Clinical pharmacology of INI + PI regimens

Clinical case-based Discussion

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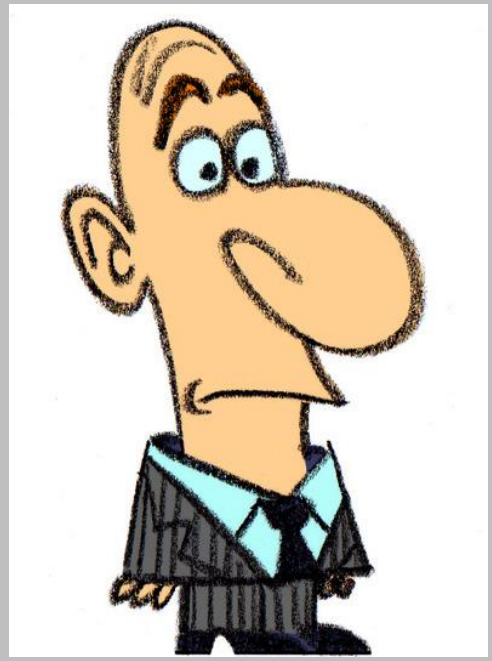
A.C.

- Male, Caucasian, 54 yrs, MSM
- Past medical history, FHx and SHx: **negative**



CLINICAL CASE
-Medical History-

- **2013: Diagnosis of AIDS** → CMV retinitis and PJP pneumonia
- BL: CD4+ 70 cell/mcl, HIV-RNA:1624844 cp/ml, clade B, WT, HLA B5701 +, CCR5 tropism.
- Admission to ID Unit ward : detection of reduced renal function and altered proteinuria 24/h

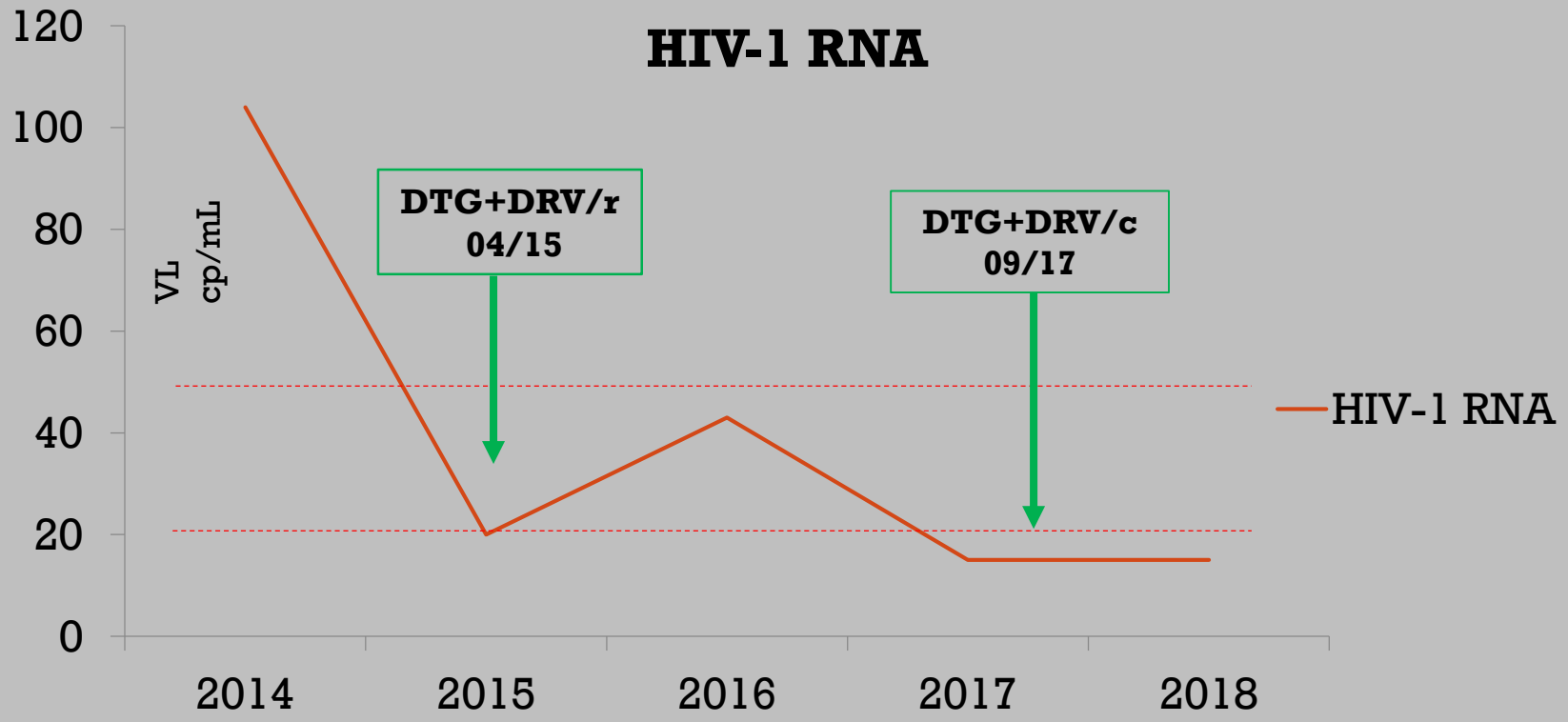
Meds at discharge: Pirimetamine, Atovaquone, Valganciclovir, **3TC/RAL/DRV/r 800/100 QD**

