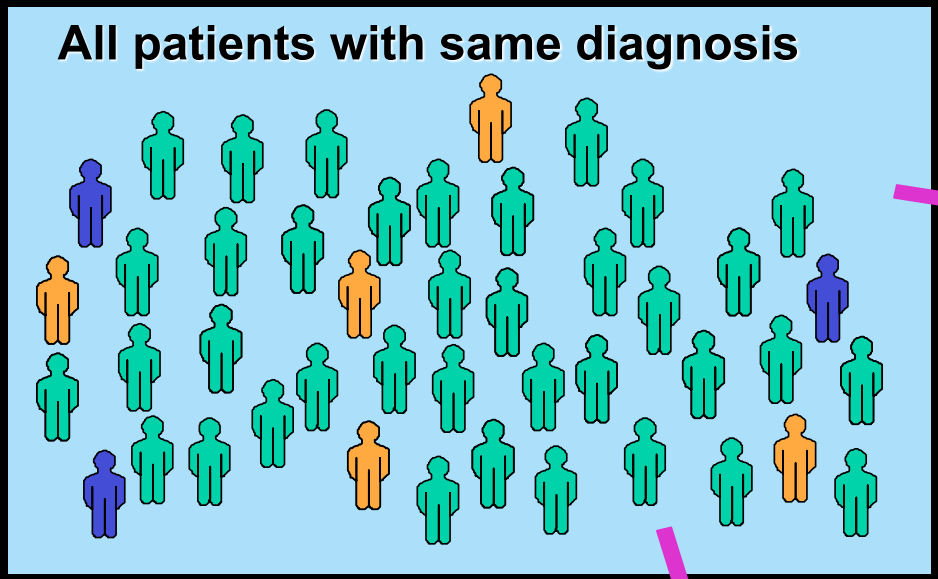
PERSONALIZZAZIONE DELLA TERAPIA ANTIRETROVIRALE

Stefano Bonora
Malattie Infettive, Università di Torino

Roma, 18 Marzo 2011

Potenzialità della farmacogenetica



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Trattare con farmaco o dosaggio alternativi

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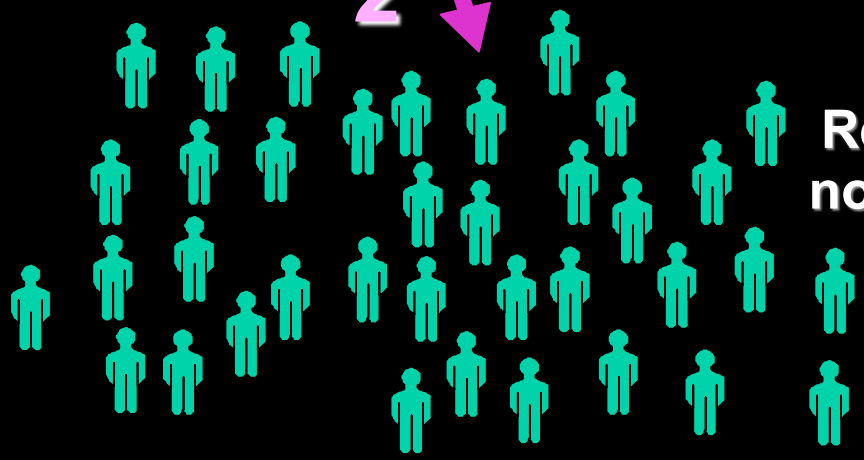


Responders and patients not predisposed to toxicity

Trattare con farmaco o dosaggio convenzionale

Ruolo dei fattori genetici

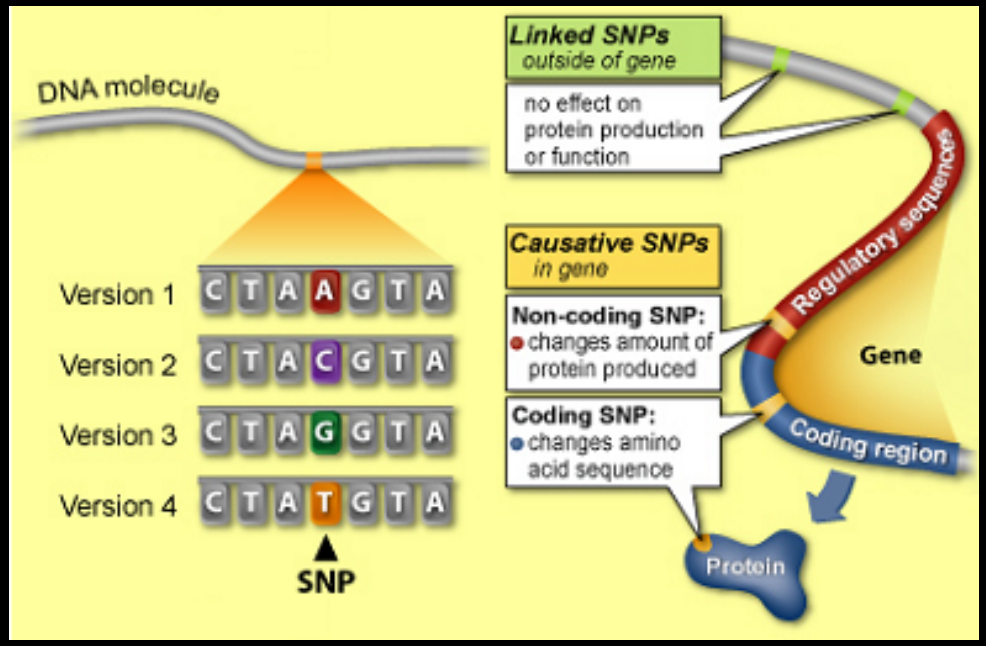
✓La farmacogenetica studia l'influenza della variabilità genetica sulla risposta ai farmaci, correlando **polimorfismi ed espressione genica di più geni all'efficienza terapeutica o alla tossicità**.

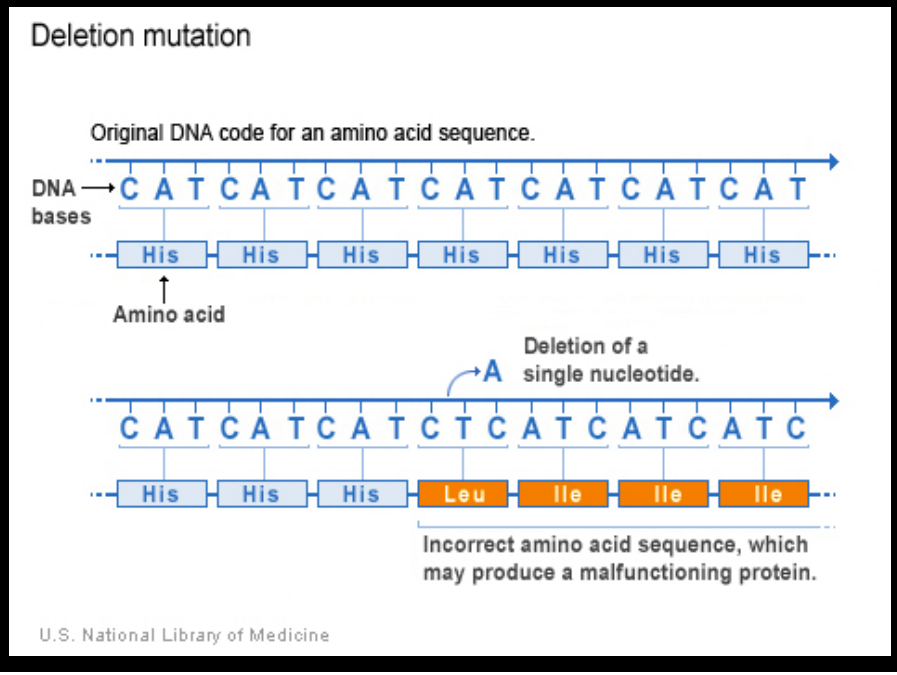
✓**Fattori genetici** possono avere un ruolo rilevante in molteplici aspetti della terapia antiretrovirale:

- **Variabilità farmacocinetica.**
- **Risposta** immunologica e virologica alla terapia.
- **Effetti tossici.**

Le principali tipologie di polimorfismi/mutazioni che possono influenzare l'espressione o l'attività dei geni sono:

Single Nucleotide Polymorphism
(SNPs)





Delezione di una o più basi nucleotidiche

- Tossicità non dose-correlate
  - ✓ Ipersensibilità

- Efficacia e tossicità dose-correlate
  - ✓ Effetto sulla PK dei farmaci

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*

N ENGL J MED 358;6 WWW.NEJM.ORG FEBRUARY 7, 2008

Biomarcatori farmacogenomici come predittori di reazioni avverse ai farmaci

Table 1. Pharmacogenomic Biomarkers as Predictors of Adverse Drug Reactions.

