AIDS Research and Human Retroviruses

DOI: 10.1089/AID.2020.0078

Overall tolerability of Integrase Inhibitors in clinical practice: results from a multicenter Italian cohort

Arturo Ciccullo[1,2], Gianmaria Baldin[1,3]*, Vanni Borghi[4], Gaetana Sterrantino[5], Giordano Madeddu[6], Alessandra Latini[7], Gabriella d'Ettorre[8], Alessandro Lanari[9,10], