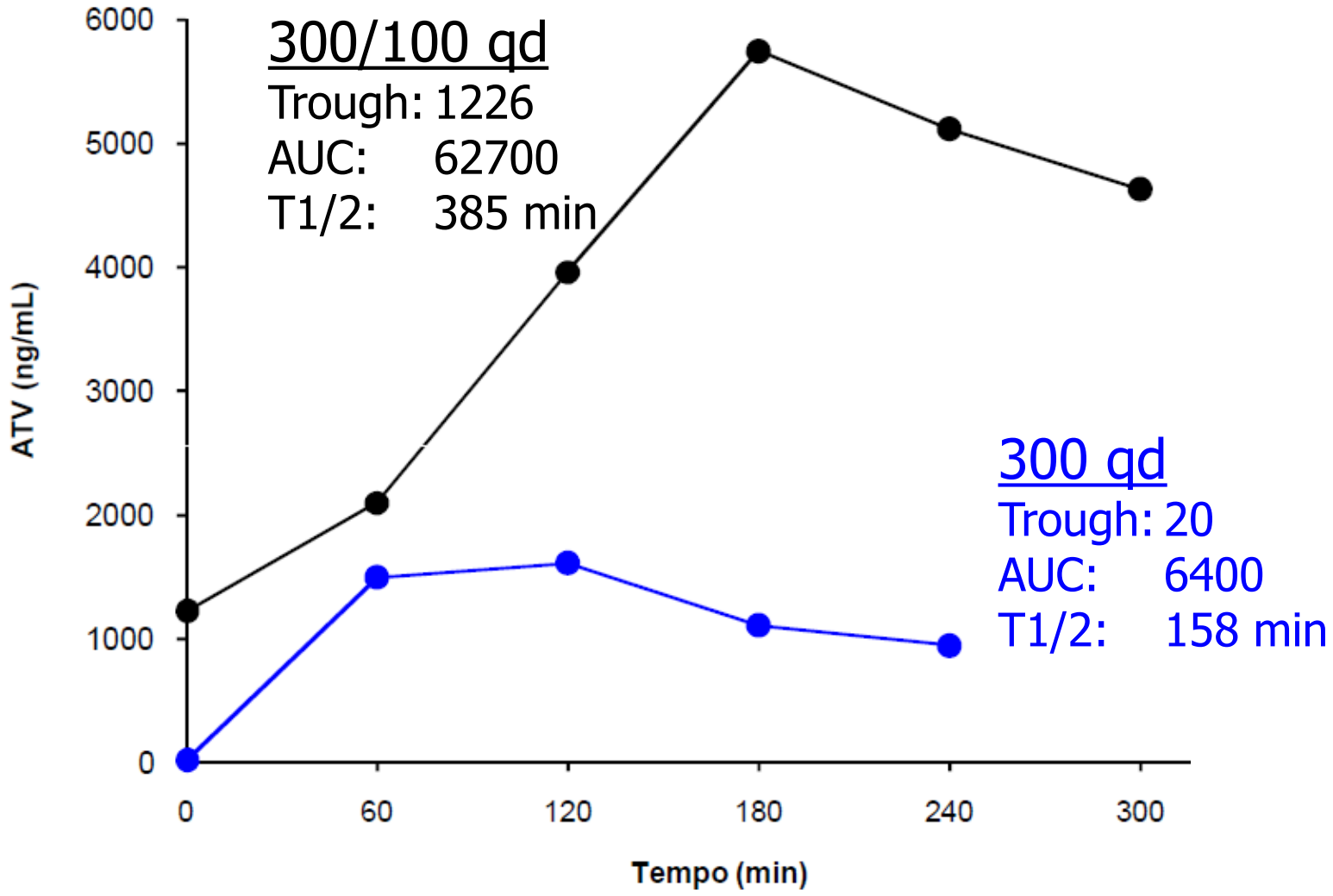
- Moltò, TDM 2007 -

Parameter	No failure ($n = 62$)	Virological failure ($n = 7$)	P value[a]
CL (liters/h)	13.3 ± 2.6	15.3 ± 2.1	0.03
V (liters)	74.7 ± 24.6	81.5 ± 19.4	0.31
k_a (h^{-1})	0.75 ± 0.28	0.38 ± 0.20	0.002
AUC_{0-24} ($mg \cdot h \cdot liter^{-1}$)	22.4 ± 11.2	10.3 ± 2.1	0.001
AUC_{target} ($mg \cdot h \cdot liter^{-1}$)	18.9 ± 11.1	7.1 ± 1.9	0.002
T_{target} (h)	22.9 ± 2.5	19.9 ± 4.9	0.045
C_{trough} (mg/liter)[b]	0.31 ± 0.22	0.11 ± 0.08	0.012
No. (%) with $C_{trough} < 0.15$ mg/liter[b]	17 (27)	4 (57)	0.19
No. (%) of low absorbers	31 (50)	7 (100)	0.014
No. (%) receiving once-daily administration	21 (34)	6 (86)	0.012

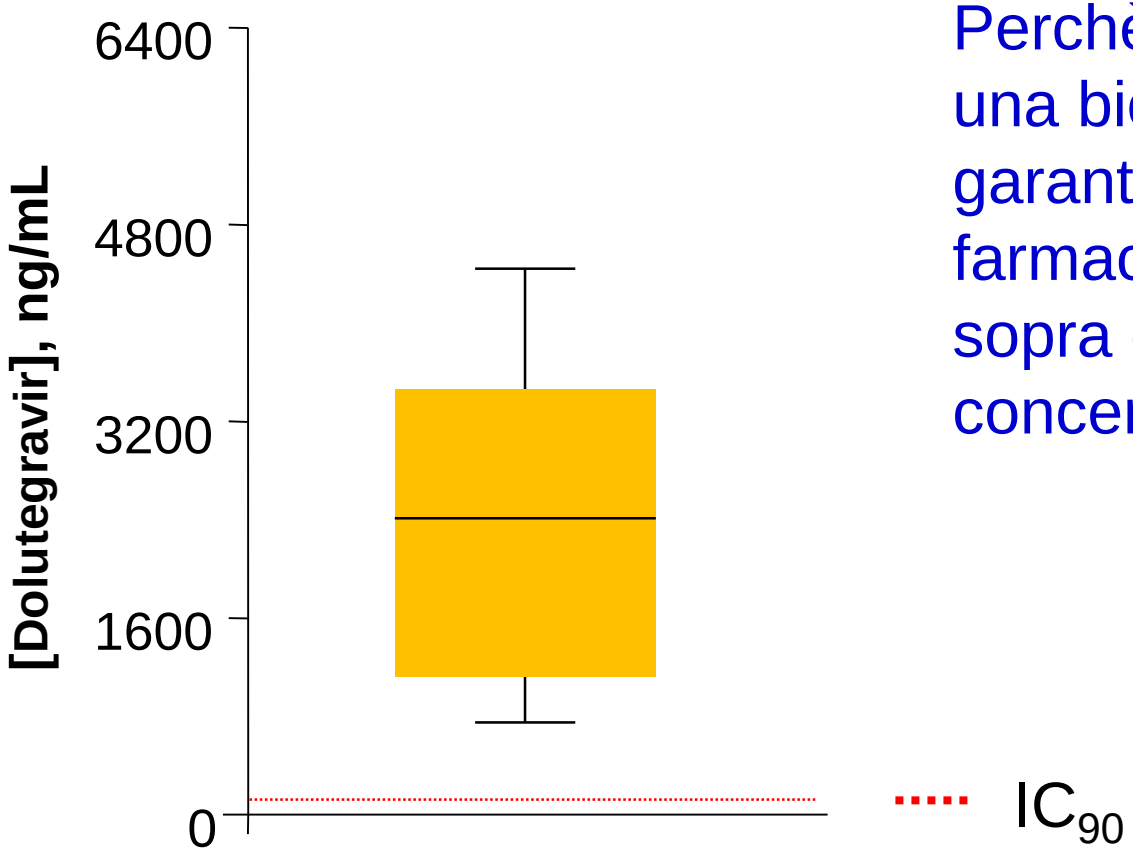
0.15 mg/L Ξ 150 ng/mL

- Goutelle, AAC 2013 -

Quanto pesa ritonavir sulla farmacocinetica di atazanavir?



Perchè alcuni farmaci non hanno bisogno del booster booster?!?



Perchè questi farmaci hanno una biodisponibilità orale che garantisce concentrazioni di farmaco ampiamente al di sopra delle minime concentrazioni inibitorie

Table 1. Inhibitory and inducing effects of ritonavir and cobicistat on cytochromes and drug transporters[3,4,10–12]

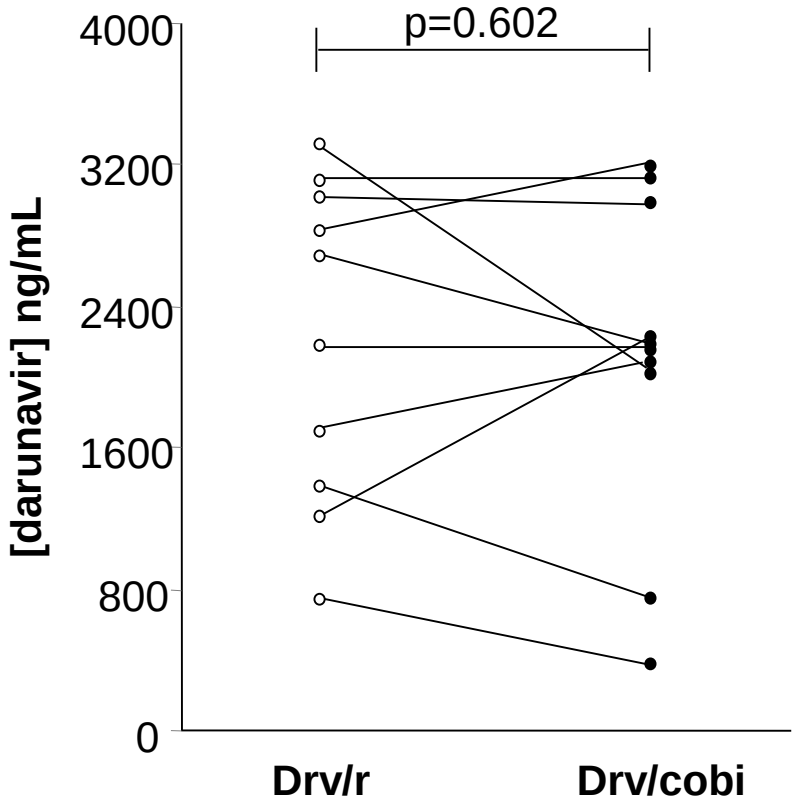
	IC_{50} (μM)	
	ritonavir	cobicistat
Cytochrome		
CYP1A2	>25	>25
CYP2B6	2.9	2.8
CYP2C8	2.8	>25
CYP2C9	4.4	>25
CYP2C19	>25	>25
CYP2D6	2.8	9.2
CYP3A4	0.11	0.15
Transporter		
P-gp	>20	36
BCRP	>20	59
OATP1B1	2.05	3.5
OATP1B3	1.83	1.88
MATE1	1.34	1.87
MATE2-K	>20	33.5
OAT1	>20	>100
OAT3	8.46	>100
OCT2	~20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

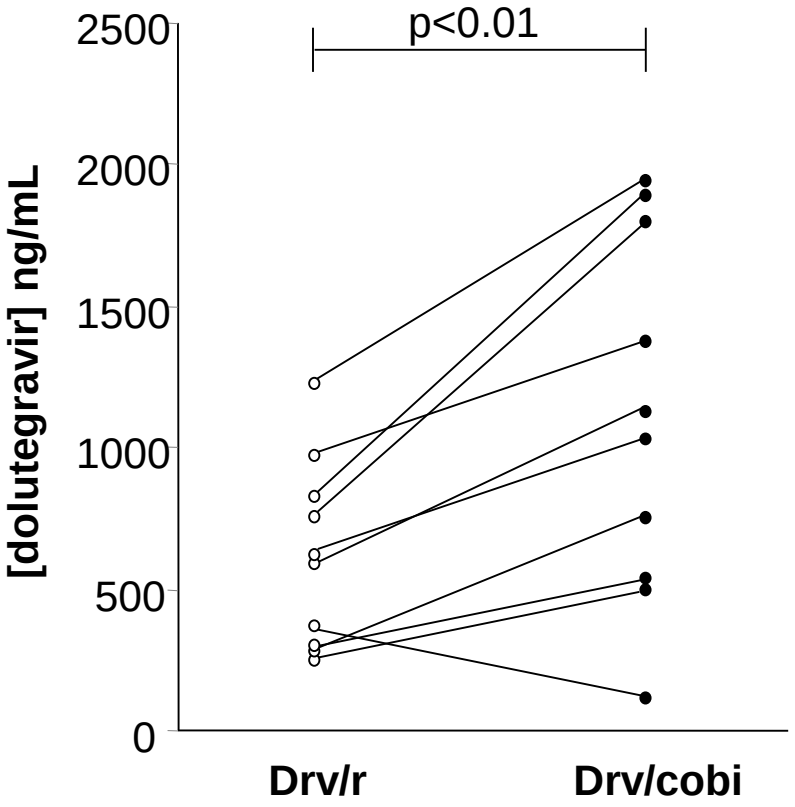
Lower value reflects greater inhibitory effect

..cambia davvero cosi tanto da ritonavir a cobi..??

- Marzolini, JAC 2016 -

Increased dolutegravir exposure in HIV patients switched from ritonavir to cobicistat





- Gervasoni, JAC 2017 -

UNIVERSITY OF LIVERPOOL

Coadministration with ritonavir alone has not been studied. Based on studies with boosted PIs, ritonavir could potentially decrease dolutegravir concentrations by induction of glucuronidation.

Antimicrobial Agents and Chemotherapy®

Differential Influence of the Antiretroviral Pharmacokinetic Enhancers Ritonavir and Cobicistat on Intestinal P-Glycoprotein Transport and the Pharmacokinetic/Pharmacodynamic Disposition of Dabigatran

November 2017 Volume 61 Issue 11 e01201-17

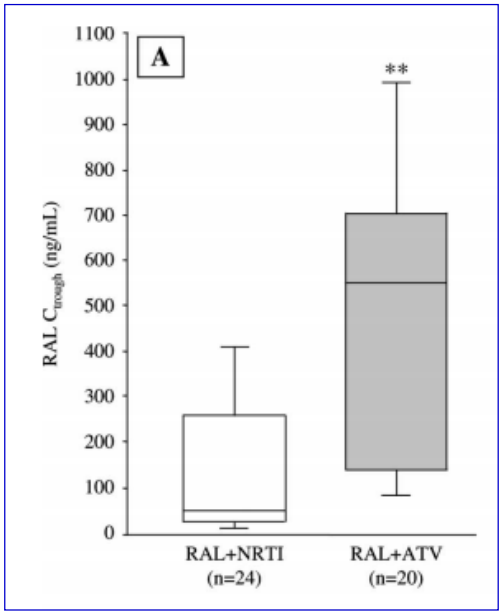
Antimicrobial Agents and Chemotherapy®

Ritonavir-Boosted Protease Inhibitors but Not Cobicistat Appear Safe in HIV-Positive Patients Ingesting Dabigatran

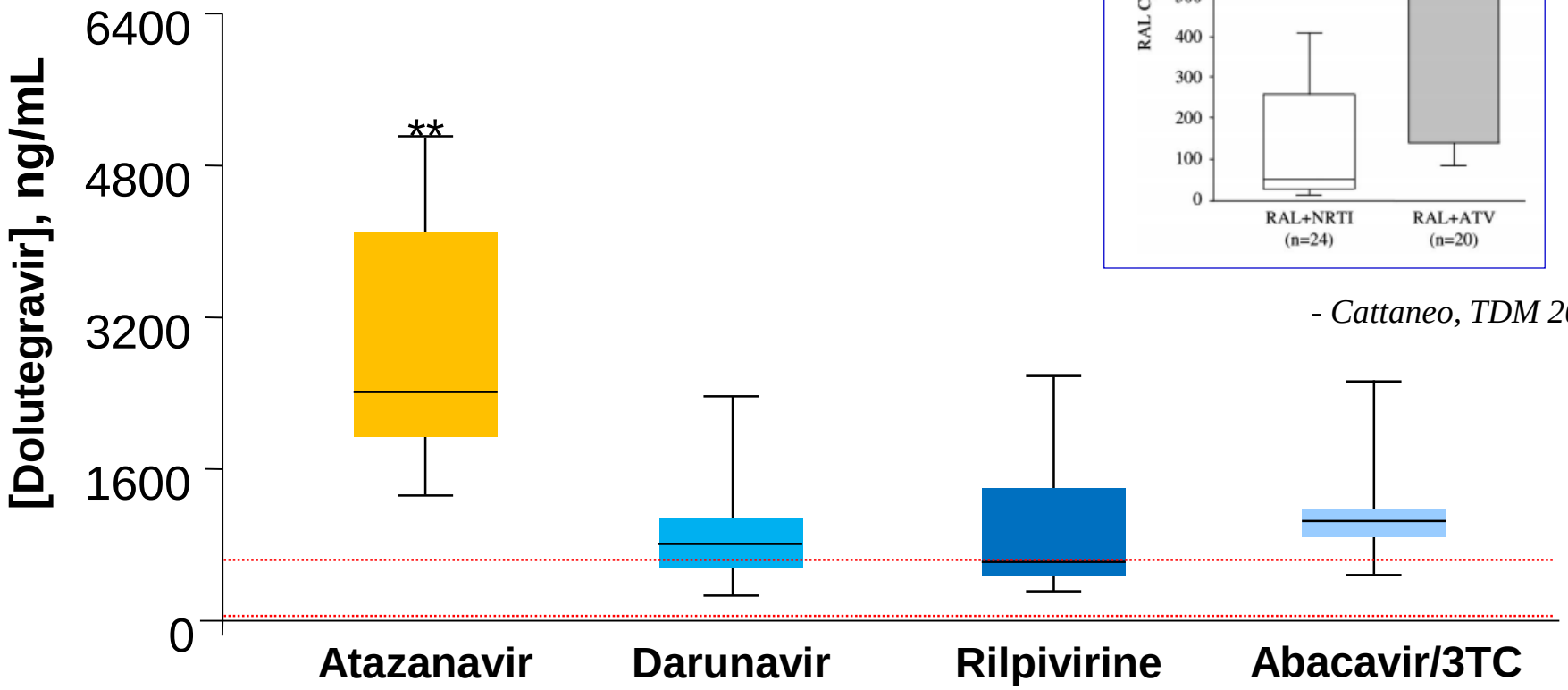
February 2018 Volume 62 Issue 2 e02275-17

Exposure-Related Effects of Atazanavir on the Pharmacokinetics of Raltegravir in HIV-1-Infected Patients

Esistono anche dei booster “atipici”….



- Cattaneo, TDM 2010 -



**p<0.001 versus other groups. Dashed lines depict the protein-adjusted 90% inhibitory concentration for wild-type and resistant virues (64 and 640 ng/mL, respectively)..

- Cattaneo, Antiviral Therapy 2017 -

Quando un'interazione può essere considerata clinicamente rilevante?

No risk of drug-drug interaction

Statistically significant drug-drug interaction but interaction unlikely to be of clinical importance (i.e. magnitude of the interaction is small, drugs with large therapeutic index).

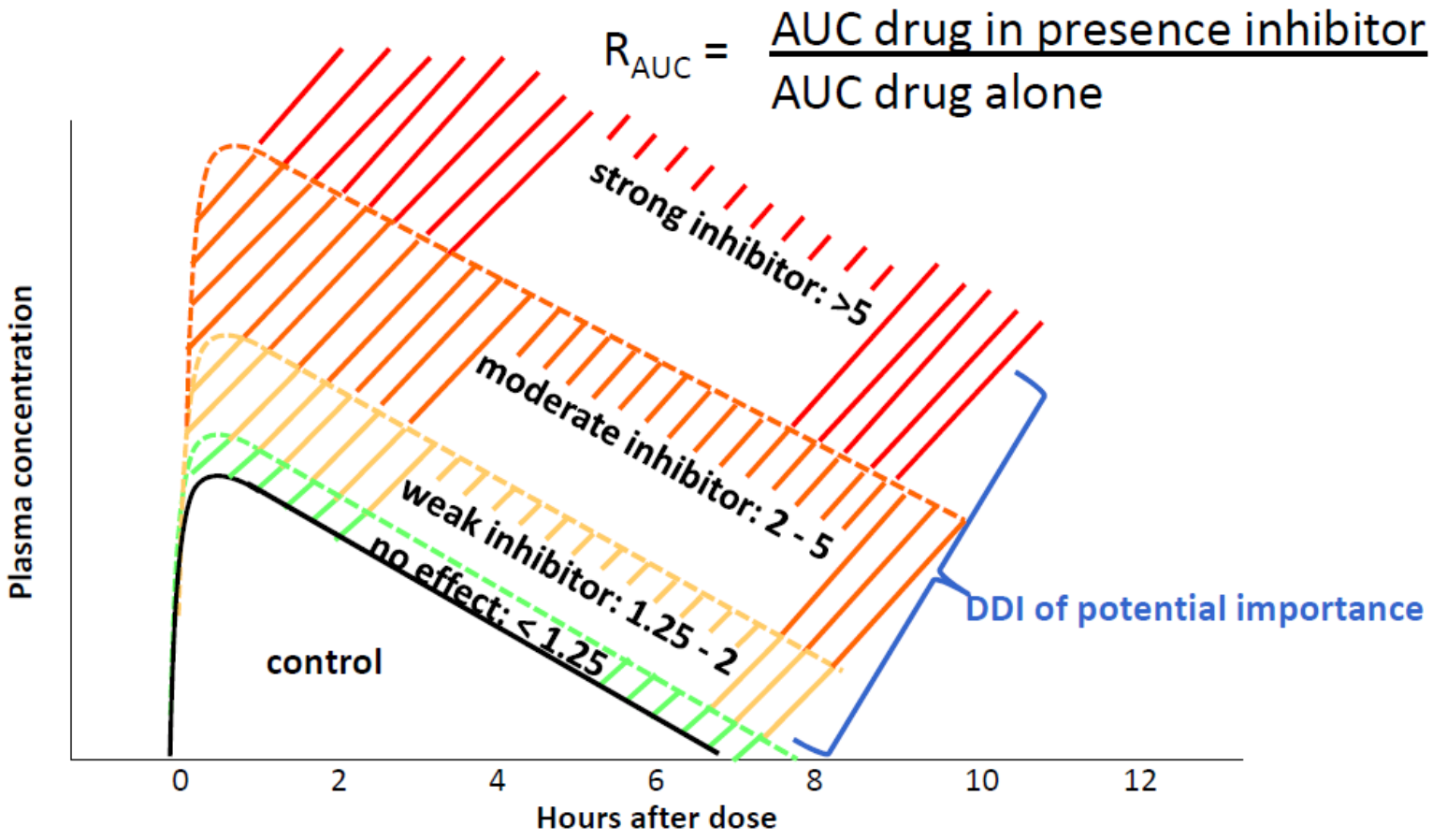
Clinically relevant drug-drug interaction manageable by dose modification, change in timing of administration, close monitoring or change to alternative drug.

