Durability of first line regimens including integrase strand inhibitors (INSTI): data from a real-life setting

Running head: **first-line INSTI-containing regimens**

Keywords: INSTI; Treatment failure; First line regimens; Observational study;

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ABSTRACT

Objective

To evaluate the durability of three INSTI+ 2NRTIs-containing in ART-naive individuals.

Design

Observational

Methods

Patients: HIV-positive, ART-naive subjects starting raltegravir (RAL), elvitegravir/cobicistat (EVG/c) or dolutegravir (DTG) with two NRTIs. Primary end-point: time to treatment failure (TF), i.e. occurrence of virological failure (VF: first of two consecutive plasma HIV-RNA >=200 copies/mL >24 weeks) or INSTI discontinuation for any reasons but simplification. Secondary end-points: INSTI discontinuation for toxicity/intolerance. Survival analysis by KM, Cox regression.

Results

2,016 patients included: 310 (15.4%) started RAL-, 994 (49.3%) DTG-, 712 (35.3%) EVG/c-based regimens. Over a median of 11 months, 167patients experienced TF: the one year-probability of TF was 6.5% for RAL; 5.4% for DTG, and 6.7% for EVG/c (p<.001). 68 patients (3.4%) discontinued INSTI for toxicity/intolerance. By multivariable analysis patients initiating RAL had a 2.03 (95% CI:1.2-3.2)-fold risk and patients on EVG/c a 1.88 (95% CI: 1.2, 2.9)-fold higher risk of TF versus DTG; there was no difference in risk of discontinuation for toxicity/intolerance when comparing DTG and RAL and marginal evidence for a difference when comparing EVG/c versus DTG (aRH: 1.94, 95%CI:1.00, 3.76; p=.05).

Conclusions

In our real-life setting, INSTI-based regimens showed high potency and durability. Among regimens currently recommended in Europe, those including DTG are associated with less risk of treatment failure.

INTRODUCTION

Integrase strand transfer inhibitors (INSTI)-based combination regimens are now recommended as first choice for initial therapy in International and National guidelines.[1-3] Each of the three currently licenced drugs in Italy, raltegravir, elvitegravir/cobicistat (EVG/c) and dolutegravir, in association with two nucleoside reverse transcriptase inhibitors (NRTIs), proved to be equivalent or superior to standard of care in randomised clinical trials.[4-7]
dolutegravir 50 mg once daily was found to be virologically non-inferior to raltegravir 400 mg twice daily in combination with two NRTIs over 96 weeks in the SPRING-2 trial;[8] there are no randomised trials comparing the response of elvitegravir/cobicistat -based combination antiretroviral therapy (cART) to any of the other licensed INSTI.

We aim to compare in a real-life setting the durability of all three INSTI- in combination with two NRTIs in previously cART-naive HIV positive individuals

PATIENTS AND METHODS

All the HIV-positive individuals enrolled in the ICONA Foundation study cohort, who started their first ever cART regimen with raltegravir, elvitegravir/cobicistat or dolutegravir with two NRTIs, after January 1, 2011 (date of licensing in Italy of first INSTI) were included. Data were frozen for analysis on June 30, 2018.

ICONA cohort is a cohort set up in Italy, in January 1997. Details of the cohort protocol are described elsewhere.[9] The main reason for discontinuing each drug are recorded in the ICONA database as: simplification/pro-active switch (either the reduction of drugs or the decrease in daily doses/pills, while viral load is undetectable), toxicity/intolerance (either side effects or demonstrated toxicity to the drug), failure (either virological, immunological or clinical or death), adherence issues and unknown/other causes.
In this analysis, patients were included if they started tenofovir disoproxil fumarate or tenofovir alafenamide (TDF or TAF)/emtricitabine (FTC) in combination with raltegravir, or with dolutegravir, or in combination with elvitegravir/cobicistat in single tablet regimen (STR) TDF(TAF)/FTC/EVG/c, or if they initiated abacavir/lamivudine in combination with raltegravir or with dolutegravir (either STR or not) from ART-naïve and had at least one clinical visit and a viral load measurement after starting.
Characteristics of participants at time of initiating cART according to the INSTI started were compared by chi-square test and Kruskal-Wallis test when appropriate.

