10° CONGRESSO NAZIONALE
ICAR Italian Conference on AIDS and Antiviral Research
Presidenza del Congresso Massimo Andreoni, Roma Andrea Antinori, Roma Carlo Federico Perno, Milano

Oral Communication **Session/Topic:** **Antiretroviral therapy: focus on integrase inhibitor**

N. **Title:**

OC 1 **Durability of integrase inhibitors (INSTI) regimens in the clinical setting: data from the Icona Foundation Cohort**

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Abstract:

Background: To date, no clinical trial has compared the efficacy and toxicity of the three EMA registered INSTI in a face-to-face study of first line regimens.

Methods: All patients initiating a first antiretroviral (ART) regimen including TDF(TAF)/FTC plus raltegravir (RAL), dolutegravir (DTG) or elvitegravir/cobicistat (EVG/c) or ABC/3TC plus RAL or DTG after January 1, 2011 were included. Primary end-point was time to treatment failure (TF) defined as discontinuation of the INSTI for any reasons or virological failure (VF: viral load (VL) >200 copies/ml after ≥24 weeks in two consecutive determinations). Secondary end-points: a) VF200: confirmed VL >200 copies/ml after ≥24 weeks; b) treatment discontinuation for any reason (TD); c) TD due to intolerance/toxicity (TDT). Follow-up accrued from the date of starting ART to the first of failure defining events, last clinical visit or death. Kaplan Maier (KM) curves and Cox regression models adjusted for potential confounders were used for statistical analyses.

Results: A total of 1,854 ART-naïve patients included: 298 (16%) initiated RAL, 874 (47%) DTG, 682 (37%) EVG/c. Median age was 37 (IQR: 28-44) years, 15% females, 53% acquired HIV through MSM, 30% were born outside of Italy. Patients on RAL had a more severe HIV infection, documented by lower median CD4 counts (RAL: 332 cells/mmc, DTG 350, EVG/c 383; p<.001) and higher VL (RAL: 4.92 log10 copies/ml, DTG 4.72, EVG/c 4.70; p<.001) at baseline. ABC/3TC was given in 28% of cases (54% of patients on DTG, 14% of RAL). The 1-year probability of TF were 11.6% (95%CI: 7.7-15.5), 5.3 (3.6-7.1), and 6.2 (4.2-8.3) for patients on RAL, DTG and EVG/c (p<.001). The probability of TD by 1 year were 12.1% (8.1-16.0), 6.1 (4.3-7.9), and 6.7 (4.3-8.7) for patients on RAL, DTG and EVG/c (p<.001). There were no differences in the probability of VF200 or TDT according to the INSTI by log-rank test. The main causes of discontinuation were: simplification for patients stopping RAL (65/116, 56%), CNS intolerance for DTG (17/58; 29%) and patient's choice for EVG/c (16/67, 24%) (Table 1). Patients initiating RAL or EVG/c showed a 5.2-fold and 1.9 higher risk of TF than DTG, respectively; the adjusted risk of TD was 4.8-fold higher and 1.6-fold higher for people initiating RAL and EVG/c vs DTG (Table 2). There was evidence that the difference RAL vs EVG/c was greater in people with CD4 count >200 than in those with ≤200 cells/mm3 (RH=3.74 vs. RH=1.43, interaction p=0.001). Main results were similar after restricting the analyses to patients starting the TDF (TAF)/FTC backbone.

Conclusions: Treatment discontinuation for reasons other than failure/toxicity, mainly simplification, rather than virological failure, were the driver of the differences in treatment failure between DTG- and the other two INSTI-based regimens. This finding and whether the RAL vs. EVG/c difference might vary according to CD4 count should be verified in randomised studies.