Hazardous drug-drug interaction potentially causing serious or life-threatening adverse reactions.

Greenblatt DJ. In: Drug Interactions in Infectious Diseases 2011, FDA Guidance for DDI studies 2012

Il punto di vista degli enti regolatori...

Controlled clinical drug-drug interactions studies



Greenblatt DJ. In: Drug Interactions in Infectious Diseases 2011, FDA Guidance for DDI studies 2012

…e le relative limitazioni…

Modifiche nell'AUC <1.25 volte:	nessun effetto rilevante
Modifiche AUC 1.25-2 volte:	interazione debole
Modifiche nell'AUC 2-5 volte:	interazione moderata
Modifiche nell'AUC >5 volte:	interazione forte

Digossina:
1.8 ug/L

↓ +100%

3.6 ug/L

lopinavir:
1000 ng/mL

↓ +100%

2000 ng/mL

Inoltre la definizione adottata dagli enti regolatori per valutare l'entità di una interazione farmacologica si fonda sull'esistenza di una relazione lineare tra il dato farmacocinetico e l'outcome clinico…

Clinical pharmacokinetics of verapamil, nifedipine and diltiazem

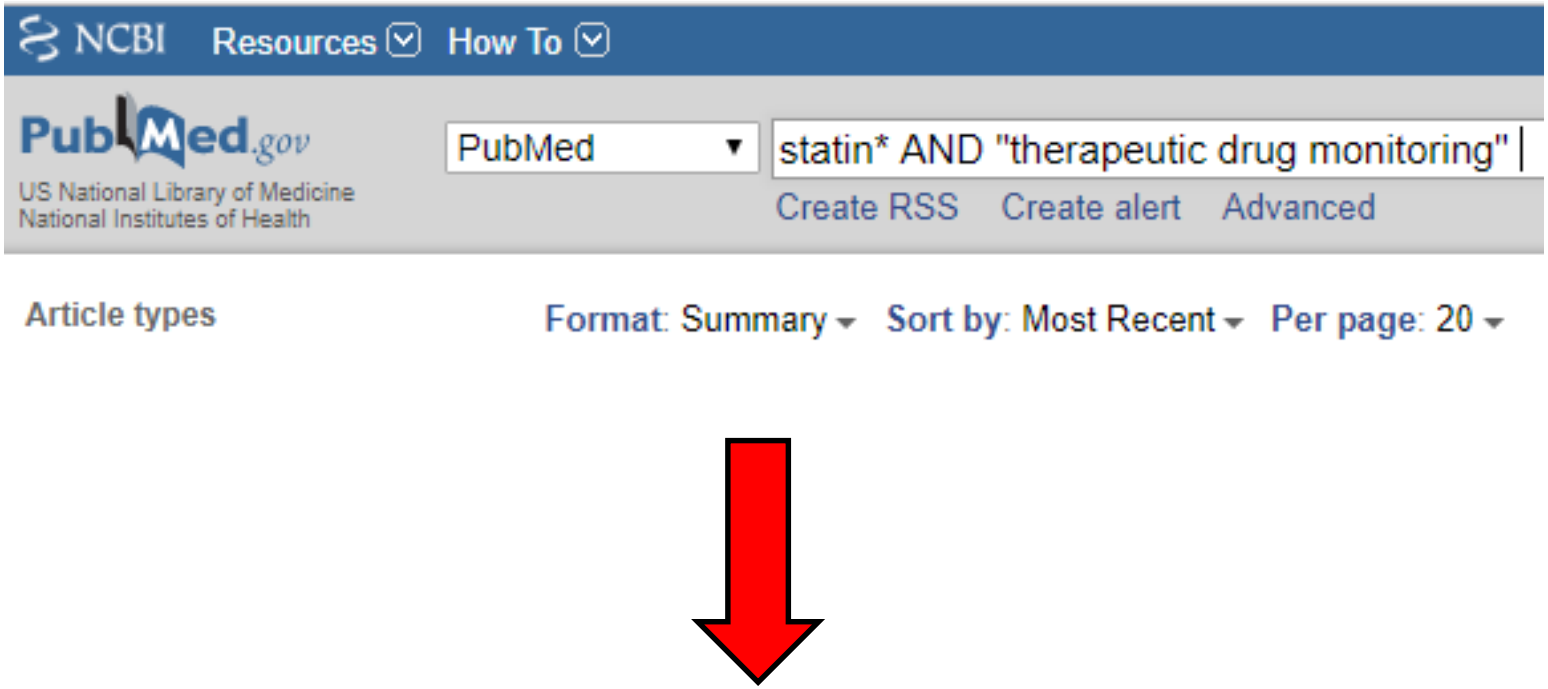
"No effective therapeutic plasma concentration range has been firmly established. As reliable clinical end-points are available for dose titration of calcium antagonists, it is doubtful whether therapeutic drug monitoring will be of great value"

- Echizen, Clin Pharmacokinet 1986 -

α1-Adrenoceptors and muscarinic receptors in voiding function – binding characteristics of therapeutic agents in relation to the pharmacokinetics

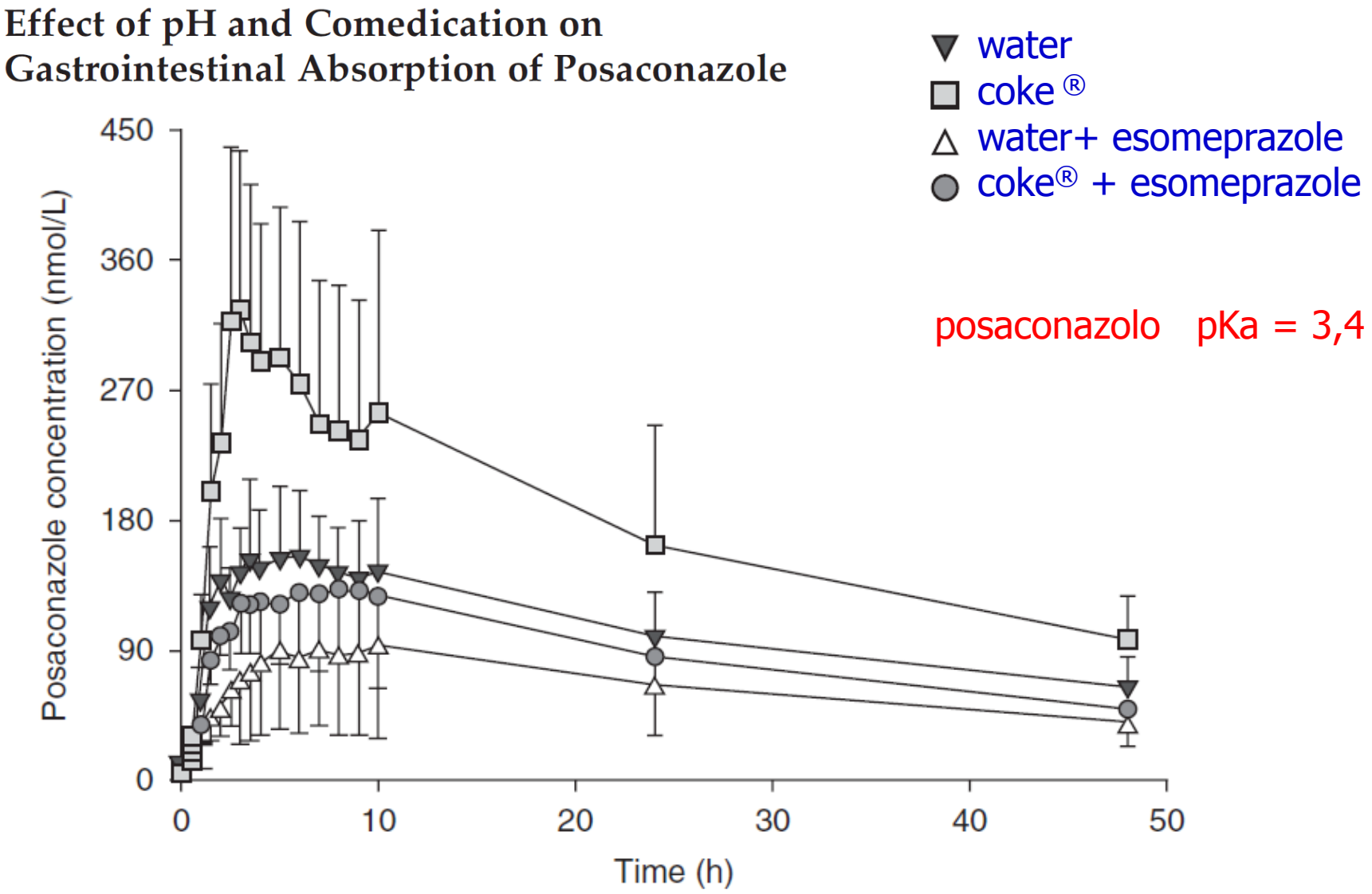
"Alpha1-blockers are characterized by a wide therapeutic window and the the lack of clear correlations between plasma concentrations of these drugs and their hemodynamic effects"

- Yamada, Br J Clin Pharmacol 2011 -



No studies showing potential associations between systemic statins concentrations and drug safety (muscle toxicity) or drug efficacy were found !!!

Le DDIs possono riguardare tutte le fasi ADME…



posaconazolo pKa = 3,4

- Walravens, Clin Pharmacokinet 2011 -

Gli Inibitori di Pompa Protonica possono però aumentare l'assorbimento di altre molecole…

Parameter	No. (%) of cases by linezolid C_{min}: ≥10 mg/liter (n = 33)	<10 mg/liter (n = 247)	P value
Linezolid administration route			
Intravenous	21 (63.6)	157 (63.6)	0.847
Oral	12 (36.4)	90 (36.4)	0.845
Linezolid dosage, median (IQ range) (mg/kg/q12h)			
Overall	9.3 (7.5–10.2)	8.0 (7.1–10.0)	0.067
Intravenous	10.0 (7.9–10.0)	8.0 (7.1–10.0)	0.071
Oral	7.9 (7.9–10.3)	8.5 (7.1–10.0)	0.876
Cotreatments			
Omeprazole	26 (78.8)	68 (27.5)	<0.001
Amiodarone	7 (21.2)	6 (2.4)	<0.001
Amlodipine	7 (21.1)	13 (5.2)	0.003

- Pea, AAC 2010 -

Pharmacokinetics of Dolutegravir When Administered With Mineral Supplements in Healthy Adult Subjects

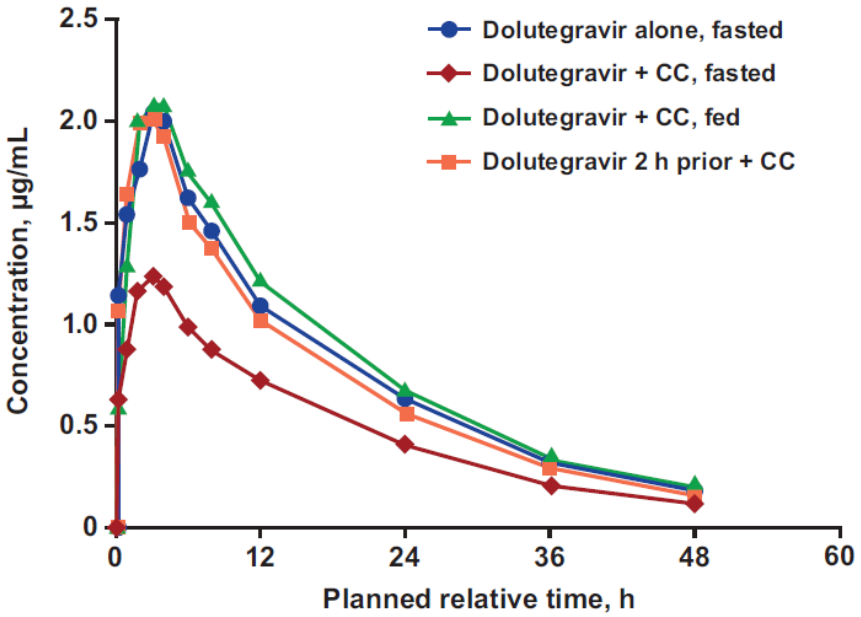


Figure 1. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without calcium carbonate (CC) (1,200 mg, single dose).

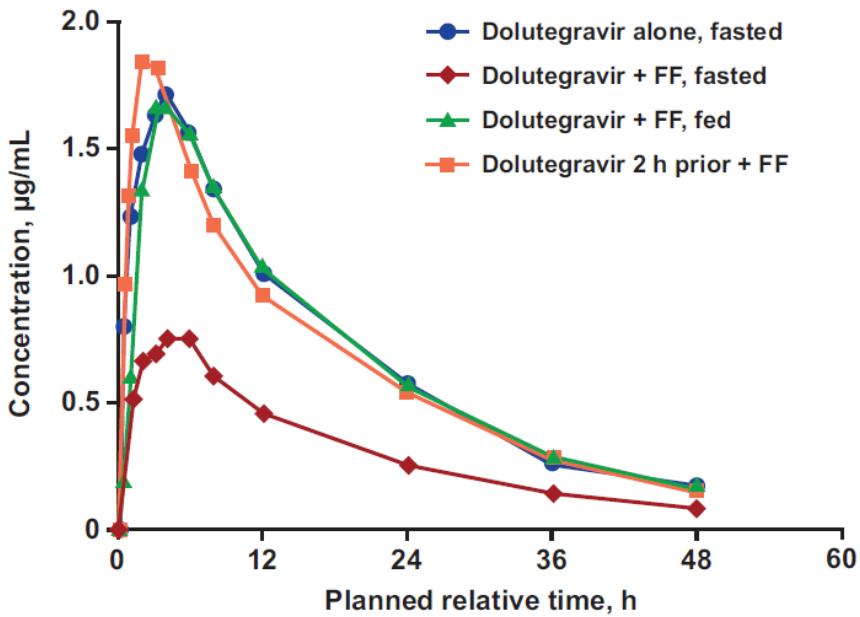


Figure 2. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without ferrous fumarate (FF) (324 mg, single dose).

40% reduction in AUC

55% reduction in AUC

Chelation of integrase inhibitors with divalent cations (magnesium, calcium, iron, aluminium)

- Song, J Clin Pharmacol, in press 2015 -

- ✓ Oltre agli integratori…cosa possiamo dire di OTC, prodotti fitoterapici, ecc…???

Ore 15.00-16.00 **SIMPOSIO IV**

Gestione della *Polypharmacy* nel paziente HIV positivo

Moderatori: *T. Bini, E. Clementi (Milano)*

Pratica clinica

C. Gervasoni (Milano)

Chiedetelo a Cristina!!!

FARMACI E CIBO

La presenza o meno di cibo condiziona la rapidità e l'entità dell'assorbimento gastrico-intestinale

STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Tablets
Product Monograph

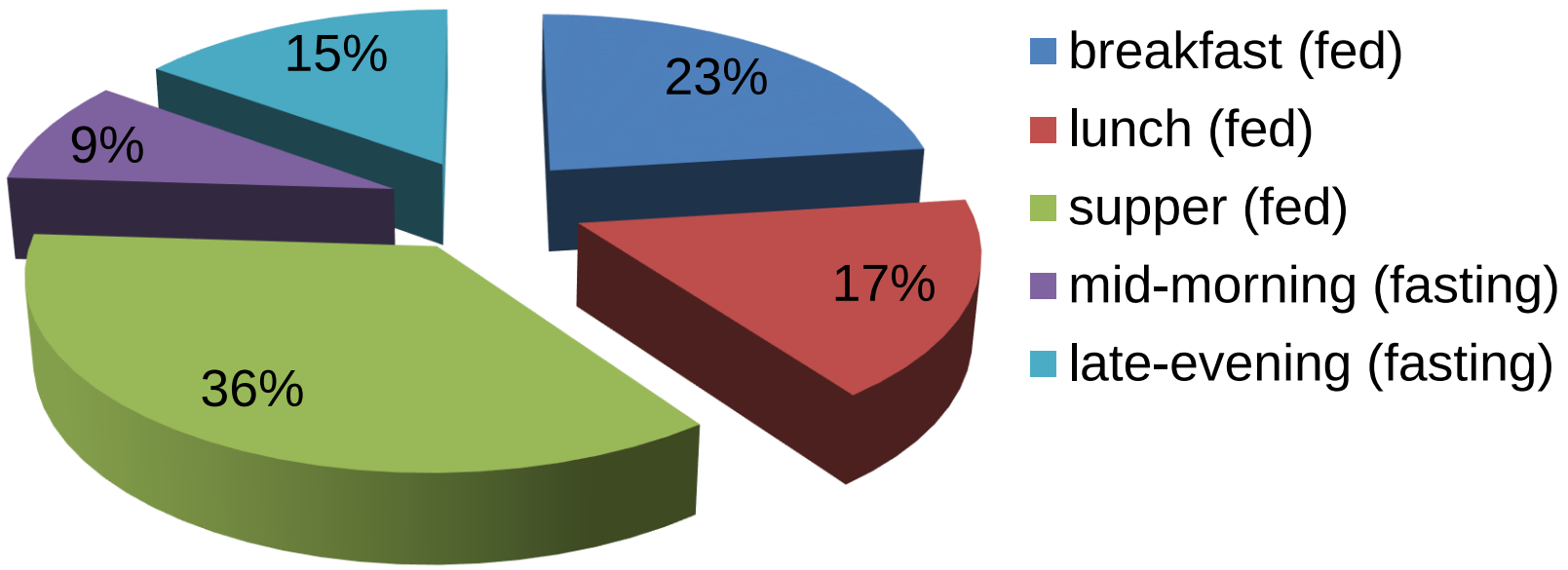
Drug-Food Interactions

Relative to fasting conditions, the administration of STRIBILD with a light meal (~373 kcal, 20% fat) or high-fat meal (~800 kcal, 50% fat) resulted in increased exposures of elvitegravir and tenofovir. For elvitegravir, C_{max} and AUC increased 22% and 36% with a light meal, while increasing 56% and 91% with a high-fat meal, respectively. The C_{max} and AUC of tenofovir increased 20% and 25% respectively with a light meal, while the C_{max} was unaffected and AUC increased 25% with a high fat meal. Cobicistat exposures were unaffected by a light meal and although there was a modest decrease of 24% and 18% in C_{max} and AUC respectively with a high-fat meal, no difference was observed in its pharmacoenhancing effect on elvitegravir. Emtricitabine exposures were unaffected by a light or high-fat meal.