- Oupatient clinic: Progressive reduction of renal function and increasing of proteinuria/24h (Crs 1.8 mg/dl; prot)→ 11/2013 renal biopsy → **Focal Segmental Glomerulosclerosis (FSGS)**

Follow-up

04/2015: **dual therapy → DRV/r+DTG QD** with immuno-virological efficacy and tolerability

- 09/2017: **simplification to DRV/c+DTG QD**
- 03/2018: FU W24 HIV-RNA: NR, CD4+ 472 cell/µL
- 08/2018: FU W48 HIV-RNA:NR, CD4+ 633 cell/µL



DTG-based Dual therapy

After approval of dolutegravir (DTG) for clinical use, trial of sperimental dual therapy strategy are ongoing on based on DTG as backbone for pharmacological characteristics as :

- High genetic barrier
- Low drug-drug interactions profile
- No need of boosting
- Once daily

DTG plasma and intracellular pharmacokinetic (PK) in dual therapy plus Protease Inhibitors (PIs)

Data from literature based on healthy subjects:

- ⌑ DTG plasma concentration increased when dosed with ATV/RTV 300/100[1].
- ⌑ DTG plasma concentration reduced when dosed with DRV/RTV 600/100[2]

Data on DTG plasma concentration from Intensive PK monitoring studies are lacking

Real life experience:

- ⌑ DTG plasma Ctrough increased after switch to COBI from RTV in DTG plus DRV/r 800/100 [3].
- ⌑ DAU Cohort: DTG plasma C_{trough} increased when dosed with ATV 400 mg unboosted[4].

[1]Song I, et al. Br J Pharmacol 2011;72:103–8

[2] Song I, et al. J Clin Pharmacol 2011;51:237–42

[3]Cristina Gervasoni et al. Luigi Sacco Univ Hosp, Milan, Italy. "INCREASED DOLUTEGRAVIR EXPOSURE IN HIV PATIENTS SWITCHED FROM RITONAVIR TO COBICISTAT | CROI Conference." (June 8, 2018); Cattaneo, D. et al. (2016). Dolutegravir plasma concentrations according to companion antiretroviral drug: unwanted drug interaction or desirable boosting effect? Antiviral Therapy, 10.3851-IMP3119

[4]Two-drug regimen with dolutegravir and unboosted atazanavir in HIV-1 infected patients with undetectable viral load and long exposure to antiretroviral therapy .On behalf of DAU Study Group

DTG plasma and intracellular pharmacokinetic (PK) in dual therapy plus Protease Inhibitors (PIs)

Gap of knowledge:

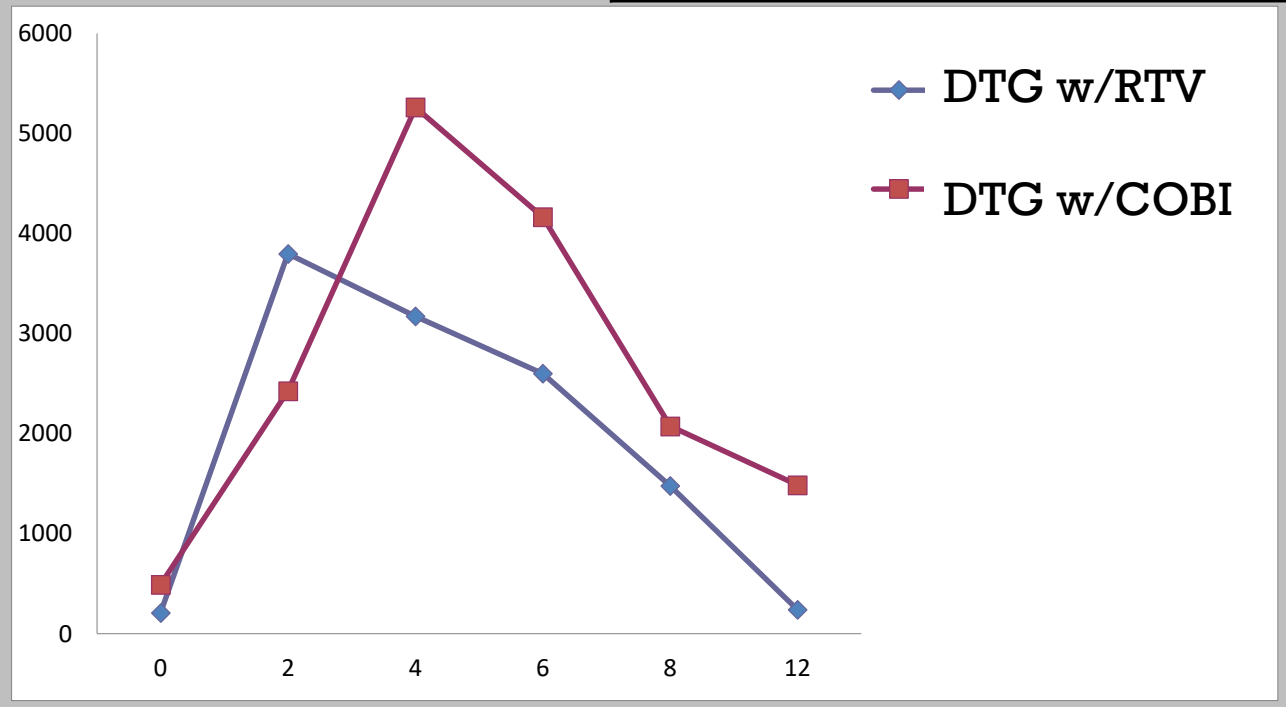
- Observational and Sperimental studies are limited at the association DTG plus DRV or absent for the association with ATV/RTV.

- Limited data on C_{trough}, lack of intracellular concentration data.

- Paucity of study number and patients included.

