15th Residential Course on Clinical Pharmacology of Antiretrovirals

Turin, January 15-17, 2020

MANAGEMENT OF POLYPHARMACY AND DDIs
A case-based discussion

Micol Ferrara
Clinica di Malattie Infettive
Università degli Studi di Torino
Ospedale Amedeo di Savoia

A.B.

CLINICAL CASE

- 48 yrs Caucasian female
- Diagnosis of Oligophrenia
- Borderline personality disorder
- HIV+ since 1999, no previous medical records
- Effective Phisical Protection Regime since 2010, frequent relocations in various Infectious Diseases Hospitals in Italy
- Living in a Residential Care Facility (Community housing)
- Scarse adherence to Antiretroviral Therapy
- Followed in our Centre since 2014 → HIV-RNA: 1857 cp/mL, CD4+: 681 cell/µl, 47%, ratio 1.4; Clade B;

NRTI: K65R;

NNRTI: Y181CY, V108I, H221H

PI: none

INSTI: none

ARV Therapy

DRV/RTV 600/100 mg BID + TDF/FTC + ETR 200 mg BID

2015 : increasing proteinuria 24h (no sign of tubulopathy)

Pharmacokinetics and antiretroviral response to darunavir/ritonavir and etravirine combination in patients with high-level viral resistance

Marta Boffito[a], Alan Winston[a], Akil Jackson[a], Carl Fletcher[a],

AIDS. 21(11):1449–1455, JULY 11TH, 2007

Parameter	
Sex: male/female	8/2
Median age [years (range)]	43 (38–56)
Race: Black/Caucasian	3/7
Median viral load [$\log_{10}$ copies/ml (range)]	4.6 (3.9–5.5)
Median CD4 cell count [cells/μl (range)]	75 (3–490)
Therapy-associated mutations [median (range)]	
NRTI	7 (2–9)
NNRTI	2 (0–6)
Primary PI	4 (0–5)
PI resistance-associated mutations	11 (2–13)

A.B.

Comedications

HIV+ → DRV/RTV 600/100 mg BID + Etravirine 200 mg BID

Dyslipidemia → Rosuvastatin 5 mg 1 cp

Psychiatric disorder → Frequent therapy modification

Citalopram 10 mg 1 cp
Delorazepam 2,5 mg

→ Citalopram
Paroxetine
Pregabalin

→ Paroxetine
Aripiprazole
Pregabalin
Flurazepam

→ **July 2018**

Pregabalin
Quetiapine
Trazodone
Citalopram

Total ACB Score: 3 **High Risk**

http://www.acbcalc.com

TOT 13: 7 + 6

PLOS ONE | RESEARCH ARTICLE October 2018

Anticholinergic burden in adult and elderly people with intellectual disabilities: Results from an Italian multicenter cross-sectional study

Luc Pieter De Vreese[1,2☯], Ulrico Mantesso[2☯], Elisa De Bastiani[2‡], Annachiara Marangoni[2‡], Elisabeth Weger[2‡], Tiziano Gomiero[2☯*]

«Over one-third (35.5%) of the people reported anticholinergic activity medicines, with 11.2% exposed to a total cumulative ACB score of 3+ (ACB score 3: n = 16; ACB score 4: n = 12, ACB score 6: n = 3).

Those living in ID specific small or large generic residential settings and those with mental health and neurologic conditions were much more likely to have higher AC exposure.»

ARV Therapy

DRV/RTV 600/100 mg BID + TDF/FTC + ETR 200 mg BID

2015 : increasing proteinuria 24h (no sign of tubulopathy)

→ STOP TDF/FTC

DRV/RTV 600/100 mg + ETR 200 mg BID

Katlama et al. *J Antimicrob Chemother 2019; 74: 2742–2751*

Dual therapy combining raltegravir with etravirine maintains a high level of viral suppression over 96 weeks in long-term experienced HIV-infected individuals over 45 years on a PI-based regimen: results from the Phase II ANRS 163 ETRAL study

→ STOP PIs

RAL 400 mg BID + ETR 200 mg BID

DDI with comedications

HIV Drug Interactions

UNIVERSITY OF LIVERPOOL

	DTG	ETV
Citalopram	◆	▲
Pregabalin	◆	◆
Quetiapine	◆	■
Trazodone	◆	■

July 2018: DTG + ETR

1_DDI between DTG and ETR

Effects of Etravirine Alone and with Ritonavir-Boosted Protease Inhibitors on the Pharmacokinetics of Dolutegravir[▽]

Ivy Song,[1] Julie Borland,[1] Sherene Min,[1] Yu Lou,[1] Shuguang Chen,[1] Parul Patel,[1] Toshihiro Wajima,[2] and Stephen C. Piscitelli[1]*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3517–3521