The primary end-point was time to treatment failure, defined as the occurrence of virological failure (at the time of the first of two consecutive HIV-RNA plasma levels >=200

copies/mL after 24 weeks) or treatment discontinuation of the INSTI component of the regimen for any reason but simplification.[10]

Secondary end-points were: time to discontinuation of the INSTI component because of intolerance/toxicity and CD4 count response, as mean CD4 count changes at 6, 12 and 24 months (time windows ±3 months of the index dates) from starting cART, by means of ANCOVA analysis, insisting on times in which HIV-RNA remained ≤50 copies/mL and correcting the p-values for multiple testing (false discovery rate adjustment).

Survival analysis has been employed to estimate the incidence of primary and secondary endpoint and to compare responses to INSTI-based regimens. Participants' follow-up accrued from the date of starting INSTI-based cART to the estimated date of a failure-defining event or participants' last viral load measurement, last clinical visit or death. Kaplan Meier (KM) curves and Cox regression models were employed. In a sensitivity analysis inverse probability of censoring weights were used instead of assuming non-informative censoring. The analysis was conducted according to the intention-to-treat (ITT) principle.

RESULTS

Patients' characteristics

A total of 2,016 patients were included: 310 (15.4%) started raltegravir -, 994 (49.3%) dolutegravir -, and 712 (35.3%) elvitegravir/cobicistat -based cART. Patients who initiated raltegravir did so in earlier calendar years, were slightly older (median age 39 years versus dolutegravir 36, versus elvitegravir/cobicistat 37, p=.002), less frequently MSM (44%, versus dolutegravir 55%, versus elvitegravir/cobicistat 56%, p=.002), more frequently co-infected with HCV (9%, versus dolutegravir 5%, versus elvitegravir/cobicistat 6%, p<.001) and with HBV (1.3%, versus dolutegravir 0.4%, versus elvitegravir/cobicistat 1.3%, p<.001). They also were in a more advanced HIV disease stage (Table 1).

Primary endpoint: treatment failure

Over a median follow-up of 11 (IQR: 3-20) months, (raltegravir 15, dolutegravir 9, elvitegravir/cobicistat 11), a total of 167 failures were observed, resulting in an estimated 1-year risk of treatment failure of 6.5% (95%CI: 3.6, 9.5) for raltegravir; 5.4% (3.7, 7.0) for dolutegravir, and 6.7% (4.6, 8.7) for elvitegravir/cobicistat (p=.001). Results were similar after relaxing the assumption of non-informative censoring by using inverse probability of weighting survival curves and when comparing specific regimens accounting also for the exact NRTI-pair used in combination (Supplementary Figure 1).

Secondary end-points

A total of 246/2,016 (12.2%) patients discontinued the INSTI component of their regimen: 39.0% of patients on raltegravir, 5.6% dolutegravir and 9.8% of elvitegravir/cobicistat. raltegravir was stopped mainly for pro-active switch (62.8% of reasons for raltegravir discontinuation), whereas both dolutegravir and on elvitegravir/cobicistat were discontinued mainly for toxicity/intolerance (47.3% and 44.3% of discontinuations, respectively). In patients on dolutegravir, discontinuation due to neuro-psychiatric symptoms occurred in a total of 13 cases (1.3%) (see supplementary Table 1).

68 patients (3.4% of total) discontinued the INSTI component of the regimen for toxicity/intolerance; the one year-probability of discontinuation for intolerance/toxicity was 3.5% (95%CI: 0.7, 6.2) for raltegravir -based regimens, 3.7% (2.2, 5.1) for dolutegravir and 4.2% (2.6, 5.9) for elvitegravir/cobicistat (p= .34).

CD4 count change from pre-ART levels

After controlling for pre-ART CD4 count level, demographics and a number of other potential confounders from fitting an ANCOVA regression model and for a given VL≤50 copies/mL, current CD4 count showed larger increases according to the initiated INSTI, with the largest CD4 count changes seen in people who started dolutegravir, followed by EVG and then by raltegravir at all three studied time points (see Supplementary Table 2).

