SHALL WE DANCE? EXTENDING TANGO'S RESULTS TO CLINICAL PRACTICE

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Dear editor,

After previous evidence from the ASPIRE trial [1], results from TANGO study [2] definitively proved the efficacy of lamivudine (3TC) plus dolutegravir (DTG) as a maintenance strategy. As trials' populations often differ from real-practice settings, we aimed to assess whether these results are reproducible in an unselected HIV-population. An observational longitudinal multicenter research study was conducted. HIV-positive patients with viral suppression (at least one HIV-RNA<50 copies/mL) were followed-up from the start of 3TC+DTG. The cohort was divided into two groups based on compliance or not with the inclusion criteria of TANGO study (absence of HBV-coinfection, of previous virological failure (VF), of a M184V-harboring virus and of previous AIDS-event other than cutaneous Kaposi's sarcoma and nadir CD4 count≤200 mm^3).

Time to VF (i.e. 2 consecutive HIV-RNA determinations ≥50 cps/mL or a single HIV-RNA≥1000 cps/mL) and to treatment discontinuation (TD, i.e. the interruption of any of the study drugs) in the 2 groups were compared through Kaplan-Meier with log-rank test and Cox-regression model after adjusting for the main clinical and demographic between-groups differences. Changes in immunological parameters were assessed by linear mixed model for repeated measures.

We analyzed 557 patients with a median follow-up time of 22 months: 145 (26.0%) met the TANGO inclusion criteria (TANGO group, TG). They were mostly men (70.4%), of Caucasians ethnicity (92.1%). Characteristics of study groups are summarized in table 1.

One VF over 248 PYFU and 11 VF over 776 PYFU occurred in the TG and non-TG, respectively. The estimated probability of maintaining virological suppression was 99.2% (SD±1.6) at 48, 96 and 144 weeks in the TG, and 98.5% (SD±1.4) at 48 weeks, 97.7 (SD±1.8) at 96 weeks and 95.7% (SD±2.6) at 144 weeks in the non-TG (log-rank p=0.189). After stratifying for the presence of M184V at historical genotype and for previous VF the results did not change (p=0.253 and p=0.186). Moreover, belonging to TG was not predictive of VF (aHR 0.35, 95%CI 0.04-2.84; p=0.327) after adjusting for age, anti-HCV serostatus and HIV duration. No resistance-associated mutations emerged after VF.

Estimated probabilities of remaining on 3TC+DTG were 86.6% (SD±5.9) at week 48 and 79.5% (SD±7.5) at both weeks 96 and 144 in the TG, and 85.8% (SD±3.5), 78.9% (SD±4.3) and 73.9% (SD±5.1) at weeks 48, 96 and 144 in the non-TG (log-rank p=0.654), with no significantly-increased hazard of TD for the TG (vs non-TG, aHR 0.97, 95%CI 0.60-1.57, p=0.894) after adjusting for confounders. A significant increase in CD4/CD8 ratio (mean change at 96 weeks, +0.05 in TG and +0.07 in non-TG) was observed over time, with no difference between groups.

Previous studies on 3TC+DTG as a switch strategy reported low rate of VF in clinical practice [3,4]. However, some demographic and viro-immunological characteristics seemed to increase the risk of VF during 3TC+DTG [5], possibly limiting the widespread use of this strategy in experienced patients.

Overall, our findings from clinical practice are in line with the TANGO study results. However, a higher, albeit not statistically-significant, number of VF was seen in the non-TG: pending results from longer follow-up studies, in our opinion caution should be advised when considering 3TC+DTG for selected patients (e.g., those with previous VF or shorter time of viral suppression).

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Table 1. Baseline patients' characteristics.

	TANGO group (n=145)	Non-TANGO group (n=412)	P value
Age (Years), Median (IQR)	49 (40-55)	53 (47-58)	<0.001
Male sex, n (%)	111 (76.6)	281 (68.2)	0.058
Ethnicity, n (%):			0.112
- Caucasians	129 (89.0)	384 (93.2)	
- Sub-Saharan	4 (2.8)	14 (3.4)	
- Central-South American	6 (4.1)	6 (1.5)	
- Other/unknown	6 (4.1)	8 (1.9)	
Risk factor for HIV, n (%):			<0.001
- Heterosexual	56 (38.6)	169 (41.0)	
- MSM	37 (25.5)	108 (26.2)	
- IDU	15 (10.4)	86 (20.9)	
- Other/Unknown	37 (25.5)	49 (11.9)	
CDC Stage C, n (%)	20 (13.8)	62 (15.0)	0.854
Anti HCV positive serostatus, n (%)	25 (17.2)	101 (24.5)	0.076
Peak HIV-RNA (log_{10} copies/mL), median (IQR)	4.95 (4.45-5.35)	4.89 (4.37-5.43)	0.780
Nadir CD4+ cell count (cells/mm^3), median (IQR)	278 (140-395)	212 (93-309)	0.001
Non-B HIV subtype, n (%)	5 (3.4)	13 (3.2)	0.875
Years from HIV diagnosis, median (IQR)	9 (5-17)	18 (10-24)	<0.001
Years of cumulative ARVs exposure, median (IQR)	7 (3-12)	13 (8-19)	<0.001
Months of virological suppression, median (IQR)	61.5 (31.5-103.1)	95.4 (51.5-126.9)	<0.001
Time of virological suppression≤6 months (%)	/	13 (3.2)	NA

Baseline CD4+ cell count (cells/mm3), median (IQR)	692 (453-912)	660 (500-876)	0.826
Previous virological failure, n (%)	/	223 (54.1)	NA
Previous ARV regimen, n (%):			<0.001
- 2NRTI + bPI	22 (15.2)	55 (13.3)	
- 2NRTI + NNRTI	90 (62.1)	55 (13.3)	
- 2NRTI + INI	33 (22.7)	57 (13.8)	
- Dual/Monotherapy	0 (0)	220 (53.4)	
- Other	0 (0)	25 (6.2)	
M184V resistance mutation detection at last genotipic resistance test, n (%)	/	45 (10.9)	NA
Reason for starting DTG+3TC, n (%):			<0.001
- Simplification/Proactive switch	49 (33.8)	106 (25.7)	
- Dyslipidemia	5 (3.4)	87 (21.1)	
- Toxicity GI tract	13 (9.0)	31 (7.5)	
- Renal toxicity	13 (9.0)	18 (4.4)	
- Osteopenia/osteoporosis	20 (13.8)	7 (1.7)	
- Other toxicity	10 (6.8)	10 (2.4)	
- Drug-drug interaction	6 (4.1)	30 (7.3)	
- Other/Unknown	29 (20.1)	123 (29.9)	

Notes: IQR, inter-quartile range; MSM, men who have sex with men; IDU, intravenous drug users; ARV, antiretroviral; (N)NRTI, (non) nucleoside-reverse transcriptase inhibitor; bPI, boosted-protease inhibitor; INI, integrase inhibitor; GI, gastro-intestinal.