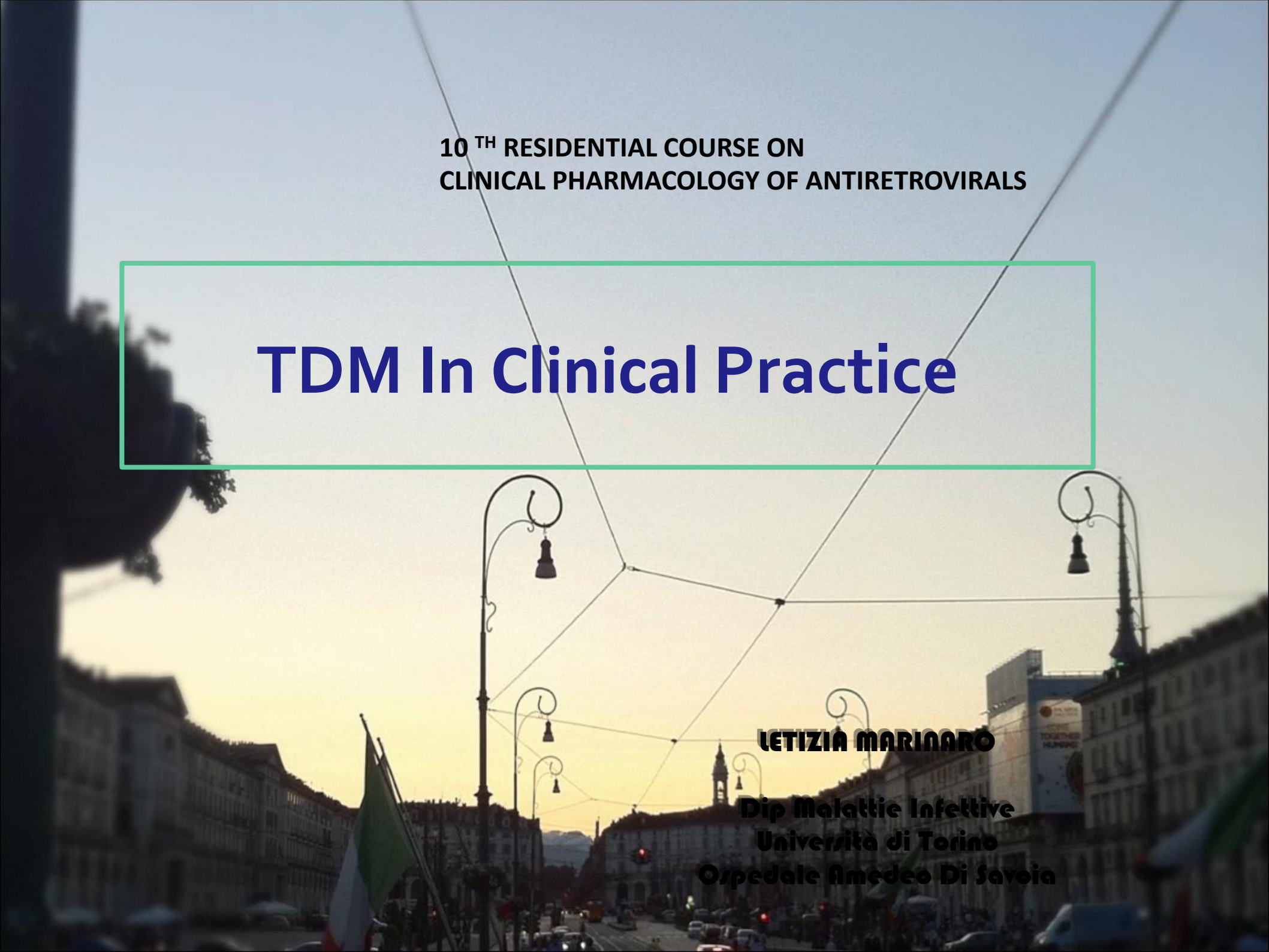


10 TH RESIDENTIAL COURSE ON
CLINICAL PHARMACOLOGY OF ANTIRETROVIRALS

TDM In Clinical Practice

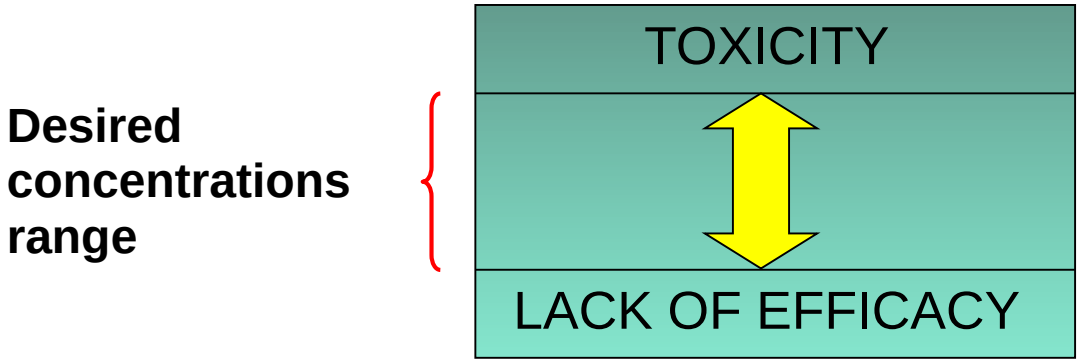
LETIZIA MARINARO

Dip Malattie Infettive
Università di Torino
Ospedale Amedeo Di Savoia

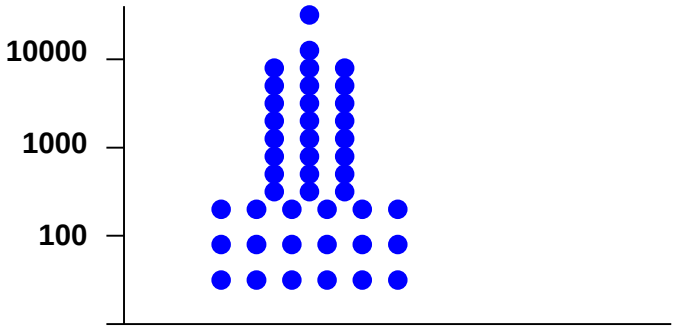
Therapeutic Drug Monitoring (Tdm) For Antiretroviral Agents

Rationale for TDM of antiretrovirals points on two **key features**:

- ✓ Relationship between drug concentration and immunovirological benefit and in some cases, toxicity



- ✓ Available clinical data show significant interpatient variability at equal dose intake



DHHS Guidelines 2014

TDM PROs

- Data showing that considerable **interpatient variability** in drug concentrations exists among patients who take the same dose
- Data indicating that relationships exist between the **concentration of drug** in the body and **anti-HIV effect** and, in some cases, **toxicities**
- Data from small prospective studies demonstrating that TDM **improved virologic response** and/or decreased the incidence of concentration-related drug toxicities .

