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

Alberto BORGHETTI - Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma Italia, UOC Malattie Infettive

Arturo CICCULLO - Dipartimento di Sicurezza e Bioetica Sezione Malattie Infettive, Università Cattolica del Sacro Cuore, Roma Italia

Gianmaria BALDIN - Mater Olbia Hospital, Olbia, Italy

Stefano RUSCONI - Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Milan, Italy.

Amedeo CAPETTI - Division of Infectious Diseases, Department of Infectious Diseases, Luigi Sacco University Hospital, Milan, Italy.

Gaetana STERRANTINO - Infectious Diseases Unit, Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy

William GENNARI - Azienda Ospedaliero Universitaria di Modena Laboratorio di Microbiologia e Virologia, Modena, Italy

Cristina MUSSINI - Azienda Ospedaliero Universitaria di Modena, Clinica Malattie Infettive e Tropicali, Modena, Italy

Vanni BORGHI - Azienda Ospedaliero Universitaria di Modena, Clinica Malattie Infettive e Tropicali, Modena, Italy

Simona DI GIAMBENEDETTI - Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma Italia, UOC Malattie Infettive; Dipartimento di Sicurezza e Bioetica Sezione Malattie Infettive, Università Cattolica del Sacro Cuore, Roma Italia
Corresponding author: Dr. Arturo CICCULLO, Section of Infectious Diseases, Department of Safety and Bioethics, Catholic University of the Sacred Heart, Rome, Italy. Telephone number: +39 06-30155366. E-mail address: arturo.ciccullo@gmail.com
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 counts<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.