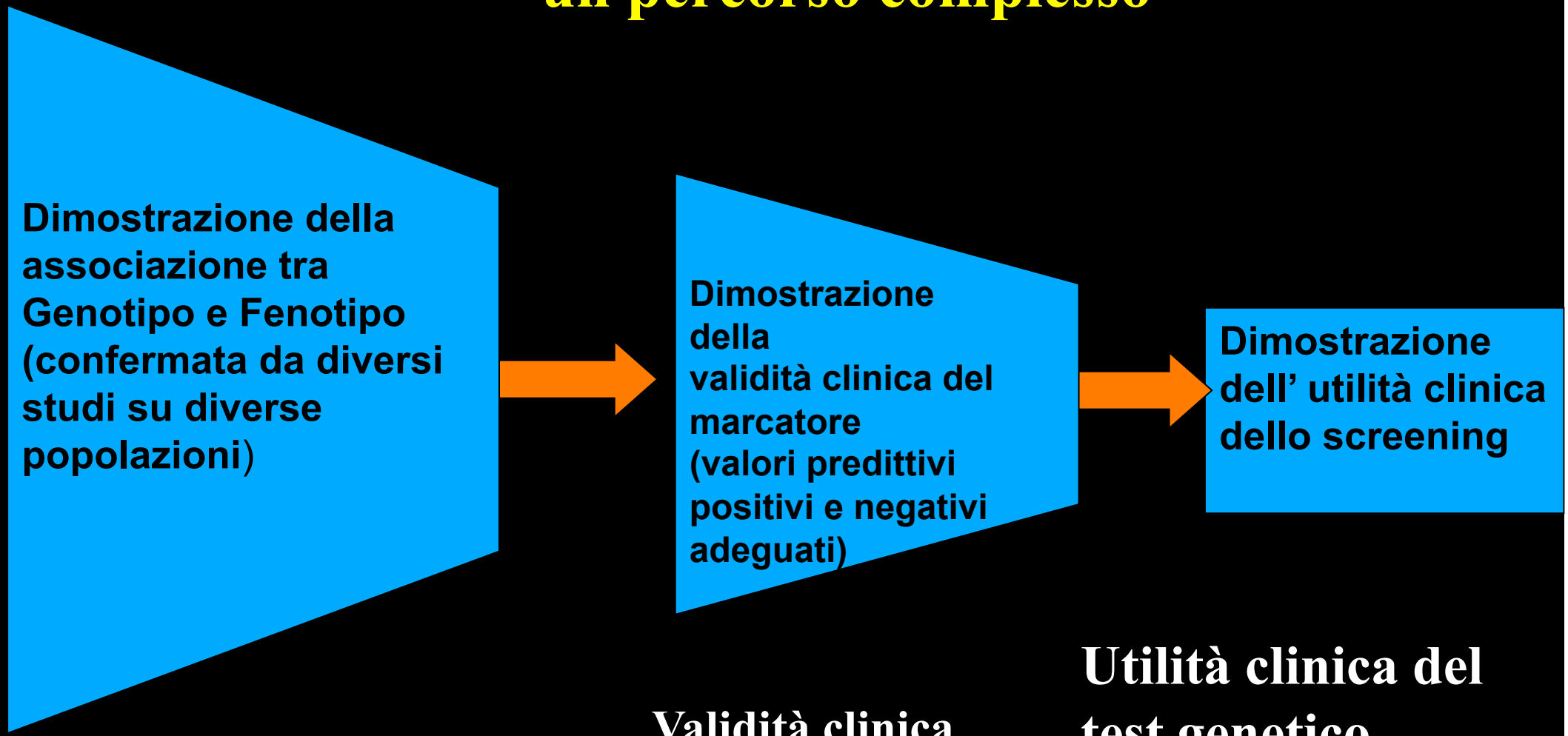
Gene or Allele	Relevant Drug	Specificity of Biomarker	Percent of Patients with an Adverse Reaction to Drug*
TPMT (mutant)	6-Mercaptopurines	Very good	1–10
UGT1A1*28	Irinotecan	Good	30–40
CYP2C9 and *VKORC1*	Warfarin†	Good	5–40
CYP2D6 (mutant)	Tricyclic antidepressants	Relatively good	5–7
HLA-B*5701	Abacavir	Very good	5–8
HLA-B*1502	Carbamazepine	Very good	10
HLA-DRB1*07 and DQA1*02	Ximelagatran	Good	5–7

* Percentages are of affected whites except that for HLA-B*1502, which is the percentage of affected Asians.
† Carriage of the *CYP2C9* and *VKORC1* alleles affects warfarin dosing.

Ingelman-Sundberg M. N Engl J Med 2008;358:637-639

The NEW ENGLAND JOURNAL of MEDICINE

Dall'evidenza scientifica all'impiego clinico: un percorso complesso

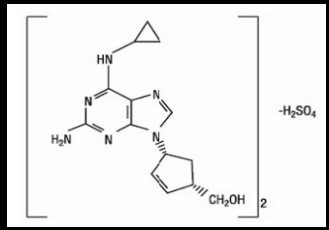


Esistenza dell'associazione

Validità clinica del marcatore

Utilità clinica del test genetico

Screening HLA-B*5701
Implicazioni per la pratica clinica



Pratica precedente

Paziente candidato ad ABV

Screening: No

↓

Controllo segni e sintomi "ABV HSR"

↓

Sospensione se comparsa "ABV HSR"

Screening HLA-B*5701

Paziente candidato ad ABV

Screening: Sì

Neg → **Controllo segni e sintomi "ABV HSR"**

Pos → **Farmaco Alternativo**

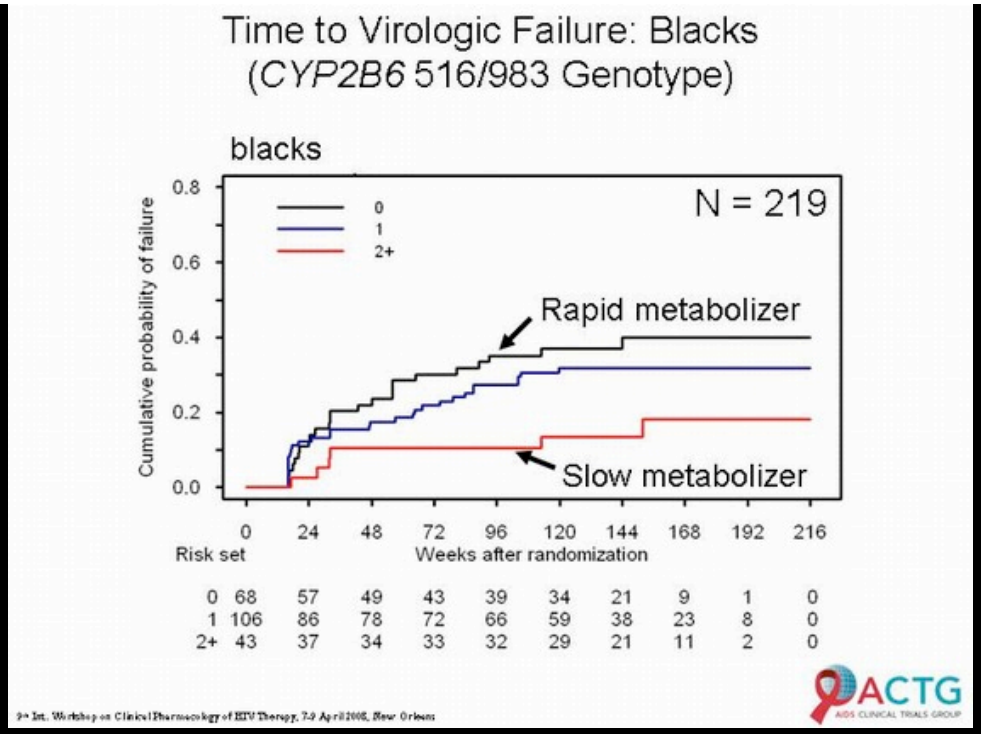
- Tossicità non dose-correlate
  - ✓ Ipersensibilità

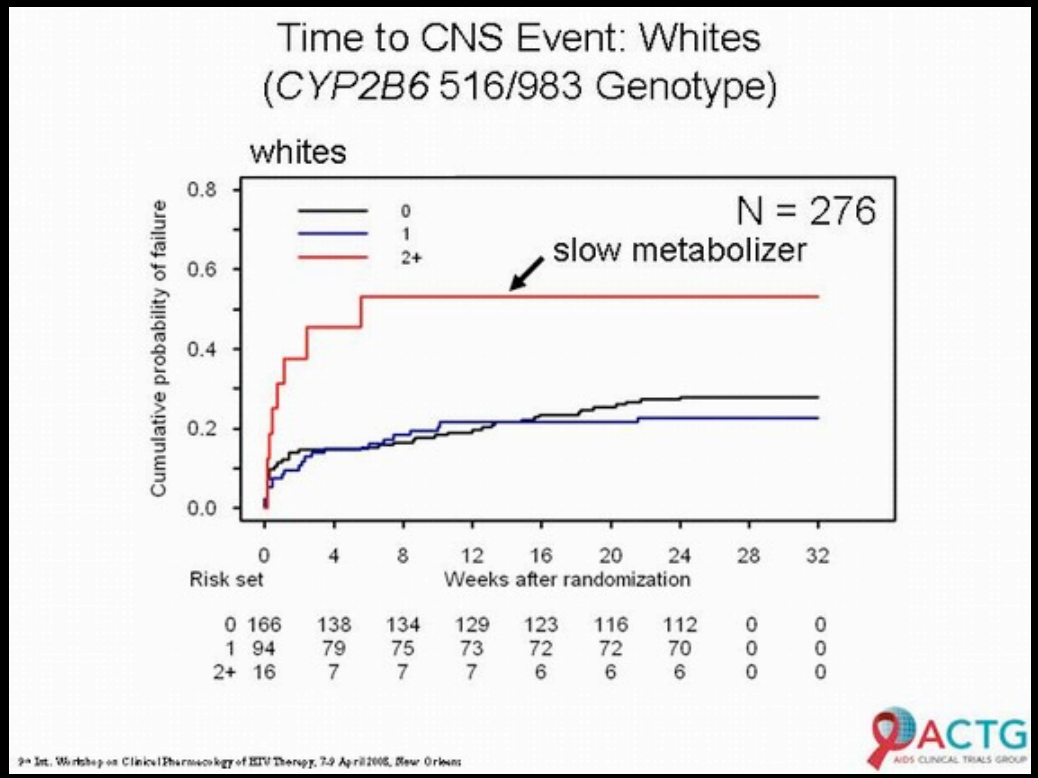
- Efficacia e tossicità dose-correlate
  - ✓ Effetto sulla PK dei farmaci

Effect of *CYP2B6*, *ABCB1*, and *CYP3A5* Polymorphisms on Efavirenz Pharmacokinetics and Treatment Response: An AIDS Clinical Trials Group Study

Heather J. Ribaudo,[1,2] Huan Liu,[1,2] Matthias Schwab,[10,11] Elke Schaeffeler,[10] Michel Eichelbaum,[10] Alison A. Motsinger-Reif,[4] Marylyn D. Ritchie,[5] Ulrich M. Zanger,[10] Edward P. Acosta,[6] Gene D. Morse,[7] Roy M. Gulick,[8] Gregory K. Robbins,[3] David Clifford,[9] and David W. Haas[5]

