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Shall We Dance? Extending TANGO's Results to Clinical Practice

To the Editor—After previous evidence from the ASPIRE trial [1], results from the 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 population living with human immunodeficiency virus (HIV). An observational, longitudinal, multicenter research study was conducted. Patients living with HIV who had viral suppression (at least 1 HIV RNA <50 copies/mL) were followed-up from the start of 3TC + DTG. The cohort was divided into 2 groups based on compliance or noncompliance with the inclusion criteria of the TANGO study (the absence of a hepatitis B virus coinfection, of previous virological failure [VF], of a M184V-harboring virus, and of a previous AIDS event other than cutaneous Kaposi's sarcoma and a nadir CD4 count ≤200 mm^3).

The times to VF (ie, 2 consecutive HIV RNA determinations ≥50 cps/mL or a single HIV RNA ≥1000 cps/mL) and to treatment discontinuation (ie, the interruption of any of the study drugs) in the 2 groups were compared through a Kaplan-Meier with log-rank test and a Cox-regression model after adjusting for the main clinical and demographic between-groups differences. Changes in immunological parameters were assessed by a 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 Caucasian ethnicity (92.1%). The characteristics of the study groups are summarized in Table 1.

There was 1 VF over 248 patient-years of follow-up (PYFU) and there were 11 VFs over 776 PYFU in the TG and non-TG, respectively. The estimated probabilities of maintaining virological suppression were 99.2% (standard deviation [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 $P = .189$). After stratifying for the presence of M184V at historical genotype and for previous VF, the results did not change ($P = .253$

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)	<.001
Male sex, n (%)	111 (76.6)	281 (68.2)	.058
Ethnicity, n (%)			
Caucasians	129 (89.0)	384 (93.2)	.112
Sub-Saharan	4 (2.8)	14 (3.4)	
Central or South American	6 (4.1)	6 (1.5)	
Other/unknown	6 (4.1)	8 (1.9)	
Risk factor for HIV, n (%)			
Heterosexual	56 (38.6)	169 (41.0)	<.001
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)	.854
Anti HCV–positive serostatus, n (%)	25 (17.2)	101 (24.5)	.076
Peak HIV RNA, log_{10} copies/mL, median (IQR)	4.95 (4.45–5.35)	4.89 (4.37–5.43)	.780
Nadir CD4+ cell count, cells/mm^3, median (IQR)	278 (140–395)	212 (93–309)	.001
Non-B HIV subtype, n (%)	5 (3.4)	13 (3.2)	.875
Years from HIV diagnosis, median (IQR)	9 (5–17)	18 (10–24)	<.001
Years of cumulative ARV exposure, median (IQR)	7 (3–12)	13 (8–19)	<.001
Months of virological suppression, median (IQR)	61.5 (31.5–103.1)	95.4 (51.5–126.9)	<.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)	.826
Previous virological failure, n (%)	/	223 (54.1)	NA
Previous ARV regimen, n (%)			
2NRTI + bPI	22 (15.2)	55 (13.3)	<.001
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 (%):			
Simplification/proactive switch	49 (33.8)	106 (25.7)	<.001
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)	

Abbreviations: 3TC, lamivudine; ARV, antiretroviral; bPI, boosted-protease inhibitor; CDC, Centers for Disease Control and Prevention; DTG, dolutegravir; GI, gastrointestinal; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, intravenous drug users; INI, integrase inhibitor; IQR, interquartile range; MSM, men who have sex with men; NA, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

and $P = .186$, respectively). Moreover, belonging to TG was not predictive of VF (adjusted hazard ratio, 0.35; 95% CI, .04–2.84; $P = .327$) after adjusting for age, anti–hepatitis C virus serostatus, and HIV duration. No resistance-associated mutations emerged after VF.

The 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 $P = .654$), respectively, with no significantly increased hazard of treatment discontinuation for the TG (vs non-TG; adjusted hazard ratio, 0.97; 95% CI, .60–1.57; $P = .894$) after adjusting for confounders. A significant increase in the CD4/CD8 ratio (mean changes 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 a 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 (eg, those with previous VF or a shorter time of viral suppression).

Notes

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