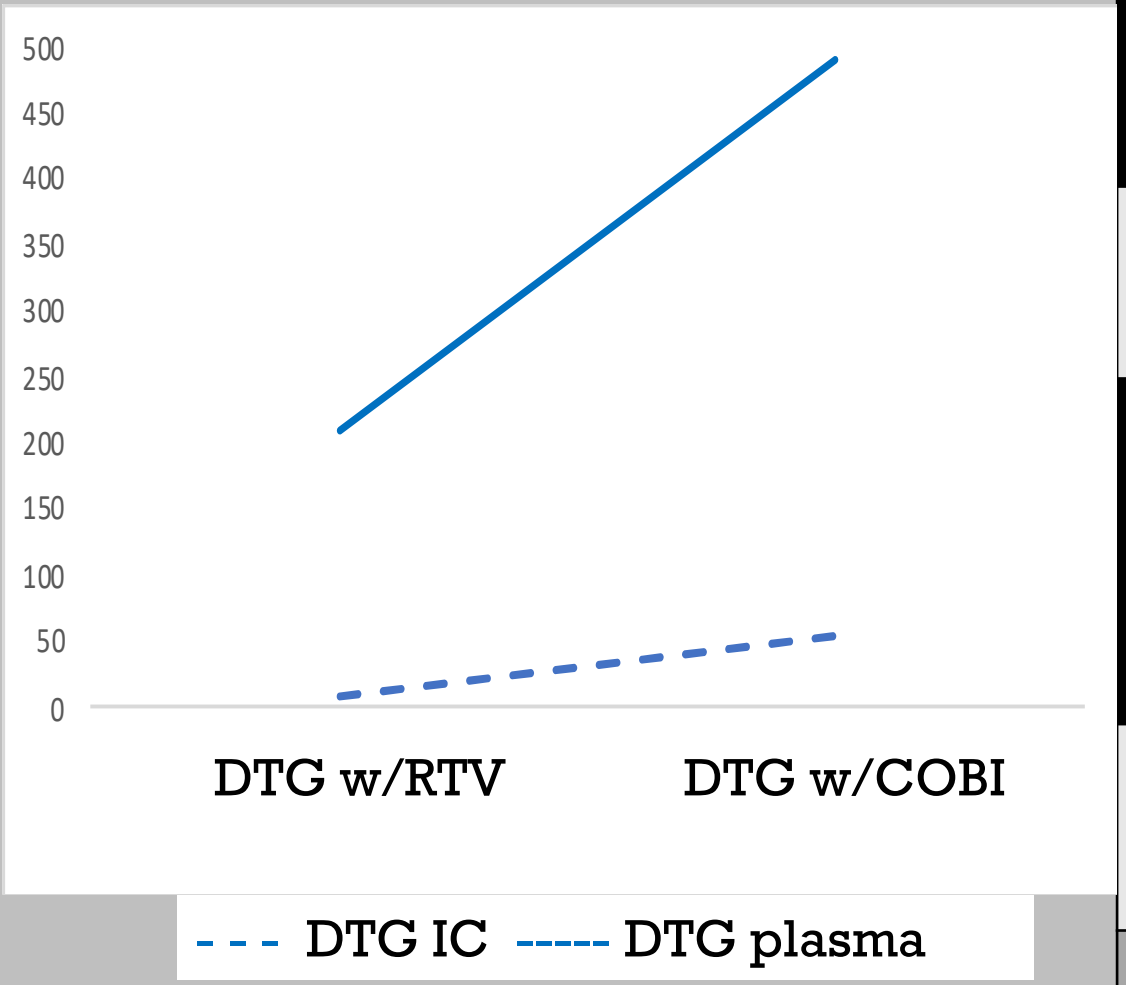
DTG plasma Ctrough and Intensive PK monitoring

	DRV w/ RTV (ng/mL)	DTG w/ RTV (ng/mL)
2016	3545	710
	DRV w/ COBI (ng/mL)	**DTG w/ COBI (ng/mL)**
2018	3225	1957
		+175%