The Journal of Infectious Diseases 2010;202(5):717–722

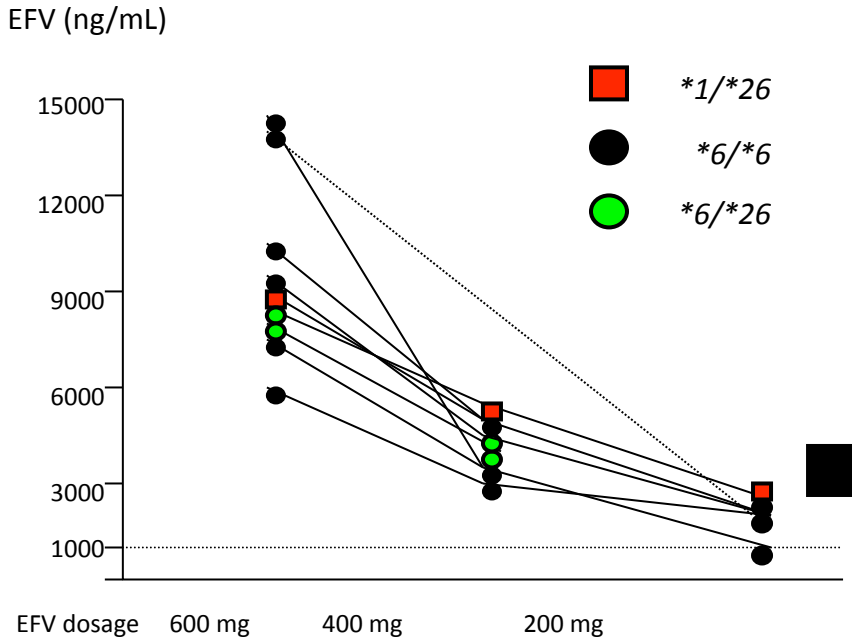


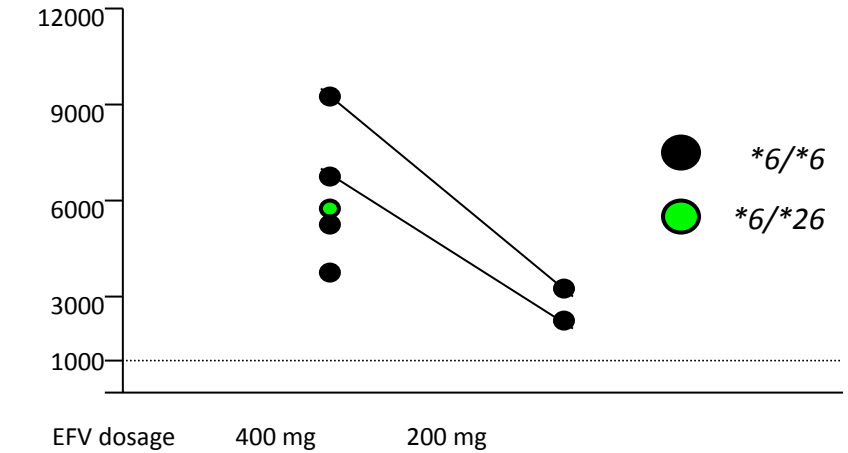


- ***CYP2B6 516/*983 genotype predicted pharmacokinetics.**
- **Slow-metabolizer genotypes were associated with increased central nervous system events among *white participants* and decreased virologic failure among *black participants*.**

Successful Efavirenz dose reduction in HIV Type 1-Infected Individuals with Cytochrome P450 2B6 *6 and *26

Gatanaga H, et al. Clin Infect Dis 2007; 45: 1230-7





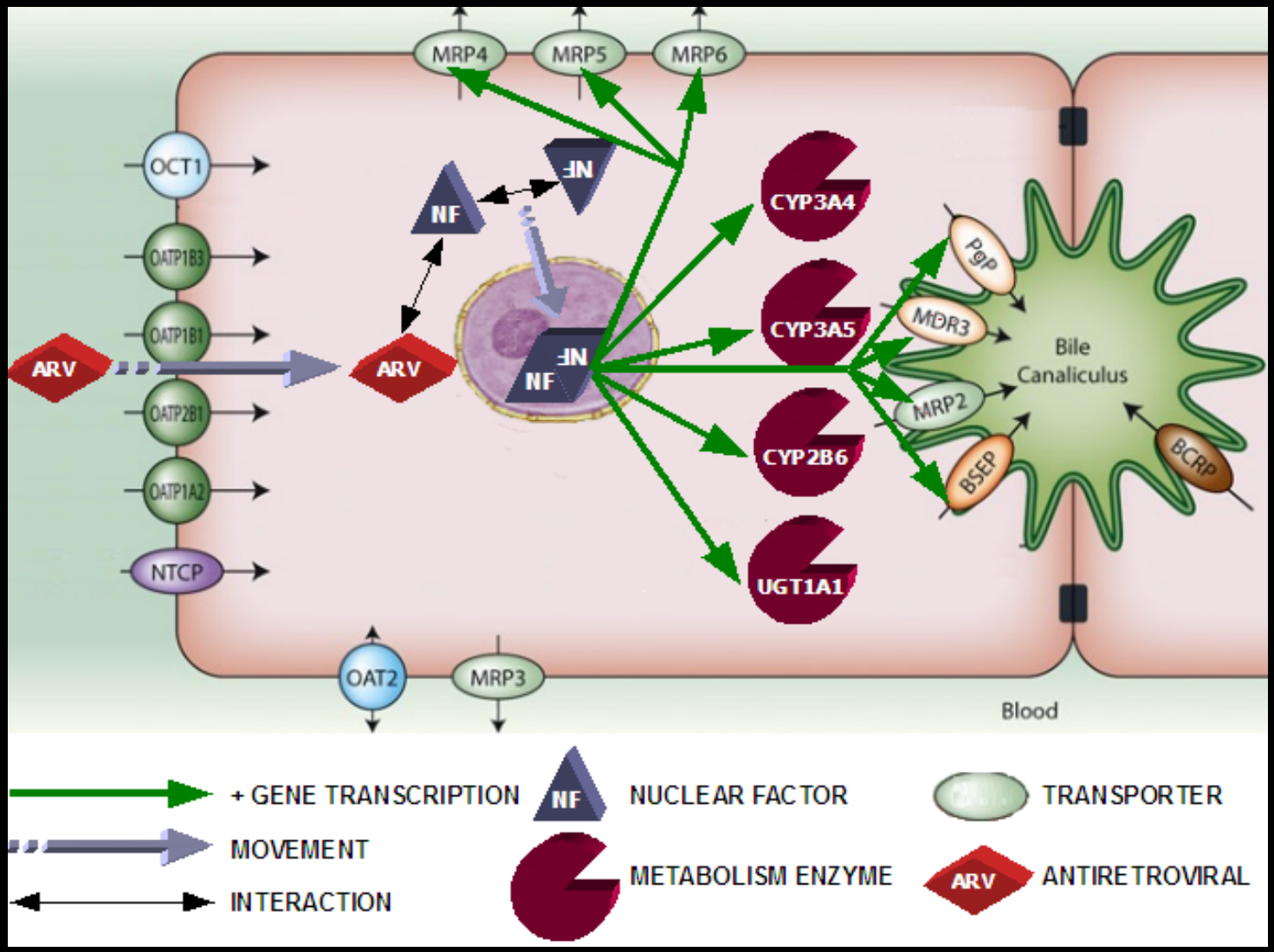
CYP2B6 genotypes determined in 456 HIV-1-infected EFV recipients

CYP2B6 516G>T was identified in the **6* allele (17.9% of patients) and a novel allele, **26* (1.3% of patients).

Genotype-based dose reduction of EFV

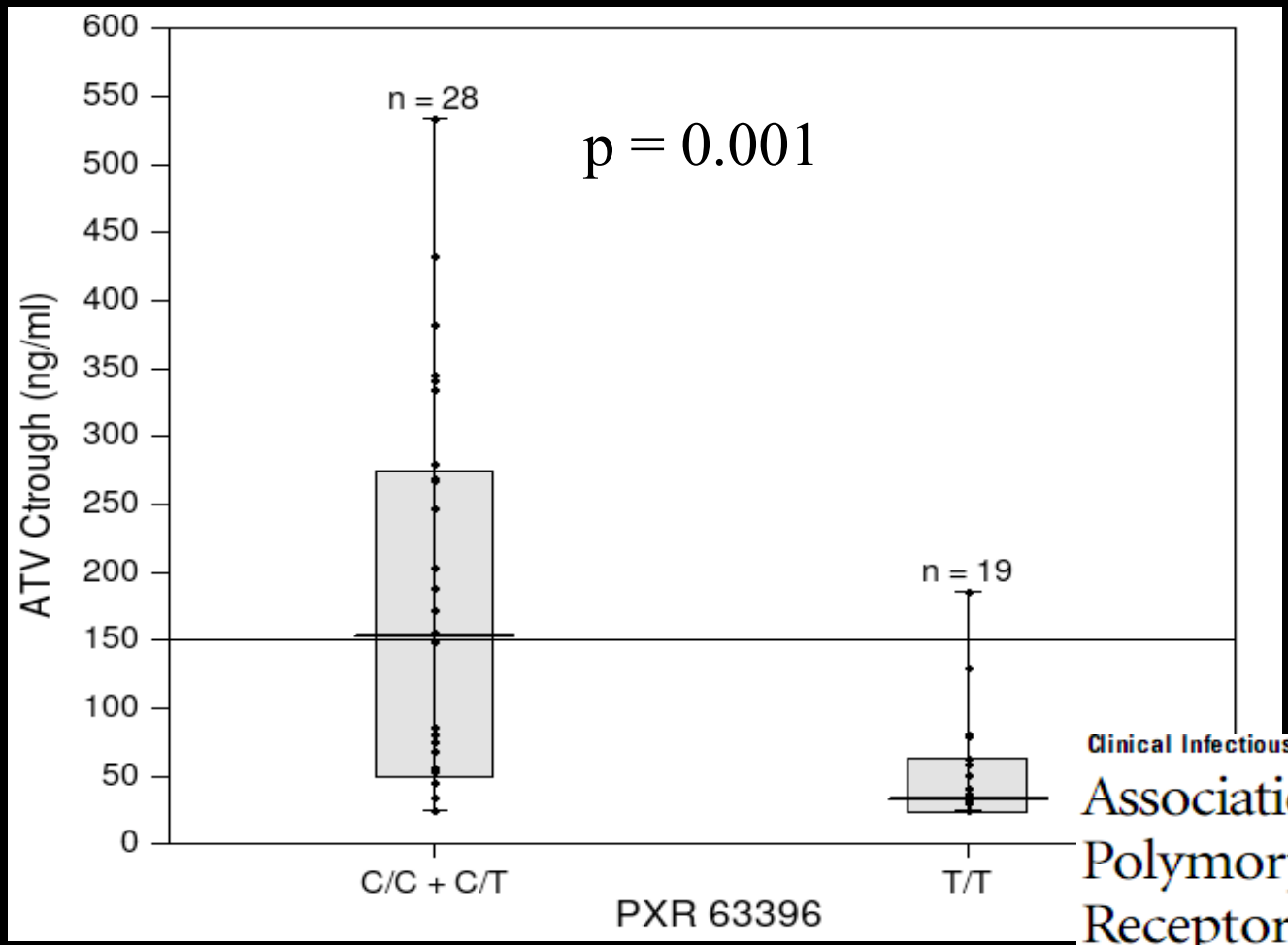
EFV-associated CNS symptoms improved in 10/14