DHHS Guidelines 2014

TDM CONs

- **lack of large prospective** studies demonstrating that TDM improves clinical and virologic outcomes
- **lack of established therapeutic** range of concentrations for all ARV drugs
- **intrapatient variability** in ARV drug concentrations
- lack of widespread availability of clinical laboratories
- **shortage of experts** to assist with interpretation of ARV concentration data.

Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs[2-9]	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1000
Nelfinavir[a] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1000
Nevirapine (NVP)	3000

[a] Measurable active (M8) metabolite

Table 10b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains	
Maraviroc (MVC)	>50
Tipranavir (TPV)	20,500
Median (Range) Trough Concentrations from Clinical Trials[12-14]	
Darunavir (DRV) (600 mg twice daily)	3300 (1255–7368)
Etravirine (ETR)	275 (81–2980)
Raltegravir (RAL)	72 (29–118)

Scenarios for use of TDM

(DHHS 2014, Italian Guidelines 2014, BHIVA 2014)

- Clinically significant drug-drug or drug-food interactions
- Changes in pathophysiological states that may impair GI, hepatic, or renal function, thereby altering PK
- Persons such as pregnant women who may be at risk for virological failure as a result of their PK characteristics
- Treatment experienced patients
- Use of alternative dosing regimens
- Concentration-dependent toxicities
- Lack of expected virological response

"We had a little trouble mixing your prescription. Can you stop back in 20 minutes?"

Risk of potentially clinically significant interactions

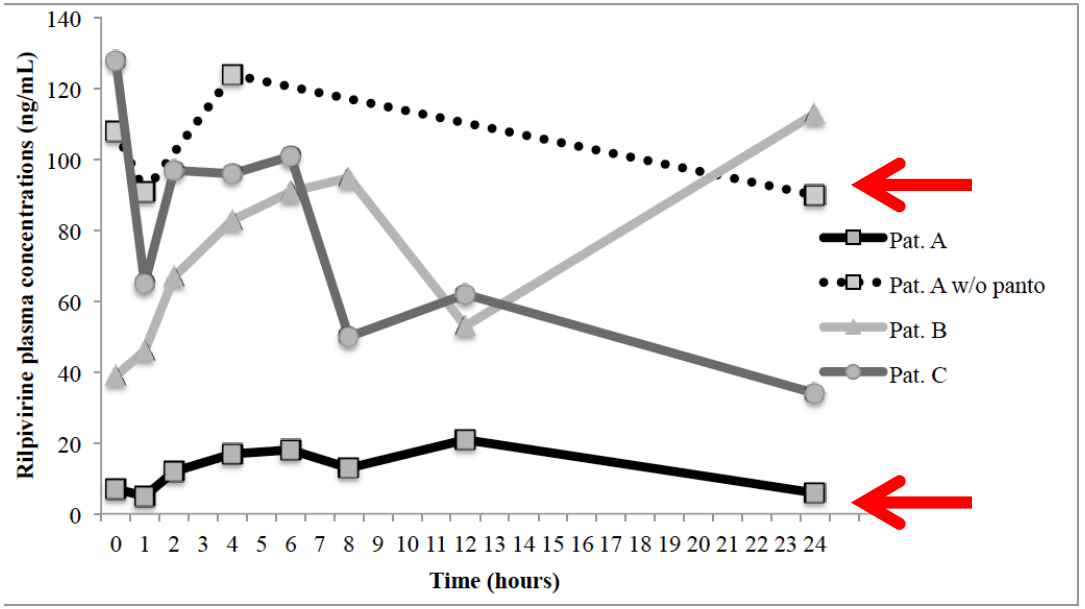
Study	Year	Setting	N	CSDI	Screening Tool	VL Effect
de Maat	2004	Netherlands (hospital)	115	26%	Liverpool website	N/A
Shah et al	2007	USA (Medicaid)	571	30%	Liverpool website; Micromedex	No VL impact
Miller et al	2007	USA (hospital)	153	41%	DHHS; PI; Micromedex	N/A
Evans-Jones et al	2010	UK (hospital)	159	27%	Liverpool website	N/A
Marzolini et al	2010	Switzerland (SHCS)	1497	40%	Liverpool website	No VL impact
Kigen et al	2011	Kenya (hospital)	996	34%	Liverpool website	N/A
Patel et al	2011	USA	190	34%	Lex-interact	N/A
Cordova et al	2013	Argentina	217	32%	Liverpool website	No VL impact
Seden K et al	2013	Uganda	2000	19%	Liverpool website	N/A

Shah et al. CROI 2007; Abstr 573
Miller et al. *Pharmacotherapy* 2007
Cordova E et al IAS 2013; MOPE031
Seden K et al; IAS 2013; MOPE035

Kigen et al. PLoS One 2011
Patel Ann Pharmacother 2011
Marzolini et al. *Antivir Ther* 2010