"Take STRIBILD with food. Take your pill with food, this helps get the right amount of medicine in your body"

When food can make the difference: The case of elvitegravir-based co-formulation

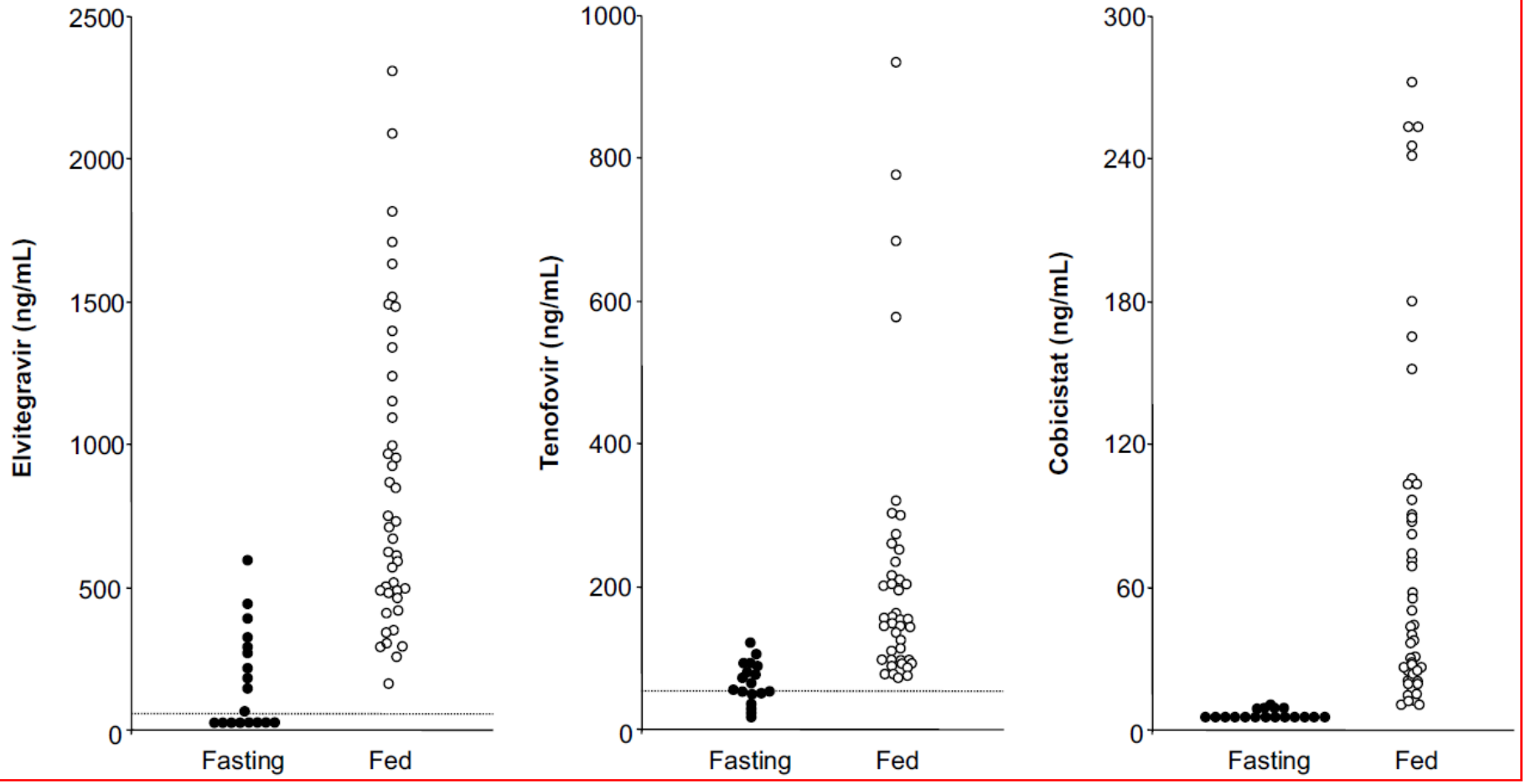
- ✓ 75 HIV-infected patients treated with Stribild for at least one month, with at least one request TDM of elvitegravir and tenofovir plasma trough concentrations, no clinical evidence of gastrointestinal impairment and not given drugs known to affect elvitegravir or tenofovir pharmacokinetics



✓24% of patients assumed Stribild® in fasting conditions

- Cattaneo et al, Int J Pharm 2016 -

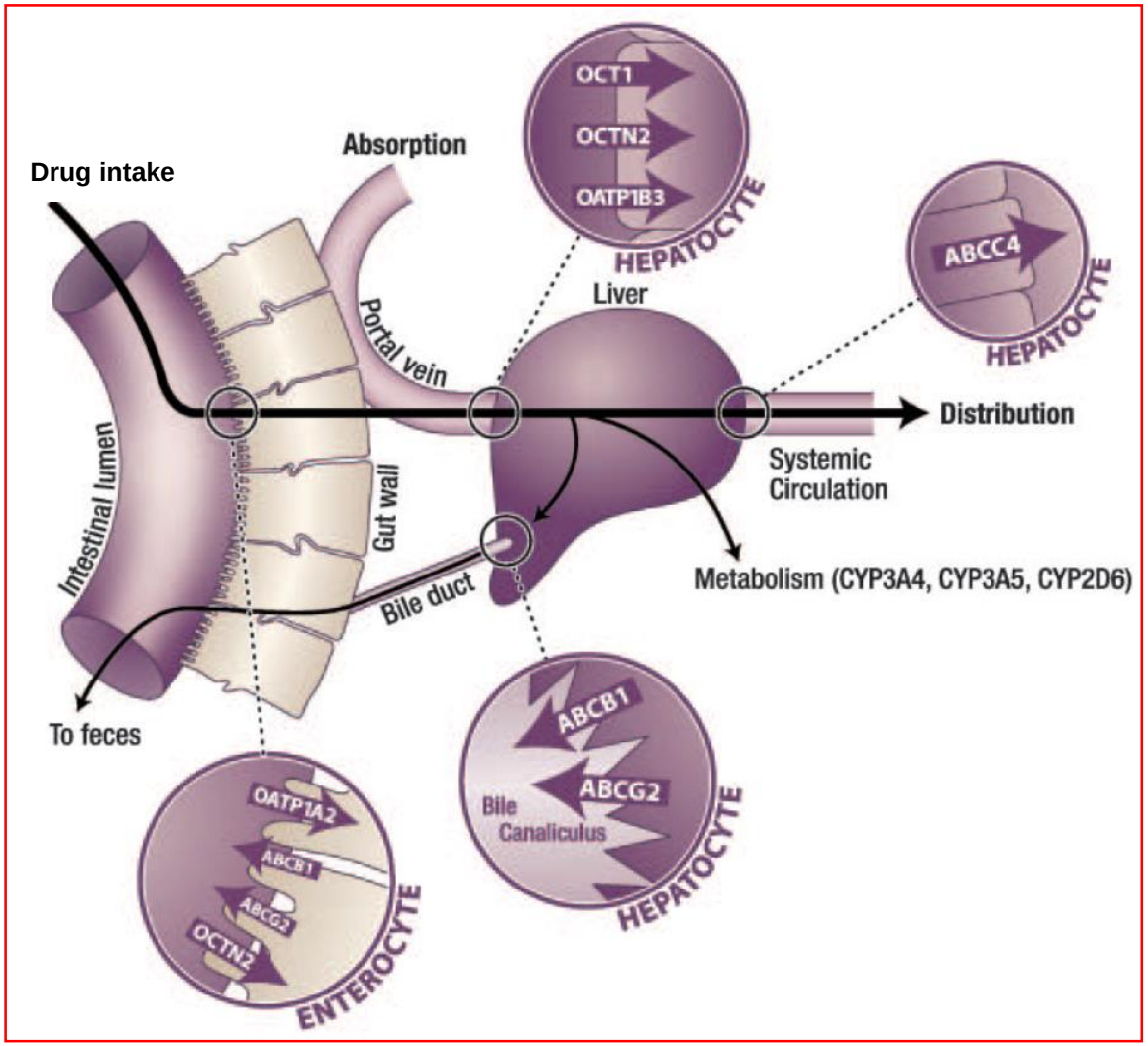
When food can make the difference: The case of elvitegravir-based co-formulation



- ✓ 12 out of the 75 patients (16%) had elvitegravir concentrations below the lower limit of quantification of the assay

- Cattaneo et al, Int J Pharm 2016 -

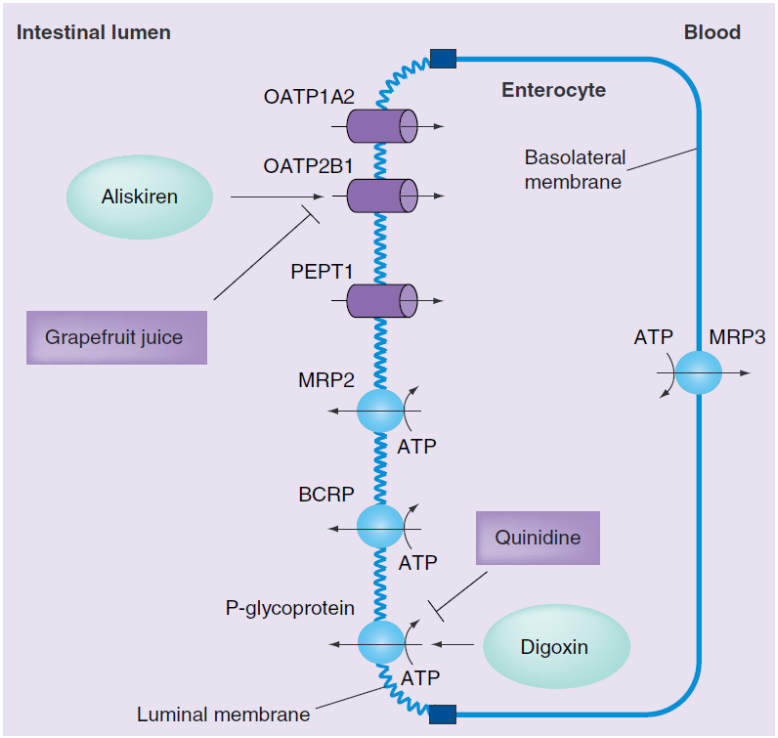
Distribuzione…

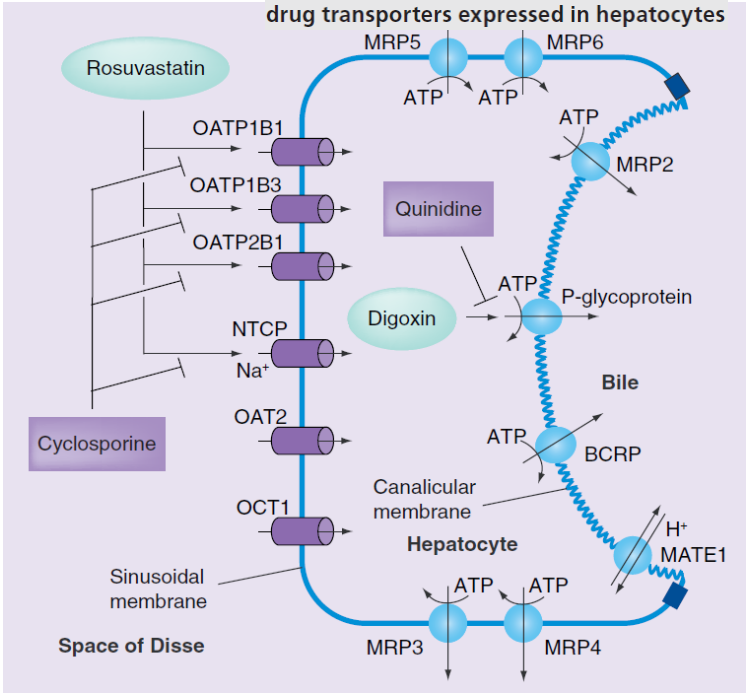


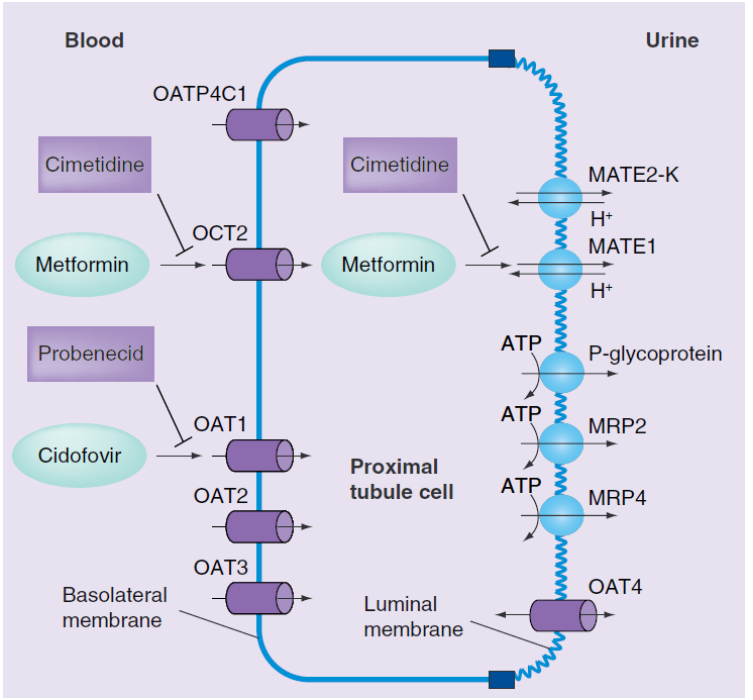
Le interazioni possono riguardare anche le proteine trans-membrana che fungono da trasportatori…

Transporter-mediated drug–drug interactions

- Muller, Pharmacogenomics 2011 -

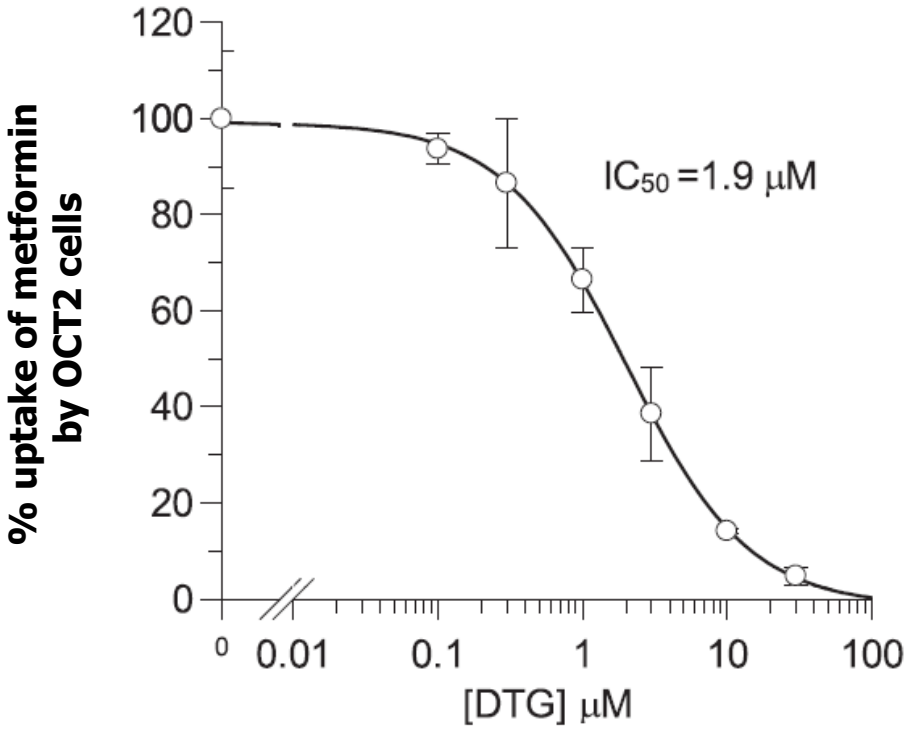






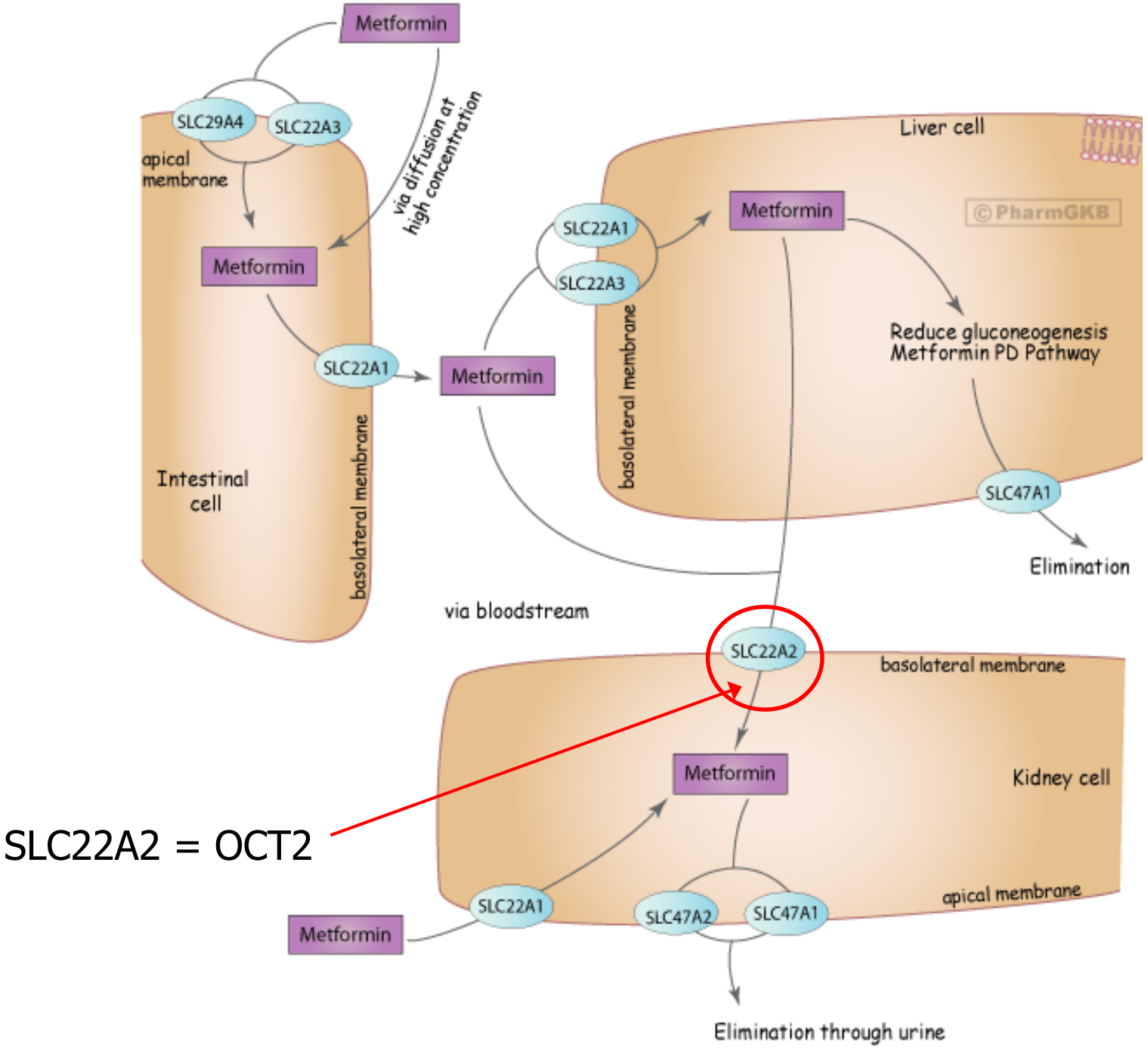
Dolutegravir is a substrate for the efflux transporters P-glycoprotein (P-gp) and human breast cancer resistance protein (BCRP)

MDCKII Cell Line	GF120918[b]	Rate Apical to Basolateral	Rate B→A	Apical Efflux Ratio
		pmol/min/cm²		
MDR1	—	7.3 ± 0.52	28 ± 3.1	3.8
MDR1	+	4.7 ± 0.04	3.5 ± 0.07	0.74
BCRP	—	2.5 ± 0.24	7.8 ± 0.29	3.1
BCRP	+	4.2 ± 0.09	3.3 ± 0.06	0.80



Dolutegravir dose-dependently inhibits the human renal oganic cation transporter 2 (OCT), providing a mechanistic basis for the increases in serum creatinine observed in clinical studies

- Reese, Drug Metab Disp 2013 -



SLC22A2 = OCT2

Abstracts of the HIV Drug Therapy Glasgow Congress 2014
Zong J et al. *Journal of the International AIDS Society* 2014, **17(Suppl 3)**:19584
http://www.jiasociety.org/index.php/jias/article/view/19584 | http://dx.doi.org/10.7448/IAS.17.4.19584

JIAS Journal of the International AIDS Society

Poster Sessions – Abstract P052

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

Zong, Jian[1]; Borland, Julie[2]; Jerva, Fred[2]; Wynne, Brian[3]; Choukour, Mike[4] and Song, Ivy[1]

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)

Published 2 November 2014

Clin Pharmacokinet (2016) 55:439–459
DOI 10.1007/s40262-015-0323-x

SYSTEMATIC REVIEW

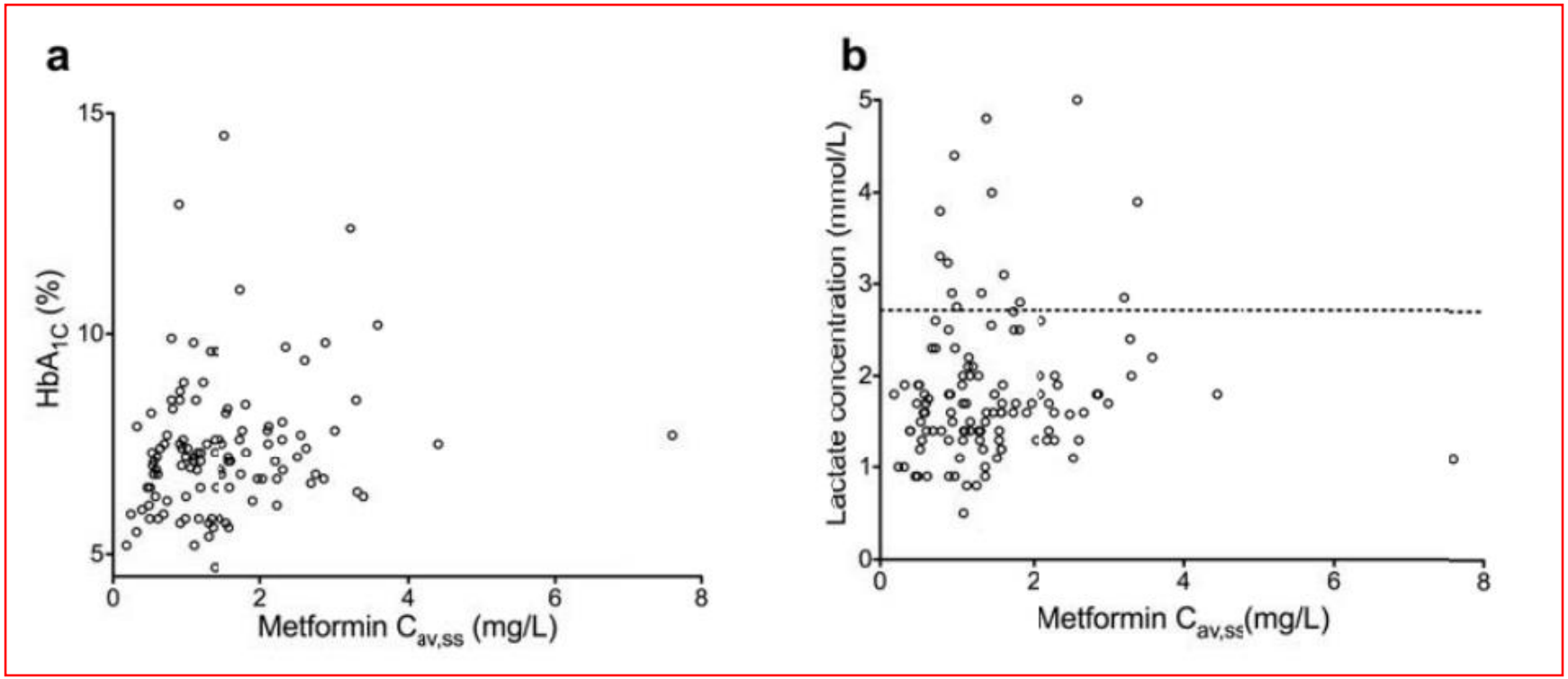
Therapeutic Concentrations of Metformin: A Systematic Review

- ✓ Great variability and heterogeneity in the “therapeutic” plasma metformin concentrations was found, with “therapeutic” values ranging from 0.13 to 90 mg/L and threshold concentrations for metformin intoxication set up to 270 mg/L
- ✓ This very wide range of drug concentrations suggests that, once those evident risk factors for inadequate drug exposure are excluded (such as renal dysfunction) most patients are likely to fall within the “therapeutic range”

Clin Pharmacokinet (2013) 52:373–384
DOI 10.1007/s40262-013-0046-9

ORIGINAL RESEARCH ARTICLE

Population Pharmacokinetics of Metformin in Healthy Subjects and Patients with Type 2 Diabetes Mellitus: Simulation of Doses According to Renal Function



"For patients with T2DM, no correlation between metformin concentrations with either lactate concentrations or glycated hemoglobin was found"

- ✓ E quindi…che rilevanza clinica può avere l'interazione tra metformina e dolutegravir nel paziente HIV-positivo ambulatoriale?

