Dolutegravir (DTG) plasma concentrations under different combinations regimens for ART- pre-treated adults living with HIV

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Background

DTG is an integrase inhibitor recommended in pre-treated people living with HIV in combination with other antiretroviral, in dual therapy or in triple therapy. The objective of this study is to compare the concentrations between different combinations regimens (DTG + RPV, DTG + ATV or DTG + 2 INTI) and to compare them with the interval therapeutic range proposed in the literature.

Methods

Measures of drug plasma level were proposed to all patients having their routine blood test between 2016 and 2018 in our outpatient HIV clinic. DTG true concentration was determined 16 h (±6) after administration of DTG OD - using HPLC coupled with Mass spectrometry detection (limit of quantification 10 ng/mL). The estimated C_{min} (C_{24h}) is based on the mean half-life of the DTG (14h)[1] described in the literature and compared to the target C_{min} (1110 ± 511 ng/mL)[1,2,3]. CD4 T cell count, HIV plasma viral load were measured. All data were collected anonymously in an Excel® data base. Statistical analysis was performed with Student test.

Results

Table 1. Characteristics at time of measurement of DTG plasma concentration

		N=39
Sex ratio (F/H)		12/27
Median age [range], years		46 [20 – 83]
Ethnicity, n (%)	Sub-Saharan Africa (21) and Caribbean (2)	23 (60.5%)
	Caucasien	7 (18.4%)
	Maghreb	6 (15.8%)
	Asian	2 (5.3%)
Median weight [range], Kg		72 [45 - 104]
Median BMI, Kg/m²		24.2 [15-34]
Median CD4 + cell count [range], cells/mm3		688 [120-1442]
Plasma HIV-1 RNA, c/mL	< 50	33 (85%)
	50-200	4 (10%)
	600-1200	2 (5%)
Time since HIV diagnosis, median [range], years		15 [0.3-31]
Time cumulative exposure to ARVs, median [range], years		8 [0.1-27]
Number of treatment lines, median [range], n=32		3 [0-15]
Previous treatment (n)	PI + 2 INTI (DRV/r =10, ATV/r=4)	14
	DRV/r+RAL+2INTI	3
	INNTI + 2 INTI (EVF = 3, NVP=1)	4
	RAL+2INTI	4
	ETG/c/FTC/TDF	3
	No treatment	3
Time between start of DTG and measurement of Concentration,	median [range], month	2 [0.5-48]
	mean ± SD, month	8 ± 11
Time between administration of DTG and blood collection,	median [range], hour	13 [1,5 – 26,5]
	mean ± SD, hour	16 ± 6

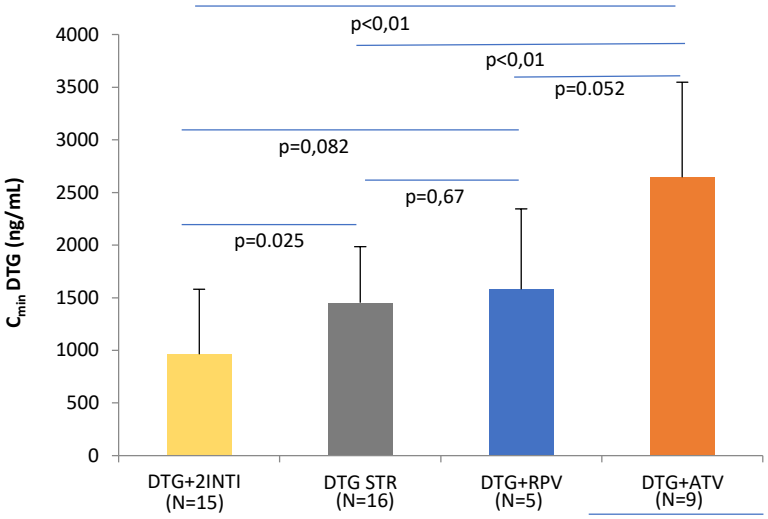

Figure 1. Comparison the estimated DTG C_{min} between different combinations regimens

2 INTI : ABC/3TC or FTC/TDF ; DTG-STR : DTG/ABC/3TC

Table 3. Distribution of DTG C_{min} according to the therapeutic target

	N	%
C_{min} < therapeutic zone (TZ)	5	11%
C_{min} In therapeutic zone	22	49%
C_{min} > therapeutic zone	18	40%

Table 2. DTG plasma true concentration and estimated C_{min}

	Concentrations ng/mL (N=45)	IV*
C_{true} (mean ± SD)	2556 ± 1641	64%
C_{min} (mean ± SD)	1508 ± 861	57%

*IV : interindividual variability

Table 4. Comparison of C_{true} and C_{min} in patients with side effects and those who tolerated the treatment well

	C_{true} ± SD (ng/mL)	C_{min} ± SD (ng/mL)
AEs (n=5)	3236 ± 671	1684 ± 297
No AEs (n=39)	2595 ± 2051	1491 ± 931
p	0,494	0,648

In this retrospective study, 39 patients were included, mostly men from sub-Saharan Africa (table 1) : 36 switches and 3 initiation to DTG-based treatment (DTG 50 mg QD). Forty-eight concentrations were determined of which 3 are less than 10 ng/mL . The $C_{trougth}$ and C_{min} of DTG and the interindividual variability are shown in Table 2. The Intra-individual variability was 42% [38 to 46] in 4 patients.

Twenty two out of 49 (48%) of the C_{min} were in the therapeutic zone (TZ) and 18 (40%) were superior to the upper limit of the TZ. Among the 18 C_{min}, 8 (44.4%) concern patients treated with DTG+ATV. All 5 concentrations < at TZ are greater than protein-adjusted IC_{90} of 65 ng/mL[1,2,3] (table 3).

The mean concentrations are 965 ng/mL (n = 15), 1452 ng/mL (n = 16), 1582 ng/mL (n = 5) and 2693 ng/mL (n = 9) respectively for treatments based on DTG + 2INTI, DTG / ABC / 3TC (STR), DTG + RPV and DTG + ATV. There is a significant difference between the C_{min} of regimens based on DTG + ATV and DTG + 2 INTI (p <0.01) and between DTG / ABC / 3TC (STR) and DTG + 2 INTI (p = 0.025) (figure 1).

Five patients had neuropsychiatric adverse events. There is no significant difference between the C_{min} of patients who tolerated the treatment well and patients who had side effects unlike the Yagura study[4] (table 4). Treatment was stopped in 4 patients, 3 for neuropsychiatric effects (dizziness, headache, severe depression) and 1 for non-compliance.

Conclusion

- There is a significant difference between the C_{min} of regimes based on DTG+ATV and DTG+2INTI (p <0.01) and between DTG-STR and DTG + 2 INTI (p = 0.025).
- Forty nine percent of C_{min} are in the TZ and 40% are higher than this TZ. The C_{min} of patients on DTG + ATV are all higher than the upper limit of the TZ.
- There is no significant difference between the C_{min} of patients with AEs and those who tolerated the treatment well.
- The limits of the study are : a small cohort ; the calculation of the C_{min}, but in real life, it is difficult to have only residual concentrations.

References

[1]SPC, Triumeq. EMA 2014 ; [2]Zhang J. et al. Br J Clin Pharmacol; 80 (3) : 503-14 ; [3]Podany AT et al. ClinPharmacokinet.2017January;56(1):25–40.
[4]Yagura et al. BMC Infectious Diseases (2017) 17:622