Effectiveness and discontinuation rate of dolutegravir (DTG)-based regimens as either first line or switch antiretroviral therapy (ART): data from the Icona cohort.

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BACKGROUND:

- DTG is now one of the most widely used antiretroviral drugs for treatment of both ART-naïve and experienced HIV patients due to its high efficacy and low potential for drug interactions [1-5].
- Despite the high tolerability demonstrated in clinical trials [1-3], recent observational studies have raised concerns about DTG safety, especially with regard to neuropsychiatric adverse events, with a higher incidence when DTG was associated to abacavir (ABC)[6-8] and in frail subgroups, as women and older patients [8]. However, these data was not uniformly confirmed in real life settings [9,10].
- The aim of this study is to estimate the **risk of virological failure** and **discontinuation of DTG-based regimens in treatment-naïve and experienced HIV patients** in a large Italian cohort.

METHODS:

- **Retrospective, observational, multicentric study** analysing data from Icona Foundation Study Cohort
- Icona is a nation-wide cohort including HIV patients, naïve from ARV, prospectively followed in 52 Italian centres
- Both **ART-naïve and virologically-suppressed** (baseline HIV-RNA < 50 copies(cp)/mL) **treatment-experienced (TE) HIV patients** enrolled in Icona cohort **who initiated, for the first time, a DTG-based regimen from January 2015 to July 2017** were included.
- **DEFINITIONS:**
  - ✓ **Virological failure (VF)**: two consecutive HIVRNA>50 cp/mL (for naïve patients, occurring ≥6 months after DTG-start).
  - ✓ **DTG discontinuation (DTG-TD)**: discontinuation of DTG from the regimen
- **STATISTICAL ANALYSIS:**
  - ✓ Characteristics at time of DTG start (baseline) were compared between naïve and TE patients using chi-square and non-parametric tests for the median as appropriate.
  - ✓ Cumulative probability of VF and DTG-TD for any reason and for toxicity were estimated by Kaplan-Meier analysis in both naïve and TE patients.
  - ✓ Predictive factors of DTG-TD for any reason and for toxicity were identified using multivariable Cox proportional hazard model in both groups.

RESULTS:

- 1057 patients were included (602 ART-naïve, 455 TE) who started DTG mainly in a standard triple ART-regimen (96% in ART-naïve group; 67% in TE group) **[Table 1]**.
- **VIROLOGICAL FAILURE**:
  - ✓ In **NAÏVE GROUP** occurred in 4 patients (**0.7%**) with a 1-year probability of **1.8%** (95%CI:0.0-3.6) [**Fig.1**]
  - ✓ In **TE GROUP** occurred in 5 patients (**1%**) with a 1-year probability of **1.3%** (95%CI:0.0-2.7) [**Fig.2**]
- **DTG DISCONTINUATION:**
  - ✓ In **NAÏVE GROUP:**
    21 patients (**3.5%**) stopped DTG, 12/21 for toxicity (**57%**) **[Fig. 5]**. The 1-year probability of DTG-TD for any reason and for toxicity was **4.6%** (95%CI: 2.6-6.7) and **2.5%** (95%CI: 0.9-4.2), respectively [**Fig. 3**].
    At multivariable analysis**, female gender and higher baseline CD4 cell count showed a trend toward significance as a predictive factor of DTG-TD for any reason** (aHR 5.32, p=0.059 and aHR 0.73, p=0.069, respectively) [**Table 2**].
  - ✓ In **TE GROUP:**
    17 patients (**3.7%**) discontinued DTG, 11/17 (**65%**) for toxicity **[Fig 6]**. The 1-year probability of DTG-TD for any reason and for toxicity was **6.2%** (95%CI: 3.1-9.4) and **2.5%** (95%CI: 0.9-4.2), respectively [**Fig 4**].
    At multivariable analysis, **dual regimens were associated to a lower risk of discontinuing DTG compared to standard triple therapies** (aHR 0.17, p=0.037) [**Table 3**]. The protective effect of dual therapies maintained a trend toward significance also when triple therapies were stratified according to the backbone (aHR 0.19, p=0.064 versus ABC; aHR 0.16, p=0.061 versus TDF) whereas no difference was observed comparing the two backbones [model not shown]. **The risk of discontinuing DTG regardless of the reason was almost significantly higher in patients starting the drug more recently** (aHR 3.44, p=0.071)[**Table 3**].