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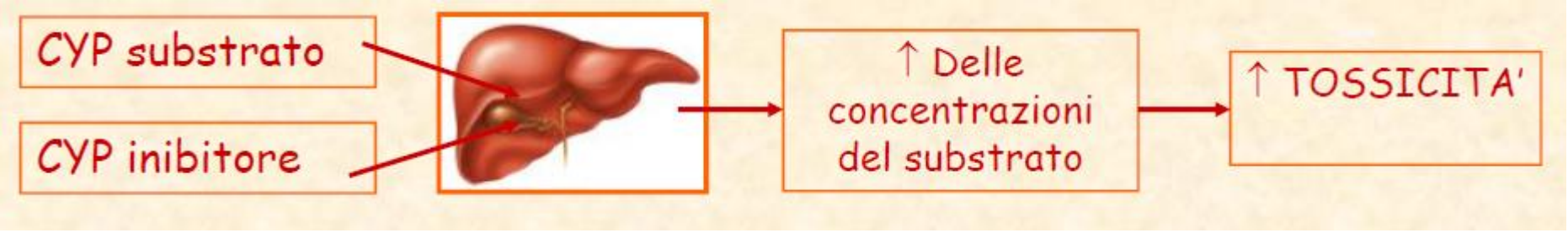
Chiedetelo a Cristina!!!

Metabolismo…



Substrates:

drugs that are metabolized as substrates by the enzyme

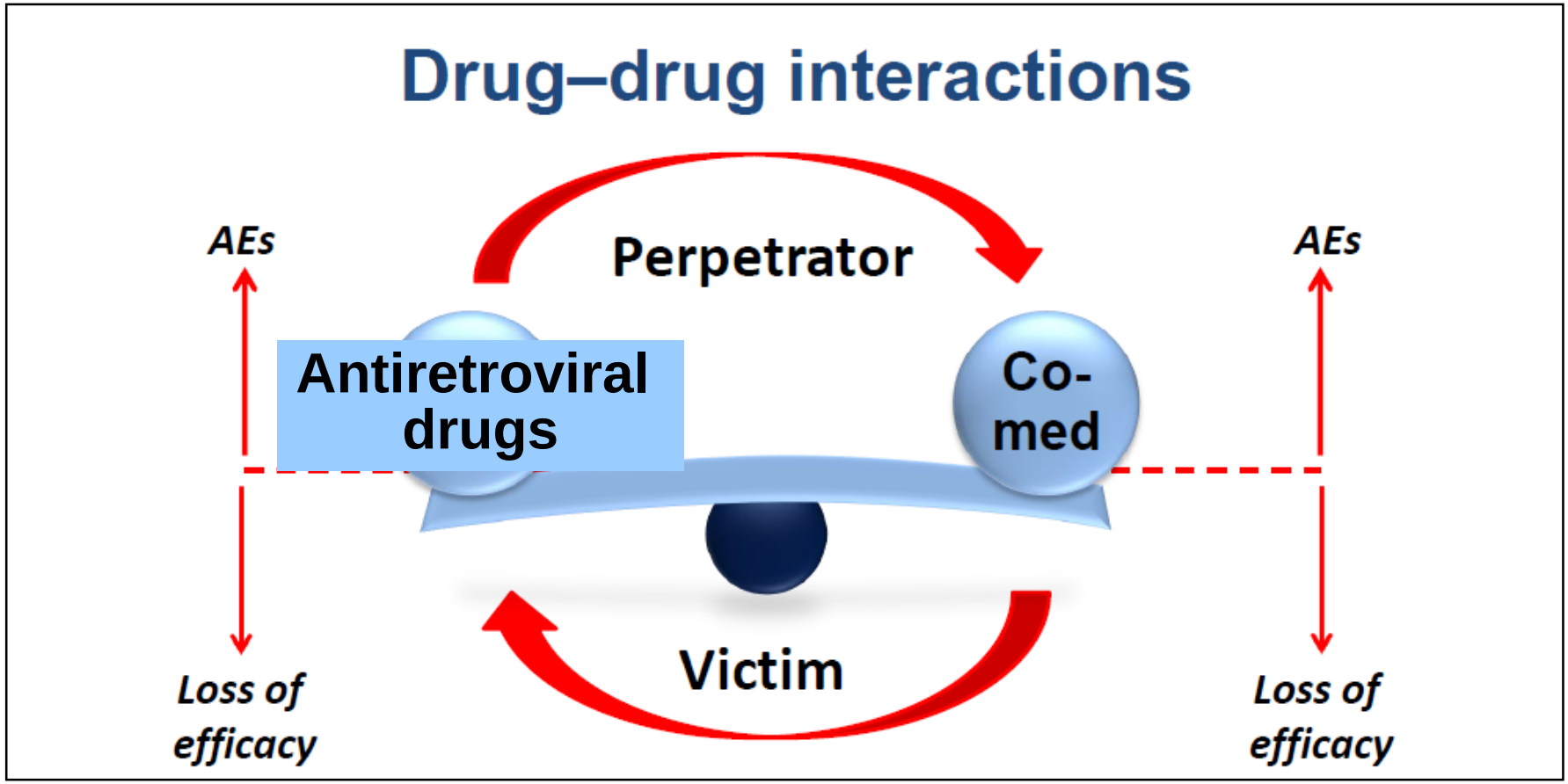
Inhibitors:

drugs that prevent the enzyme from metabolizing the substrates

Inducers:

drugs that increase the enzyme's ability to metabolize the substrates

Noi siamo abituati a pensare agli ARVs come dei "perpetrators" della DDI. Ricordiamoci però che possono a loro volta essere "vittime" di DDI…



ALCUNI FARMACI CHE PROVOCANO INDUZIONE ENZIMATICA

Alcool

Aloperidolo

Antistaminici

Barbiturici

Meprobamato

Fenacetina

Fenilbutazone

Rifampicina

Clorofenolato

Griseofulvina

Imipramina

Nicotina

* **Fenobarbital**

* **Pentobarbital**

Pesticidi

Prednisone

Probenecid

Promazina

Protossido d'azoto

Uretano

* **FENITOINA**

* **CBZ**

desametazone

ALCUNI FARMACI CHE PROVOCANO INIBIZIONE ENZIMATICA

Allopurinolo

Androgeni

Anticolinesterasici

Clofibrato

Cloramfenicolo

Clorpromazina

Contraccettivi orali

Disulfiram

IMAO

Sulfaniluree

D-tiroxina

Warfarina

Cimetidina

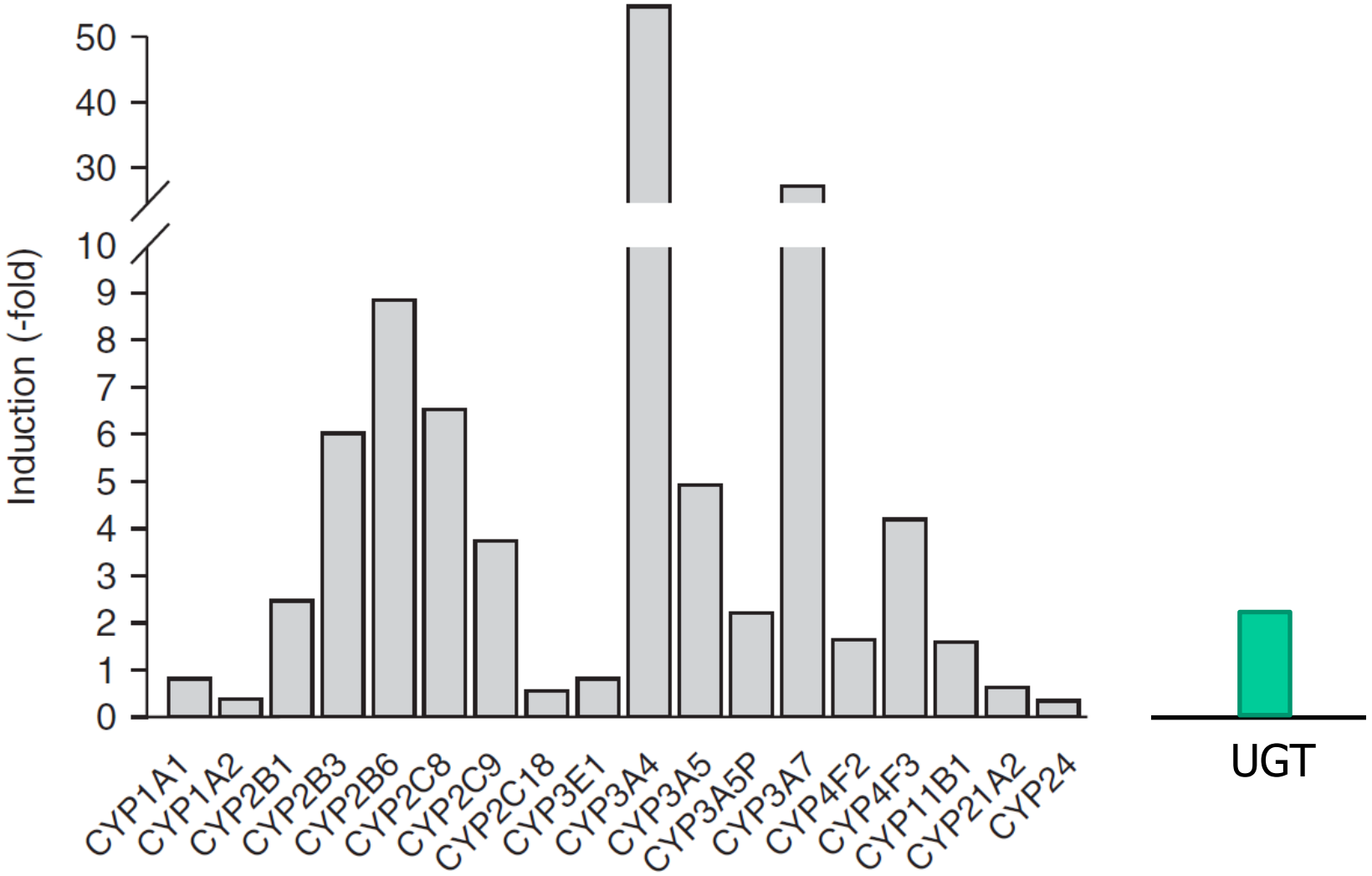
Eritromicina

Ciprofloxacina

Ofloxacina

Enoxacina

L'effetto di un'interazione si può prevedere? Il caso della rifampicina…



Clin Pharmacokinet 2003; 42 (9): 819-850
0312-5963/03/0009-0819/$30.00/0

Quanto può durare l'effetto di un'interazione?

N° di t½	% farmaco rimanente
0	100%
1	50%
2	25%
3	12.5%
4	6.25%
5	3.125%
6	1.56%
7	0.78%
8	0.39%
9	0.195%
10	0.0975%

Rifampicin: terminal $t_{1/2}$: 4-6 h….

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

LETTER TO THE EDITORS

Prolonged inductive effect of rifampicin on linezolid exposure

The novelty of our findings relates to the fact that we observed a significant effect of rifampicin on linezolid concentrations up to 2–3 weeks after its discontinuation. Such prolonged inductive effect of rifampicin, formerly described when this drug was given in combination with propranolol, prednisolone, digoxin, and midazolam, underlines the importance of the time-course characterization not only for enzyme induction but also for enzyme deinduction [6, 7].

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

Quali strumenti abbiamo?

Check DDIs by TDM if available !!!!

Ospedale Luigi Sacco
POLO UNIVERSITARIO
Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

Ospedale L.Sacco – Azienda Ospedaliera – Polo Universitario
UOSD Medicina di Laboratorio-Farmacologia Clinica
Farmacocinetica Tel. 02 50319619 Fax 02 50319646

UNIVERSITÀ DEGLI STUDI DI MILANO

CODICE A BARRE DEL PRELIEVO

COGNOME_____NOME_____

□ M □ F Data di nascita_____/_____/_____

Reparto:_____ Data e ora del prelievo:_____

Medico Richiedente_____

SETTORE DI FARMACOCINETICA (PK) – Modulo di richiesta esami M FACL C 01 Rev.17 /P FACL 06

SANGUE: provetta da 4 ml con **EDTA** (tappo **VIOLA** cod 368861);
per dosaggi di 1-2 farmaci usare 1 provetta, per più di due farmaci usare 2 provette.
NON congelare prelievo

Antiretrovirali

- ❑ cod.51 P-Atazanavir
- ❑ cod.52 P-Darunavir
- ❑ cod.53 P-Efavirenz
- ❑ cod.54 P-Etravirina
- ❑ cod.55 P-Lopinavir
- ❑ cod.56 P-Maraviroc
- ❑ cod.57 P-Nevirapina
- ❑ cod.58 P-Raltegravir
- ❑ cod.59 P-Tipranavir
- ❑ cod.42 P-Amprenavir
- ❑ cod.43 P-Tenofovir
- ❑ cod.28 P-Saquinavir
- ❑ cod.14 P-Ritonavir
- ❑ cod.8016 P-Rilpivirina
- ❑ cod.8017 P-Elvitegravir
- ❑ cod.8018 P-Dolutegravir

Altri Antinfettivi

- ❑ cod.37 P-Teicoplanina
- ❑ cod.38 P-Levofloxacina
- ❑ cod.39 P-Rifampicina
- ❑ cod.45 P-Linezolid
- ❑ cod.46 P-Ciprofloxacina
- ❑ cod.47 P-Sulfametoxazolo
- ❑ cod.48 P-Trimetoprim
- ❑ cod.8012 P-Meropenem (**cons. +4°C**)
- ❑ cod.8013 P-Piperacillina (**cons. +4°C**)
- ❑ cod. 9 P-Voriconazolo
- ❑ cod.8007 P-Posaconazolo
- ❑ cod.8020 P-Isavuconazolo
- ❑ cod.8021 P-Itraconazolo
- ❑ cod.8019 P-Caspofungina
- ❑ cod. 44 P-Ribavirina

Antiepilettici

- ❑ cod.21 P-Lamotrigina
- ❑ cod.22 P-Etosuccimide
- ❑ cod.23 P-Zonisamide
- ❑ cod.24 P-Rufinamide
- ❑ cod. 2 P- Levetiracetam
- ❑ cod.15 P-Topiramato
- ❑ cod.18 P-Felbamato
- ❑ cod.20 P-Oxcarbazepina
- ❑ cod.8014 P-Perampanel
- ❑ cod.8015 P-Lacosamide

Antipsicotici/antidepressivi

- ❑ cod. 25 P-Citalopram/ Escitalopram
- ❑ cod. 29 P-Quetiapina
- ❑ cod. 30 P-Paroxetina
- ❑ cod. 31 P-Aripiprazolo
- ❑ cod. 32 P-Olanzapina (**cons. +4°C**)
- ❑ cod. 33 P-Risperidone (**cons. +4°C**)
- ❑ cod. 34 P-Haloperidolo
- ❑ cod. 35 P-Clozapina
- ❑ cod. 36 P-Paliperidone (**cons. +4°C**)
- ❑ cod. 41 P-Fluoxetina (**cons. +4°C**)
- ❑ cod. 93 P-Duloxetina
- ❑ cod. 94 P-Flufenazina
- ❑ cod. 95 P-Clomipramina (**cons. +4°C**)
- ❑ cod. 96 P-Venlafaxina (**cons. +4°C**)
- ❑ cod. 98 P-Ziprasidone
- ❑ cod. 99 P-Sertralina

Varie

- ❑ cod.49 P-Ibuprofene
- ❑ cod.461 Sg-Ciclosporina

SANGUE:
una provetta da 4 ml tappo **ROSA** cod 368813

- ❑ cod. 550 S-Chinidina
- ❑ cod. 500 S-Valproato
- ❑ cod. 546 S-Carbamazepina
- ❑ cod. 431 S-Fenobarbitale
- ❑ cod. 597 S-Fenitoina
- ❑ cod. 460 S-Primidone
- ❑ cod. 521 S-Gentamicina
- ❑ cod. 522 S-Vancomicina
- ❑ cod. 433 S-Litio
- ❑ cod. 472 S-Teofillina
- ❑ cod. 8005 S-Amikacina
- ❑ cod. 8006 S-Paracetamolo

Profilo farmacocinetico (AUC)
Per misure del farmaco/i ripetute nell'arco della giornata indicare tempi dei prelievi:

- ❑C0 ora prelievo .....
- ❑ **ora assunzione farmaco** .....
- ❑ C1 ora prelievo .....
- ❑ C2 ora prelievo .....
- ❑ C3 ora prelievo .....
- ❑ C4 ora prelievo .....
- ❑ C5 ora prelievo .....

DDIs: do not rely on general beliefs...

"Azoles are strong inhibitors of CYP enzymes…"

	CYP3A4		CYP2C9		CYP2C19		P-gp	
	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate	Inhibitor	Substrate
Fluconazole	++	0	++	0	+	+	0	0
Itraconazole	+++	+++	+	0	0	0	+++	++
Voriconazole	++/+++	+	+	0	++	+++	0	0
Posaconazole	++	0	0	0	0	0	++	+
Isavuconazole	+/++	++	0	0	0	0	+	0

+, weak; ++, moderate; +++, potent

✓ add voriconazole to clopidogrel (CYP2C19 substrate) is an issue…
✓ add isavuconazole to clopidogrel is not an issue…


www.hep-druginteractions.org
Interaction Charts
News & Archive
About Us
Pharmacology Resources
Links
Meetings
Feedback
Home
LATEST ARTICLES
Meeting Report - 13th HIV Pharmacology Workshop, Barcelona.
Case Report - Possible interaction with ribavirin and oseltamivir.
Review - Optimising antiretroviral regimens in HIV/HCV co-infected patients.
Guidelines - UK guidelines for boceprevir and telaprevir.
Meeting Report - 19th CROI, Seattle.
Review - Interactions with boceprevir and telaprevir.
Click here for previous news items
Updated printable charts
The printable charts have been updated to include all the recent additions to the list of comedicati...
>>more
Additional Comedications
In response to feedback about commonly prescribed comedications, ~40 new drugs have been added to th...
>>more
DRUG INTERACTION CHARTS
Access our comprehensive, user-friendly, free, drug interaction charts
CLICK HERE
UNIVERSITY OF LIVERPOOL
ASSOCIATED SITES
www.hiv-druginteractions.org
A comprehensive HIV drug-drug interaction resource, freely available to healthcare workers, patients and researchers.
These drugs should not be coadministered
Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration
No clinically significant interaction expected
There are no clear data, actual or theoretical, to indicate whether an interaction will occur
n/a
Data not available
NEW - click here to generate a personalised report in PDF format
welcome to the www.hiv-druginteractions.org website
UNIVERSITY OF LIVERPOOL
Interaction Charts
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TDM
Feedback
Drug Interaction Charts
Printable charts | View all | View all Protease Inhibitors | View all NNRTIs | View all NRTIs | View all Entry/Integrase Inhibitors | Back to start
Step 1
Choose one or more HIV drugs
Step 2
Choose one or more combination classes
Step 3
Choose one or more combination drugs
Step 4
View results

…ricordandosi però che questi siti non possono prevedere tutto….

...cosa succede se somministro rifampicina in un paziente in terapia con efavirenz?

www.hiv-druginteractions.org

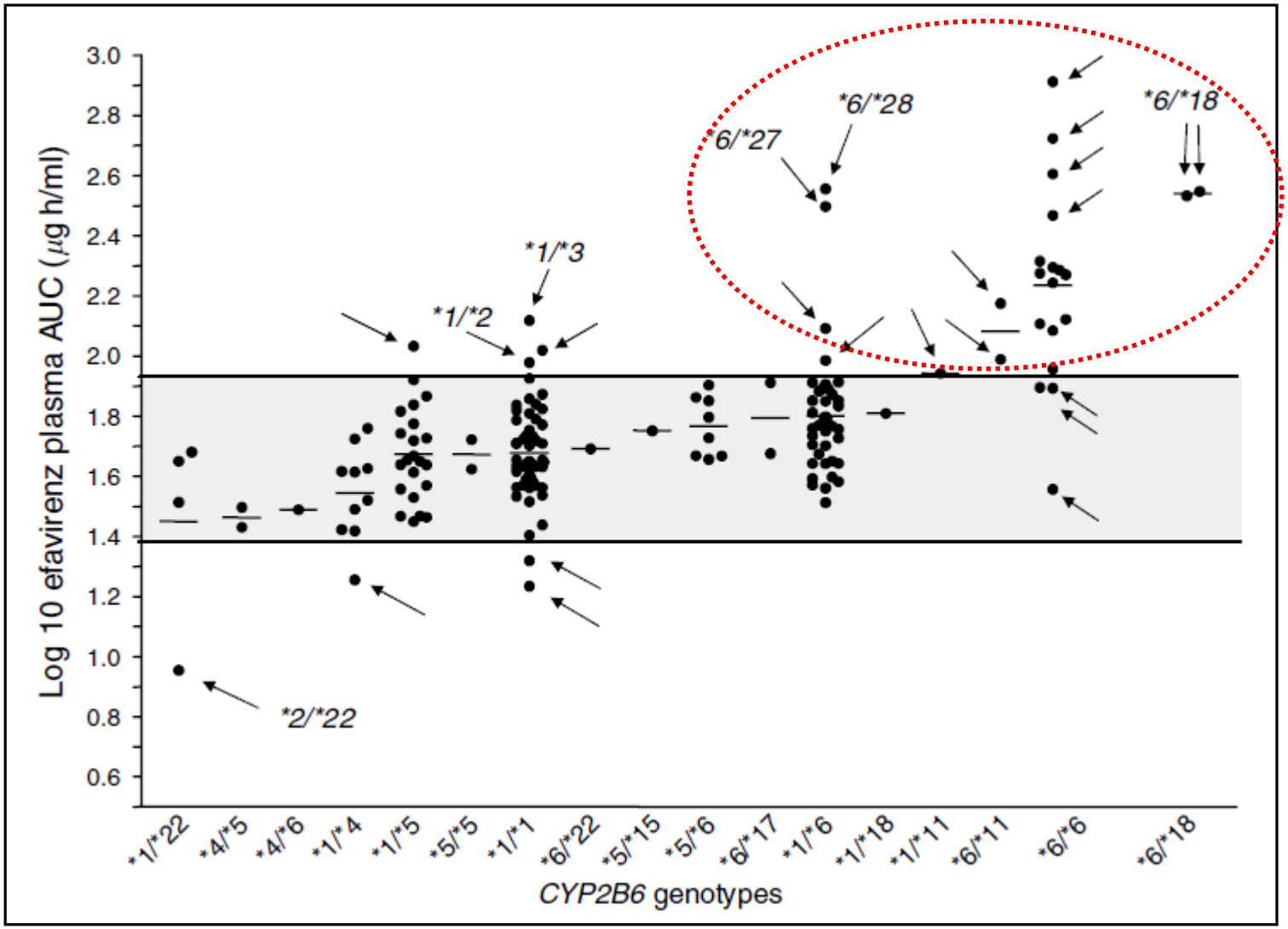
Class:	Drug:	HIV Drug:
Antibacterials	Rifampicin	Efavirenz

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

AIDS 2011, Vol 25 No 3

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

Predictive value of CYP2B6 alleles for efavirenz plasma concentrations in HIV patients



- Rotger, CPT 2007 -

- ✓ rifampicin is an inductor of CYP2B6…
- ✓ efavirenz is metabolized by CYP2B6..
- ✓ rifampicin reduces efavirenz concentrations by inducing its metabolism…

But…

- ✓ if a patient does not express CYP2B6…
- ✓ rifampicin has no effect on efavirenz metabolism…
- ✓ the metabolism of efavirenz is blocked…
- ✓ efavirenz concentrations increase…

- ✓ Quale rilevanza clinica delle DDIs…???
- ✓ Come gestire le DDIs nella routine ambulatoriale quotidiana…???