Independent predictors of primary and secondary end-points

Compared to patients who started dolutegravir -based regimens and after adjusting for a number of confounders (specified in the footnote of Table 2), patients who initiated raltegravir including regimens had a 2.03-fold (95% CI:1.2-3.2) higher risk of treatment failure and those who started elvitegravir/cobicistat had 1.88-fold (95% CI: 1.2, 2.9) higher risk of failure (p<.005).

There was no evidence for a difference in risk of discontinuation due to toxicity/intolerance when comparing dolutegravir and raltegravir adjusted relative hazard (aRH): 1.55 raltegravir versus dolutegravir (95%CI: 0.69, 3.50, p=.29) and marginal evidence for a difference in those initiating elvitegravir/cobicistat versus dolutegravir (aRH: elvitegravir/cobicistat versus dolutegravir: 1.94, 95% CI: 1.00, 3.76, p=.05) (Table 2).
These results were confirmed when restricting the analysis to patients who initiated tenofovir disoproxil fumarate or tenofovir alafenamide fumarate /emtricitabine backbone (data not shown).

DISCUSSION

Our analysis from a large data set of HIV-positive patients seen for HIV care in Italy confirms that INSTI-based regimens, used as initial therapy with either tenofovir disoproxil fumarate or tenofovir alafenamide fumarate /emtricitabine or abacavir/lamivudine, are very potent and well tolerated regimens associated with very few failure events: over 1 year follow-up, only 246 out of 2,016 (12.2%) patients discontinued their INSTI regimen for any reasons, 68 (3.4%) patients discontinued for toxicity and only 13 (0.6%) showed evidence of virological failure. In our real-life setting, dolutegravir -based regimens showed a superiority over the other two regimens when compared in regards of the composite end-point of treatment failure. The difference in durability appeared to be reflected also in a marginal difference in CD4 count response. Our data are not completely consistent with those of the SPRING trial,[8] in which raltegravir showed virological non-inferiority and the same rate of discontinuations due to adverse events.

All the studied regimens were well tolerated, with only a marginally significant difference between elvitegravir/cobicistat and dolutegravir but only for toxicity-related discontinuations. The rate of discontinuation due to adverse events of all the INSTI-based regimens has also been shown to be very low (less than 2% at 48 weeks) in fully powered randomised clinical trials.[4-8] In our clinical setting, the rate of discontinuation due to toxicity/intolerance was slightly higher at 3.5%, 2.0% and 4.3% for raltegravir, dolutegravir and elvitegravir/cobicistat respectively, over a median of one year follow-up. Interestingly, discontinuation due to neuro-psychiatric symptoms occurred only in 13 cases, i.e. 1.3% of all patients on dolutegravir, data which are consistent with those shown in a similar analysis of the Swiss HIV cohort study (1.7% neuropsychiatric toxicity).[11] However, this rate is considerably lower compared to that shown in other observational studies showing rates of dolutegravir interruptions ranging from 7.6% to 13.7%.[12-14]
Gastrointestinal intolerance was the main cause of discontinuation for intolerance/toxicity in participants who started elvitegravir/cobicistat -based regimens (29%), followed by renal toxicity (19%) also confirming the data of clinical trials.[5] Renal toxicity can be attributable mainly to the combined use of TDF.[15]

Some limitations of this analysis need to be mentioned. First, we cannot exclude that the found differences could be due to unmeasured confounding. Also, our analysis could be biased against elvitegravir/cobicistat. This is because, unlike dolutegravir, elvitegravir/cobicistat is always given as a single tablet regimen in co-formulation with NRTIs.

In conclusion, in our real life population, we demonstrated high efficacy and tolerability of all studied INSTI-based regimens currently available in Europe, and a lower risk of treatment failure in those using dolutegravir.

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The authors have no competing interests in this study that might influence the results and/or discussion reported in this paper.