Rilpivirine and PPIs in HCV-coinfected pts

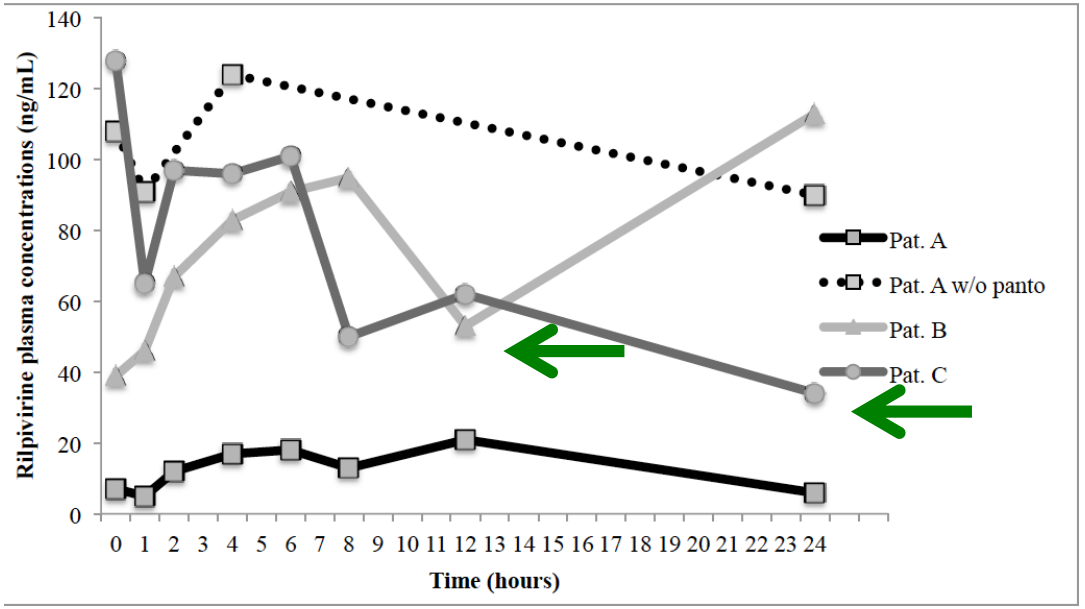
	AUC (ng h/mL)	Cmax (ng/mL)	Cmin (ng/mL)
Patient A	339	21	5
Patient A without pantoprazole	2562	124	90
Patient B	1901	113	39
Patient C	1518	128	34



A. Calcagno, in press

Rilpivirine and PPIs in HCV-coinfected pts

	AUC (ng h/mL)	Cmax (ng/mL)	Cmin (ng/mL)
Patient A	339	21	5
Patient A without pantoprazole	2562	124	90
Patient B	1901	113	39
Patient C	1518	128	34



In two patients, the degree of hepatic impairment (Child B and C) counterbalanced the decrease in drug absorption

A. Calcagno, in press

DDIs and Pharmacogenetics

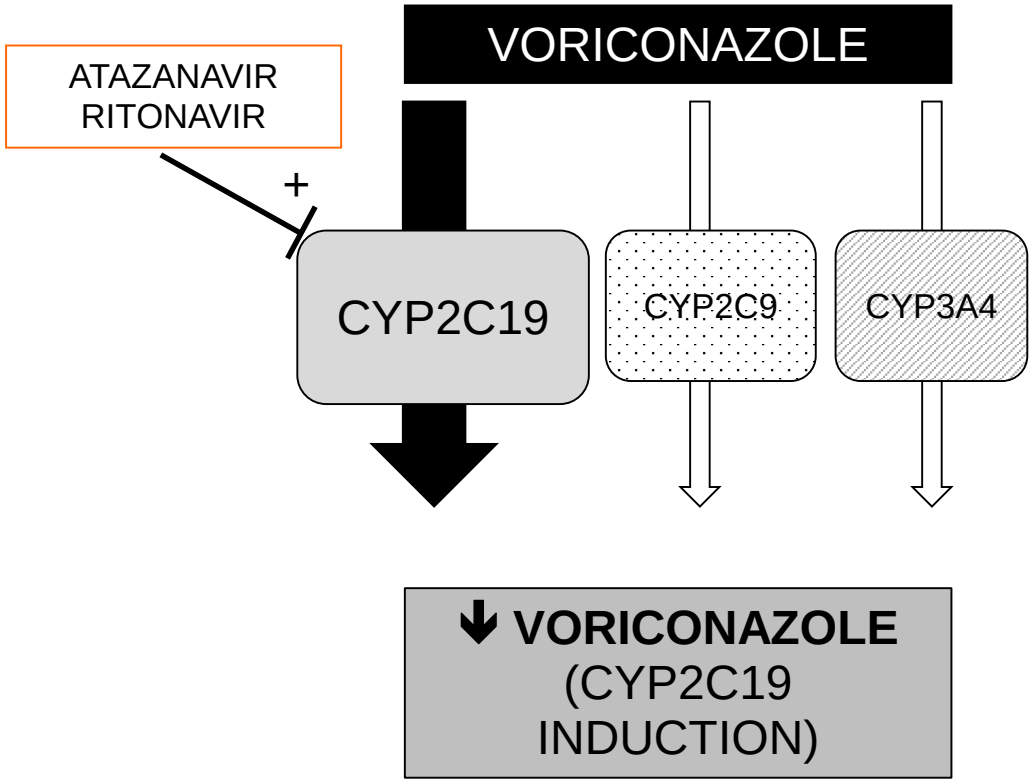
- Entity and “direction”of DDI determined by enzymes activity
- Interaction influenced by single nucleotide polymorphism (SNPs) of genes encoding for metabolizing enzymes

Calcagno et Al. Voriconazole and atazanavir: a CYP2C19-dependent manageable drug-drug interaction. Pharmacogenomics. 2014 Jul;15(10):1281-6.