- ✓ Quale rilevanza clinica delle DDIs…???
- ✓ Come gestire le DDIs nella routine ambulatoriale quotidiana…???

Ore 15.00-16.00 **SIMPOSIO IV**

Gestione della *Polypharmacy* nel paziente HIV positivo

Moderatori: *T. Bini, E. Clementi (Milano)*

Pratica clinica

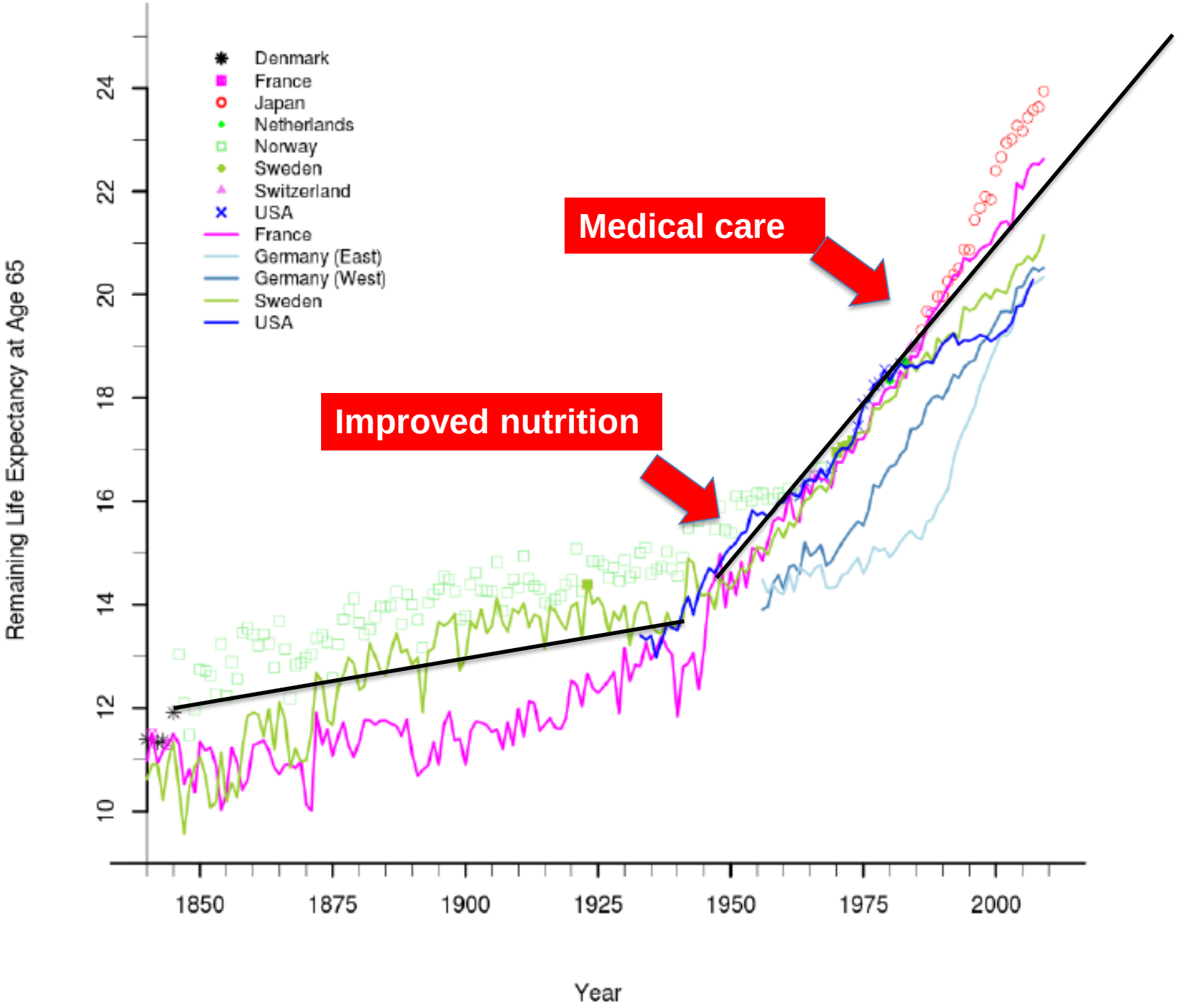
C. Gervasoni (Milano)

Chiedetelo a Cristina!!!

Gestione della polypharmacy nel paziente HIV positivo

….. dopo le “noiose” ma scientifiche basi teoriche…….

La pratica clinica


Denmark
France
Japan
Netherlands
Norway
Sweden
Switzerland
USA
France
Germany (East)
Germany (West)
Sweden
USA
Medical care
Improved nutrition
Remaining Life Expectancy at Age 65
10
12
14
16
18
20
22
24
1850
1875
1900
1925
1950
1975
2000
Year

February 1, 2004 THE AMERICAN JOURNAL OF MEDICINE®

The End of the Disease Era

Mary E. Tinetti, MD, Terri Fried, MD

Disease-Oriented Model	Integrated, Individually Tailored Model
Clinical decision making is focused primarily on the diagnosis, prevention, and treatment of individual diseases.	Clinical decision making is focused primarily on the priorities and preferences of individual patients.
Discrete pathology is believed to cause disease; psychological, social, cultural, environmental and other factors are secondary factors, not primary determinants of disease.	Health conditions are believed to result from the complex interplay of genetic, environmental, psychological, social, and other factors.
Treatment is targeted at the pathophysiologic mechanisms thought to cause the disease(s).	Treatment is targeted at the modifiable factors contributing to the health conditions impeding the patient's health goals.
Symptoms and impairments are best addressed by diagnosing and treating "causative" disease(s).	Symptoms and impairments are the primary foci of treatment even if they cannot be ascribed to a discrete disease.
Relevant clinical outcomes are determined by the disease(s).	Relevant clinical outcomes are determined by individual patient preference.
Survival is the usual primary focus of disease prevention and treatment.	Survival is one of several competing goals.

Multiple health problems in elderly people

The problem is that in health care the specialist medical view predominates. And, as a direct result, multiple diagnoses lead almost inevitably to polypharmacy as each condition is treated in perverse isolation from the others. Research findings are extrapolated from younger age groups and interpreted overoptimistically in the context of what inevitably are limited life expectancies. As a direct result, older people are taking an ever increasing number of prescribed drugs, but because of diminished physiological reserve they are also more susceptible to adverse drug reactions and interactions. Nevertheless, the all too easy accusation of age discrimination means that the limited time available for older people to derive clinical benefit is not seen as a legitimate reason for "underprescribing."

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

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals

JAMA. 2007;297:1233-1240

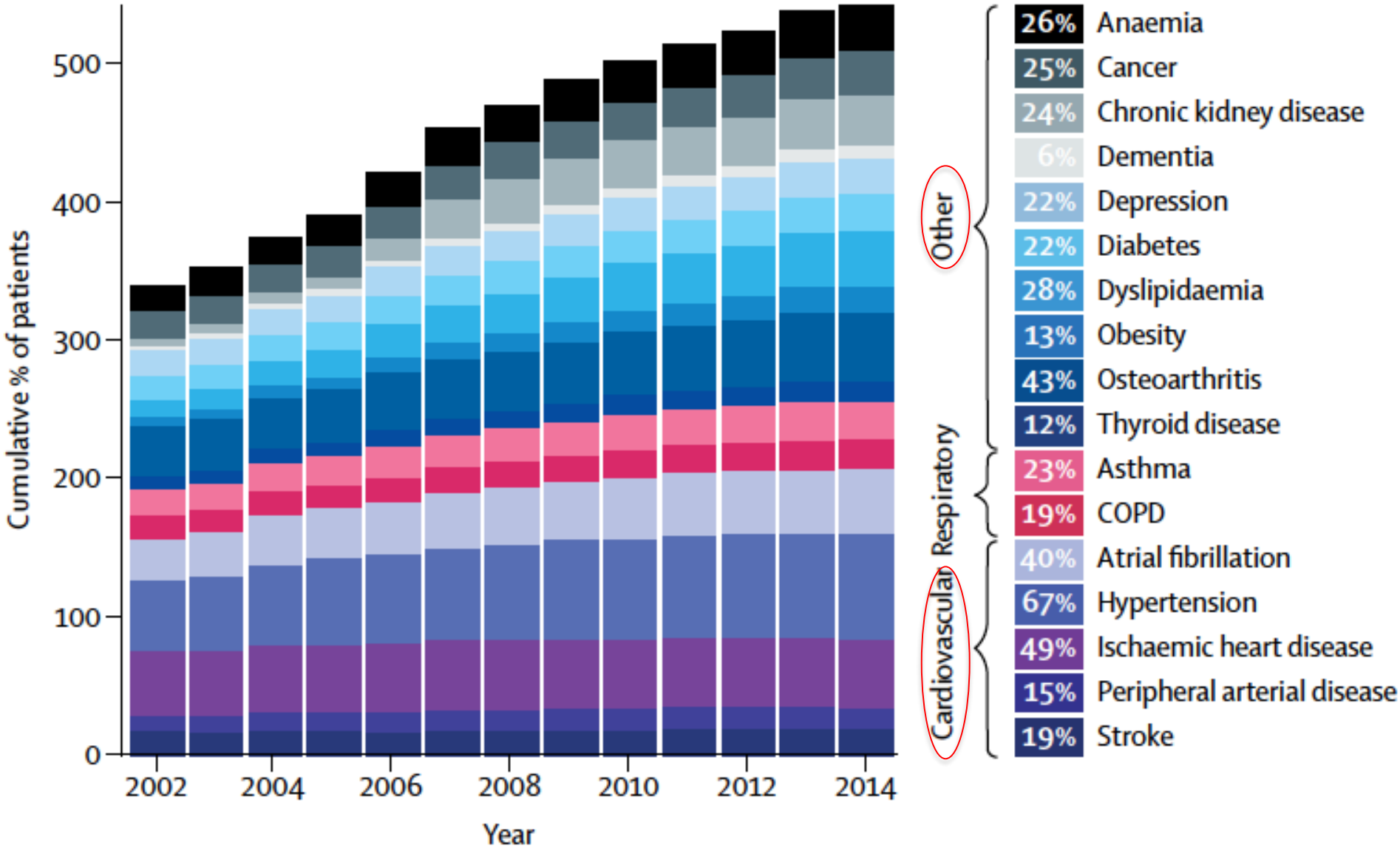
- I pazienti risultavano esclusi in base a:

età	72.1% dei trial
sesso femminile	47.0% dei trial
multimorbidità	→ 81.3% of trials
polifarmacoterapia	54.1% of trials

- I trials sui farmaci tendono ad escludere più facilmente, così come quelli sponsorizzati dall'industria farmaceutica.

Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals

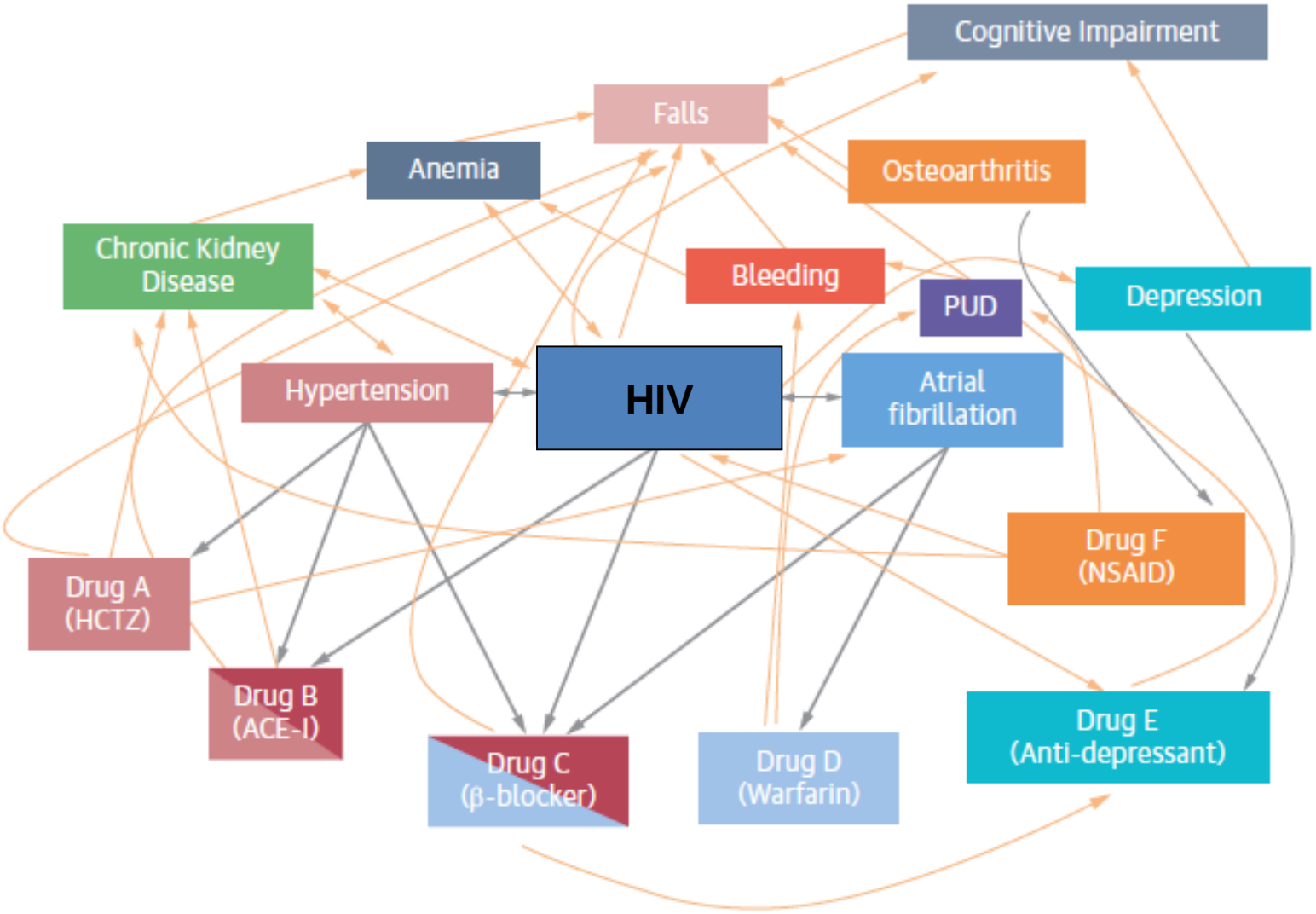
Lancet 2018; 391: 572–80



Multimorbidity in Older Adults With Cardiovascular Disease

JACC VOL. 71, NO. 19, 2018
MAY 15, 2018:2149-61

Diseases and Medications Impacting One Another in Multimorbidity



Making more of multimorbidity: an emerging priority

Multimorbidity would seem a relatively straightforward term, denoting multiple medical conditions within a single patient. Yet an Academy of Medical Sciences report, *Multimorbidity: a priority for global health research*, published in April, 2018, suggests that competing definitions in the medical literature have impeded research and improvements in patient care. The report recommends that a path forward must include a standardised definition that can be incorporated into research agendas to identify the evidence gaps and to inform the organisation of health-care systems globally.

Multimorbidity, as emphasised by the authors, is distinct from comorbidity because there is no primary or index condition. Frailty is a related construct in ageing populations, but is different since patients with multimorbidity might not necessarily be frail. Researchers

Most of the evidence on multimorbidity has come from cross-sectional studies sampling specific populations in various settings. The report largely focuses on where the research agenda must be extended, including refining descriptive epidemiology, especially for LMICs and younger patients, and underscoring the need for longitudinal cohort data to understand clustering of conditions across the lifespan. But it also highlights the challenges for patients and clinicians. The majority of health-care systems are organised to treat single conditions. For patients with multimorbidity, that can mean interfacing with multiple health-care providers, increased risk of inappropriate polypharmacy from lack of provider communication, and potentially suboptimal care.

To update health-care systems in the face of the increasing burden of multimorbidity will require a shift for

To update health-care systems in the face of the increasing burden of multimorbidity will require a shift for physicians from specialists to generalists, likely through

and is the norm in this age group in high-income countries. It is also more prevalent in women, possibly because of greater exposure to the adverse effects of poverty. Multimorbidity is increasing globally, likely driven by the ageing population but also by factors such as high body-mass index, urbanisation, and the growing burden of NCDs (such as type 2 diabetes) and tuberculosis in low- and middle-income countries (LMICs). Predictably, certain morbidities cluster together, such as coronary heart disease and cerebrovascular disease. These conditions are called concordant multimorbidities since they can share a common aetiology. Depression, cardiometabolic disorders, and musculoskeletal disorders are most commonly present within multimorbidity clusters. Notably, multimorbidity clusters comprising concurrent physical and mental

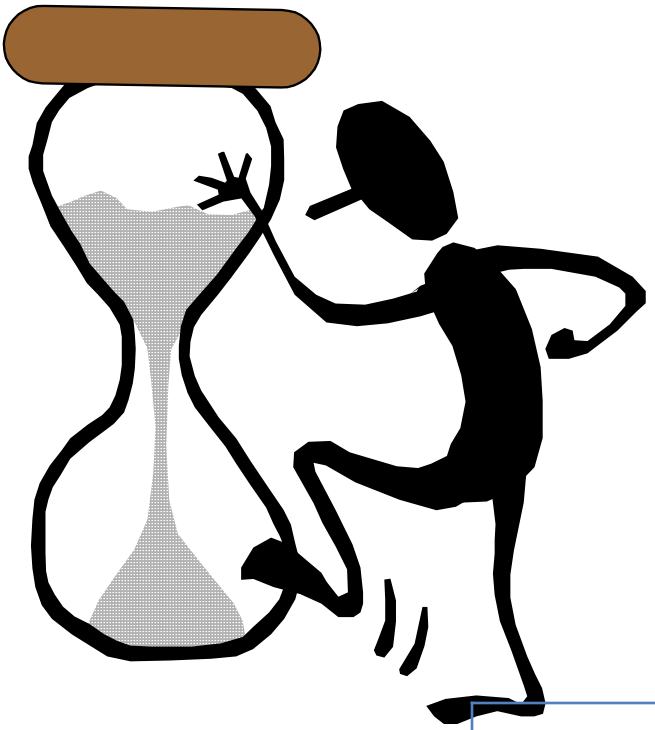
Although not yet well characterised, multimorbidity is extremely costly to individuals and health-care systems. While actively engaging in efforts to adapt to increasing demand, identifying the determinants of the acceleration of multimorbidity is crucial. Appreciating that multimorbidity clusters are linked with the increase in NCDs is essential as well. The report backs up the findings and recommendations in *The Lancet*'s Taskforce on NCDs and Economics, also published this month, highlighting greater investment in prevention and control of NCDs to disrupt the cycle of chronic illness and economic impoverishment.

The multimorbidity perspective adds a timely dimension, suggesting an important window of opportunity to curtail this complex and expanding challenge. Aggressively targeting NCDs as preventable and with identifiable (and

For **Multimorbidity: a priority for global health research** see https://acmedsci.ac.uk/policy/policy-projects/multimorbidity

The Lancet's Taskforce on NCDs and Economics see http://www.thelancet.com/series/taskforce-NCDs-and-economics

Ogni individuo è responsabile per il 70% del proprio invecchiamento



FISIOLOGICO

NORMALE EVOLUZIONE DEI PROCESSI BIOLOGICI

PATOLOGICO

COMPARSA PRECOCE O ABNORME DI SEGNI E SINTOMI DI DECADIMENTO PSICO-FISICO


WHEY
GF-PRO
MASS
V12

Sistema Sanitario Regione Lombardia

RICHIESTA DI APERTURA NUOVO AMBULATORIO

Unità Operativa	MALATTIE INFETTIVE III DIVISIONE
Nome Ambulatorio	GAP - GESTIONE AMBULATORIALE DELLE POLITERAPIE
Ubicazione ambulatorio	PADIGLIONE 56 PIANO -1
Tipologia Agenda	☐ Classica ☒ Gestione Diretta

Se Agenda Classica specificare anche:

			Lunedì	Martedì	Mercoledì	Giovedì	Venerdì	Sabato
ORARIO	M	DALLE ORE						
		ALLE ORE						
	P	DALLE ORE						
		ALLE ORE						

Data inizio attività : __/__/____

DESCRIZIONE PRESTAZIONE	Tempo esecuz.	Cod. Minist.	Lu q.tà	Ma q.tà	Me q.tà	Gi q.tà	Ve q.tà	Sa q.tà
VISITA MULTIDISCIPLINARE	1/2 h	89,03						
L'EQUIPE								
(INFETTIVOLOGO + FARMACOLOGO)								

Dichiarazione rispetto condizioni Preliminari:

- L'U.O. rispetta i TMA di tutte le prestazioni soggette a rilevazioni da non meno di tre mesi;
- L'U.O. dispone di di spazi/locali adeguati alle nuove attività;
- L'U.O. ha verificato la disponimilità, eventualmente fornita direttamente, di personale infermieristico e/o tecnico di supporto;
- L'U.O. dispone od ha garanzia di acquisizione della strumentazione necessaria;
- L'U.O. ha verificato la preesistenza di attività ambulatoriali simili, in caso positivo allega indicazioni per la corretta attivazione delle prenotazioni da parte dei Sistemi di Accesso.