TABLE 1 –BASELINE CHARACTERISTICS

Characteristic	ART-naïve (n=602)	ART-experienced (n=455)	p-value	Total Population (n=1057)
Female gender*	110 (18.3)	113 (24.8)	**0.010**	223 (21.1)
Age, years**	41 (32- 49)	48 (40-56)	**<0.001**	44 (35-53)
Non italian born*	114 (18.9)	42 (9.2)	0.430	156 (14.8)
Risk Factor for HIV*			**<0.001**	
- Homosexual contacts	303 (50.9)	188 (41.3)		491 (46.8)
- Heterosexual contacts	204 (33.9)	205 (45.1)		409 (38.7)
- IDU	25 (4.2)	43 (9.5)		68 (6.5)
- Other/unknown	63 (10.6)	19 (4.2)		82 (7.8)
AIDS diagnosis*	86 (14.3)	89 (19.6)	**0.022**	175 (16.6)
HBV co-infection*	0 (0)	10 (2.2)	**<0.001**	10 (0.9)
HCV co-infection*	20 (3.3)	63 (13.8)	**<0.001**	83 (7.9)
CD4 cells count nadir, cell/mm3**	330 (123-541)	273 (140-373)	**<0.001**	293 (132-460)
Calendar year*			**<0.001**	
- 2015	216 (35.9)	209 (45.9)		425 (40.2)
- 2016-2017	386 (64.1)	246 (54.1)		632 (59.8)
BL CD4 cells count, cell/mm3**	350 (123-570)	640 (463-858)	**<0.001**	506 (260-720)
Type of regimen started*				
- **Standard triple therapy**	580 (96.3)	303 (66.6)	**<0.001**	883 (83.5)
• ABC-based	280 (48.3)	227 (75.0)		507 (57.4)
• TDF-based	300 (51.7)	76 (25.0)		376 (42.6)
- **Dual therapy**	7 (1.2)	139 (30.5)	**0.001**	146 (13.8)
• 3TC+DTG	1 (14.3)	83 (59.7)		84 (57.5)
• DRV/r + DTG	5 (71.4)	20 (14.4)		25 (17.1)
• RPV + DTG	1 (14.3)	26 (18.7)		27 (18.5)
• Other dual therapies	0 (0)	10 (7.2)		10 (6.9)
- **Other**	15 (2.5)	13 (2.9)	0.714	28 (2.7)

*n (%); ** median (interquartile range)

VIROLOGICAL FAILURE:

FIGURE 1: PROBABILITY OF VIROLOGICAL FAILURE ART-NAÏVE PATIENTS- KAPLAN-MEIER ANALYSIS

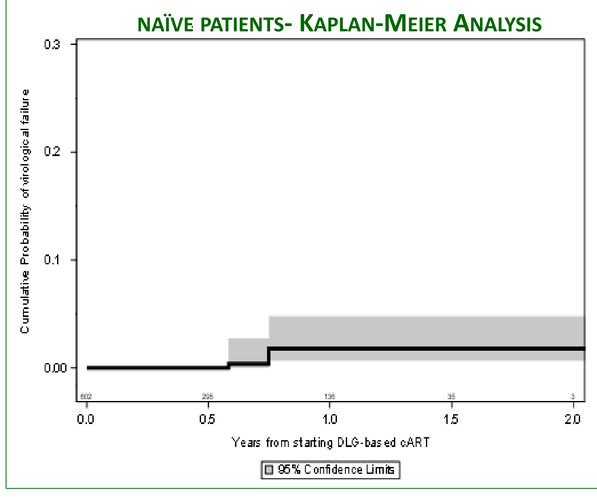
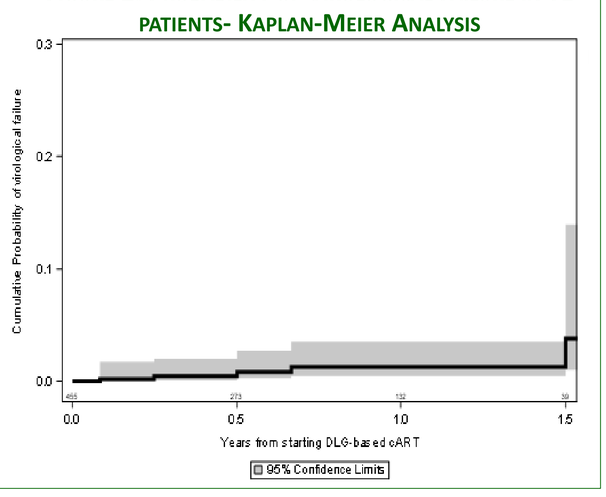