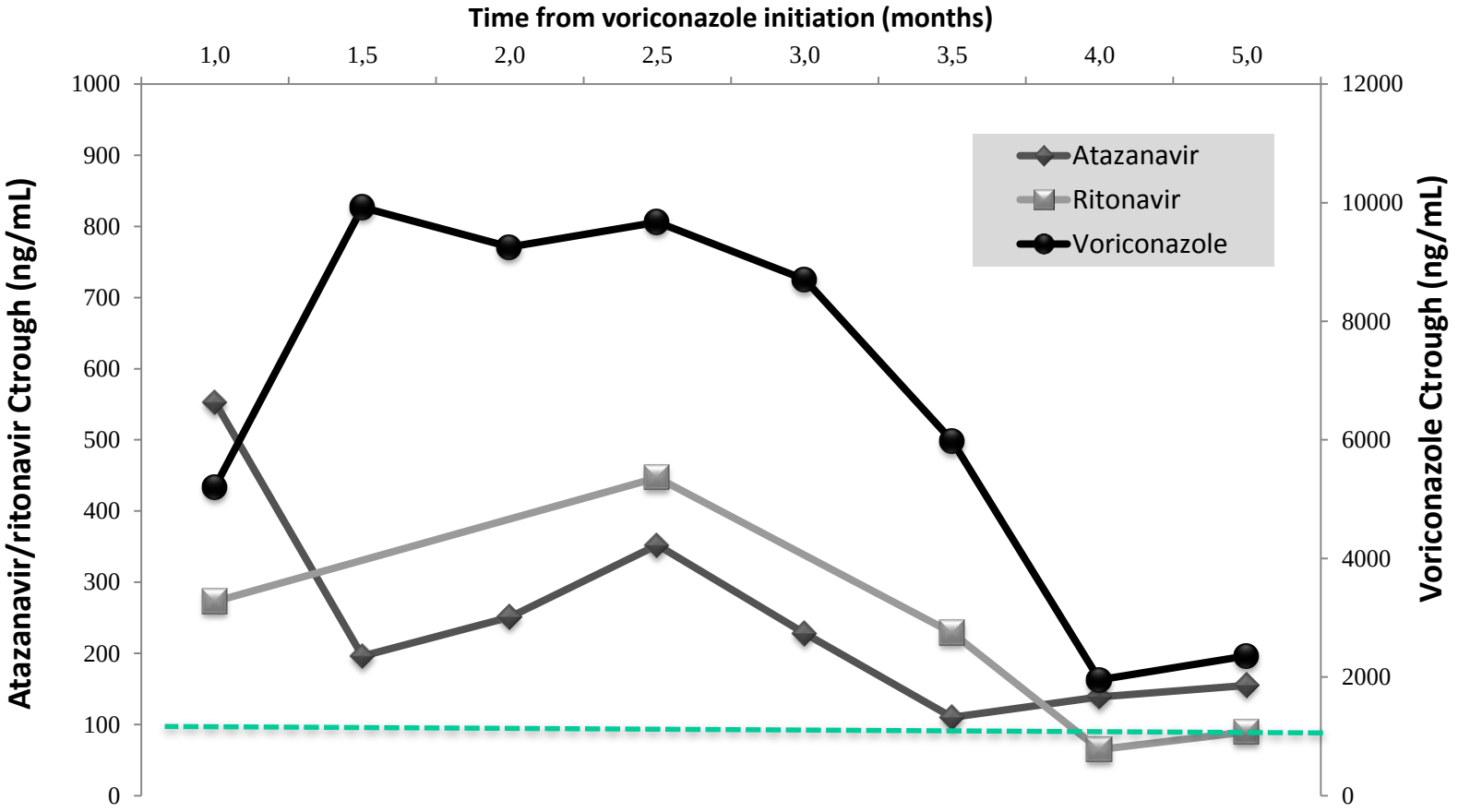
- VORICONAZOLE metabolized by CYP2C19 (lesser extent by CYP2C9 and CYP3A4)
- RITONAVIR **INDUCES** CYP2C19 (inhibits 2C9 and 3A4)
- **Coadministration contraindicated** due 40% VOR Ctrough reduction

DDIs and Pharmacogenetics
Ritonavir and Voriconazole

"Normal metabolizers"

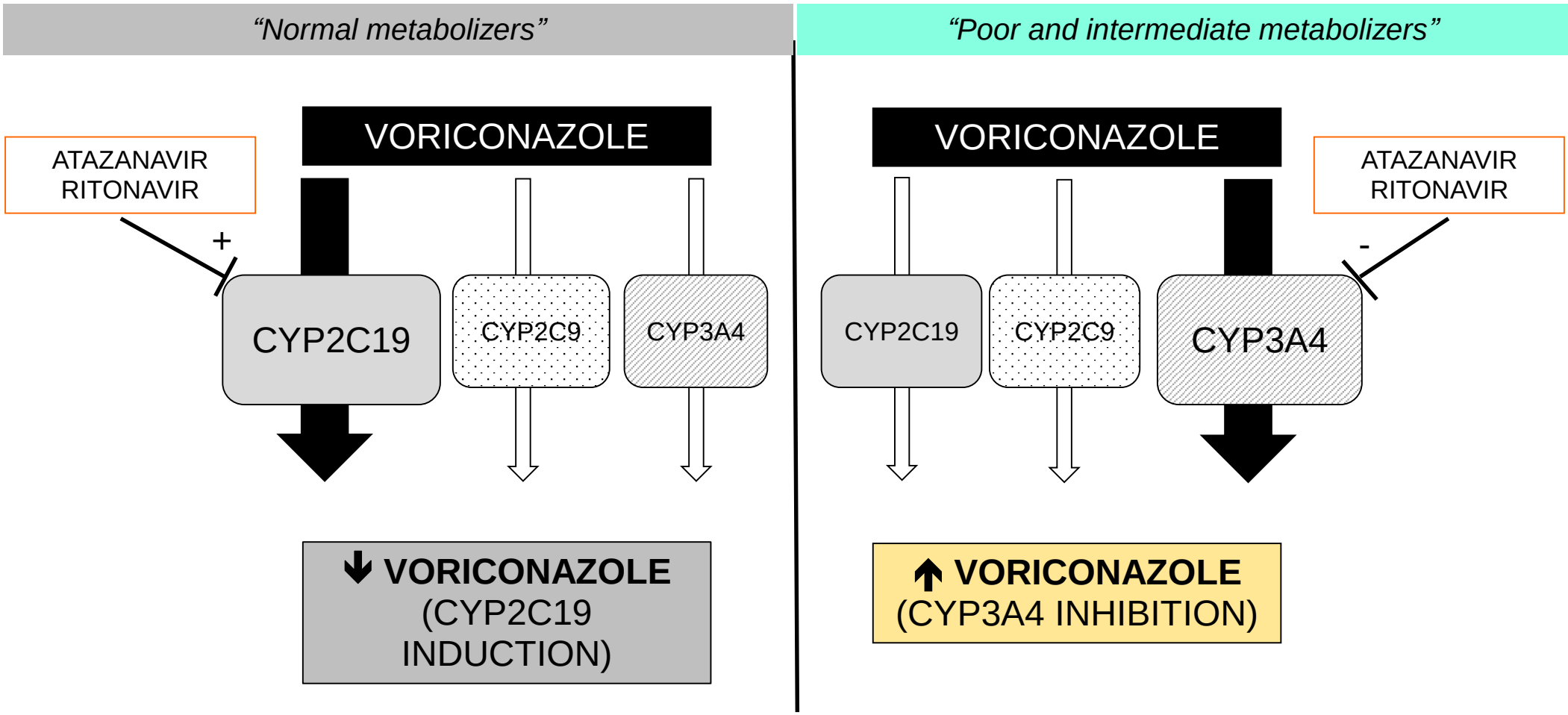


DDIs and Pharmacogenetics Ritonavir and Voriconazole



	1	1,5	2	2,5	3	3,5	4	5
ATV	553	196	251	352	228	110	139	155
RTV	273			447		229	65	90
VOR	5207	9921	9252	9673	8704	5984	1954	2357
dose VOR	**200x2**	**200x2**	**200x2**	**150x2**	**100x2**	**100x2**	**50x2**	**50x2**

DDIs and Pharmacogenetics
Ritonavir and voriconazole



Italian HIV Guidelines 2014

- ✓ **Magnitude of a known interaction is unpredictable** in single patient, therefore TDM can be useful to check individual extent of such interaction [CIII].