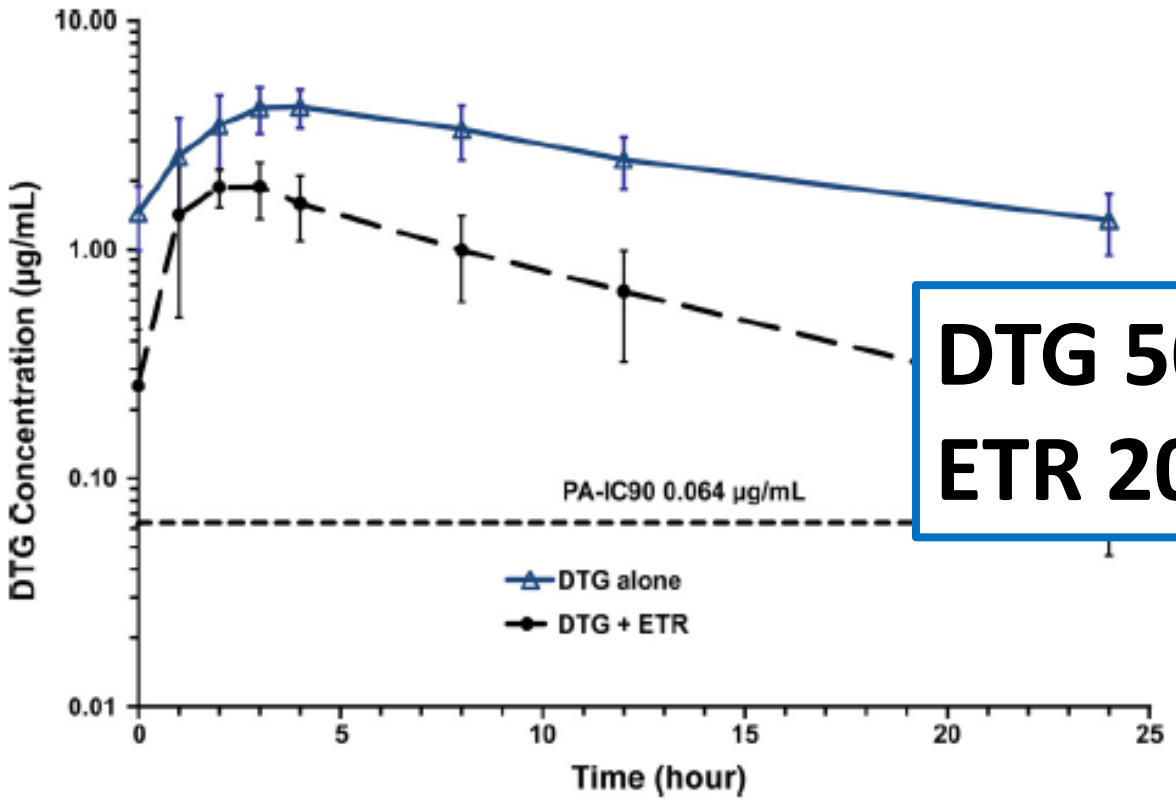
Clinical Pharmacokinetics and Pharmacodynamics of Etravirine: An Updated Review

Joshua P. Havens[1,2] · Anthony T. Podany[2] · Kimberly K. Scarsi[1,2] · Courtney V. Fletcher[1,2]

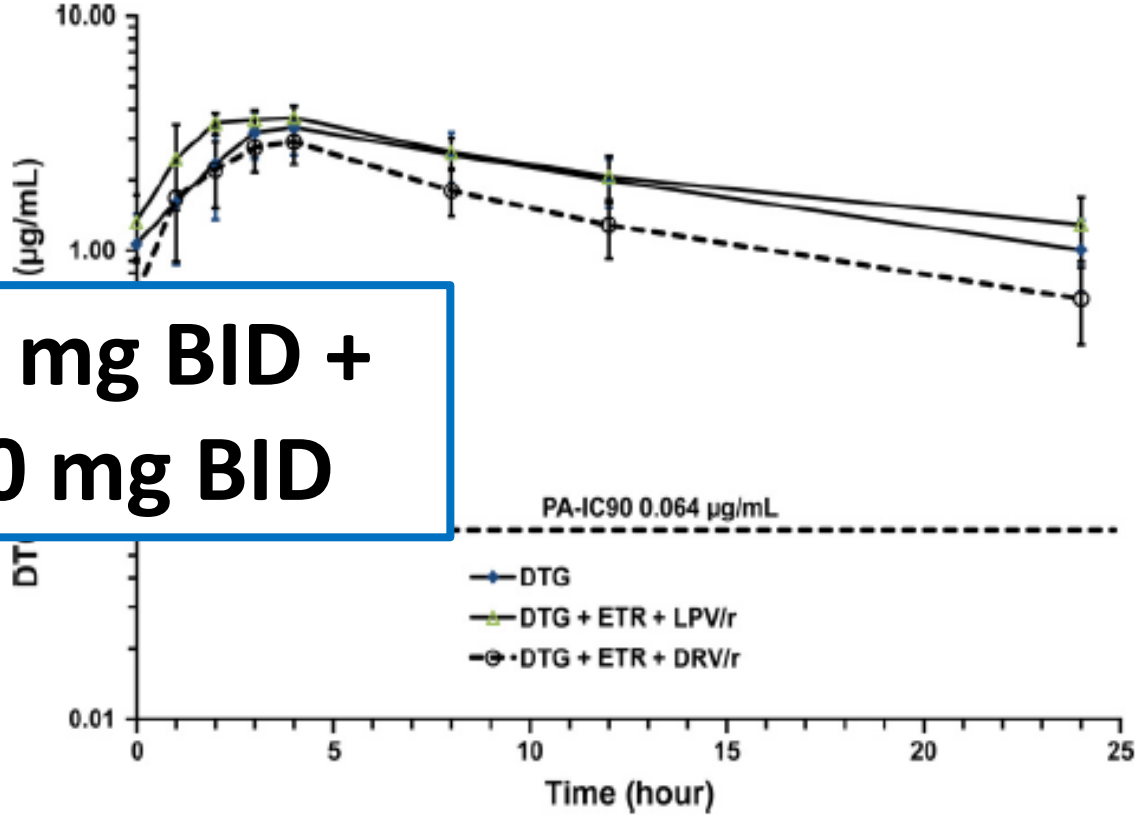
Clinical Pharmacokinetics 2019

Drug Transporters
NOT p-glycoprotein inhibitor,
NOT ABC transporters substrate
BCRP/ABCG2 both an inducer and inhibitor

Cytochrome
CYP3A4, CYP2C9, and CYP2C19 substrate
CYP3A inducer
CYP2C9 and CYP2C19 inhibitor



DTG 50 mg BID + ETR 200 mg BID



Dolutegravir (50 mg daily) combined with etravirine (200 mg twice daily) resulted in a 71% and 88% decrease in dolutegravir AUC and C24 , respectively

CONCLUSIONS: The combination of DTG and ETR alone should be avoided, DTG can be coadministered with ETR/DRV/RTV with no dose adjustment.

September 2018: Balanced Psychiatric disorder
Improvemente in mood

REVISION PSYCHIATRIC THERAPY

- Pregabalin
- Quetiapine
- Trazodone
- Citalopram

- VALPROATE Since 2 months

→**HIV-RNA**: 550 cp/mL
→**TDM**
→**Genotyping Resistance Test**: No INSTI resistance

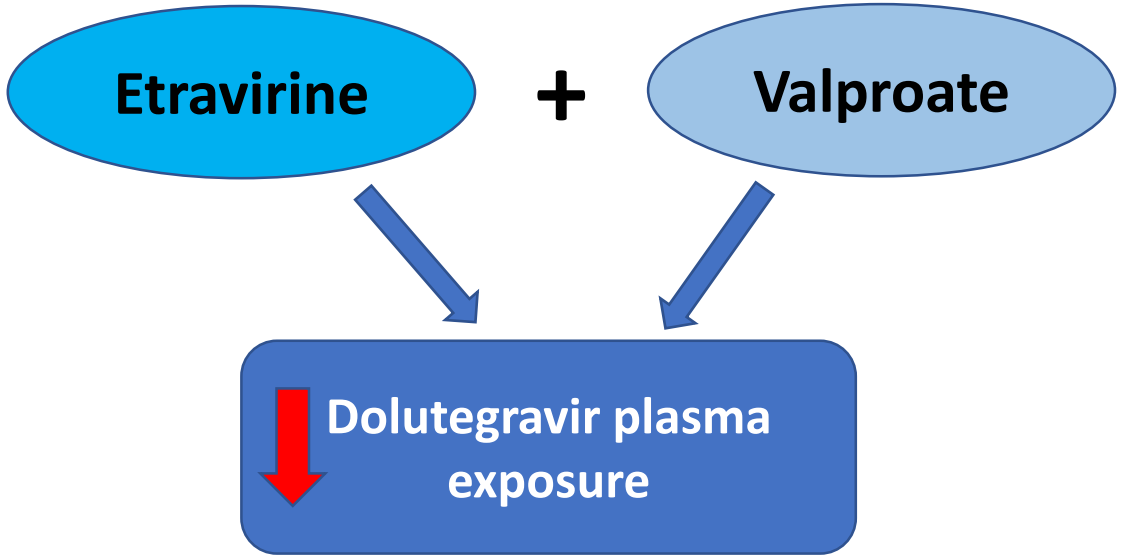
DTG 50 mg + ETR 200 mg BID

Palazzo A.et al
Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid
Journal of Antimicrobial Chemotherapy, 2018

2_DDI between Valproate and Dolutergravir

TDM September 2018

Plasma Ctrough (ng/mL)	A.B.	Havens et al. (2019) *	Song I. et al (2011)**
ETR	931	297 (75-2710)	
DTG	105		160



Treatment regimen	*n*	Geometric mean (CV%)[a]		
		$AUC_{0-\tau}$ (μg · h/ml)	C_{max} (μg/ml)	C_{τ} (μg/ml)
DTG	15	60.4 (22)	4.34 (19)	1.29 (29)
DTG + ETR	15	17.8 (39)	2.10 (24)	0.16 (84)

*J. P. Havens et al. «Clinical Pharmacokinetics and Pharmacodynamics of Etravirine: An Updated Review» (adapted from the IMPAACT 1090, PIANO, and DUET trials) *Clinical Pharmacokinetics 2019*

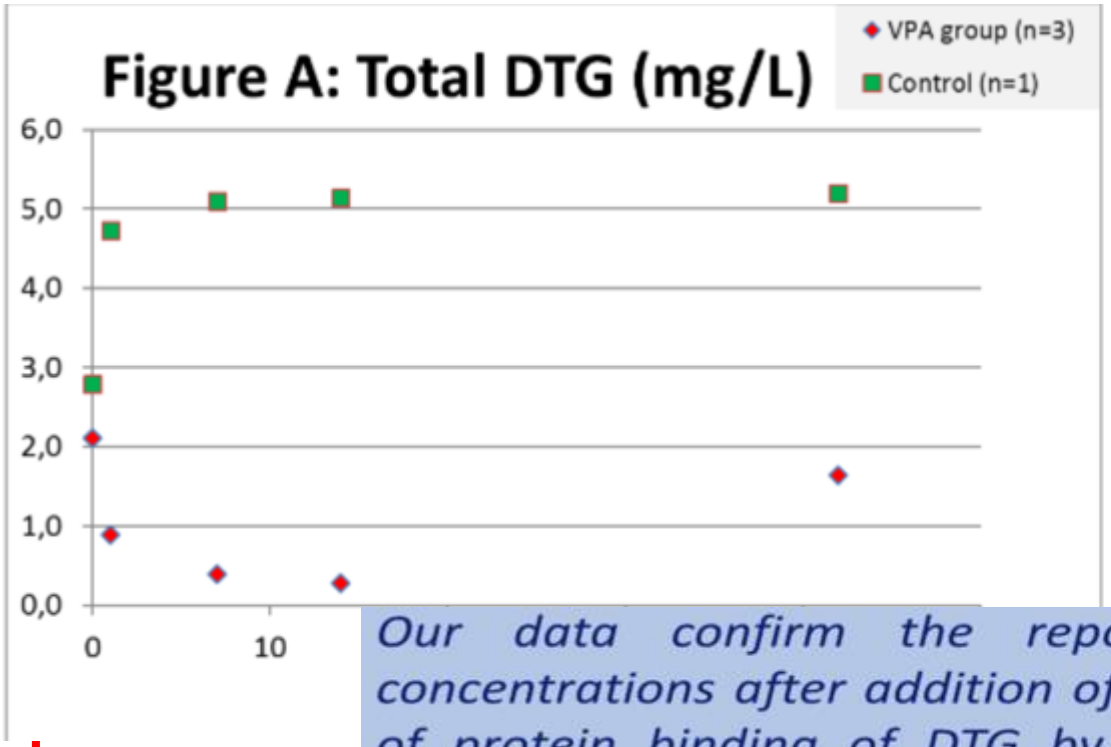
** Song I. et al. «Effects of Etravirine Alone and with Ritonavir-Boosted Protease Inhibitors on the Pharmacokinetics of Dolutegravir» *ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011*

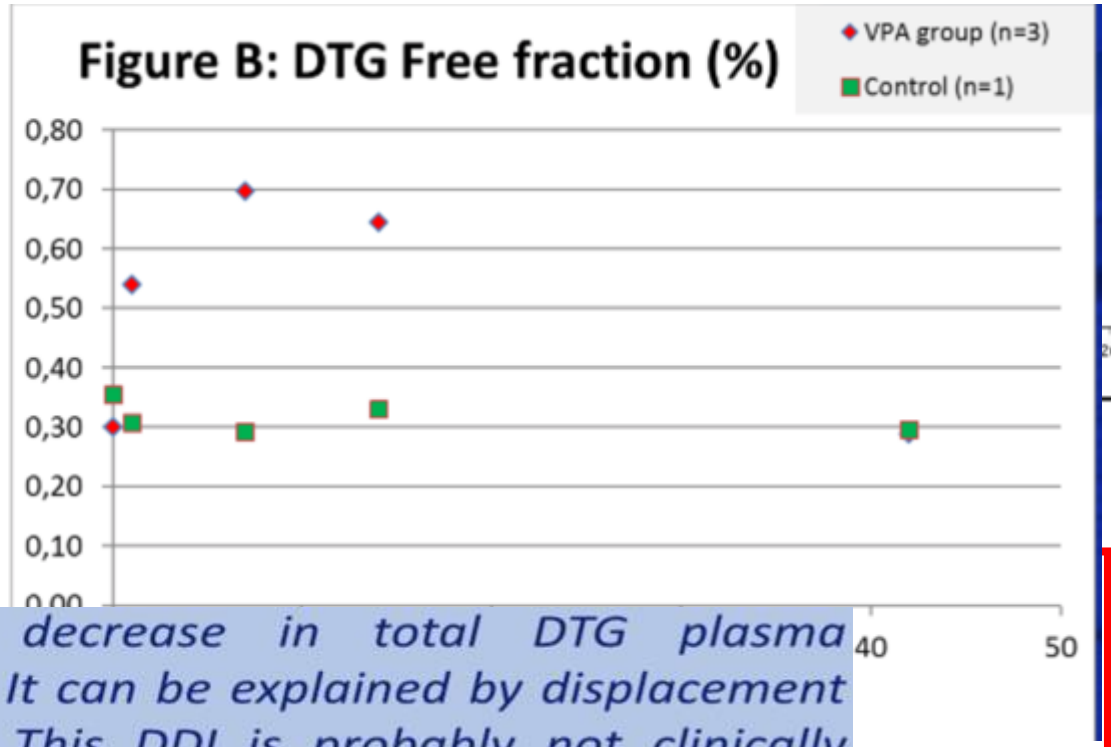
Drug interactions are not always predictable: the curious case of valproic acid and dolutegravir and a possible explanation

Alice
AIDS

The valproic acid - dolutegravir drug-drug interaction is based on displacement of protein binding and unlikely to be clinically relevant

H. Prins qt al. PK Workshop 2019, EACS 2019



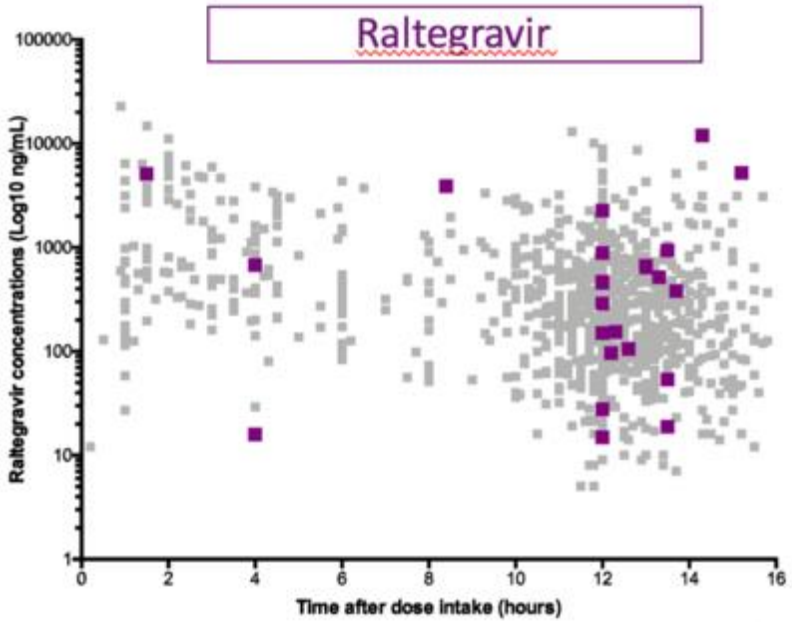


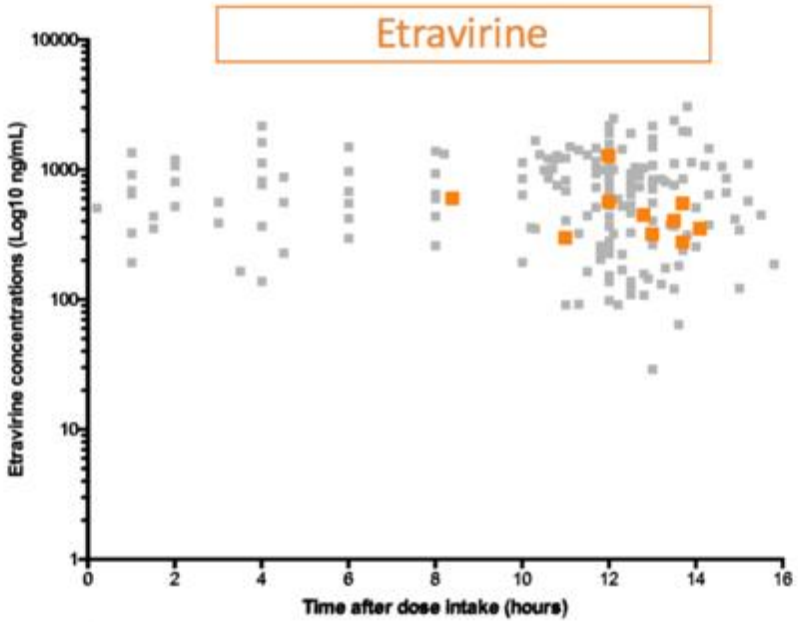
Our data confirm the reported decrease in total DTG plasma concentrations after addition of VPA. It can be explained by displacement of protein binding of DTG by VPA. This DDI is probably not clinically relevant.

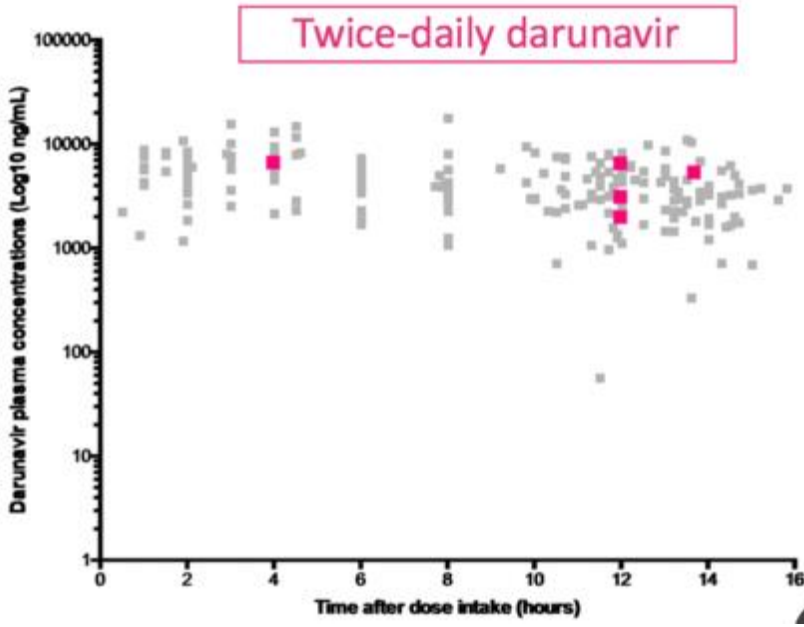
Valproic Acid Co-administration and Antiretrovirals' Exposure in a Therapeutic Drug Monitoring Registry

Calcagno A, Cusato J, Ferrara M, De Nicolò A, Lazzaro A, Manca A, D'Avolio A, Di Perri G and Bonora S.

submitted to JAC







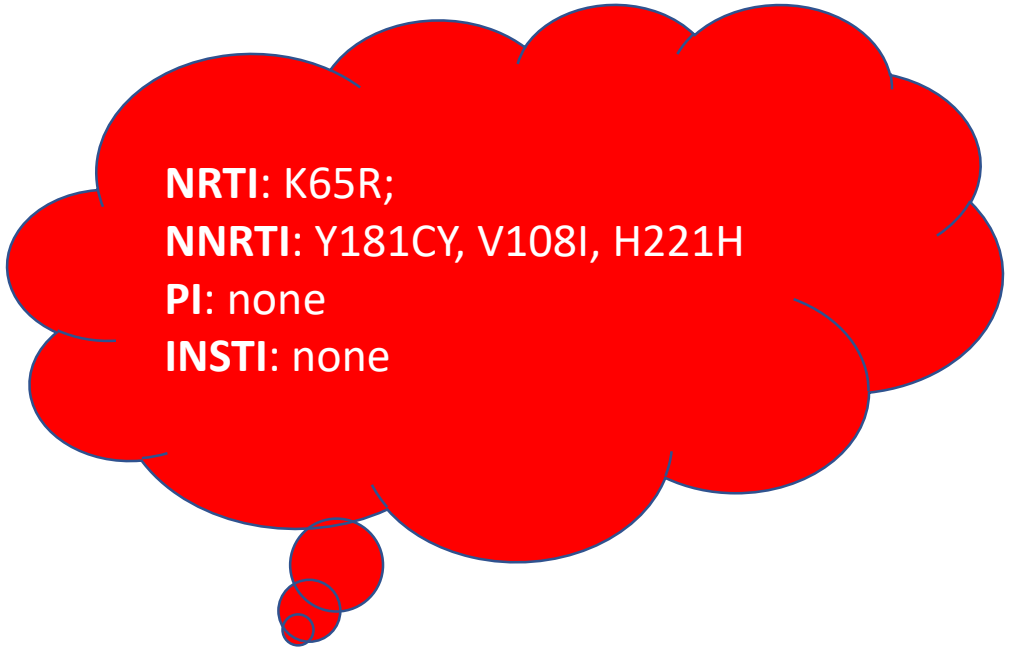
Conclusion: Variable binding to plasma proteins (raltegravir 83%, atazanavir 86%, darunavir 95%, etravirine 99.9%) No reduction observed in these ARVs' exposure comparable to the one observed with dolutegravir.

Lack of a clear effect on highly protein-bound compounds suggest that protein displacement may not be the only mechanism underlying the dolutegravir-valproic acid interaction.

ARV Therapy

DTG 50 mg BID + ETR 200 mg BID

STOP DTG
Reintroduction of PI



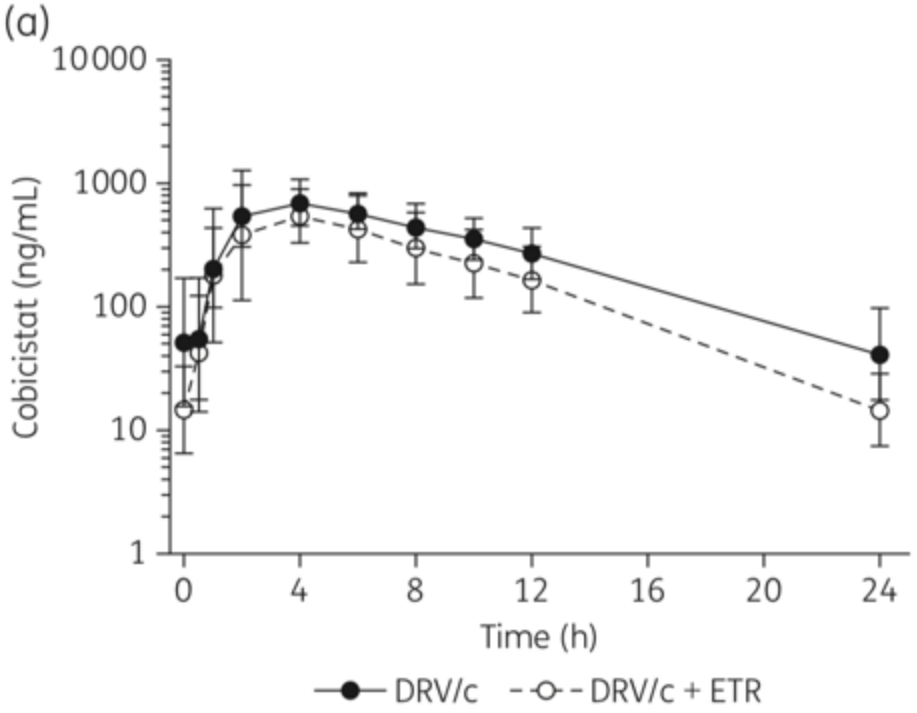
ETR 200 mg BID + TAF/FTC/DRV/COBI QD + DRV/COBI 800/150 mg QD

3_DDI between Cobicitstat and Etravirine

Pharmacokinetics of darunavir/cobicistat and etravirine alone and co-administered in HIV-infected patients

José Moltó[1–3], Adrian Curran[3,4], Cristina Miranda[1], Elizabeth Challenger[5], José Ramón Santos[1,2], Esteban Ribera[3,4], Saye Khoo[5], Marta Valle[3,6]

J Antimicrob Chemother 2018;



	Cobicistat		
	day 0 (reference)	day 14 (test)	LSM ratio (90% CI)
C_{max} (ng/mL)	822.7±269.0	689.7± 170.2	0.86 (0.75–0.98)
AUC_{0-24} (ng·h/mL)	7736.4±2951.7	5490.0± 1900.4	0.70 (0.56–0.87)
C_{24} (ng/mL)	63.1±83.1	17.3± 10.6	0.34 (0.23–0.50)
$t_{1/2}$ (h)	5.3±3.2	3.6± 0.6	–

- Unchanged ETR pharmacokinetics by DRV/COBI
- Decrease in cobicistat exposure and C24 when DRV/COBI was co-administered with ETR.
- Boosting DRV with RTV instead of with COBI may be preferred if DRV is to be combined with ETR in clinical practice.

ARVs TDM

	Plasma Ctrough (ng/mL)	*Reference Liverpool HIV drug inteactions QD*
ETR 200 mg BID	1206	297 (75-2710)
DRV 800 mg BID	4245	2043±1257 **QD**
COBI 150 mg BID	104	70±70 **QD**
FTC 200 mg QD	103	90 ± 70

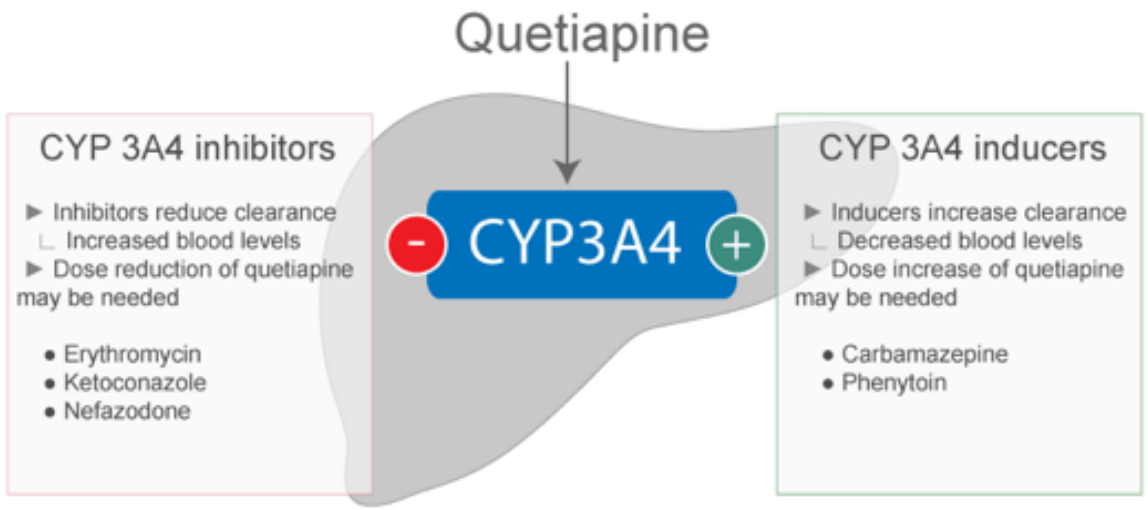
DON’T FORGET COMEDICATIONS!!!

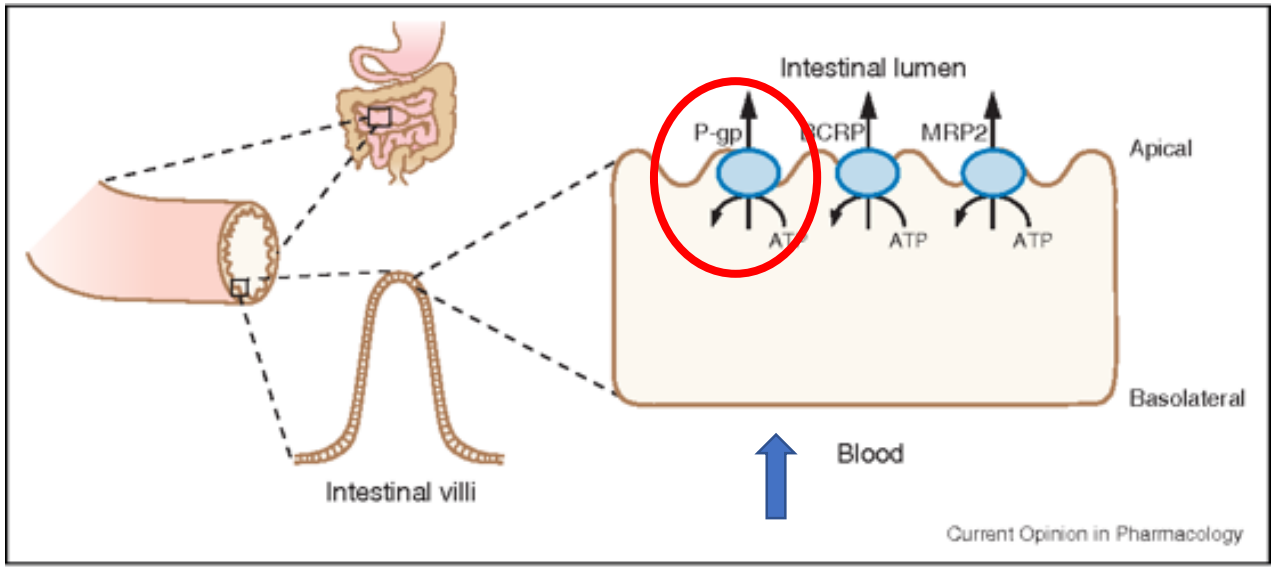
Pregabalin 75 mg BID
Trazodone 100 mg BID
Quetiapine 25 mg BID
Citalopram 10 mg QD
Valproate 250 mg BID