DTG w/ RTV (ng*h/mL)	DTG w/ COBI (ng*h/mL)	%
21879	64355	**+194%**

DTG plasma and IC PK evaluation



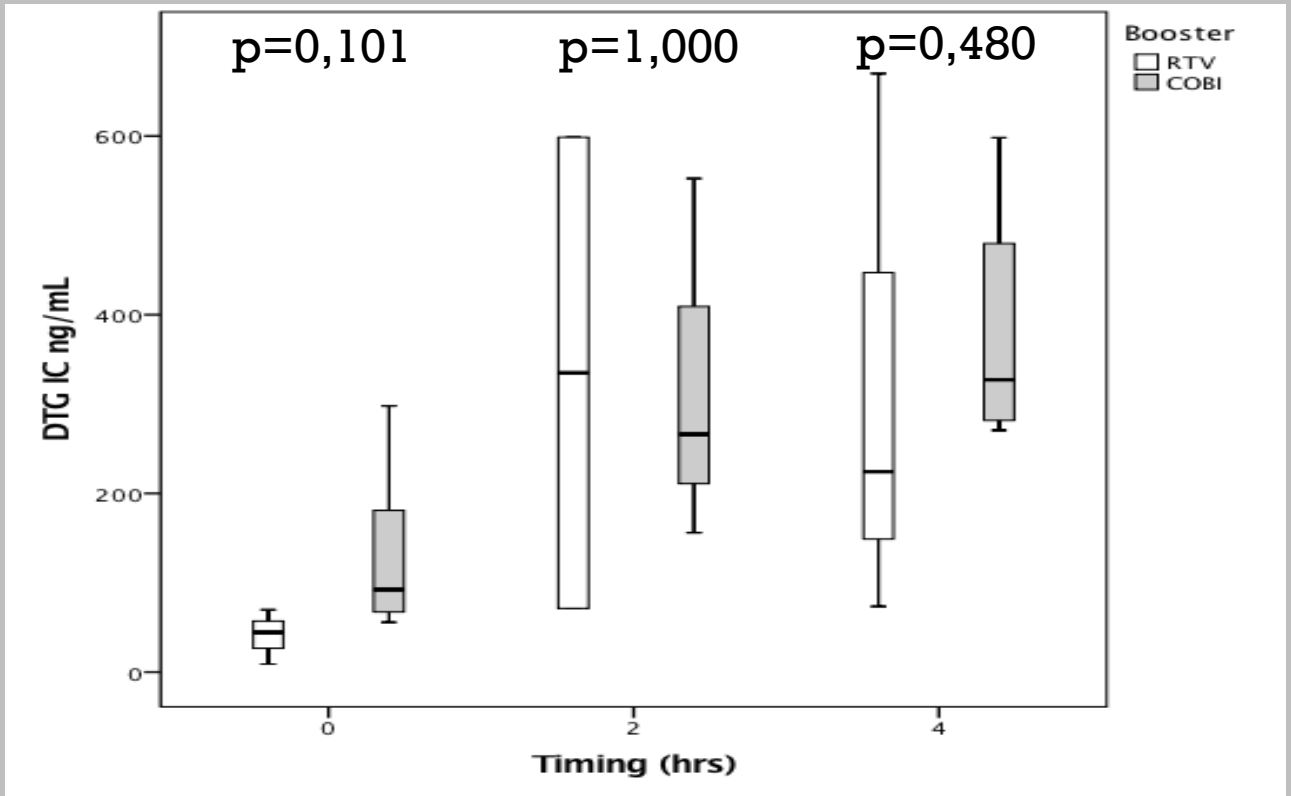
DTG w/RTV IC (ng/dL)	DTG w/RTV Plasma (ng/dL)	DTG w/RTV IC/plasma Ratio
8,9	209,0	0,043
DTG w/COBI IC (ng/dL)	**DTG w/COBI Plasma (ng/dL)**	**DTG w/COBI IC/plasma Ratio**
55,8	490,0	0,114
+84%	**+57,3%**	**+62%**

DTG plasma intensive PK with DRV/r 800/100 *vs* DRV/c 800/150 (n=5)

	*DTG + DRV/r	*DTG + DRV/c	Ratio COBI/RTV	p
AUCss (ng/mL*h)	18537.8 (6935.1; 30140.6)	63613.1 (3313.7; 123912.5)	2,9 (-2,215-7,910)	0.142
Cmin (ng/mL)	192.3 (167.7; 216.8)	579.6 (-168.2; 1327.3)	2,5 (-2,668-7,763)	**0.014**
Cmax (ng/mL)	1934.3 (-40.2; 3909.0)	3567.6 (-1897.9; 9033.0)	1,3 (-1,887-4,606)	0.327

* Geometric means (IC95%)