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Table 1. Patients characteristics according to the different integrase inhibitor containing regimens

Characteristics	Regimen started				
	RAL-based N= 310	**DTG-based N= 994**	**EVG-based N= 712**	**p-value**	**Total N= 2,016**
Gender, n(%)				.088	
Female	67 (21.6)	167 (16.8)	115 (16.2)		349 (17.3)
Age, years				.002	
Median (IQR)	39 (31, 47)	36 (27, 41)	37 (28, 44)		37 (28, 44)
Mode of HIV Transmission, (%)				.002	
Intravenous drug users	21 (6.8)	44 (4.5)	38 (5.4)		103 (5.2)
Homosexual contacts	137 (44.3)	542 (55.1)	396 (56.3)		1075 (53.9)
Heterosexual contacts	133 (42.9)	322 (32.4)	231 (32.4)		686 (34.0)
Other/Unknown	18 (5.8)	76 (7.7)	38 (5.4)		132 (6.6)
Nationality, n(%)				.075	
Not Italian	62 (20.0)	218 (21.9)	170 (23.9)		450 (22.3)
Calendar year of baseline				<.001	
Median (IQR)	2015 (2014, 2016)	2016 (2016, 2017)	2016 (2015, 2016)		2016 (2015, 2017)
HBsAg, n(%)				<.001	
Positive	4 (1.3)	4 (0.4)	9 (1.3)		17 (0.8)
HCVAb, n(%)				<.001	
Positive	27 (8.7)	49 (4.9)	41 (5.8)		117 (5.8)
AIDS diagnosis, n(%)				.006	
Yes	26 (8.4)	48 (4.8)	26 (3.7)		100 (5.0)
CD4 count, cells/mmc				<.001	
Median (IQR)	330 (133, 494)	343 (121, 548)	380 (225, 553)		356 (151, 540)
CD4 count, n(%)				<.001	
<=200 cells/mmc	107 (35.4)	326 (33.3)	162 (22.9)		595 (29.9)
CD8 count, cells/mmc				.018	
Median (IQR)	852 (553, 1214)	853 (542, 1251)	900 (648, 1325)		867 (588, 1272)
Viral load, log10 copies/mL				.005	
Median (IQR)	4.93 (4.23, 5.43)	4.73 (4.10, 5.31)	4.71 (4.18, 5.13)	.089	4.75 (4.14, 5.27)
Time from HIV diagnosis to starting cART, months				<.001	
Median (IQR)	2 (1, 9)	1 (1, 3)	2 (1, 8)		2 (1, 5)
NRTIs started				<.001	
ABC+ 3TC	43 (13.9)	527 (53.0)	0 (0.0)		570 (28.3)
TDF+FTC	267 (86.1)	375 (37.7)	594 (83.4)		1236 (61.3)
TAF+FTC	0 (0.0)	92 (9.3)	118 (16.6)		210 (10.4)

*Chi-square or Kruskal-Wallis test as appropriate

RAL= raltegravir; DTG=dolutegravir; EVG=elvitegravir; 3TC=lamivudine; FTC=emtricitabine; TDF= tenofovir disoproxil fumarate; TAF= tenofovir alafenamide fumarate; NRTIs= nucleoside reverse transcriptase inhibitors

Table 2. Relative hazards of reaching the end-points by univariate and multivariate Cox analyses

	Unadjusted and adjusted relative hazards			
Outcomes	**Unadjusted RH (95% CI)**	**p-value**	**Adjusted* RH (95% CI)**	**p-value**
Treatment failure				
Regimen				
RAL-based	2.03 (1.36, 3.03)	<.001	2.00 (1.24, 3.21)	.004
DTG-based	1.00		1.00	
EVG/c-based	1.61 (1.12, 2.31)	.011	1.88 (1.20, 2.95)	.006
Discontinuation for toxicity				
Regimen				
RAL-based	1.33 (0.66, 2.68)	.419	1.55 (0.69, 3.50)	.286
DTG-based	1.00		1.00	
EVG/c-based	1.43 (0.87, 2.34)	.154	1.94 (1.00, 3.76)	.051

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

RAL= raltegravir; DTG=dolutegravir; EVG=elvitegravir;