DATA 27/6/15

Firma del Responsabile dell'UO.

Massimo Galli

Autorizzazione della D.M.P.

_____

Motivo mancata autorizzazione:

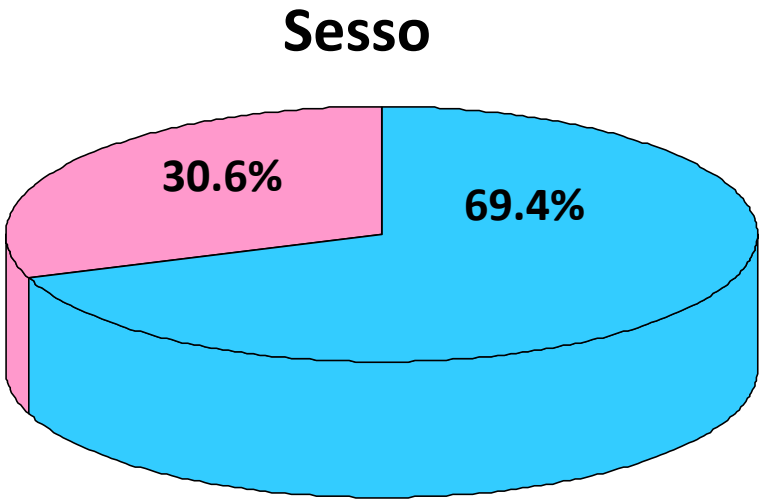
_____

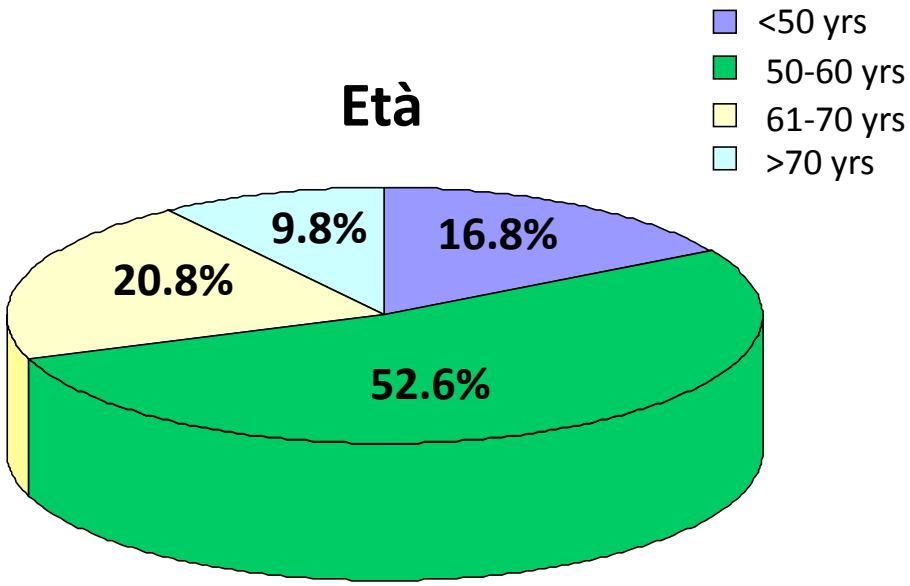
_____

A settembre 2018


AGE 0-4
AMOXICILLIN
4-12
RITALIN
12-18
APPETITE SUPPRESSANTS
18-24
NO-DOZ
24-38
PROZAC
38-65
VIAGRA
65 —
EVERYTHING ELSE

Caratteristiche demografiche della popolazione arruolata in GAP



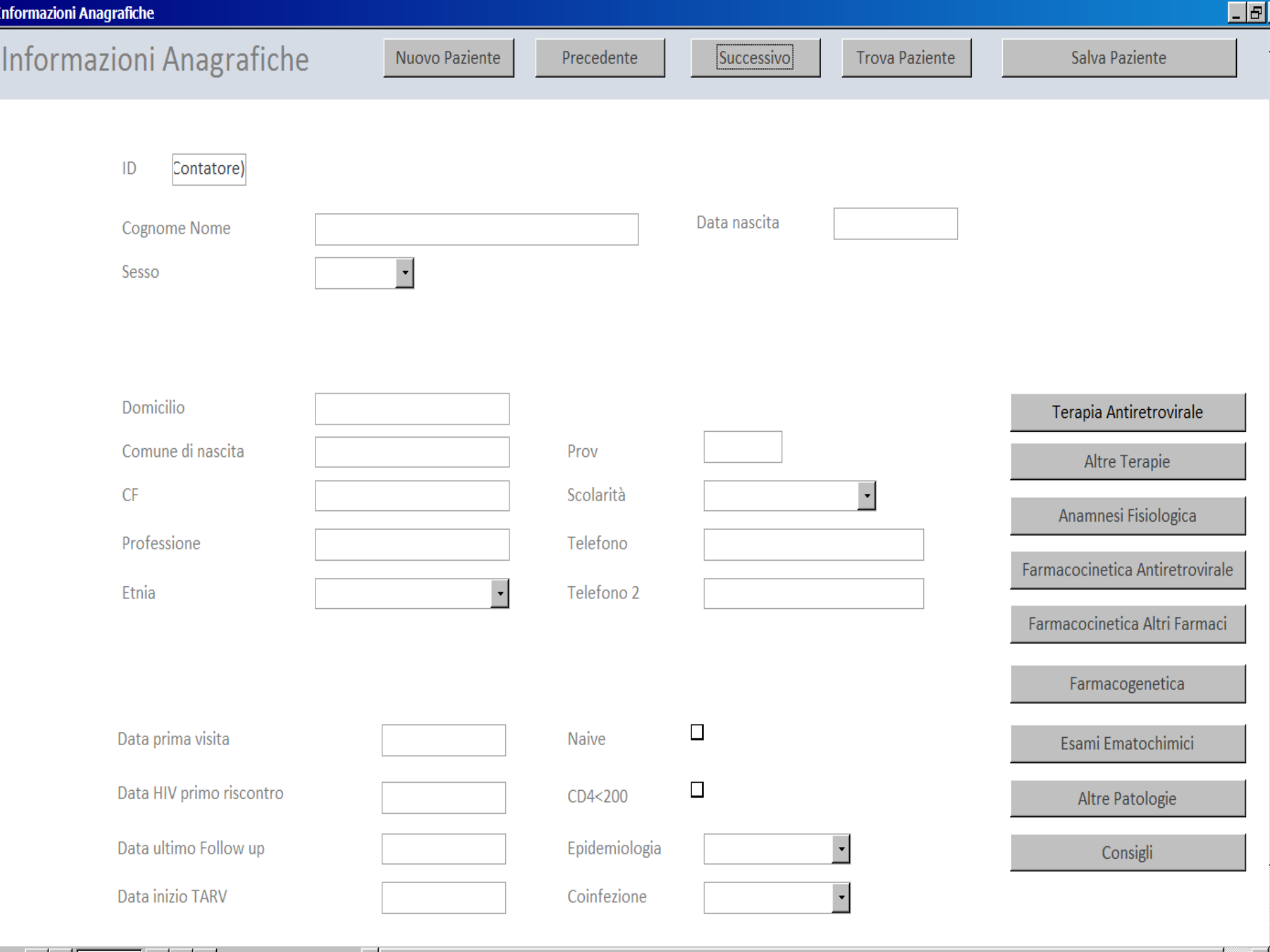


GAP is aimed to:

I) check if the patients are treated with contraindicated drug combinations due to known or predictable DDIs
II) assess the clinical and/or pharmacokinetic relevance of these DDIs
III) provide written advices on how the patient's therapy should be modified in order to limit DDIs (if any)

Chi sono i pazienti che accedono a GAP

- **in politerapia (pluritrattati in terapia cronica con farmaci per patologie non necessariamente o esclusivamente di natura infettiva)**
- **con insufficienza renale e/o epatica cronica**
- **anziani**
- **pazienti con condizioni cliniche predisponenti ad inadeguato dosaggio (obesità, gravidanza,ecc)**
- **popolazioni “speciali” (pazienti di diversa etnia; donne in menopausa; ecc)**
- **pazienti che assumono integratori o prodotti naturali**
- **epatopatici in terapia con i nuovi farmaci antivirali**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Informazioni Anagrafiche
Nuovo Paziente
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Trova Paziente
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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

Throughout medication history

"Brown Bag" asking patient to bring in all prescription, OTC, and herbal medications

"Teach-back" method, patient shows how taking medication

Determine patient adherence to medication and barriers if not adherent

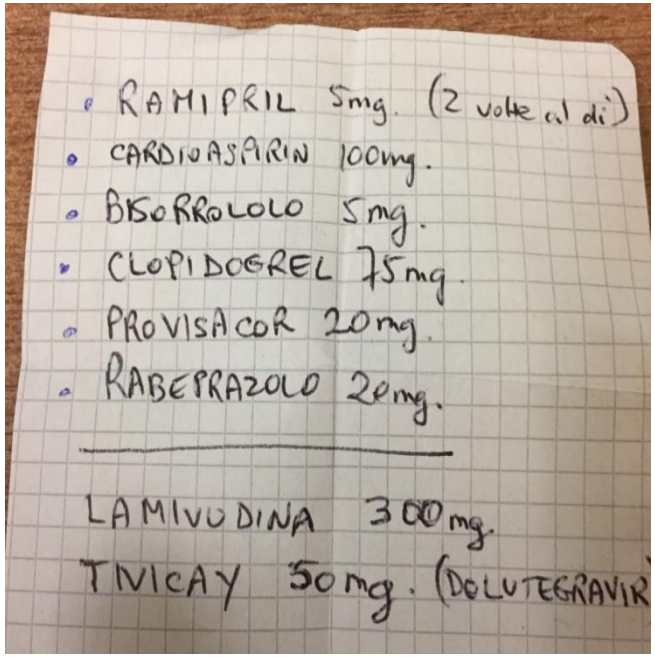
Is the patient forgetting to take?

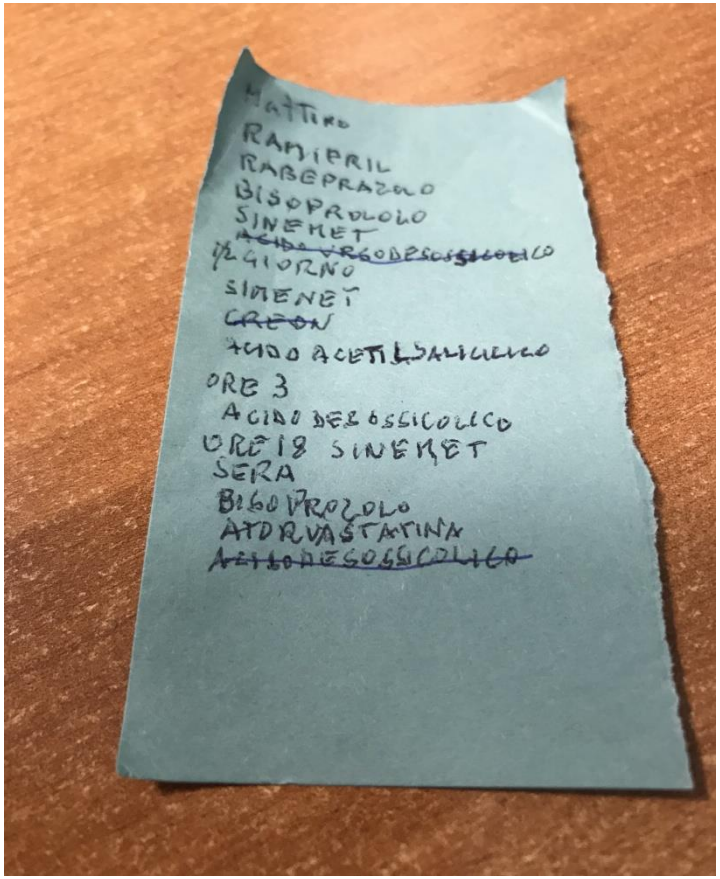
Is the pill difficult to take?

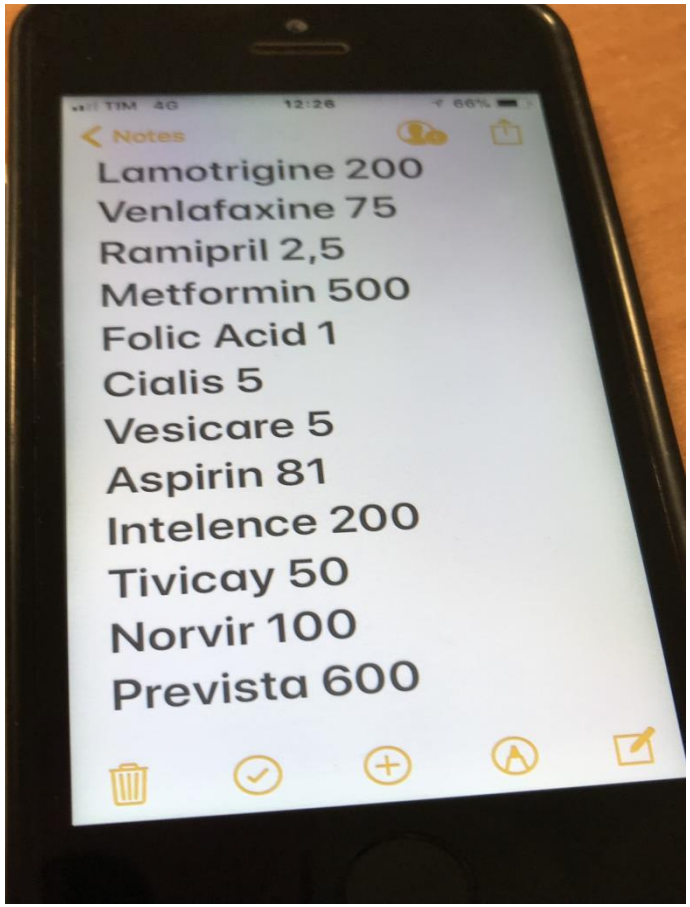
Is the pill costly?

Does the patient believe that the drug is not needed?

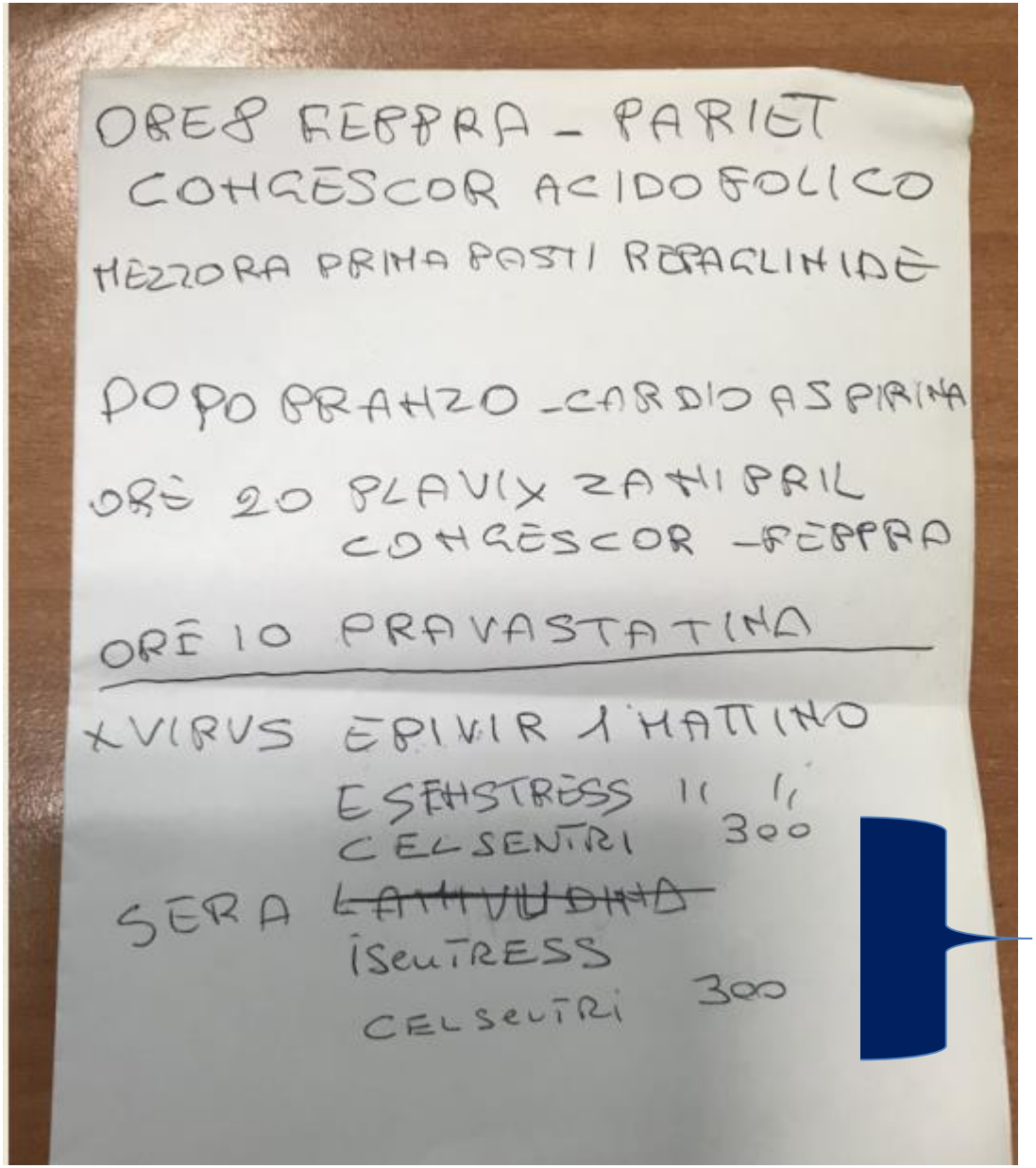

Colf e Badanti


RAMIPRIL 5mg. (2 volte al di')
CARDIOASPIRIN 100mg.
BISOPROLOLO 5mg.
CLOPIDOGREL 75mg.
PROVISACOR 20mg.
RABEPRAZOLO 20mg.
LAMIVUDINA 300mg.
TIVICAY 50mg. (DOLUTEGRAVIR



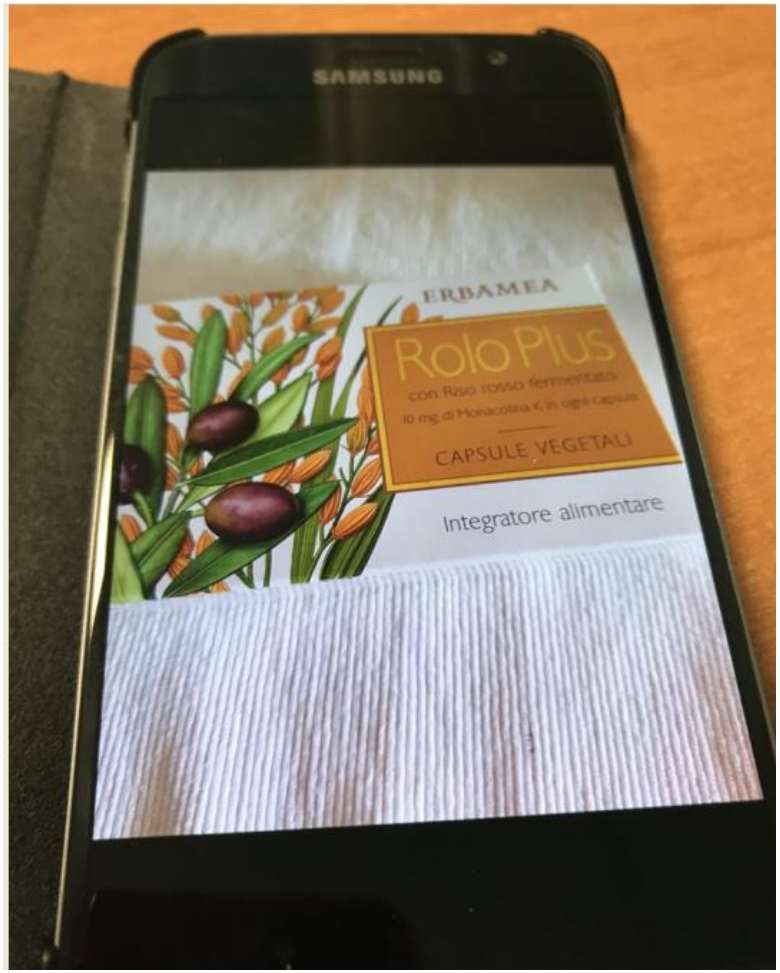


….nel portafoglio……



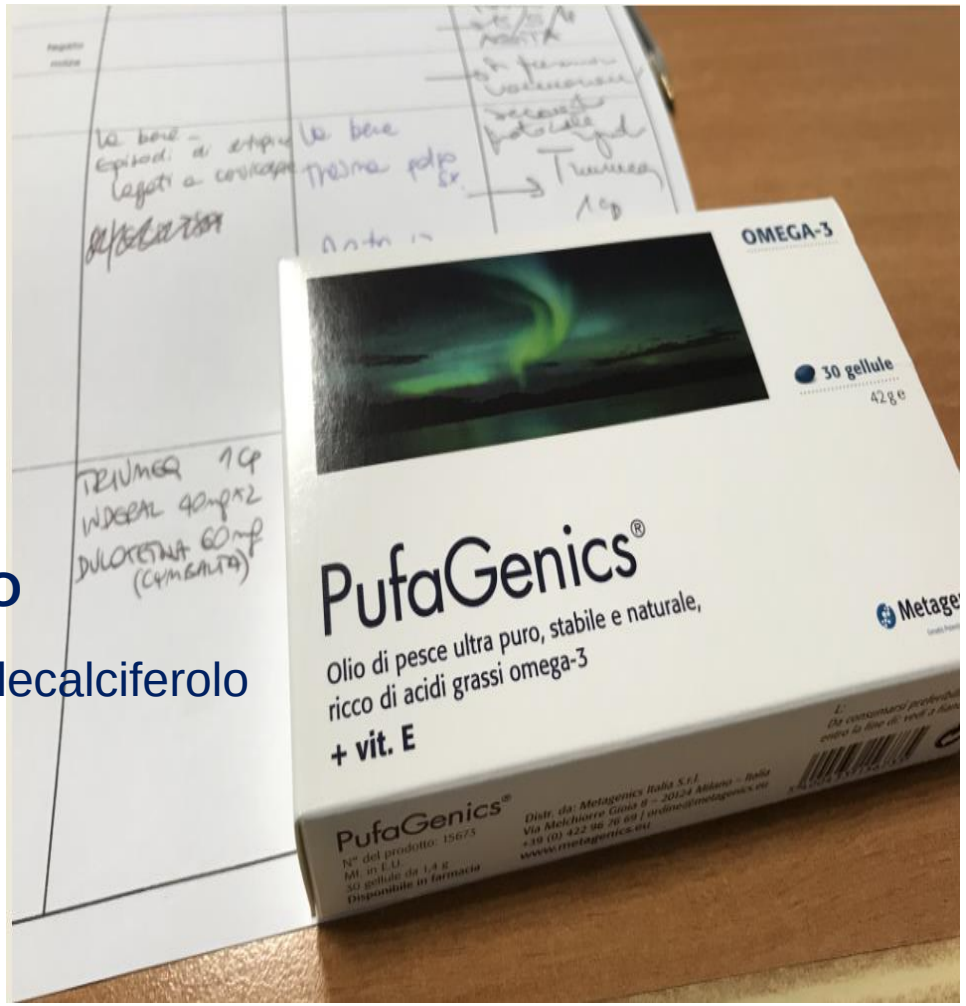
…. corretto da GAP ..