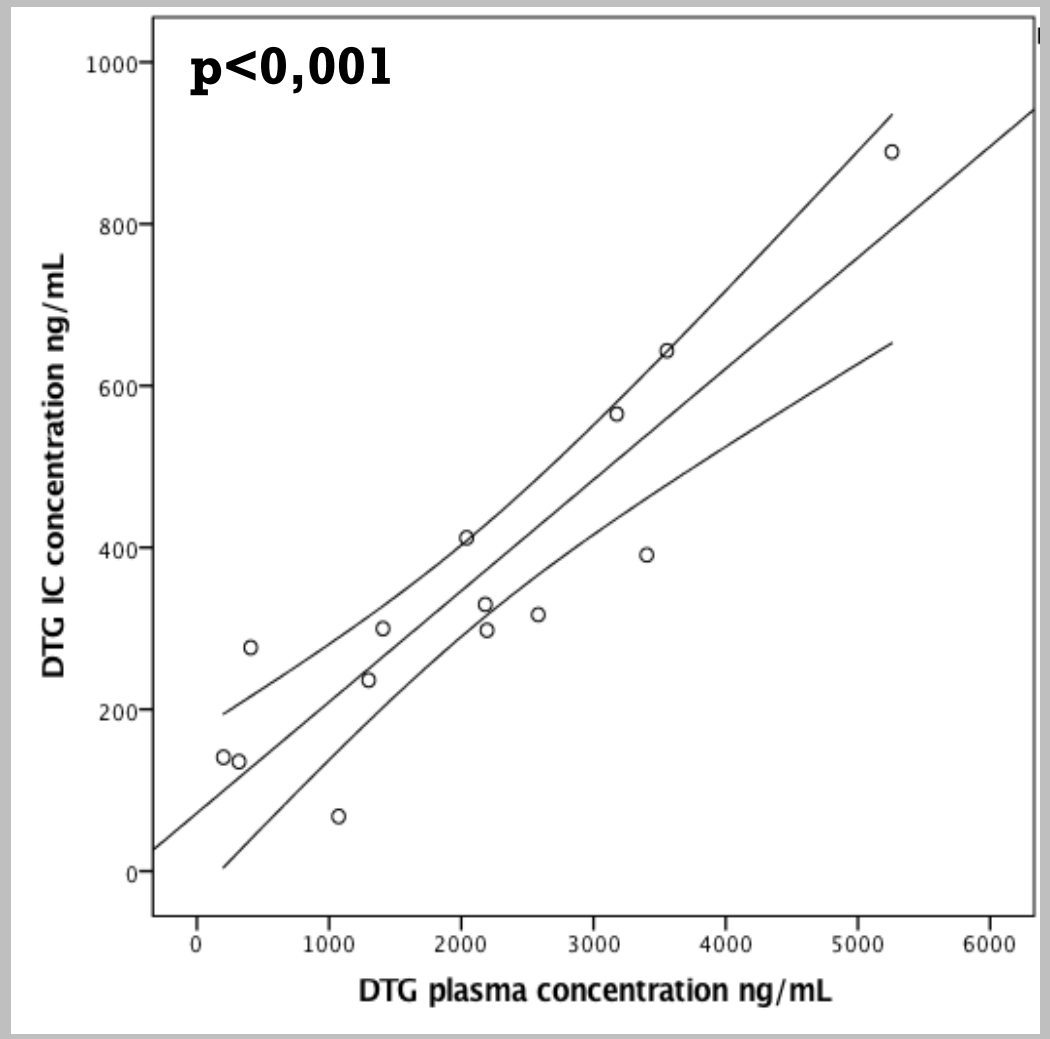
DTG IC determinations at timing T 0-2-4 with DRV/RTV *vs* DRV/COBI