The analysis of this study have been conducted thanks to the unconditional sponsorship of Gilead Sciences

Table 1- Reasons for discontinuation according to INSTI

Reason for discontinuation	Regimen			
	RAL-based	**DTG-based**	**EVG-based**	**Total**
	N= 116	N= 58	N= 67	N= 241
Failure, n(%)	12 (10.3%)	12 (20.7%)	15 (22.4%)	39 (16.2%)
Death	0 (0.0%)	3 (25.0%)	0 (0.0%)	3 (7.7%)
Virological	12 (100.0%)	9 (75.0%)	13 (86.7%)	34 (87.2%)
Immunological	0 (0.0%)	0 (0.0%)	2 (13.3%)	2 (5.1%)
Intolerance, n(%)	8 (6.9%)	17 (29.3%)	16 (23.9%)	41 (17.0%)
CNS	3 (37.5%)	9 (52.9%)	0 (0.0%)	12 (29.3%)
Allergic reactions	2 (25.0%)	3 (17.6%)	5 (31.3%)	10 (24.4%)
Gastrointestinal intolerance	1 (12.5%)	3 (17.6%)	9 (56.3%)	13 (31.7%)
Lipodystrophy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Osteopenia/osteoporosis	1 (12.5%)	0 (0.0%)	2 (12.5%)	3 (7.3%)
Arthromyalgias	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin and skin structures disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clinical contraindications	1 (12.5%)	2 (11.8%)	0 (0.0%)	3 (7.3%)
Pro-active[&], n(%)	65 (56.0%)	3 (5.2%)	5 (7.5%)	73 (30.3%)
Toxicity, n(%)	5 (4.3%)	13 (22.4%)	13 (19.4%)	31 (12.9%)
Cardiovascular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hepatic	0 (0.0%)	1 (7.7%)	1 (7.7%)	2 (6.5%)
Renal	2 (40.0%)	3 (23.1%)	6 (46.2%)	11 (35.5%)
Peripheral nervous system	0 (0.0%)	2 (15.4%)	0 (0.0%)	2 (6.5%)
Metabolic/Increase in lipids	1 (20.0%)	0 (0.0%)	2 (15.4%)	3 (9.7%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Adherence, n(%)	5 (4.3%)	1 (1.7%)	0 (0.0%)	6 (2.5%)
Temporary complete interruptions, n(%)	1 (0.9%)	0 (0.0%)	2 (3.0%)	3 (1.2%)
Other, n(%)	20 (17.2%)	12 (20.7%)	16 (23.9%)	48 (19.9%)
Patient's choice	6 (30.0%)	5 (41.7%)	2 (12.5%)	13 (27.1%)
Drug-drug interactions	0 (0.0%)	1 (8.3%)	6 (37.5%)	7 (14.6%)
Pregnancy or pregnancy planning	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inclusion or discharge from clinical trials	7 (35.0%)	4 (33.3%)	0 (0.0%)	11 (22.9%)
Adherence to new guidelines	1 (5.0%)	0 (0.0%)	1 (6.3%)	2 (4.2%)
Availability of more effective drugs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	6 (30.0%)	1 (8.3%)	7 (43.8%)	14 (29.2%)

[&]regimen modification with a VL<=50 copies/mL to prevent toxicityor to improve adherence/simplify the regimen/reduce pill burden

Table 2- Univariate and multivariate hazard ratio to reach the different end-points

	Unadjusted and adjusted relative hazards			
Outcomes	**Unadjusted RH (95% CI)**	**p-value**	**Adjusted* RH (95% CI)**	**p-value**
Treatment failure				
Regimen				
RAL-based	4.38 (3.11, 6.18)	<.001	5.27 (3.51, 7.91)	<.001
DTG-based	1.00		1.00	
EVG-based	1.51 (1.04, 2.19)	0.031	1.88 (1.21, 2.92)	0.005
Discontinuation (any reason)				
Regimen				
RAL-based	3.96 (2.88, 5.44)	<.001	4.86 (3.33, 7.09)	<.001
DTG-based	1.00		1.00	
EVG-based	1.27 (0.89, 1.81)	0.180	1.58 (1.04, 2.39)	0.033
Discontinuation for toxicity				
Regimen				
RAL-based	0.81 (0.41, 1.58)	0.533	1.11 (0.51, 2.42)	0.790
DTG-based	1.00		1.00	
EVG-based	1.11 (0.66, 1.85)	0.693	1.59 (0.81, 3.11)	0.178
Confirmed VL>200 copies/mL				
Regimen				
RAL-based	6.88 (0.75, 63.15)	0.088	6.98 (0.62, 79.18)	0.117
DTG-based	1.00		1.00	
EVG-based	5.52 (0.64, 47.26)	0.119	4.11 (0.42, 40.35)	0.225

**adjusted for age, gender, nation of birth, mode of HIV transmission,hepatitis co-infection status, AIDS diagnosis, baseline CD4 count and viral load andyear of starting cART*