PXR: Pregnane X Receptor



- Fattore nucleare
- Risposta a varie sostanze (rifampicina, corticosteroidi, fenobarbital...)
- Aumenta sintesi enzimi "detossificanti" e trasportatori

Unboosted ATV and PXR SNPs



Clinical Infectious Diseases 2008; 47:1222–5

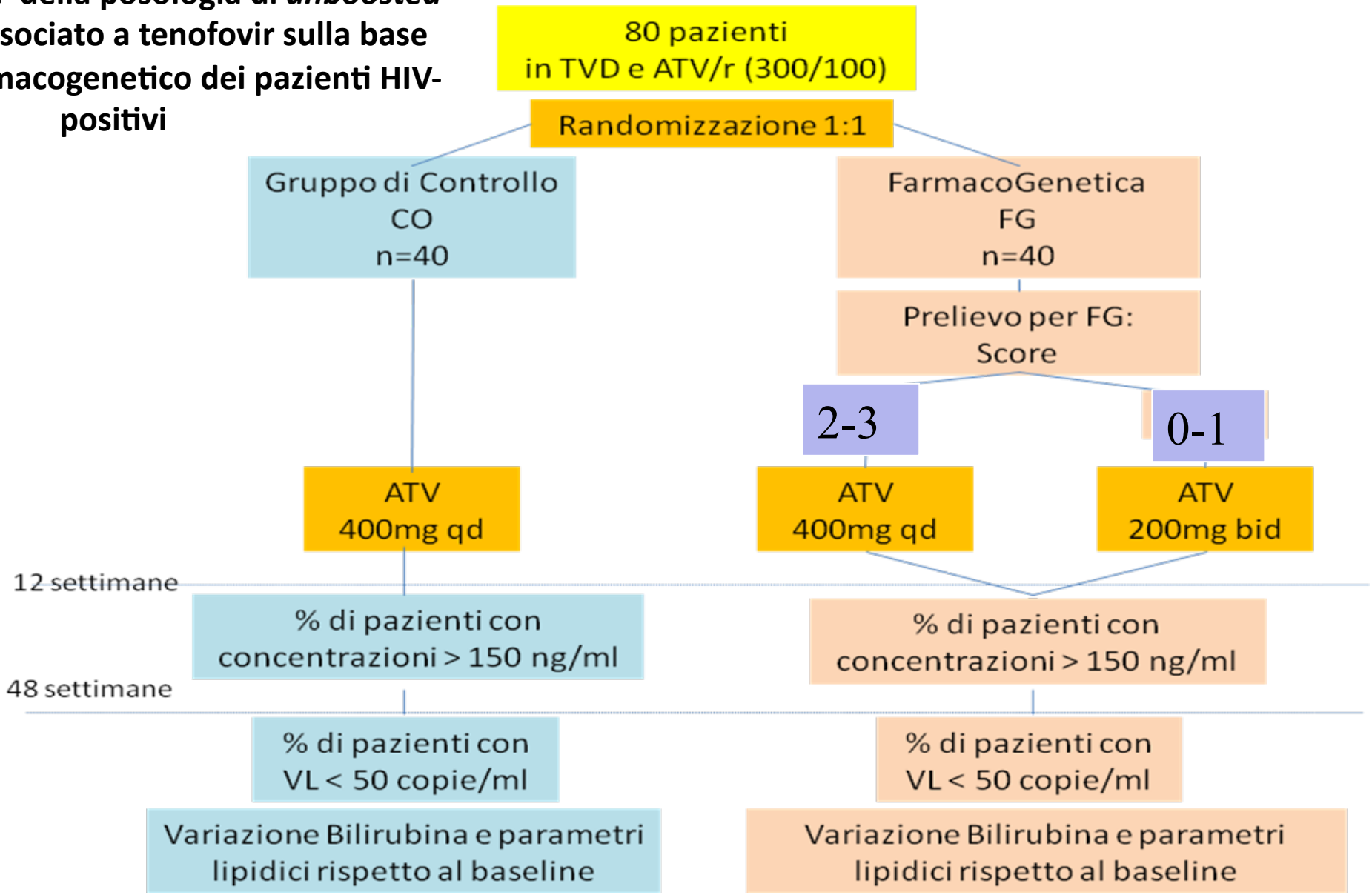
Association of a Single-Nucleotide Polymorphism in the Pregnane X Receptor (*PXR* 63396C→T) with Reduced Concentrations of Unboosted Atazanavir

Marco Siccardi,[1,2] Antonio D'Avolio,[1] Lorena Baietto,[1] Sara Gibbons,[2] Mauro Sciandra,[1] Daniela Colucci,[1] Stefano Bonora,[1] Saye Khoo,[2] David J. Back,[2] Giovanni Di Perri,[1] and Andrew Owen[2]

Studio REYAGEN

(Studio in corso c/o Torino e Milano Sacco)

Ottimizzazione della posologia di *unboosted* atazanavir associato a tenofovir sulla base del profilo farmacogenetico dei pazienti HIV-positivi



Riduzioni di dose/posologia?

Alcune evidenze che vi siano farmaci sovradosati (d4T!)

Vari studi di riduzione di dose soprattutto nei paesi a risorse limitate: IDV, ATV, LPV/r

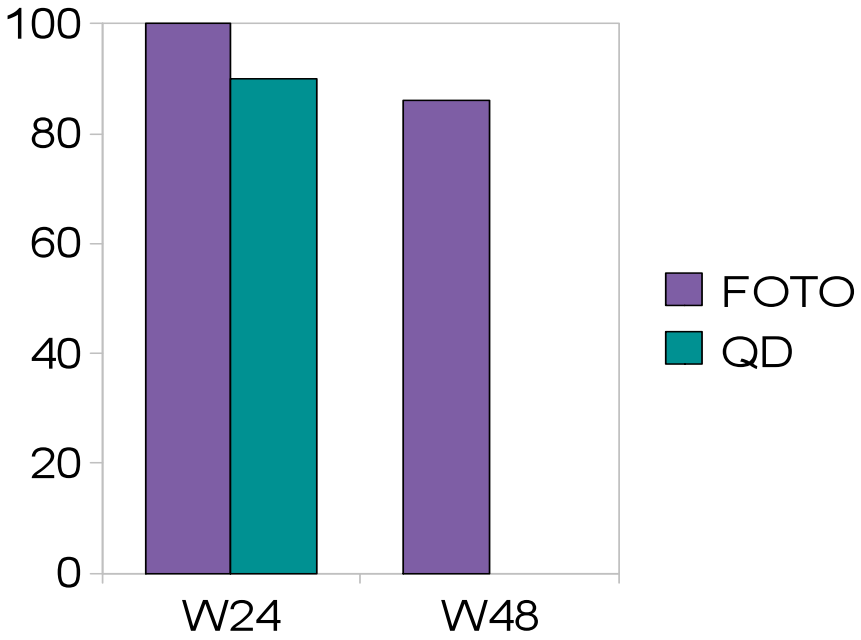
Pharmacokinetics of low-dose protease inhibitors and efavirenz in low- and middle-income countries

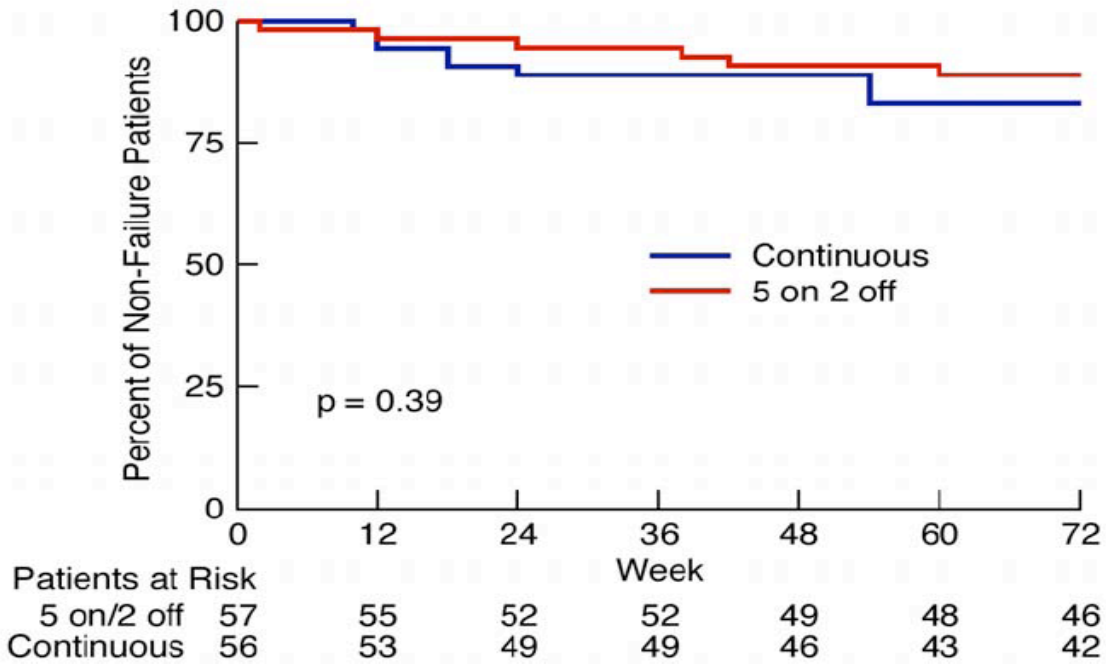
Meena Gorowara[a,b], David Burger[c], Andrew Hill[d] and Kiat Ruxrungtham[a,b]