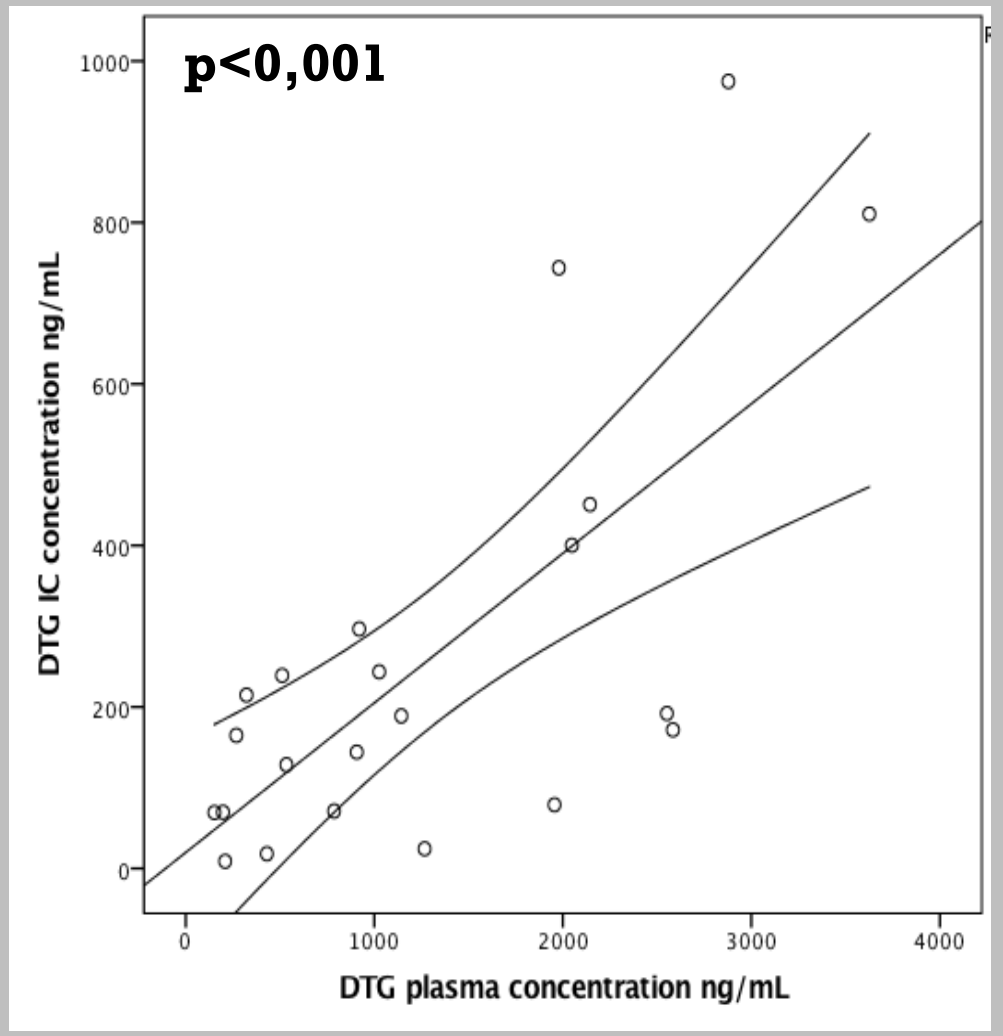
TO		T2		T4	
DTG + RTV	DTG + COBI	DTG + RTV	DTG + COBI	DTG + RTV	DTG + COBI
30.2 (-45.5; 106.0)	113.3 (-12.7; 239.4)	206.4 (-3143.2: 3556.1)	284,05 (-224,2-792,3)	222.7 (-547.6; 993.2)	361.8 (175.6; 547.9)
p = 0.101		p = 1.000		p = 0.480	

