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Session Topic Resistance. Is it still a problem?

Title **Impact of resistance mutations on virological efficacy of DTG-based maintenance two-drug regimens: an ARCA cohort study**

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Abstract **Background**: Two-drug regimens (2DR) are largely prescribed as maintenance therapy, nowadays mainly based on DTG. While many data have been reported about PI-based 2DR, the impact of resistance mutations and duration of virological suppression on DTG-based 2DR remains to be clarified. The aim of this study was to evaluate the impact of resistance mutations on virological outcome of DTG-based 2DR maintenance ART.

Material and methods: Virologically suppressed patients (pts) switching to DTG+3TC or DTG+RPV with pre-baseline (time of switch=baseline, BL) resistance genotype (at least PR/RT) were selected from the ARCA database. Primary endpoint was virological failure (VF: an HIV-RNA, VL, >200 cps/mL or 2 consecutive >50 cps/mL). The probability of VF was estimated by Kaplan-Meier analysis. Resistance to 2DR was defined as occurrence of at least Stanford HIVdb (v.8.5) low-level resistance (LLR) to at least one drug included in the current 2DR, based on cumulative genotype. CD4 changes were assessed using Student's t-test for paired samples. A secondary analysis comparing 2DR with DTG-based 3D regimens was also performed.

Results: A total of 318 2DR pts were analysed: 260 (82%) switching to DTG+3TC, 58 (18%) to DTG+RPV; 68% were males, median age was 51 (44-56) years, 12 (6-23) years of HIV infection, 5 (3-8) years of virological suppression, nadir CD4 231 (121-329), 5 (3-9) previous ARV lines, 59% previously exposed to INSTI, 11% with resistance to current 2DR. The integrase sequence was available in 14% of patients, none harbouring resistance to DTG. 20 VF were observed, of whom 4 (3/17 VF in DTG+3TC, 1/3 in DTG+RPV) in patients with at least LLR at BL (M184V+K219Q; D67N+K70R+K219Q; D67N+K70R+T215Y+219Q; E138A), in a median FU of 1.3 years (IQR 0.6-2). The 2-year estimated probability of VF was 8.7% (95% CI 4.4;13); 8.6% (4.1;13.1) in those without resistance and 9.7% (-4.4;23.8) in those with resistance (Log rank: p=ns, figure 1). No factor was significantly associated with VF at multivariate analysis, but in pts with <6 years of virological suppression, BL resistance was associated with a higher probability of VF (p=0.003). After 48 weeks, a statistically significant increase in CD4+ was detected (+56 cells/mmc, p<0.001), independently from baseline resistance. The 2-year estimated probability of VF in the reference 3DR group (n=564) was not different from that for the 2DR group: 8.8% (5.9;11.7) in the whole case file and 9.7% (6.6;12.8) in the presence of baseline resistance. Longer time of virological suppression was the only factor associated with a lower risk of VF in the 3DR dataset.

Conclusions: DTG-based 2DRs show high virological efficacy, even in the context of predicted incomplete activity, at least within a short-term follow-up. A longer duration of virological suppression seems to decrease the impact of resistance on virological outcome, however further studies are warranted to confirm this hypothesis and possibly define a clinically useful threshold.