Current Opinion in HIV and AIDS, 2010; 5:90-96

Studi in corso su altre molecole: 3TC

Studio FOTO
Five days On Two days Off





A 6 mesi 100% vs. 86% con VL < 50 copie/ml

Cohen C, et al. IAS 2009

Non inferiorità del regime FOTO

(Interrotto braccio 7on/7off)

Reynolds SJ, et al. PLoSOne 2010; 5(4): e10307cv

Results: PK and QOL

EFV LEVEL (MEC=1000 ng/ml)	FOTO* Mean 60 hours post last dose	DAILY** Mean 12 hours post last dose
> 1000 ng/ml	48%	90%
500-999 ng/ml	37%	1%
< 500 ng/ml	15%	9%

*13 subjects, 92 samples **15 subjects, 74 samples

Quality of Life

0 ——— 10

I prefer taking HIV medications 7 days per week

I prefer 5 days on and 2 days off HIV medications

- **n=54; Median Response 9.5 (IQR 8-10) four weeks after change from daily to FOTO treatment schedule:**

Dosing of Maraviroc	
	Coadministered antiretroviral medications
300 mg BID	▪ all NRTIs ▪ nevirapine ▪ tipranavir ▪ enfuvirtide
150 mg BID	CYP3A inhibitors (with or without with a strong CYP3A inducer): ▪ protease inhibitors (other than tipranavir) ▪ delavirdine
600 mg BID	CYP3A inducer (if used without a strong CYP3A inhibitor [see above]): ▪ efavirenz ▪ etravirine

Dose adjustements for interactions:

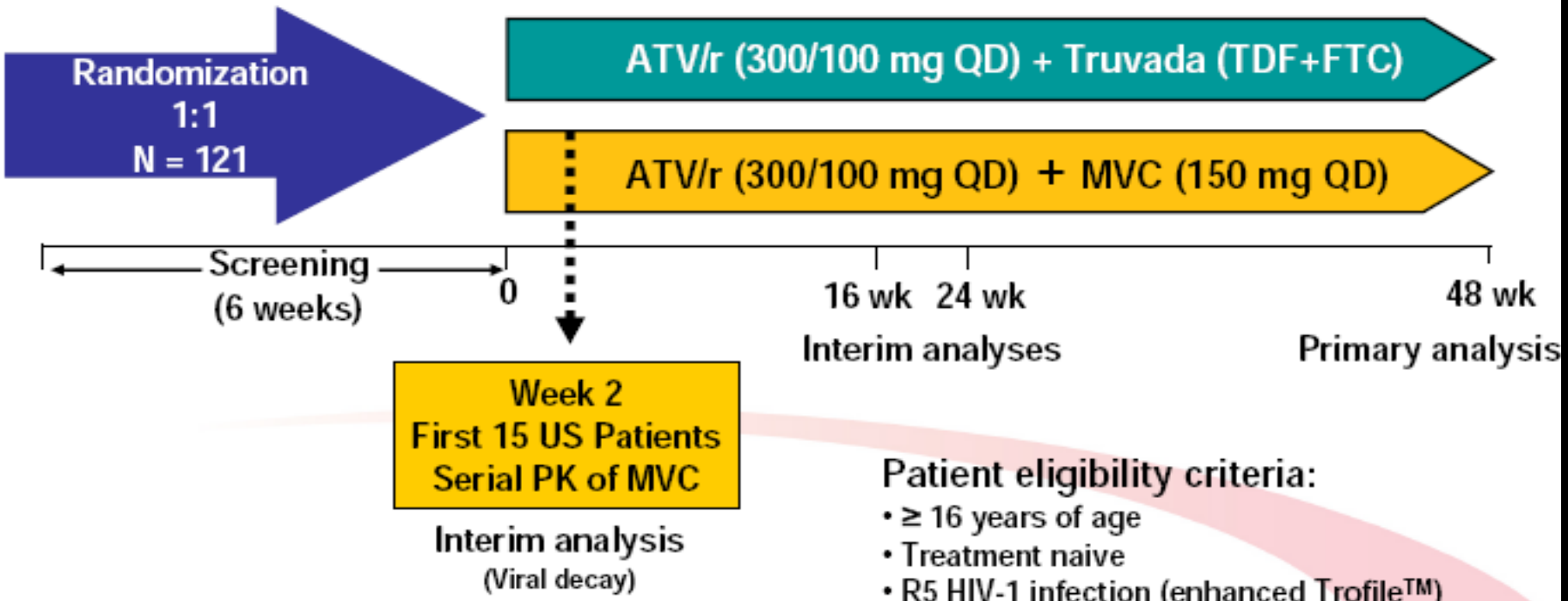
one size probably does not fit all due to genetic-related variability

In some patients 150 mg QD could be enough

In some patients 300 mg BID could be enough

Study A4001078

Open-label, randomized, international phase 2b study
Primary endpoint: Proportions < 50 copies/mL at week 48*



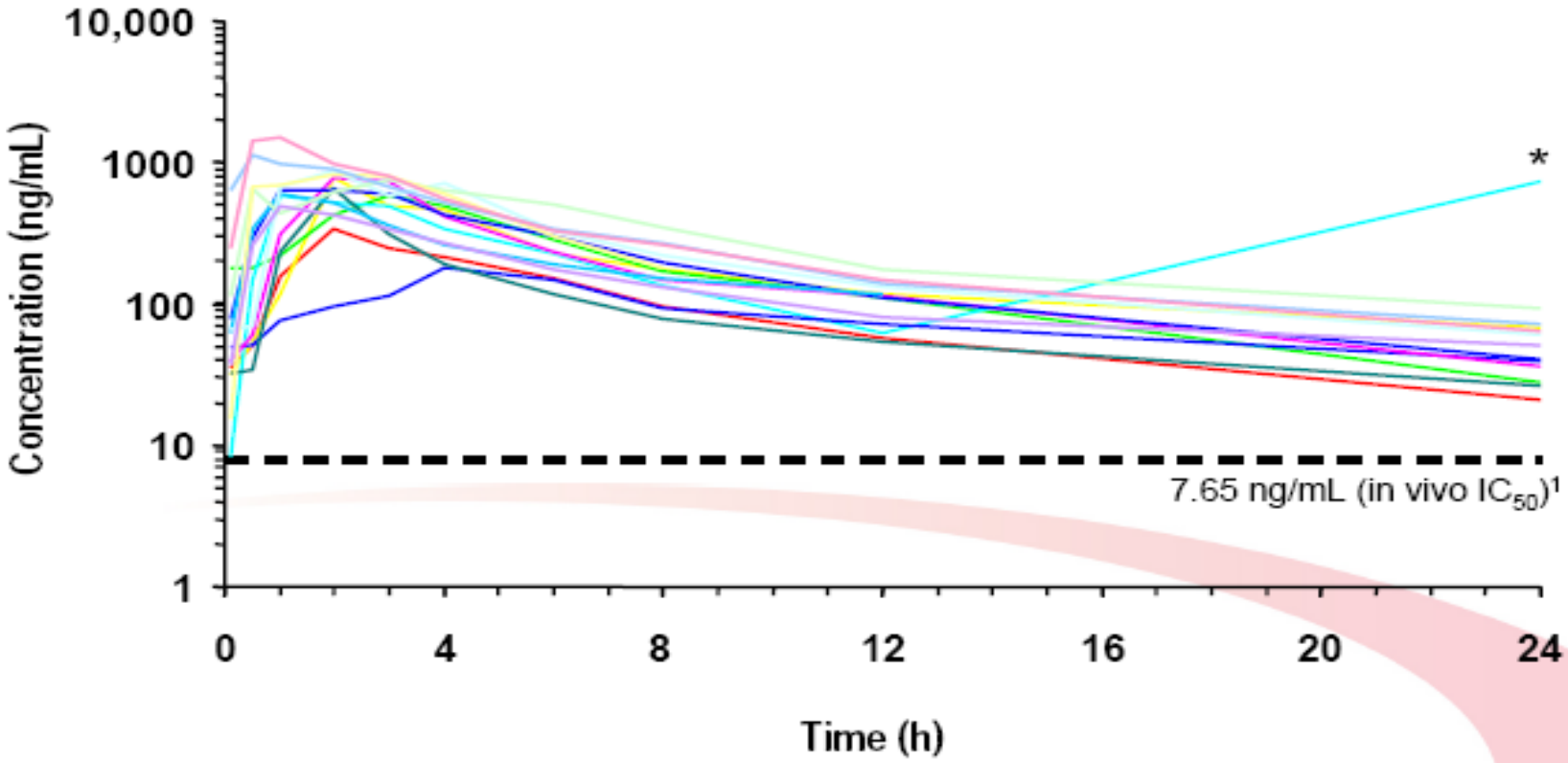
Patient eligibility criteria:

- ≥ 16 years of age
- Treatment naive
- R5 HIV-1 infection (enhanced Trofile™)
- HIV-1 RNA ≥ 1000 copies/mL
- CD4 ≥ 100 cells/mm^3
- No evidence of resistance to ATV/r, TDF, or FTC

* Study is not powered to show a treatment difference and no comparative statistics will be performed.
Sparse PK sampling on all patients at Weeks 2 (non-PK substudy), 12 and 24.

Presented at the 11th International Workshop on Clinical Pharmacology of HIV Therapy - 2010

All patients had plasma MVC concentrations above the in vivo IC_{50} across the dosing interval (150 mg QD + ATV/r)



* One patient accidentally dosed with MVC prior to the 24-hour sample draw.