Correlations between plasma and IC DTG when dosed with RTV and COBI

DTG+COBI plasma-IC concentration

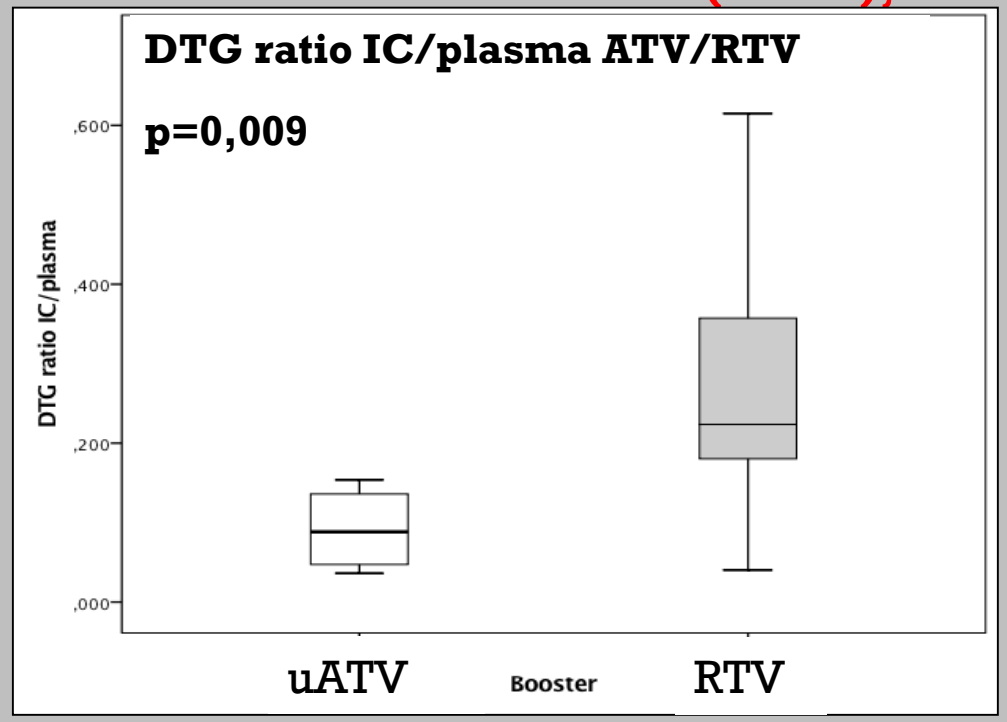


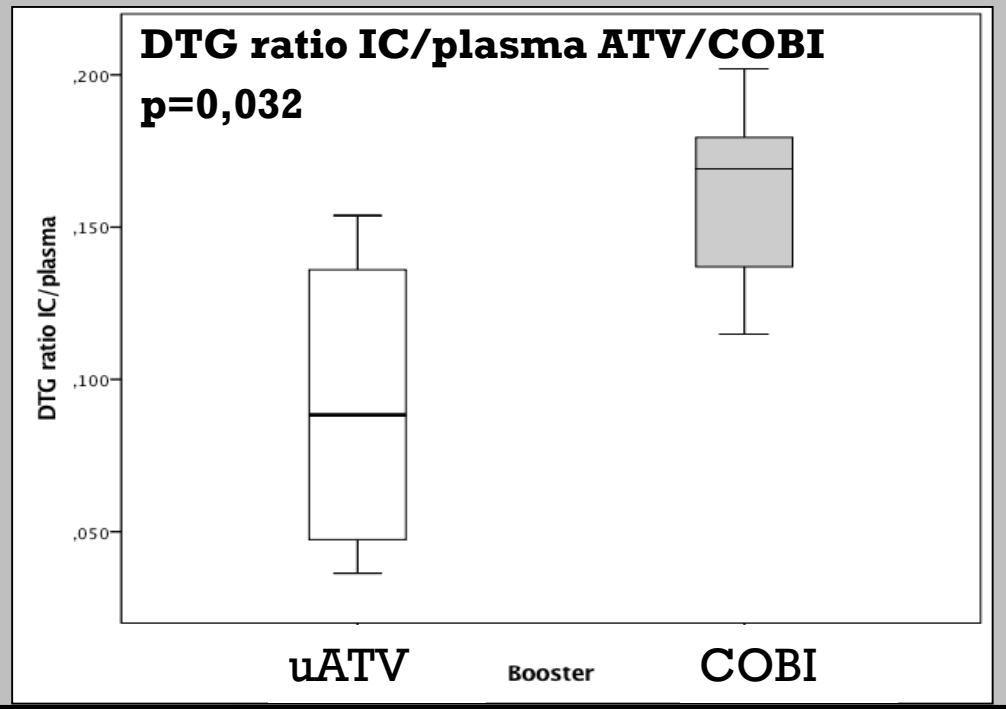
DTG+RTV plasma-IC concentration



Dosing with Boosted therapy, which impact on DTG intracellular accumulation?

DTG PLASMA, IC AND IC/PLASMA RATIO IN 3 DIFFERENT ATV-BASED DUAL REGIMENS: ATV/RTV (N=11), ATV/COBI (N=7) AND UATV (N=6)





Parameters	*ATV/RTV	*uATV	p
DTG plasma (ng/mL)	1401,8 (696,1; 2107,5)	2133,7 (894,8; 3372,5)	0.421
DTG IC	316,4 (113,8; 519,1)	137,3 (49,6; 225,0)	0.056
DTG IC/plasma ratio	0,226 (0,091; 0,360)	0,064 (0,003; 0,125)	**0.009**

Parameters	*ATV/COBI	*uATV	p
DTG plasma (ng/mL)	3025,4 (2291,6; 3759,3)	2133,7 (894,8; 3372,5)	0.253
DTG IC	474,7 (335,5; 614,1)	137,3 (49,6; 225,0)	**0.003**
DTG IC/plasma ratio	0,157 (0,135; 0,178)	0,064 (0,003; 0,125)	**0.032**

CONCLUSIONS

1. DTG-based Dual therapy plus PIs could be an option in experienced patients needing a full high genetic barrier due to tolerability, adherence and resistance reasons

2. bPIs are known to have a boosting effect on DTG plasma exposure.

3. For the first time, our study evaluated the PI boosting effect on DTG both at IC level and plasma intensive PK analysis.

Our findings confirm the increasing of DTG plasma concentration after switch to COBI with a consensual increase within PBMCs.

Higher DTG IC/plasma ratio in presence of booster, both RTV and COBI, than unboosted therapy (uATV 400 mg).

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