FIGURE 2: PROBABILITY OF VIROLOGICAL FAILURE IN TE PATIENTS- KAPLAN-MEIER ANALYSIS



TREATMENT DISCONTINUATION:

FIGURE 3: PROBABILITY OF DTG-TD FOR ANY REASON (3A) AND FOR TOXICITY (3B) IN ART-NAÏVE PATIENTS– KAPLAN-MEIER ANALYSIS

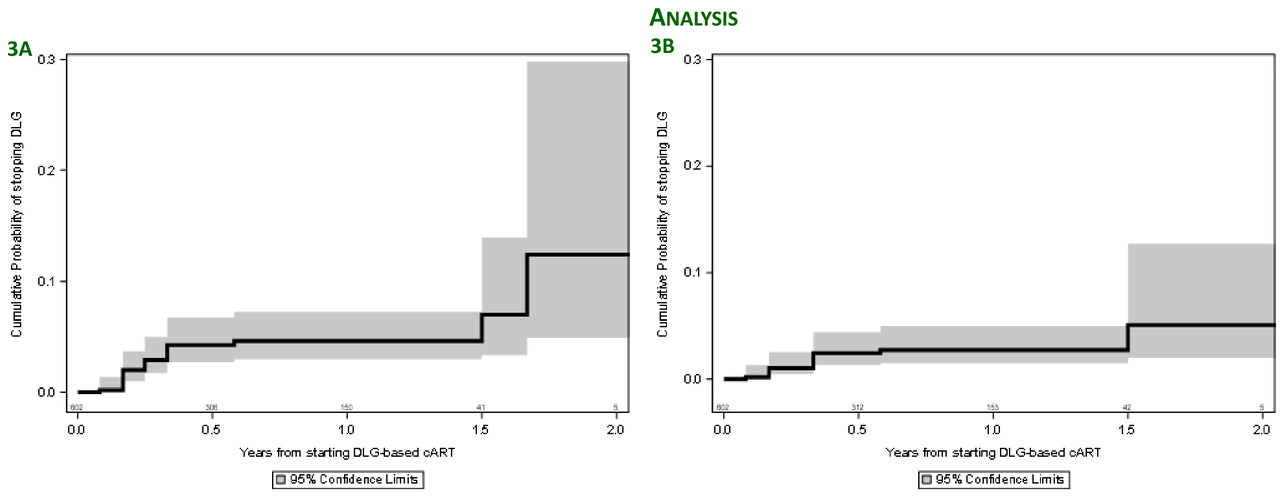


FIGURE 4: PROBABILITY OF DTG-TD FOR ANY REASON (4A) AND FOR TOXICITY (4B) IN TE PATIENTS– KAPLAN-MEIER ANALYSIS

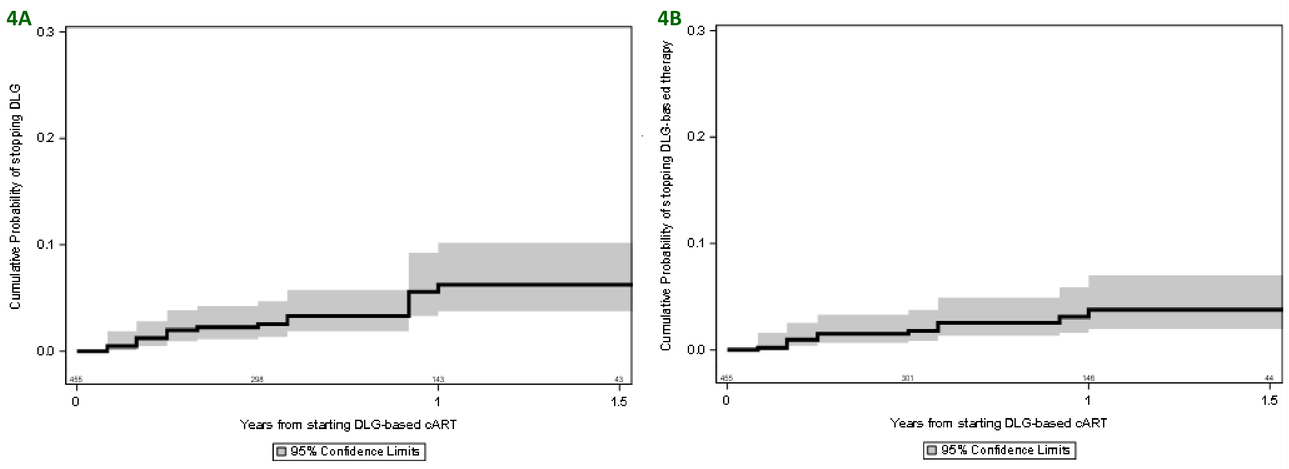


TABLE 2: PREDICTIVE FACTORS OF DTG-TD FOR ANY REASON IN ART-NAÏVE PATIENTS - COX REGRESSION MODEL

	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Female gender	2.84 (1.13-7.10)	**0.026**	5.32 (0.94-30.12)	**0.059**
AIDS diagnosis (Yes vs No)	2.80 (1.10, 7.13)	**0.030**	1.17 (0.24-5.74)	0.850
Baseline CD4 cells count, cell/mm3 (per 100 higher)	0.73 (0.55, 0.97)	**0.028**	0.73 (0.52-1.02)	**0.069**

* adjusted for age, mode of HIV transmission, nationality ,year of DTG-start and ART-backbone.

TABLE 3: PREDICTIVE FACTORS OF DTG-TD FOR ANY REASON IN TE PATIENTS - COX REGRESSION MODEL

	Unadjusted RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Risk Factor for HIV				
- Homosexual contacts	1.00	-	1.00	-
- Heterosexual contacts	2.69 (0.84-8.60)	**0.095**	2.55 (0.59-10.97)	0.208