- ✓ **Net effect of multiple concomitant interactions is unpredictable, TDM is recommended** [CIII].

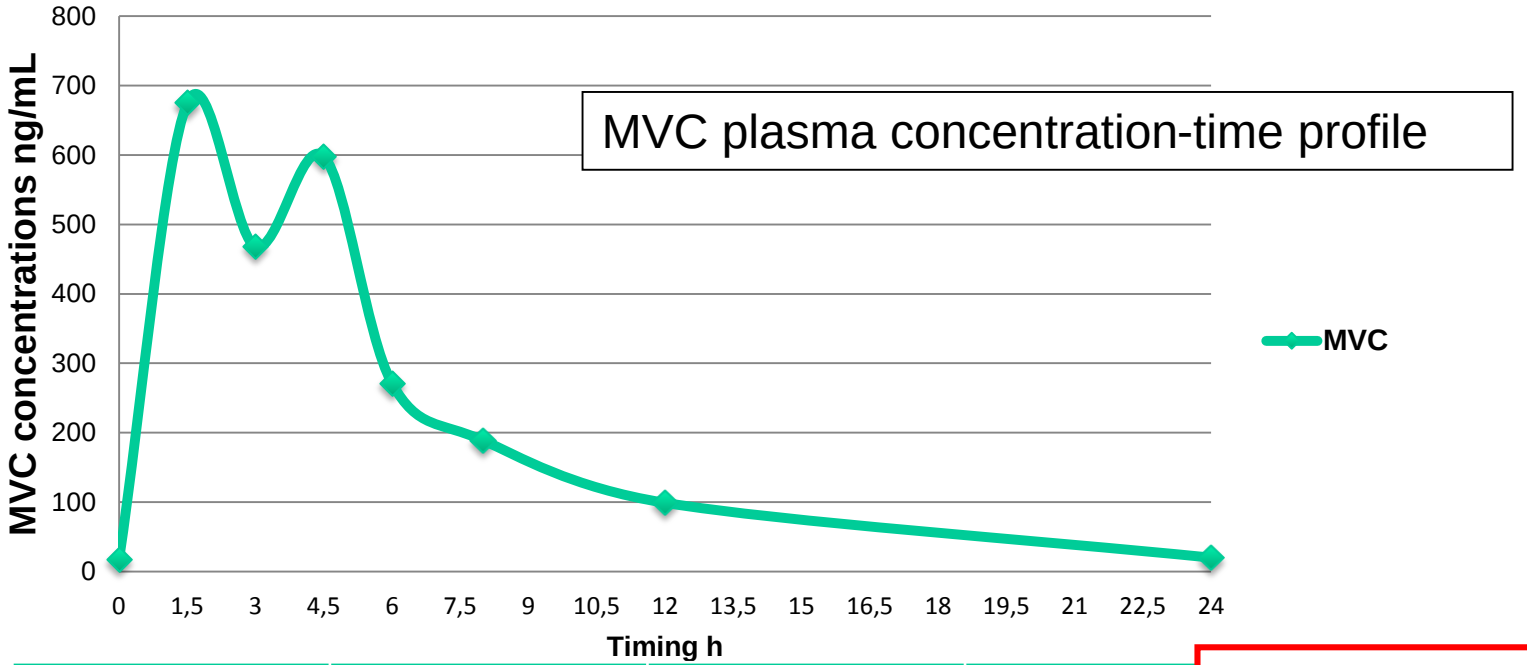
- ✓ CLINICAL SIGNIFICANCE of an interaction could vary according to individual clinical variables, such as:

- Genetic barrier of drugs involved
- Immuno-virological status of the patient
- Lenght of coadministration

- ✓ Combined evaluation of the latter with **TDM results** could allow the clinical management also of interactions otherwise considered at risk of therapeutical failure and/or toxicity

MVC+COBI ?

- No data available
- Maraviroc 300 mg QD + Stribild → COBI boosting effect



	AUCss	Cmin	Cmax
	ng/mL*h	ng/mL	ng/mL
MVC 300 QD	**4356**	**17**	**675**
MEC (naive MERIT)		**>25**	

Unconventional regimen

TDM at different timepoints confirms adequate plasma exposure

Italian HIV Guidelines 2013

- ✓ **Magnitude of a known interaction is unpredictable** in single patient, therefore TDM can be useful to check individual extent of such interaction [CIII].

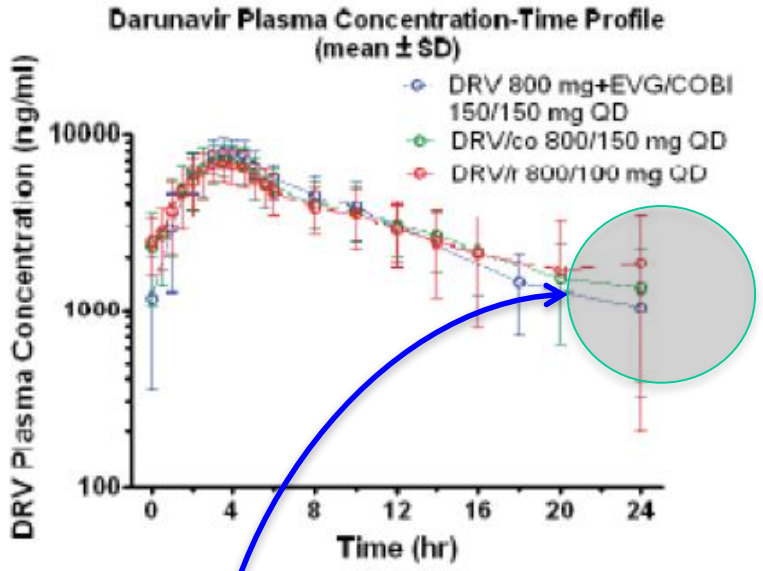
- ✓ **Net effect of multiple concomitant interactions is unpredictable, TDM is recommended** [CIII].