1. Rosario MC, et al. *J Acquir Immune Defic Syndr*. 2006;**42**:183-191.

Presented at the 11th International Workshop on Clinical Pharmacology of HIV Therapy - 2010

A Low Dose of Ritonavir-Boosted Atazanavir Provides Adequate Pharmacokinetic Parameters in HIV-1-Infected Thai Adults

A Avihingsanon[1], J van der Lugt[1,2], SJ Kerr[1,3], M Gorowara[1], S Chanmano[1], P Ohata[1], J Lange[2], DA Cooper[3], P Phanuphak[1], DM Burger[4] and K Ruxrungtham[1,5]

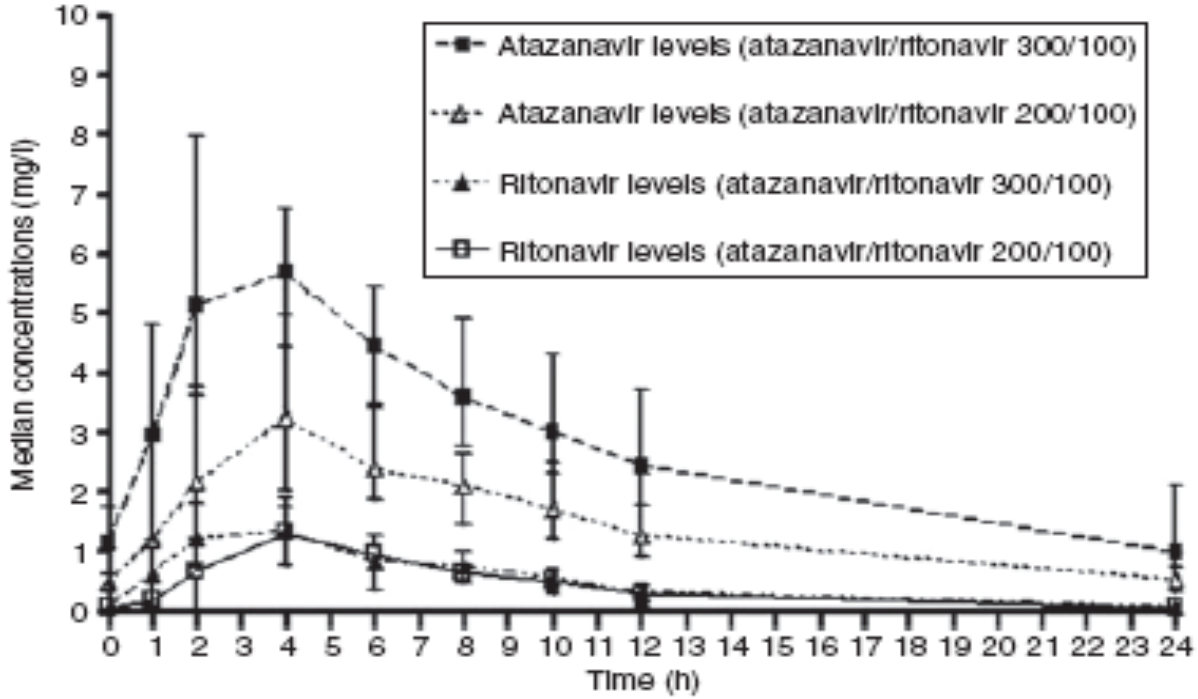


Figure 1 Median atazanavir and ritonavir concentration–time curves, with bar indicating interquartile range (IQR).

PK e modifiche di dosaggio

Pazienti stabili (< 50 copie/ml)

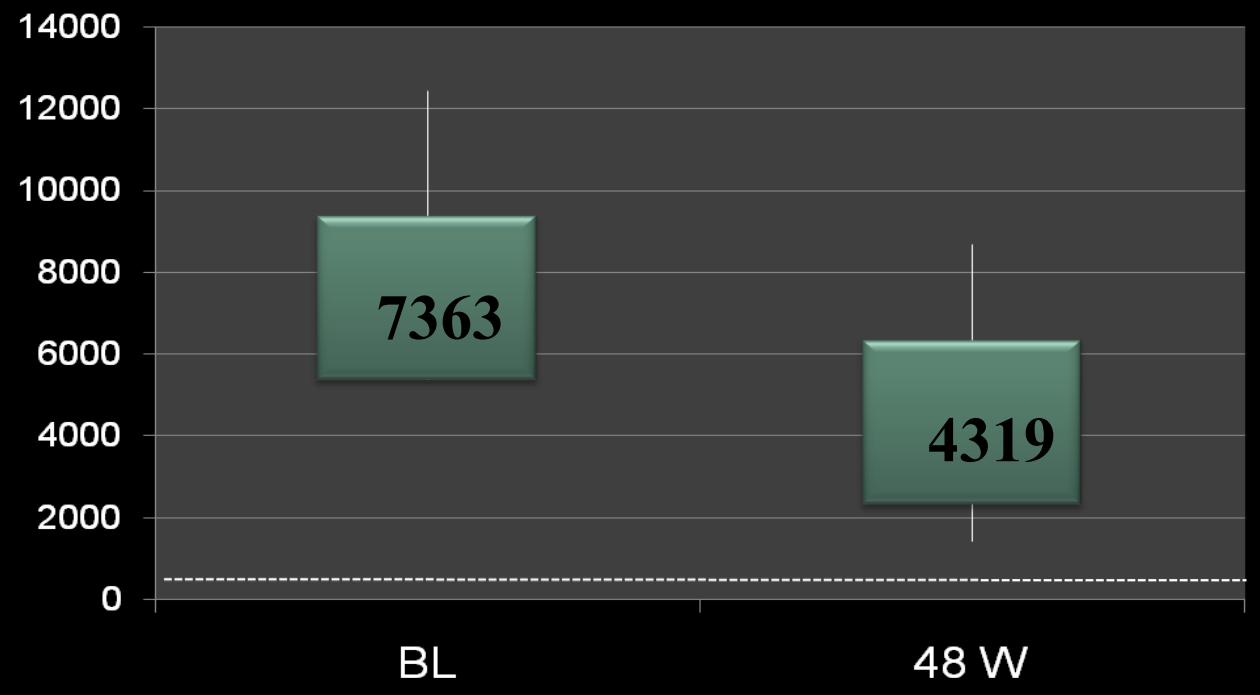
In Terapia con LPV/r

No esposizione a PIs

Non farmaci interagenti

Cmin > 5000 ng/ml

LPV/r ridotto a 267/67 mg



89.3% soppressi a 48w

Riduzione dei TG

Maynard JL, et al. JAC 2010

(Provocative) piano di ricerca futura per IP

Pazienti:

✓Molto aderenti

✓Backbone pienamente attivo

✓Successo virologico a lungo termine

✓Peso? Genere? Genetica?

Possibili strategie di switch:

✓DRV /r 600/100 QD?

✓LPV/r 200/50 BID? 600/150 QD?

✓ATV 200/100 QD?

Linee Guida Italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostico-clinica delle persone con infezione da HIV-1

Luglio 2010

Su mandato del *Ministro della Salute*

CENTRO NAZIONALE AIDS

In collaborazione con

Ministero della Salute

Commissione Nazionale per la lotta contro l'AIDS
Consulta delle Associazioni per la lotta contro l'AIDS

e

SIMIT
Società Italiana di Malattie Infettive e Tropicali

Tabella 2 - Scenari clinici di possibile uso del TDM

SCENARIO	FORZA/EVIDENZA
Alterazioni significative della funzionalità gastroenterica, epatica o renale	[CIII]
Gravidanza	LPV/r, SQV/r [CIII]
Pregressi fallimenti con virus resistente	IP con uso di IQ [CII]
Tossicità concentrazione-correlata	IDV/r [BII], EFV [CII], ATV [CIII]
Schemi posologici non convenzionali	[CIII]
Aderenza terapeutica	[CIII]
Interazioni farmacologiche	[BIII]

Epidemiology of HIV Drug Interactions

The Netherlands [de Maat et al, J Clin Pharm Ther 2004;29:121-30]

- Clinically significant DIs in 23-26% of 220 HIV outpatients (with prior screening of community pharmacy records)
- prior Pharmacy screening (but not clinical pharmacist input) was able to reduce frequency

New York City [Shah, et al, CROI 2007. Abstr 573]

- Review of Medicaid dataset for 571 HIV+ individuals (342 on ARVs)
- Overall, 1:5 patients on ARVs had a potential drug interaction
- 1:5 of these could have led to lowered ARV concentrations

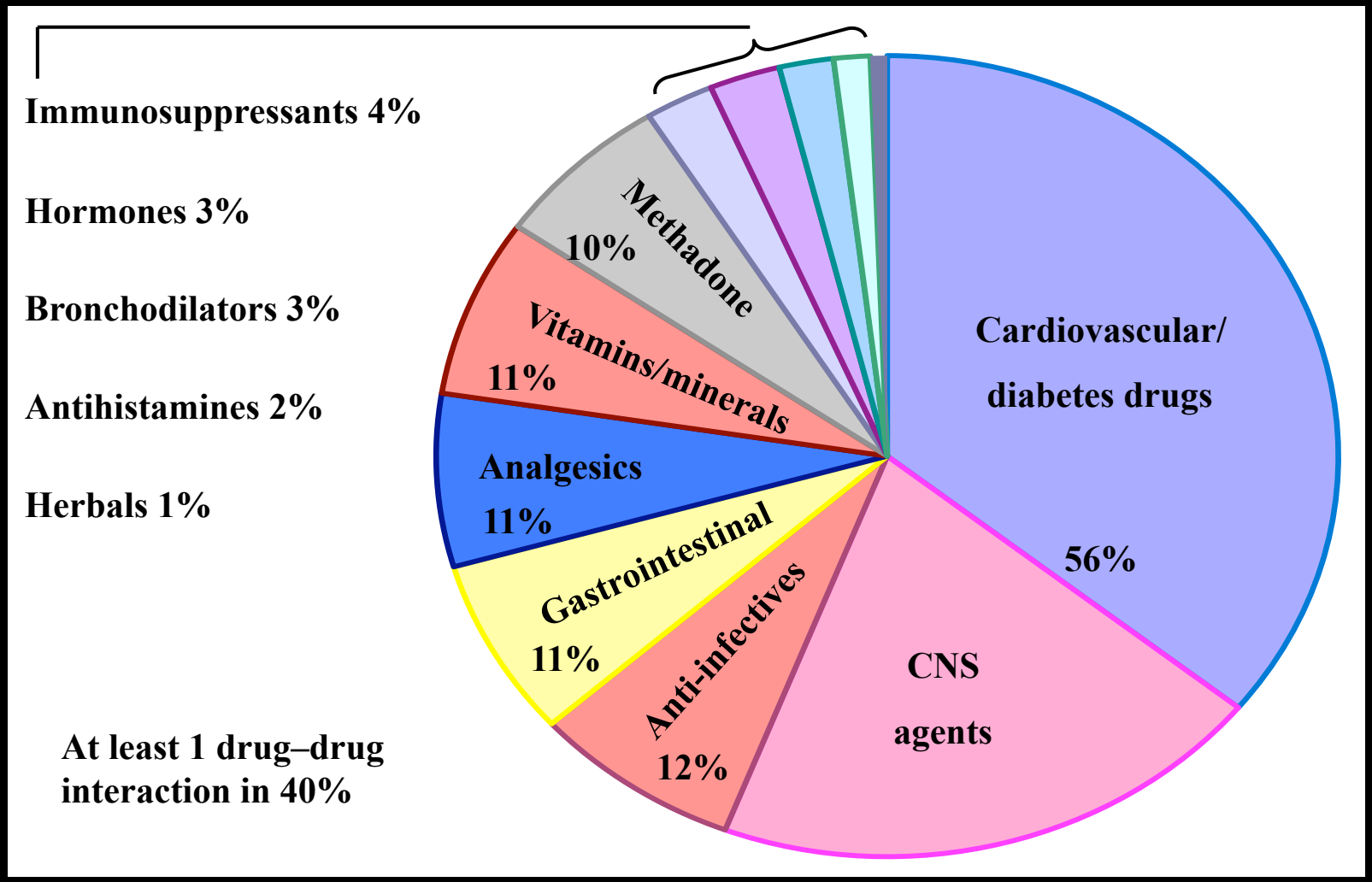
Baltimore [Rastegar, et al, CID 2006;43:933-8]