Calendar year of baseline (per more recent)	4.82 (1.48-15.73)	**0.009**	3.44 (0.90-13.18)	**0.071**
Type of regimen started				
- Standard triple therapy	1.00	-	1.00	-
- Dual therapy	0.22 (0.05-0.98)	**0.048**	0.17 (0.03-0.90)	**0.037**

* adjusted for age, nationality. AIDS diagnosis, baseline CD4 cell count, hepatits co-infection, duration of cART and virological suppression, history of previous VF and reasons for stopping previous regimen.

FIGURE 5 : REASONS FOR DTG-TD IN ART-NAÏVE PATIENTS

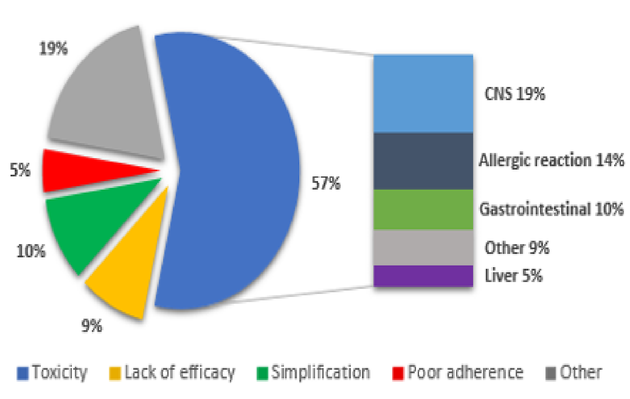
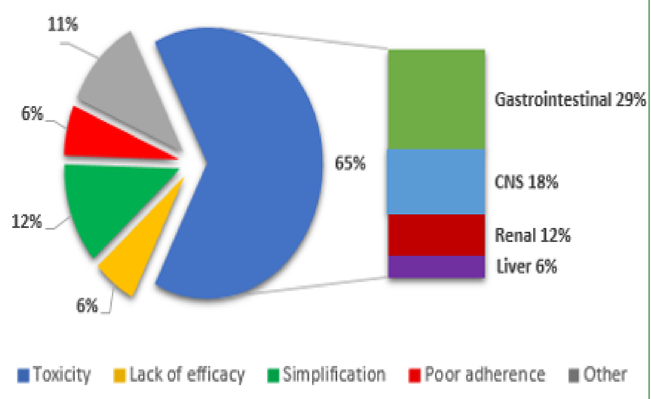


FIGURE 6 : REASONS FOR DTG-TD IN TE PATIENTS



CONCLUSIONS:

In this large cohort, DTG showed **an optimal efficacy and tolerability**, with **a low rate of discontinuations over the first year of treatment**, both in **ART-naïve and ART-experienced patients.** In ART-experienced population, **starting DTG as a part of a two-drug regimen was associated with a lower risk of DTG discontinuation compared to switching to a standard triple therapy, possibly due to more options left in those on 3-drugs regimens**. However, confounding by indication cannot be ruled out and we aim to re-perform this comparison after further follow-up is cumulated.

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