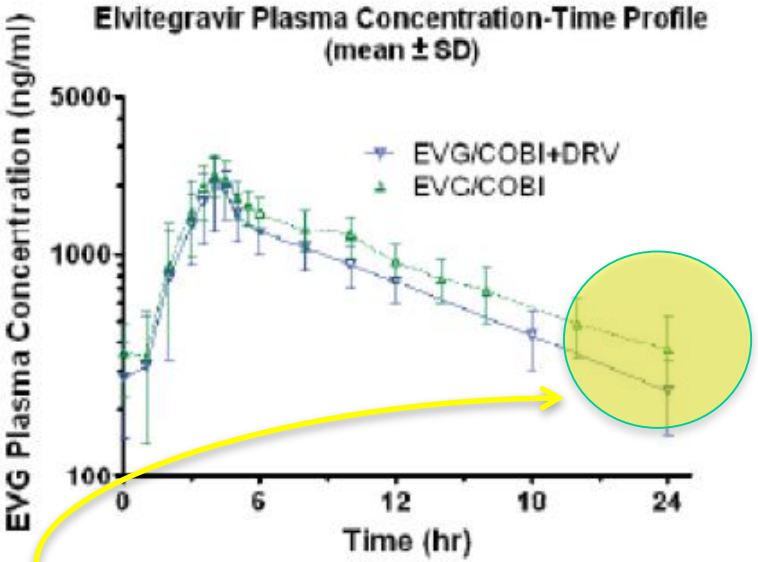
- ✓ CLINICAL SIGNIFICANCE of an interaction could vary according to individual clinical variables, such as:

- Genetic barrier of drugs involved
- Immuno-virological status of the patient
- Lenght of coadministration

- ✓ Combined evaluation of the latter with **TDM results** could allow the clinical management also of interactions otherwise considered at risk of therapeutical failure and/or toxicity

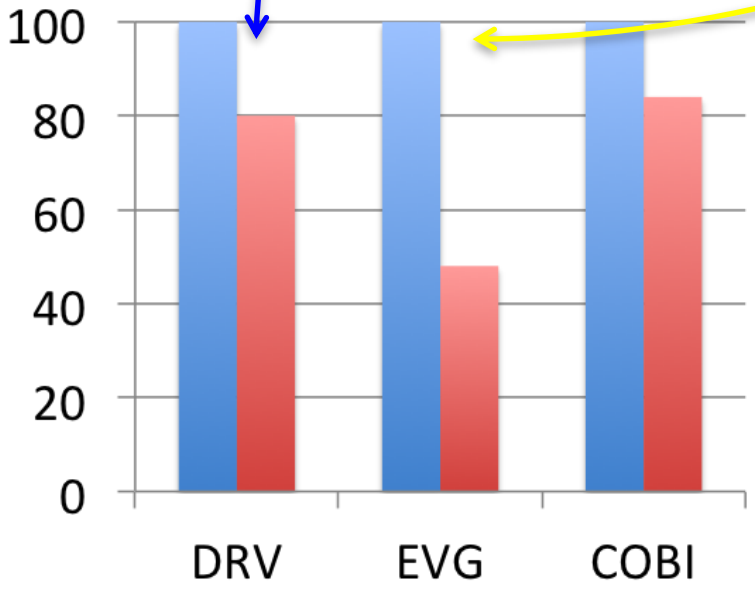
PROTEASE INHIBITORS + COBI ? STRIBILD + DRV 800



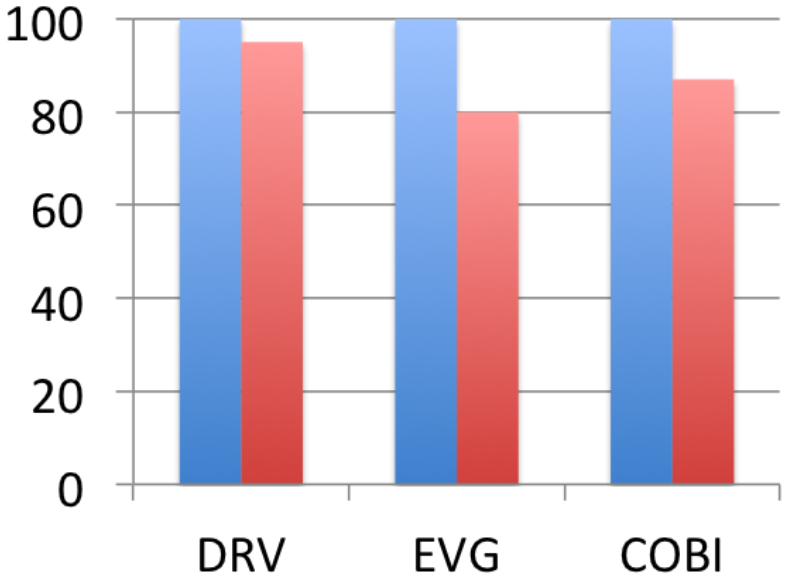


Ramanathan S, et Al 13th International Workshop on Clinical Pharmacology of HIV Therapy [poster P08].