….scritto dalla moglie per GAP ……



NO

Colecalciferolo



Il paziente perfetto per GAP

FARMACI

Per la pressione:

ATENOLOLO HEXAL 100 mg. (sera)

ENALAPRIL 20 mg. (mattino)

Per il colesterolo:

PRAVASTATINA GmbH 20 mg. (sera)

Per la prostata:

TAMSULOSINA 0,4 mg. (mattino)

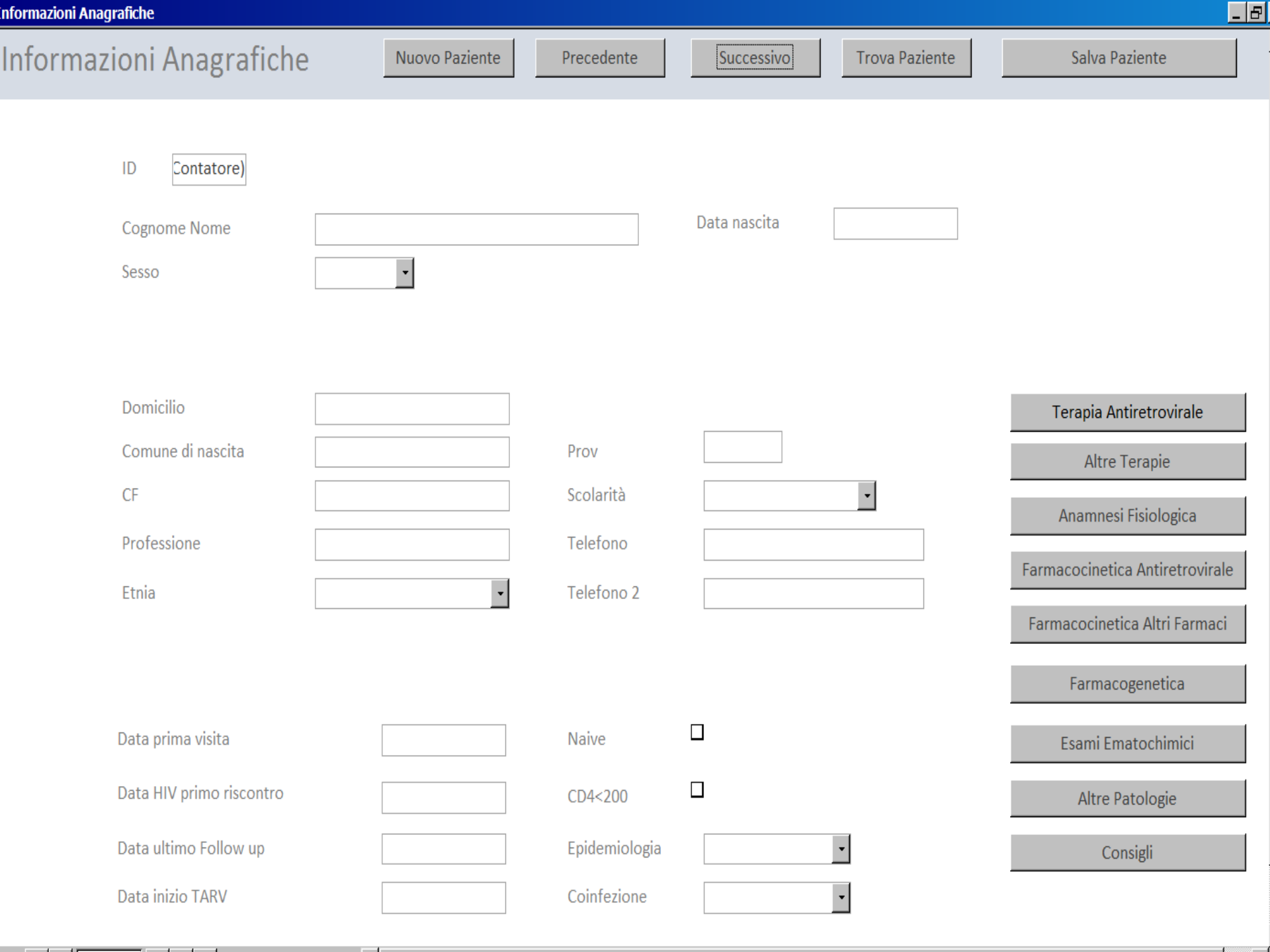
Farmaci antivirali:

ISENTRESS 400 mg. (mattino e sera)

VIRAMUNE 400 mg. (sera)

PRESSIONE:

115 - 82 (ore 8,15 di oggi)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ASST Fatebenefratelli Sacco

Ospedale L.Sacco – Azienda Ospedaliera – Polo Universitario
UOSD Medicina di Laboratorio-Farmacologia Clinica
Farmacocinetica Tel. 02 50319619 Fax 02 50319646

UNIVERSITÀ DEGLI STUDI DI MILANO

CODICE A BARRE DEL PRELIEVO

COGNOME_____NOME_____

□ M □ F Data di nascita_____/_____/_____

Reparto:_____ Data e ora del prelievo:_____

Medico Richiedente_____

SETTORE DI FARMACOCINETICA (PK) – Modulo di richiesta esami

M FACL C 01 Rev.17 /P FACL 06

SANGUE: provetta da 4 ml con **EDTA** (tappo **VIOLA** cod 368861);
per dosaggi di 1-2 farmaci usare 1 provetta, per più di due farmaci usare 2 provette.
NON congelare prelievo

Antiretrovirali

- ❑ cod.51 P-Atazanavir
- ❑ cod.52 P-Darunavir
- ❑ cod.53 P-Efavirenz
- ❑ cod.54 P-Etravirina
- ❑ cod.55 P-Lopinavir
- ❑ cod.56 P-Maraviroc
- ❑ cod.57 P-Nevirapina
- ❑ cod.58 P-Raltegravir
- ❑ cod.59 P-Tipranavir
- ❑ cod.42 P-Amprenavir
- ❑ cod.43 P-Tenofovir
- ❑ cod.28 P-Saquinavir
- ❑ cod.14 P-Ritonavir
- ❑ cod.8016 P-Rilpivirina
- ❑ cod.8017 P-Elvitegravir
- ❑ cod.8018 P-Dolutegravir

Altri Antinfettivi

- ❑ cod.37 P-Teicoplanina
- ❑ cod.38 P-Levofloxacina
- ❑ cod.39 P-Rifampicina
- ❑ cod.45 P-Linezolid
- ❑ cod.46 P-Ciprofloxacina
- ❑ cod.47 P-Sulfametoxazolo
- ❑ cod.48 P-Trimetoprim
- ❑ cod.8012 P-Meropenem (**cons. +4°C**)
- ❑ cod.8013 P-Piperacillina (**cons. +4°C**)
- ❑ cod. 9 P-Voriconazolo
- ❑ cod.8007 P-Posaconazolo
- ❑ cod.8020 P-Isavuconazolo
- ❑ cod.8021 P-Itraconazolo
- ❑ cod.8019 P-Caspofungina
- ❑ cod. 44 P-Ribavirina

Antiepilettici

- ❑ cod.21 P-Lamotrigina
- ❑ cod.22 P-Etosuccimide
- ❑ cod.23 P-Zonisamide
- ❑ cod.24 P-Rufinamide
- ❑ cod. 2 P- Levetiracetam
- ❑ cod.15 P-Topiramato
- ❑ cod.18 P-Felbamato
- ❑ cod.20 P-Oxcarbazepina
- ❑ cod.8014 P-Perampanel
- ❑ cod.8015 P-Lacosamide

Antipsicotici/antidepressivi

- ❑ cod. 25 P-Citalopram/ Escitalopram
- ❑ cod. 29 P-Quetiapina
- ❑ cod. 30 P-Paroxetina
- ❑ cod. 31 P-Aripiprazolo
- ❑ cod. 32 P-Olanzapina (**cons. +4°C**)
- ❑ cod. 33 P-Risperidone (**cons. +4°C**)
- ❑ cod. 34 P-Haloperidolo
- ❑ cod. 35 P-Clozapina
- ❑ cod. 36 P-Paliperidone (**cons. +4°C**)
- ❑ cod. 41 P-Fluoxetina (**cons. +4°C**)
- ❑ cod. 93 P-Duloxetina
- ❑ cod. 94 P-Flufenazina
- ❑ cod. 95 P-Clomipramina (**cons. +4°C**)
- ❑ cod. 96 P-Venlafaxina (**cons. +4°C**)
- ❑ cod. 98 P-Ziprasidone
- ❑ cod. 99 P-Sertralina

Varie

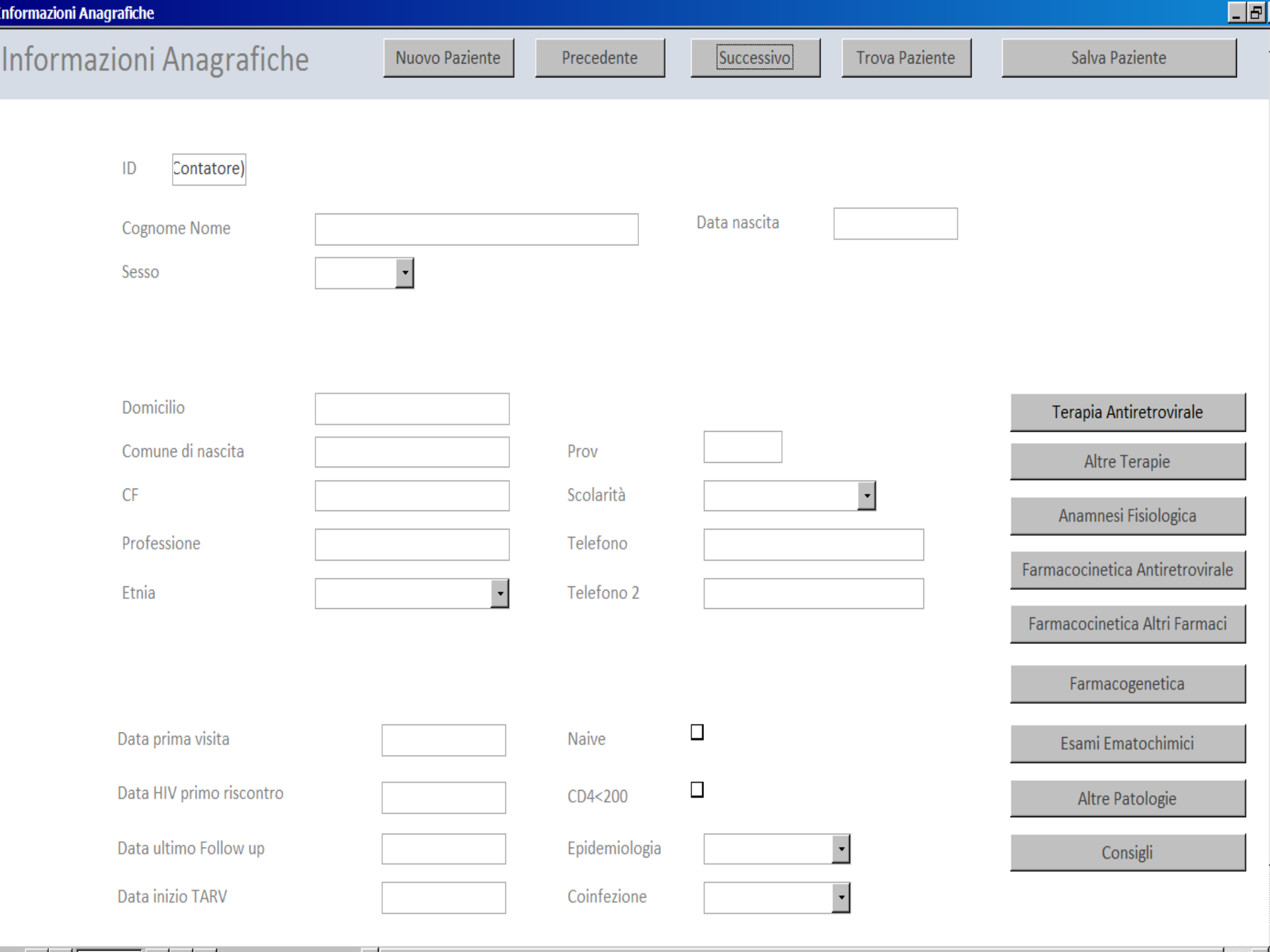
- ❑ cod.49 P-Ibuprofene
- ❑ cod.461 Sg-Ciclosporina

SANGUE:
una provetta da 4 ml tappo **ROSA** cod 368813

- ❑ cod. 550 S-Chinidina
- ❑ cod. 500 S-Valproato
- ❑ cod. 546 S-Carbamazepina
- ❑ cod. 431 S-Fenobarbitale
- ❑ cod. 597 S-Fenitoina
- ❑ cod. 460 S-Primidone
- ❑ cod. 521 S-Gentamicina
- ❑ cod. 522 S-Vancomicina
- ❑ cod. 433 S-Litio
- ❑ cod. 472 S-Teofillina
- ❑ cod. 8005 S-Amikacina
- ❑ cod. 8006 S-Paracetamolo

Profilo farmacocinetico (AUC)
Per misure del farmaco/i ripetute nell'arco della giornata indicare tempi dei prelievi:

- ❑C0 ora prelievo .....
- ❑ **ora assunzione farmaco** .....
- ❑ C1 ora prelievo .....
- ❑ C2 ora prelievo .....
- ❑ C3 ora prelievo .....
- ❑ C4 ora prelievo .....
- ❑ C5 ora prelievo .....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Nuovo Paziente
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Successivo
Trova Paziente
Salva Paziente
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Cognome Nome
Data nascita
Sesso
Domicilio
Comune di nascita
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Scolarità
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Telefono
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Terapia Antiretrovirale
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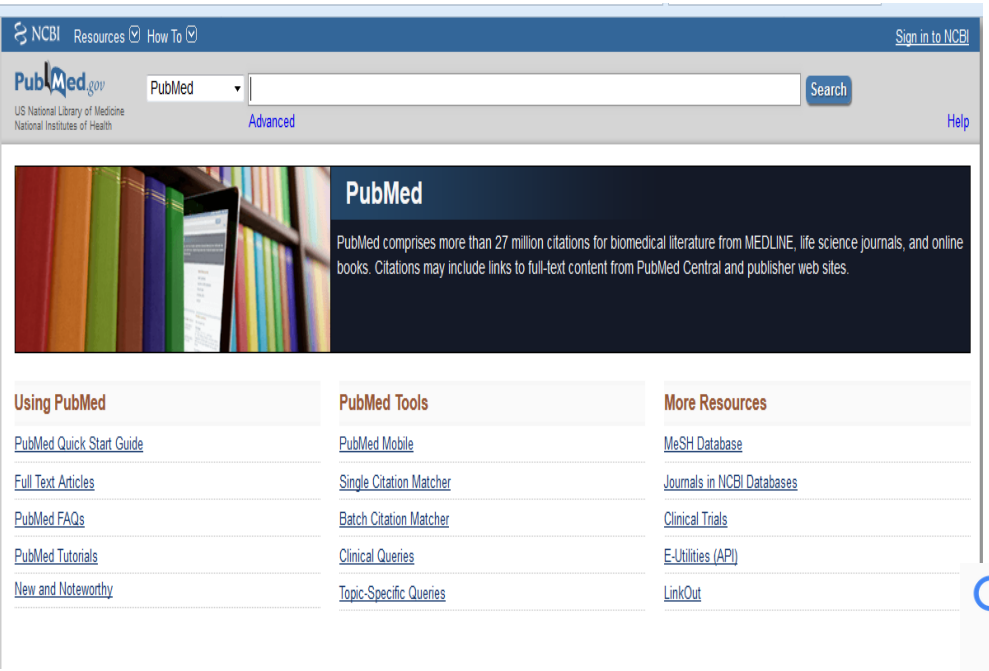
Farmacocinetica Antiretrovirale
Farmacocinetica Altri Farmaci
Farmacogenetica
Esami Ematochimici
Altre Patologie
Consigli
Data prima visita
Naive
Data HIV primo riscontro
CD4<200
Data ultimo Follow up
Epidemiologia
Data inizio TARV
Coinfezione

A pagamento		
Drug-Reax (Micromedex)	USA	https://www.thomsonhc.com
British National Formulary	UK	http://www.bnf.org/bnf/
Vidal	F	http://www.vidal.fr/
SFINX	Fin/Se	http://www.medbase.fi
FASS	Se	http://www.fass.se
Gratuite		
INTERCheck	I	https://clinicalweb.marionegri.it/intercheckweb
Medscape	USA	https://reference.medscape.com/drug-interactionchecker
University of Liverpool	UK	https://www.hiv-druginteractions.org
Medscape D-I checker	USA	http://www.medscape.com/druginfo
Drugs.com D-I checker	USA	http://www.drugs.com/drug_interactions.html
DrugDigest	USA	http://www.drugdigest.org/wps/portal/ddigest
P4 HealthCare Oncology	USA	http://www.p4healthcare.com/go/Oncology/p4programs
HealthAtoZ	USA	http://www.healthatoz.com/healthatoz/Atoz/drugdb/drugSearch.jsp
University of Maryland	USA	http://www.umm.edu/medref/index.htm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Topic-Specific Queries
More Resources
MeSH Database
Journals in NCBI Databases
Clinical Trials
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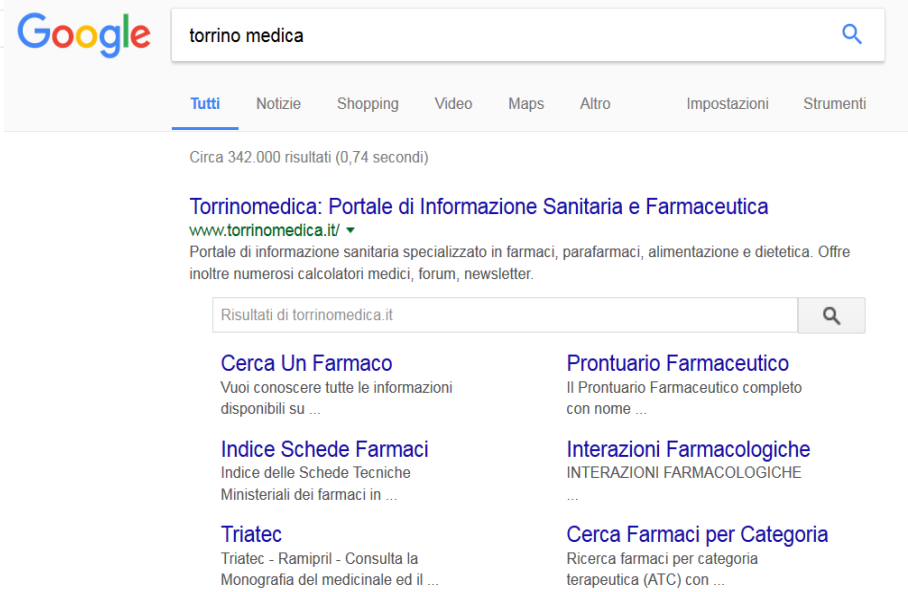
LinkOut


Google
torrino medica
Tutti
Notizie
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Maps
Altro
Impostazioni
Strumenti
Circa 342.000 risultati (0,74 secondi)
Torrinomedica: Portale di Informazione Sanitaria e Farmaceutica
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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 ...

Ospedale Luigi Sacco
POLO UNIVERSITARIO
Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

UNIVERSITÀ DEGLI STUDI DI MILANO

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

Milano, …….

Alla cortese attenzione del medico curante

In data…… è pervenuta al Nostro servizio richiesta di consulenza per un controllo delle possibili interazioni farmacologiche tra i farmaci assunti dalla Sig.ra ……..

Nello specifico, sono stati valutate le seguenti molecole

…….

…….

DATO FARMACOCINETICO

Dario

INTERAZIONI FARMACOLOGICHE IPOTIZZABILI SU BASE TEORICA*

Co-somministrazione controindicata (considerare regimi alternativi se possibile)

Co-somministrazioni che richiedono un attento monitoraggio

Interazioni di minore rilevanza clinica

Cri

CONSIGLI

*Le possibili interazioni farmacologiche tra questi farmaci sono state valutate utilizzando banche dati specifiche (pubmed, intercheck web, medscape drug interaction checker). Le interazioni farmacologiche identificate sono state suddivise in base alla possibile rilevanza clinica.

Margherita, 55 aa, HIV RNA < 37, CD4 800 c/mm^3

Ex TD, HIV noto da più di 20 anni, pregressa epatite B, cirrosi HCV correlata (SVR dopo due trattamenti), IA, DMID, LES, pregresso IMA, stenosi carotidea bilaterale, stenosi aortica, insufficienza mitralica, osteoporosi, IRC, necrosi bilaterale testa femore, BPCO, anemia multifattoriale, sindrome di Mikulicz, un ricovero per sepsi, *recentemente dimessa per sostituzione valvolare*

→ **Paziente 1.0**

→ **Paziente 1.1**

raltegravir 1 cp x 2
etravirina 1cp x 2

clopidogrel 75 mg
rabeprazolo 20 mg
nitroglicerina cerotto 5 mg
insulina lispro 8+8 UI
bisoprololo 1.25 mg x 2
furosemide 25 mg x 2
spironolattone 25 mg
eritropoietina 1 fl ogni 3 settimane
tiotropio bromuro soluzione x inalazione 5 microgrammi
budesonide e formoterolo 1 inalaz x 2
mesoglicano 50 mg x 2

Interazioni attese e clinicamente rilevanti

Pazienti non soppressi per interazioni farmacologiche

Loss of control of HIV viremia with OTC weight-loss drugs: A call for caution?