- 209 admissions of patients receiving ARVs over 1 year
- Contraindicated medications were prescribed in 5.2%

Kenya [Kigen et al. HIV8, 2008 Abstract O121]

- 993 consecutive patients receiving ARVs
- Moderate / Major drug interactions identified in 28%
- 47% of these could have lowered ARV concentrations
- Rifampicin > Azoles > Steroids > Antimalarials > PPIs

Two thirds of patients in the Swiss HIV Cohort Study received co-medication (1013/1497 patients)



- ✓ L'entità di una interazione nota può essere imprevedibile nel singolo caso osservato, per cui il TDM è utile a verificare se e quanto si discosti dall'atteso [CIII].
- ✓ La risultante di più interazioni farmacologiche contemporanee (più di due farmaci concomitanti interagenti tra di loro) è spesso di difficile prevedibilità e consiglia l'uso del TDM [CIII].
- ✓ L'entità dell'interazione, quantificabile con il TDM, può avere un peso specifico diverso a seconda delle variabili cliniche del singolo caso: per esempio la barriera genetica del/dei farmaci interessati, lo status virologico del paziente, la presenza di mutazioni di resistenza per il/i farmaci in oggetto, la durata della co-somministrazione. La valutazione congiunta del TDM e di queste variabili, meglio se con il parere di un esperto, può permettere la gestione razionale di molte interazioni considerate a rischio di fallimento terapeutico e/o tossicità [CIII].
- ✓ Una interazione farmacologica può essere imprevedibile e pertanto, seppur non segnalata in precedenza, deve essere sospettata in caso di eventi clinici e terapeutici inattesi in termini di tossicità ed efficacia [CIII].

Linee Guida Italiane, 2010

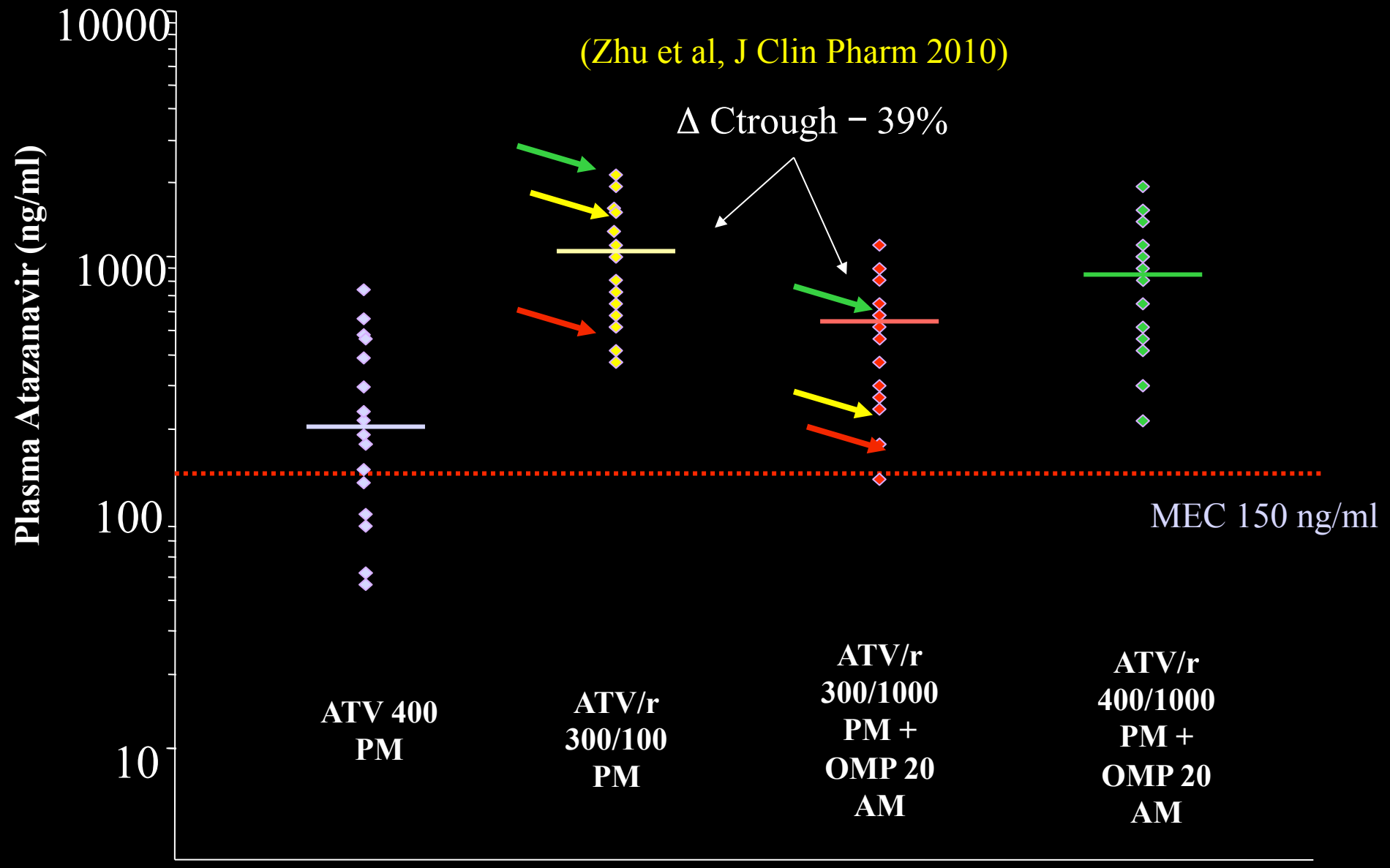
ATV and PPIs

•Coadministration is contraindicated for treatment-experienced patients in the US Prescribing Information and not recommended for all patients in the European SPC.

•If coadministration is judged unavoidable, close clinical monitoring is recommended and doses of omeprazole should not exceed 20 mg and must be taken approximately 12 hours prior to the atazanavir/ritonavir The European SPC recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.

DHHS guidelines, 2010

Effect of omeprazole 20 mg daily on the bioavailability of multiple-dose atazanavir in healthy subjects



- ✓ L’entità di una interazione nota può essere imprevedibile nel singolo caso osservato, per cui il TDM è utile a verificare se e quanto si discosti dall’atteso [CIII].

- ✓ - La risultante di più interazioni farmacologiche contemporanee (più di due farmaci concomitanti interagenti tra di loro) è spesso di difficile prevedibilità e consiglia l’uso del TDM [CIII].

Linee Guida Italiane, 2010

Esempio: Paziente N.R.

PCR HIV < 50 copie/ml

289 CD4/mm3, 0.3 ratio

DRV/r +TDF + FTC

DRV

RTV

?

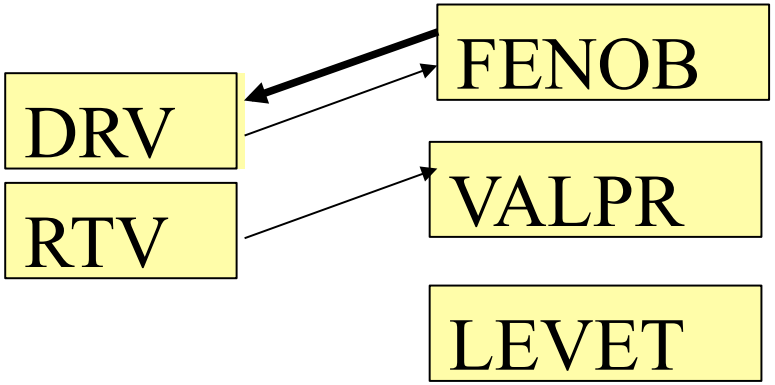
FENOB

VALPR

LEVET

www.hiv-druginteractions.org

Anticonvulsivants	Darunavir	Ritonavir
Levetiracetam		
Phenobarbital (Phenobarbitone)		
Valproate (Divalproex)		



Interazioni: evidenze?

Summary

The European SPC contraindicates coadministration as it may significantly decrease darunavir concentrations. However, the US Prescribing Information predicts no change in darunavir concentrations, but decreased phenobarbital concentrations and advises monitoring of phenobarbital.

Description

LHPG Comment: *Note the difference between the European SPC (contraindicated) and the US Prescribing Information (monitor phenobarbital). The charts reflect the more cautious option.*

Darunavir coadministered with low dose ritonavir should not be used in combination with phenobarbital. This interaction has not been studied, but phenobarbital is expected to decrease plasma concentrations of darunavir by induction of CYP450 enzymes.
Prezista Summary of Product Characteristics, Janssen-Cilag Ltd, October 2009.