Cmin



AUC

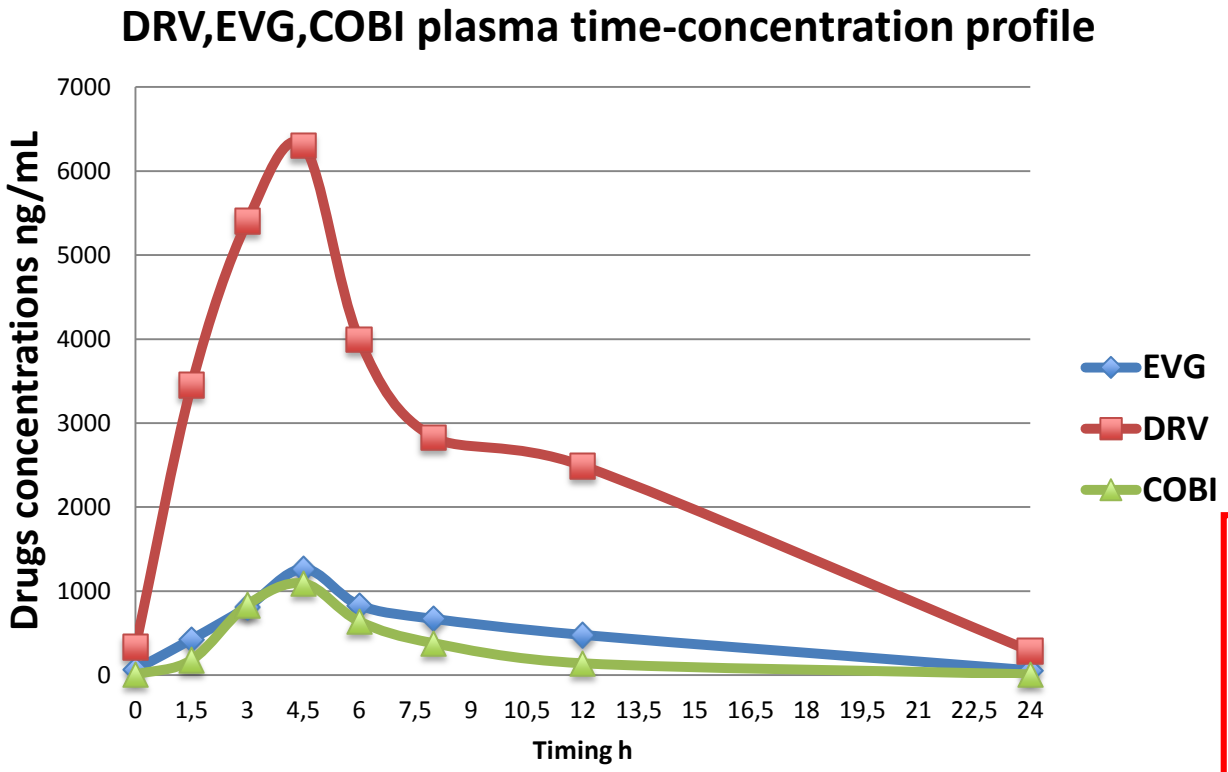


Ref

STRIBLD + DRV 800

PROTEASE INHIBITORS + COBI ? STRIBILD + DRV 800 QD

Patient with PHI



	T0	T1,5	T3	T4,5	T6	T8	T12	T24
DRV	334	3449	5405	6302	3996	2830	2491	287
EVG	68	426	812	1264	833	670	479	58
COBI	8	180	836	1092	640	380	141	10

Unconventional regimen

TDM confirms inadequate plasma exposure

DOSE OPTIMIZATION

CASE HISTORY

- Female, caucasian, 53 years old, HIV + since1986, nadir CD4+ 4 cells/mL
- Starts ARV 1996:

- 1996 AZT/3TC +IDV
- 1998 D4T+3TC+ SQV
- 1999 DDI+ D4T + EFV: DIZZINES
- 2001 AZT/3TC + LPV/RTV: GI SYMPTOMS
- 2004 AZT/3TC +EAP ATAZANAVIR/RTV improved GI SYMPTOMS
- **2006 TDF/FTC + ATV/RTV …HYPERBILIRUBINEMIA (3-4.5 mg/dL)**

UNSTABLE THERAPY ACCEPTABILITY DUE TO MAJOR DEPRESSIVE DISORDER

ATV dose optimization

- **Low-Dose, Once-Daily Atazanavir/Ritonavir (200/100): An Effective Treatment for HIV Infected Patients in Thailand**
  Chetchotisakd P, JAIDS 2008

- **Simultaneous Population Pharmacokinetic Modelling of Atazanavir and Ritonavir in HIV-Infected Adults and Assessment of Different Dose Reduction Strategies**
  Schipani A, JAIDS 2013

- **A Maintenance Dose of Atazanavir/Ritonavir 200/100 mg Once Daily Is Effective in Virologically Suppressed HIV-1–Infected Patients**
  Lanzafame M, JAIDS 2013