ARV Therapy
ETR 200 mg BID
TAF/FTC/DRV/**COBI** QD
DRV/**COBI** 800/150 mg QD

4_DDI between Quetiapine and ARVs

Quetiapine metabolism

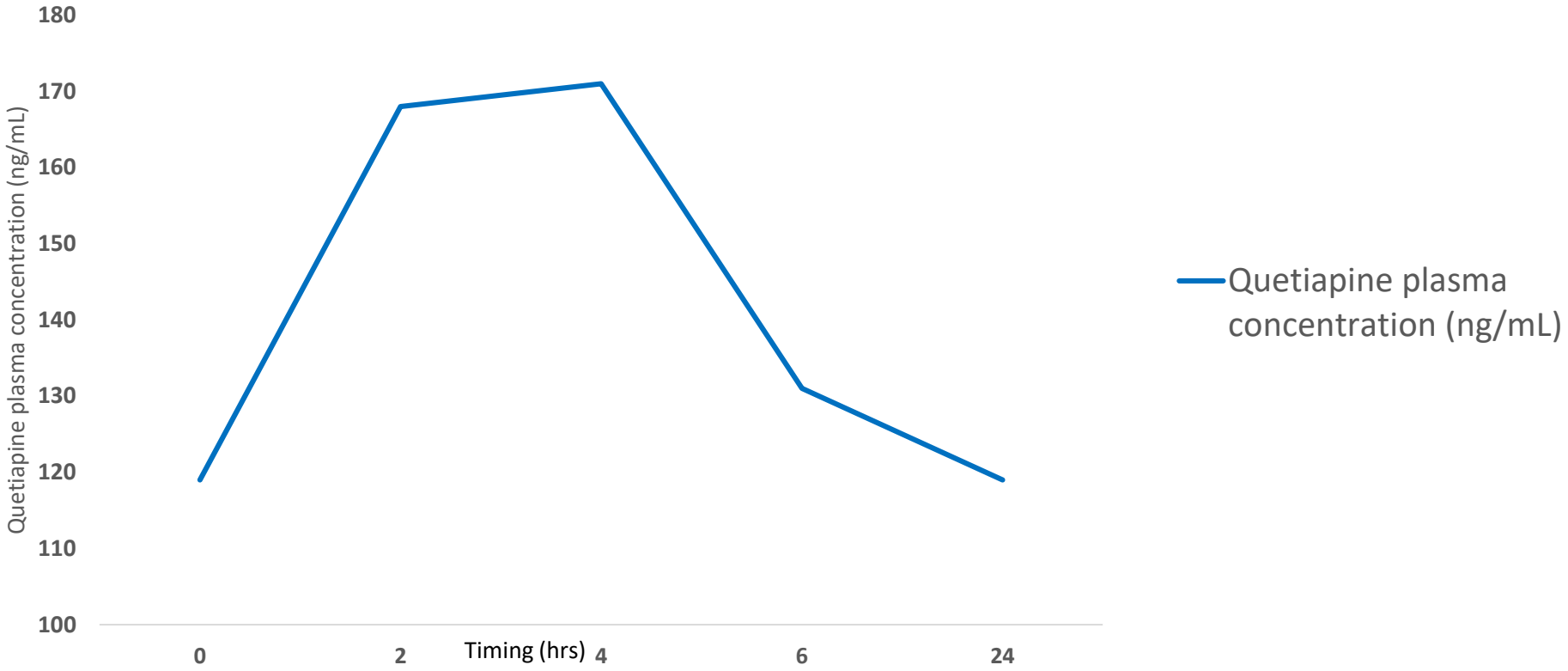




Etravirine

Cobicistat

Quetiapine plasma Intensive PK Monitoring



Plasma concentration (ng/mL)	T0	T2	*T4*	*T6*	*T24*	*Reference Ctrough Heimke 2017**
Quetiapine	**119**	**168**	**171**	**131**	**121**	**100-500**

*Heimke et al. Therapeutic drug monitoring in neuropsychopharmacology : Summary of the consensus guidelines 2017 of the TDM task force of the AGNP

A.B.

CLINICAL CASE

November 2019

HIV-RNA undetectable
CD4 983 cell/microL, 23%, ratio 0,6

Psychiatric disorder: clinically balanced

CONCLUSIONS

Lessons learnt:

- Role of ID physician as a widewalker reaching the ancing between multiple DDIs
- Polydoctoring and Polypharmacy in the setting of al disabilities can be very problematic
- Tailoring ARVs drug on chronic comorbidities

Acknowledgements

Unit of Infectious Diseases

Prof. Giovanni Di Perri
Prof. Stefano Bonora
Andrea Calcagno
Mariacristina Tettoni
Chiara Alcantarini
Laura Trentini
Letizia Marinaro
Alessandro Lazzaro
Stefano Biffi
Alessandro Di Stefano

Clin. Pharm. Lab.

Antonio D'Avolio
Mauro Sciandra
Jessica Cusato
Amedeo De Nicolò
V. Avataneo