Co-administration of darunavir/ritonavir may cause a decrease in the steady-state concentrations of phenytoin and phenobarbital. Phenytoin and phenobarbital levels should be monitored when co-administering with darunavir/ritonavir.
Prezista Prescribing Information, Tibotec Inc, January 2010.

Interazione RTV – Carbamazepina

Letteratura

Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir.

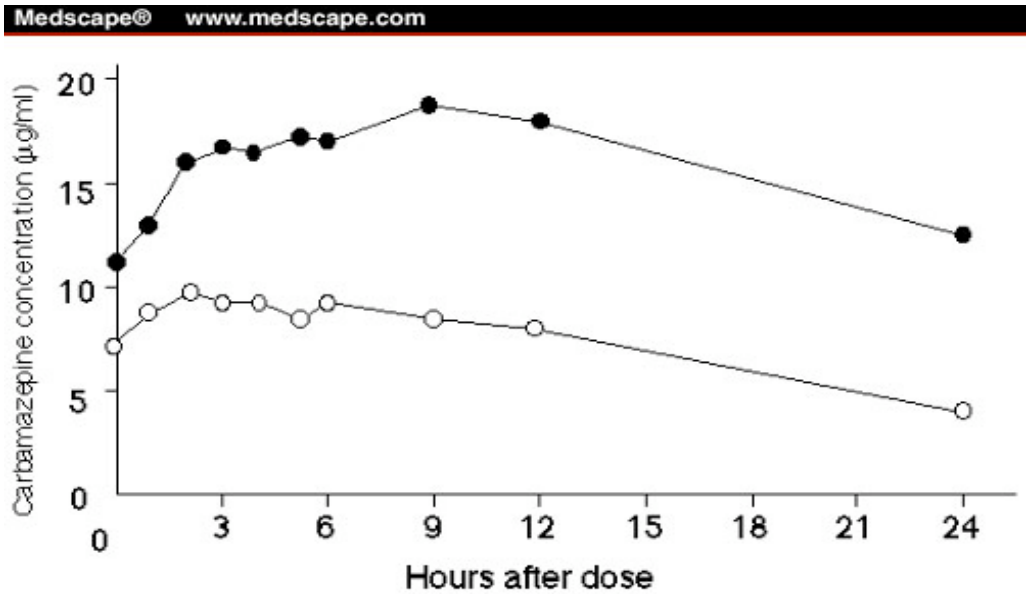
Bates DE, Herman RJ.

Ann Pharmacother. 2006 Jun;40(6):1190-5.
Epub 2006 May 23.

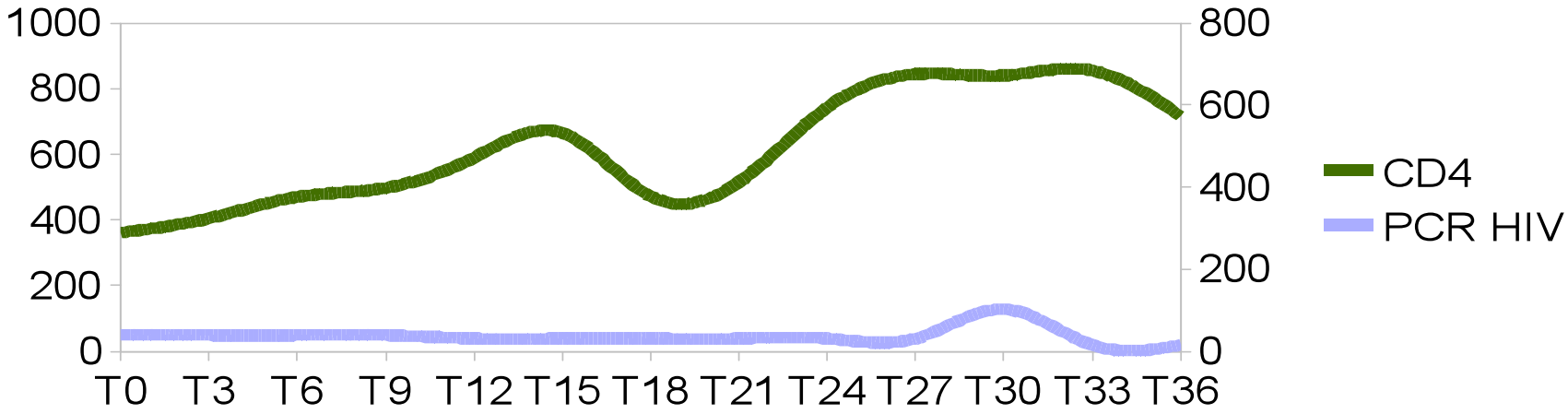
Ritonavir-induced carbamazepine toxicity.

Mateu-de Antonio J, Grau S, Gimeno-Bayón JL, Carmona A.

Ann Pharmacother. 2001 Jan;35(1):125-6.



TDM e follow up



	T1	T6	T9	T12	T18	T24	T30	T36
DRV 600/100 bid	1823	2177	-	-	-	-	3116	-
FENOB 100 mg	26,4	28,1	27,5	25,2	28,7	27,4	20,6	22,2
VALPR	31,7	71,5	65,9	59,5	80,8	80,3	0	64,5

Il TDM di DRV e fenobarbital supporta l'associazione in questo paziente

- ✓ L'entità di una interazione nota può essere imprevedibile nel singolo caso osservato, per cui il TDM è utile a verificare se e quanto si discosti dall'atteso [CIII].

- ✓ La risultante di più interazioni farmacologiche contemporanee (più di due farmaci concomitanti interagenti tra di loro) è spesso di difficile prevedibilità e consiglia l'uso del TDM [CIII].

- ✓ **L'entità dell'interazione, quantificabile con il TDM, può avere un peso specifico diverso a seconda delle variabili cliniche del singolo caso: per esempio la barriera genetica del/dei farmaci interessati, lo status virologico del paziente, la presenza di mutazioni di resistenza per il/i farmaci in oggetto, la durata della co-somministrazione. La valutazione congiunta del TDM e di queste variabili, meglio se con il parere di un esperto, può permettere la gestione razionale di molte interazioni considerate a rischio di fallimento terapeutico e/o tossicità [CIII].**

Linee Guida Italiane, 2010

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LHPG

UNIVERSITY OF LIVERPOOL

Interaction Report from www.hiv-druginteractions.org

Report ID: h

Date Produced: 18 October 2010

Antiretroviral treatment	Co-medications
Atazanavir	Lansoprazole

This report lists the potentially clinically significant interactions (i.e. "red" and "amber" classifications) for the drugs in the table above. Interactions with a "green" classification (i.e. no clinically significant interaction expected) have been checked but are not shown on this report.

For full details of all interactions, see www.hiv-druginteractions.org.

Description of the interactions

Drugs that should not be co-administered **(RED)**

- **Atazanavir and Lansoprazole**: Lansoprazole decreased atazanavir (alone) AUC by 94%; omeprazole decreased atazanavir (+ ritonavir) AUC by 75%. Coadministration with proton pump inhibitors is contraindicated for treatment-experienced patients in the US Prescribing Information and not recommended for all patients in the European SPC. If coadministration is judged unavoidable, close clinical monitoring is recommended and doses of proton pump inhibitors comparable to omeprazole 20 mg should not be exceeded and must be taken approximately 12 hours prior to the atazanavir/ritonavir. The European SPC recommends increasing the dose of atazanavir to 400 mg with 100 mg of ritonavir.

Information supplied and monitored by The Liverpool HIV Pharmacology Group. This report is provided for information only. It is not intended to replace a consultation with an appropriately qualified health professional. We aim to ensure that the information published in this report is accurate and consistent with current knowledge and practice. However, medical knowledge and practice is constantly evolving and individual cases may require specific advice that cannot be addressed through this report. The University of Liverpool, eMedFusion and their servants or agents shall not be responsible or in any way liable for the continued currency of the information or for any errors, omissions or inaccuracies in this publication whether arising from negligence or otherwise howsoever or for any consequences arising therefrom. The University of Liverpool and eMedFusion expressly exclude liability for errors, omissions or inaccuracies to the fullest extent permitted by law.

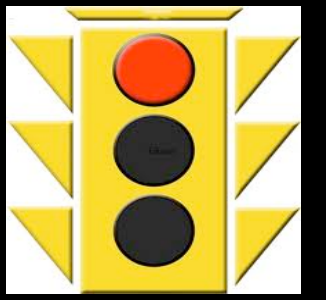
Patient on TDF/FTC + ATV/RTV, he started lansoprazole 30 mg/die, required lenght of treatment is 8-10 weeks

ATV C_{trough} 185 ng/ml

1st line HAART since 1 month

HIV-RNA: BL 560.000, current 2490 copies/ml

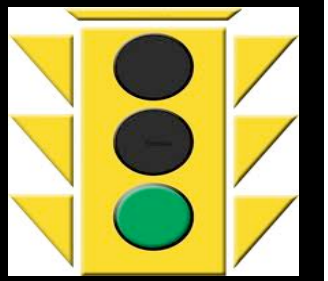
CD4+ BL 38 cell/uL, current 78 cell/ul



1st line HAART since 17 months

HIV-RNA < 20 copie/ml since 13 months

CD4+ 478



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- ✓ Una interazione farmacologica può essere imprevedibile e pertanto, seppur non segnalata in precedenza, deve essere sospettata in caso di eventi clinici e terapeutici inattesi in termini di tossicità ed efficacia [CIII].

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HIV Medicine (2008), 9, 389–396

REVIEWS IN ANTIRETROVIRAL THERAPY

Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature

MM Foisy,[1,2] EMK Yakiwchuk,[2] I Chiu[3] and AE Singh[3]

28 cases (25 inhlaed, 3 intranasal)

14 adults and 10 paediatric

Onset in 2.75 months – faster in HCV related cirrhosis (2)

Marked interaction in formal PK study:

Serum Fluticasone AUC increased 350-fold!

QUAL È LO STATO DELLA RICERCA?
STIAMO TENTANDO DI CAPIRE CHE MALATTIE VUOLE AVERE LA GENTE.