ATV dose optimization

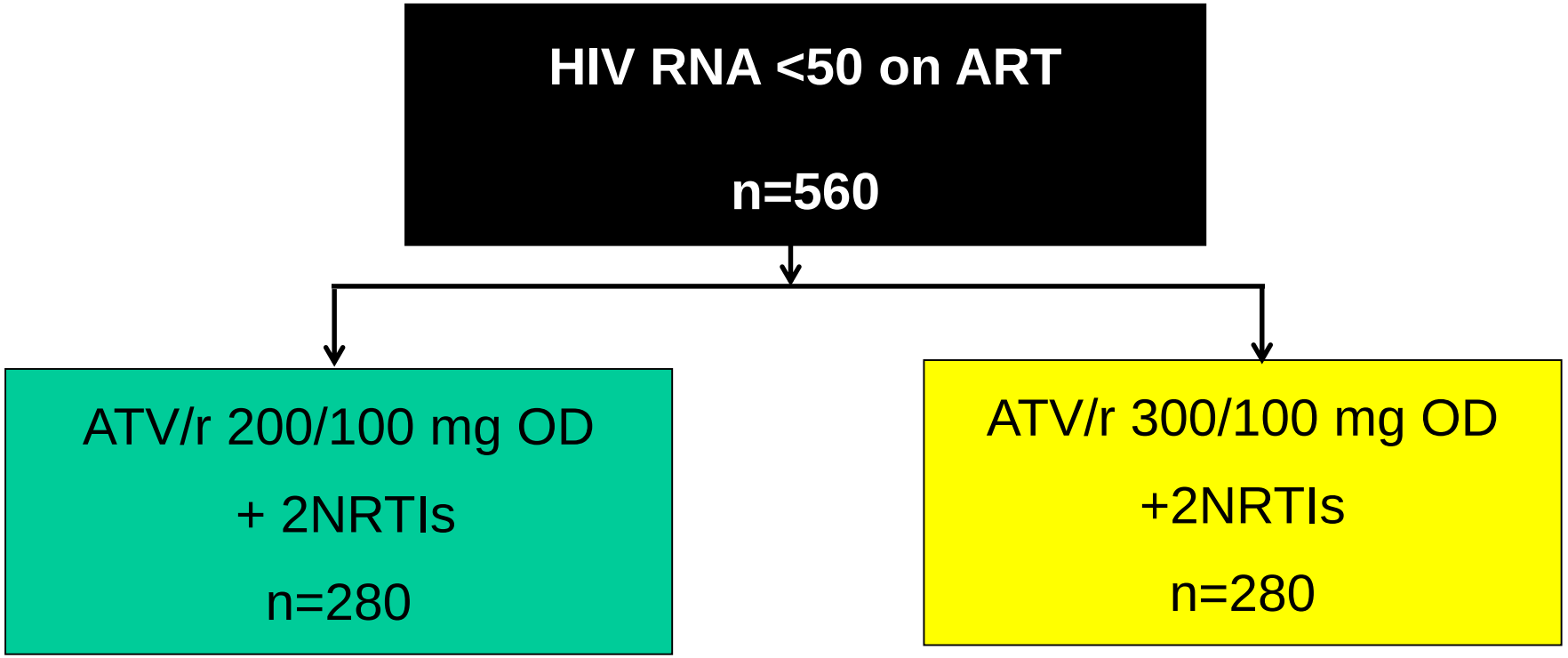
JAN 2012 : TDF/FTC + ATV/RTV

- **HIV RNA not detectable, CD4+ 750 cells/µl, 35%**
- BMI 20, hyperbilirubinemia 3.50 mg/mL, complains of scleral jaundice
- TDM : C trough ATV 799 ng/mL, RTV 59 ng/mL

March 2012: ATV 200/RTV100+TDF/FTC

	PCR HIV	CD4+	BIL TOT	Ctrough ATV	Ctrough RTV
Jul 2012	<20	689	1.56		
Dec 2012	<20	730	0.63		
Jun 2013	Not detectable	917	1.88		
Dec 2013	Not detectable	650	2.01	345 ng/mL	76 ng/mL
May 2014	Not detectable	584	1.75		
Oct 2014	Not detectable	874	1.28	380 ng/mL	

LASA trial: ongoing



Patients enrolled in Thailand. Maintenance trial, with primary analysis at Week 48 (HIV RNA suppression endpoint). Estimated Primary Completion Date: December 2014

ATV dose optimization

- Reduced ATV dosing to 200 + RTV100: effective option in induction maintenance strategy
- Better compliance and tolerance due to reduced bilirubin levels
- Diminished risk of renal stones given the suggested correlation between stones development and ATV exposure
- Lowering dose could provide significant cost containment in resource-limited settings

"Frankly, darling, I think your doctor is a little obsessive about this compliance thing."

Drug schedule and polymedication

- 74-years old, diabetes, hypertension, IMA
- TDF/FTC + ATV/RTV, fully suppressed since 3 years, last VLs 230-350 copies/ml
- Insulin, aspirin, bisoprolol, rosuvastatin 10 mg, furosemide

Drug schedule and polymedication

Doc: “What’s going on, dear patient, are you sure you’re always taking your pills as I told you?”

PT:“It’s true, doctor, I’m taking all my pills well!”

- TDM: ATV $_{C12h}$ 170 ng/ml (lower than expected)

Doc: “What’s going on, dear patient, are you sure you’re always taking your pills as I told you?”

PT:“I’m fully adherent, every single day I take Truvada and Norvir in the morning and Reyataz in the evening”

Doc: “……!”

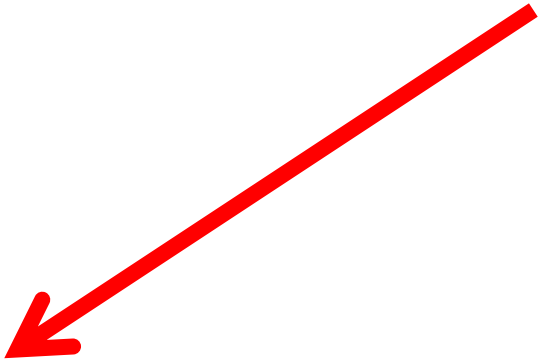
Treatment failure & adherence

TDM can:

- confirm poor adherence (low or undetectable)

TDM cannot:

- confirm good adherence



Adequate concentration may only indicate patient has taken medications shortly before visit

Challenges for TDM

- Knowledge of therapeutic ranges for ARVs (for wild type HIV and viruses with ↓ susceptibility)
- Widespread availability of quality controlled laboratories and timing of TDM results
- Interpretation and lack of dose adjustment strategies
- Lack of powered, prospective, controlled trials to demonstrate TDM improves outcome

Future of TDM

- Evaluating TDM by RCT difficult: TDM must be integrated with all clinical factors
- ARVs are for life, on individual basis TDM can be a useful clinical tool
- Current drug levels for long term clinical response are not defined – studies warranted
- TDM-guided cost saving strategies

Acknowledgments

All the Staff of the Infectious Diseases Unit, University of Turin, Ospedale Amedeo Di Savoia

In particular:
Prof. Giovanni Di Perri
Prof. Stefano Bonora

A special thanks to
Doctor Andrea Calcagno for clinical data and slides kindly made available.

Chiara Alcantarini
Sabrina Audagnotto
Roberto Bertucci
Lucio Boglione
Paolo Bigliano
Marino Bonasso
Margherita Bracchi
Chiara Cardellino
Giuseppe Cariti
Sinibaldo Carosella
Silvia Corcione
Cecilia Costa
Micol Ferrara
Filippo Lipani
Anna Lucchini
Maurizio Milesi
Chiara Montrucchio
Simone Mornese
Ilaria Motta
Giancarlo Orofino
Nicole Pagani
Francesca Patti
Stefania Raviolo
Bernardino Salassa
Silvia Scabini
Maria Elisabetta Scarvaglieri
Maria Laura Stella
Maria Cristina Tettoni
Alice Trentalange
Laura Trentini

All the Staff of the Clical Pharmacological Laboratory

In particular:
Antonio D'Avolio
Sara Allegra
Alessandra Ariaudo
Lorena Baietto
Jessica Cusato
Amedeo De Nicolò
Debora Pensi
Marco Simiele
Mauro Sciandra

All the Staff of the Molecular Biology Laboratory

In particular:
Valeria Ghisetti
Tiziano Allice
Tina Ruggiero
Maria Grazia Milia