Clinical characteristics of the 4 patients from the GAP cohort experiencing virologic failure

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

Obesity in press

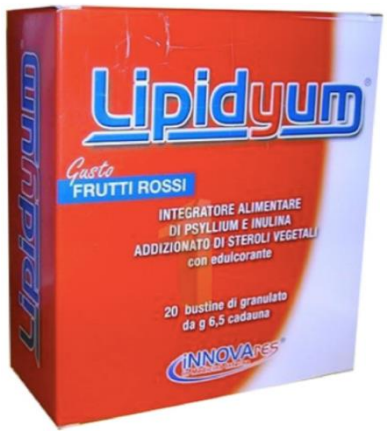
- ✓ Orlistat 120 mg thrice daily: Requires medical prescription
- ✓ Orlistat 60 mg thrice daily: Freely available as over-the counter (OTC) medication

Orlistat is a lipase inhibitor reported to inhibit the intestinal absorption of dietary fats and of highly lipophilic drugs[1-3]

1. Zhi J, et al. Effects of orlistat, a lipase inhibitor, on the pharmacokinetics of three highly lipophilic drugs (amiodarone, fluoxetine, and simvastatin) in healthy volunteers. J Clin Pharmacol. 2003 Apr;43(4):428-35.
2. Hilger E, et al. The effect of orlistat on plasma levels of psychotropic drugs in patients with long-term psychopharmacotherapy. J Clin Psychopharmacol. 2002 Feb;22(1):68-70.
3. Nägele H, et al. Effect of orlistat on blood cyclosporin concentration in an obese heart transplant patient. Eur J Clin Pharmacol. 1999 Nov;55(9):667-9.

Sinetrol contains mainly **naringin,** a flavanone-7-O-glycoside which inhibits the activity of carrier proteins (p-glycoprotein and organic anion transporting polypeptide), ultimately resulting in impaired drug absorption[1-3]

1. Surampalli G, et al. Corroboration of naringin effects on the intestinal absorption and pharmacokinetic behavior of candesartan cilexetil solid dispersions using in-situ rat models. Drug Dev Ind Pharm. 2015;41(7):1057-65.
2. Catalán-Latorre A, et al. In situ study of the effect of naringin, talinolol and protein-energy undernutrition on intestinal absorption of saquinavir in rats. Basic Clin Pharmacol Toxicol. 2011 Oct;109(4):245-52.
3. Shirasaka Y, et al. Concentration-dependent effect of naringin on intestinal absorption of beta(1)-adrenoceptor antagonist talinolol mediated by p-glycoprotein and organic anion transporting polypeptide (Oatp). Pharm Res. 2009 Mar;26(3):560-7.



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[1-3]

1. Asvarujanon P, et al. Inhibitory effects of psyllium on rat mineral absorption were abolished by reduction of viscosity with partial hydrolysis. Biosci Biotechnol Biochem. 2004 Aug;68(8):1737-42.
2. Chiu AC, et al. Effects of pharmacological fiber supplements on levothyroxine absorption. Thyroid. 1998 Aug;8(8):667-71.
3. Heaney RP, et al. Effect of psyllium on absorption of co-ingested calcium. J Am Geriatr Soc. 1995 Mar;43(3):261-3.

Interazioni attese e per ora clinicamente non rilevanti

Pazienti “per ora” soppressi con interazioni farmacologiche

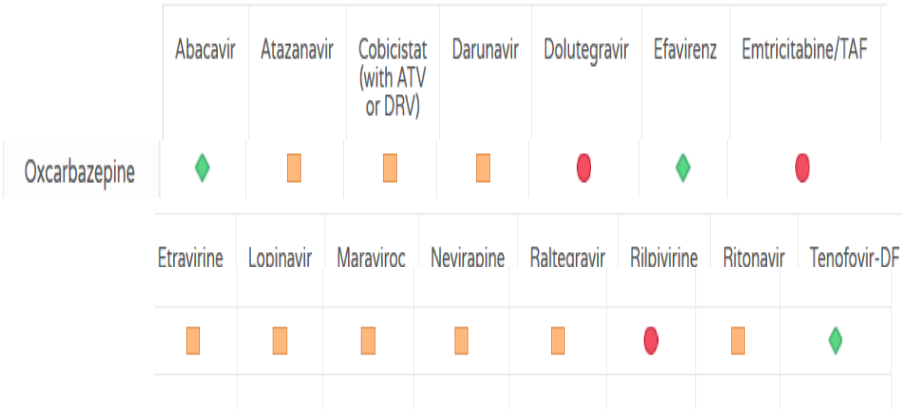
Angelo, 55 aa, HIV RNA < 37 NR, CD4 603 c/mm^3

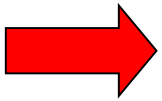
HIV noto da 30 anni, epilessia farmacoresistente (angioma cavernoso)

TDF FTC RPV da un anno

Clobazam 10 mg (no Liverpool)
Ramipril 5 mg
Oxcarbazepina 600 x 3 (in range)

No Interaction Expected





Contraindicated

oxcarbazepine + rilpivirine

oxcarbazepine decreases levels of rilpivirine by affecting hepatic/intestinal enzyme CYP3A4 metabolism. Contraindicated. Contraindicated. Rilpivirine should not be co-administered with strong CYP 3A4 inducers. Potential for loss of virologic response and possible resistance to rilpivirine or to the NNRTI class.

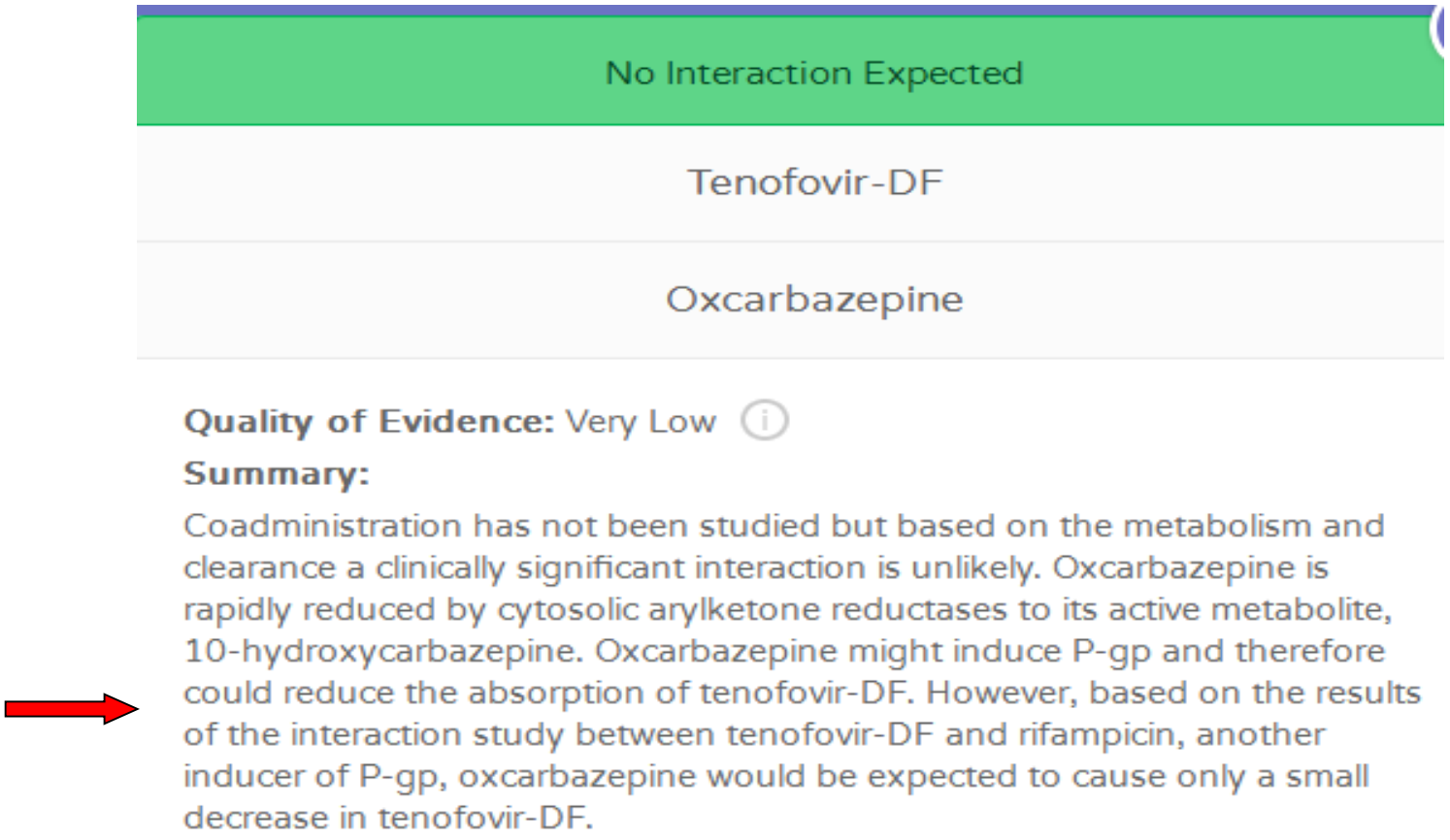
Monitor Closely

oxcarbazepine + clobazam

oxcarbazepine, clobazam. Other (see comment). Use Caution/Monitor. Comment: Concomitant administration can increase the potential for CNS effects (e.g., increased sedation or respiratory depression).

TDF (45 ng/mL)
RPV (<20 ng/mL)

TDF (45 ng/mL)


No Interaction Expected
Tenofovir-DF
Oxcarbazepine
Quality of Evidence: Very Low
Summary:
Coadministration has not been studied but based on the metabolism and clearance a clinically significant interaction is unlikely. Oxcarbazepine is rapidly reduced by cytosolic arylketone reductases to its active metabolite, 10-hydroxycarbazepine. Oxcarbazepine might induce P-gp and therefore could reduce the absorption of tenofovir-DF. However, based on the results of the interaction study between tenofovir-DF and rifampicin, another inducer of P-gp, oxcarbazepine would be expected to cause only a small decrease in tenofovir-DF.

Dolutegravir plasma concentrations according to companion ARV: unwanted drug interaction or desirable boosting effect?

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

Qd: once daily; *Data were given as median [interquartile range]

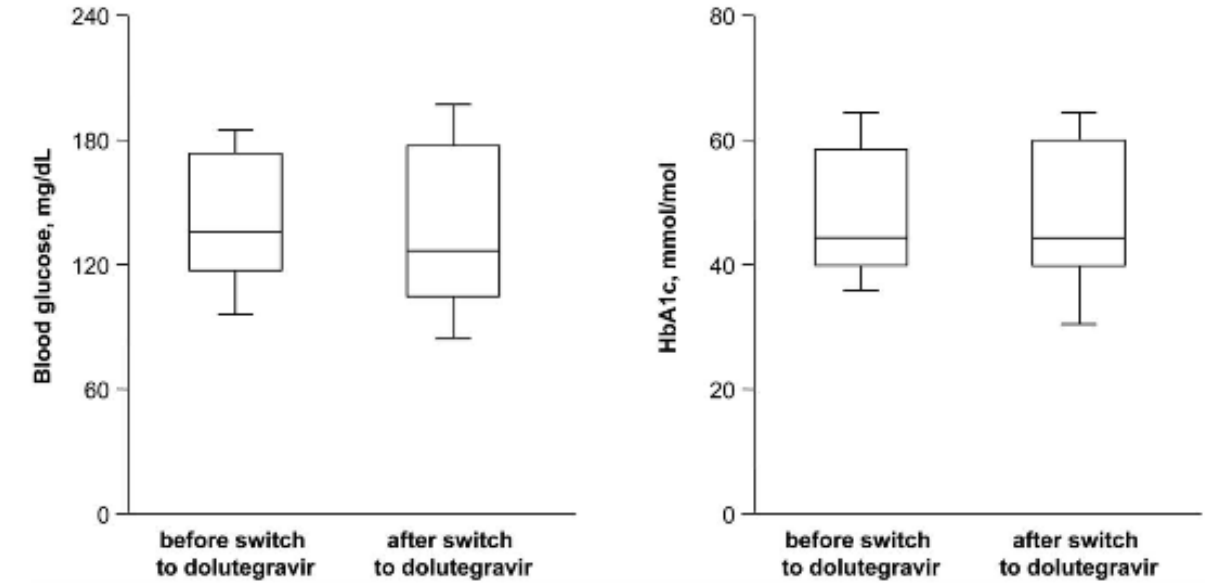
Cattaneo, D. Antiviral Therapy 2017

Interazioni potenziali ma non clinicamente rilevanti

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.



Mean age of 59 ± 10 years

AIDS. 2017 Sep 24;31(15):2176-2177. doi: 10.1097/QAD.0000000000001617.

Dolutegravir and metformin: a case of hyperlactatemia.

Naccarato M[1], Yoong D, Fong IW.

Dolutegravir and metformin: a clinically relevant or just a pharmacokinetic interaction?

Dario Cattaneo[1], Chiara Resnati[2], Giuliano Rizzardini[2,3], Cristina Gervasoni[2]

……All the 15 patients are still on treatment with dolutegravir plus metformin, given at a median (interquartile range) dose of 1250 (1000-1913) mg/daily (minimum dose 500 mg daily; maximum dose 2550 mg/daily)…….

……After having established that the discrepant findings between our experience [2] and the case reported by Naccarato et al. [1] were not related to differences in the dosage of metformin or by adherence issues of patients to therapy, we attempted to identify potential confounding factors as detailed below…….

Antivir Ther. 2018 Jan 4. doi: 10.3851/IMP3214. [Epub ahead of print]

The relevance of drug-drug interactions in clinical practice: the case of concomitant boosted protease inhibitors plus alpha1-blocker administration.

Gervasoni C[1,2], Resnati C[1], Formenti T[1], Fossati A[3], Minisci D[1], Meraviglia P[1], Cattaneo D[2,4].

- We focused on the potential DDIs between alpha1-blockers and boosted PIs

Drug	Metabolic pathway
Alfuzosin	CYP3A4/5
Tamsulosin	CYP3A4/5, CYP2D6
Silodosin	CYP3A4/5, UDP-gluycuronosyltransferase

plus ritonavir or cobicistat (CYP3A4/5 inhibitors)

increased alpha1-blockers exposure and development of severe hypotension

Clinical safety outcome

Systolic blood pressure, mmHg	135 (121 - 147); - minimum recorded: 105
Diastolic blood pressure, mmHg	82 (76 - 90); - minimum recorded: 60
Pts with episodes of hypothension	0%
Pts treated with antihypertensives - ACE inhibitors - beta blockers - diuretics - sartans - calcium channel blockers	12/14 (86%) n=6 n=5 n=4 n=2 n=1

Data were expressed as median (interquartile range).

Conclusions

- We have provided preliminary evidence from real life setting arguing against a clinical relevance of the predicted DDIs between alpha1-blockers and boosted PIs

- Tamsulosin or silodosin might be more suitable than alfuzosin for the treatment of benign prostatic hyperplasia in patients receiving PIs

- Instead of defining a priori contraindicated combinations, we suggest to monitor blood pressure as per clinical practice. In most cases, it is likely that nothing happens and no drug withdrawal/avoidance be required

J Antimicrob Chemother
doi:10.1093/jac/dky139

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]*

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Conclusions

In conclusion, we provide some useful insights into the previously under-studied DDIs between boosted antiretrovirals and CCBs, which are frequently co-administered in HIV-infected patients. The findings of this albeit small cohort study seem to suggest that such DDIs can be adequately managed by adjusting CCB doses and clinically monitoring BP and electrocardiographic assessment; it is likely that no discontinuation of the CCBs or change in antiretroviral regimen is required.

La paura delle interazioni

AIDS. 2018 Jan 2;32(1):127-128. doi: 10.1097/QAD.0000000000001656.

Psychoactive drugs and HIV: are we sure to treat our patients adequately?

Cattaneo D[1], Rizzardini G[2,3], Gervasoni C[2].

Distribution of ARV drug concentrations in HIV-infected patients from the GAP cohort

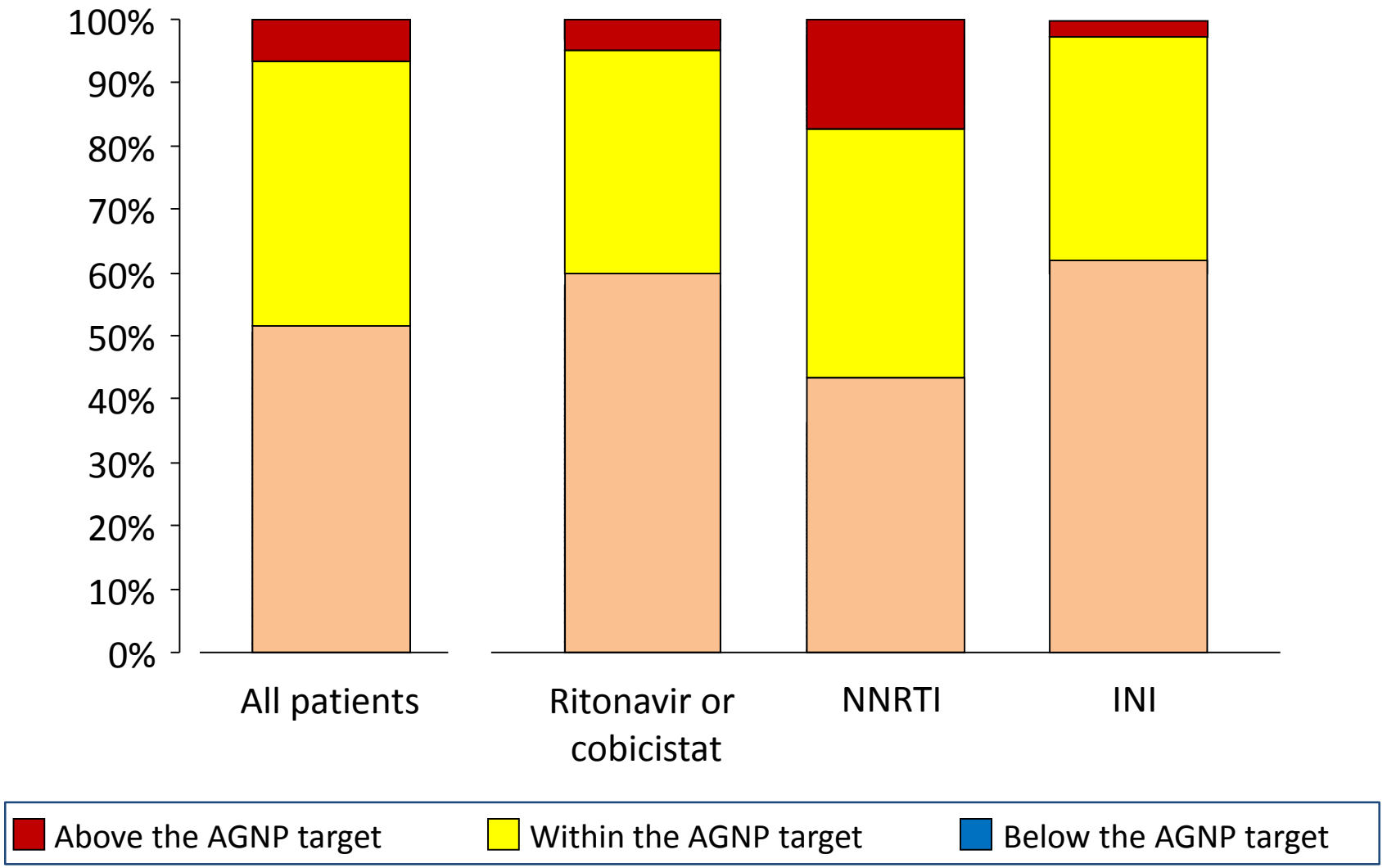
ARV drug	Patients (n)	Trough levels (ng/mL)	Reference ranges (ng/mL)	Sub-therapeutic samples, %
Tenofovir (TDF)	26	149±159	50-180	4%
Tenofovir (TAF)	15	16±7	5-30°	0%
Efavirenz	2	2309±656	1000-4000	0%
Etravirine	11	424±296	>300	9%
Nevirapine	3	5102±1191	3000-6000	0%
Rilpivirine	13	146±109	>20	0%
Atazanavir	6	1273±1042	150-850	0%
Darunavir	19	2816±1754	>550	5%
Dolutegravr	21	1316±919	>100	0%
Elvitegravir	9	622±403	>25	0%
Raltegravir	19	395±795	>40	26%

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

Drug	HIV-pos patients, n	Trough levels (ng/mL)	Sub-therapeutic samples, %	HIV-neg controls, 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%
Venlafaxine	4	223±52	0%	44	288±239	23%
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%

* patients undergoing TDM of antidepressant and/or antipsychotic concentrations in our lab in the same period

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



Conclusions

- ✓ In everyday clinical practice psychotropic drugs are frequently under-dosed in HIV-infected patients with optimal compliance to therapy
- ✓ A contribution of DDIs between ARV and psychotropic drugs was excluded because we found a higher frequency of sub-therapeutic psychotropic concentrations in the patients treated with boosting agents than in those treated with NNRTIs
- ✓ We hypothesize that psychiatrists may be reluctant to prescribe full doses of psychotropic drugs for HIV-infected patients because of the risk that DDIs may lead to virological failure

……il futuro di GAP……..

- Beers List → list of potentially inappropriate medications to be avoided in older adults

- Medication Appropriateness Index

- Anticholinergic burden → the cumulative effect of taking one or more drugs that are capable of developing anticholinergic adverse effects

- STOPP/START

Appropriatezza prescrittiva/riconciliazione terapeutica

THANK YOU !

Paola Meraviglia

Noemi Astuti

Davide Minisci

Tutti i colleghi che inviano pazienti

…e i pazienti…che chiedono informazioni!!!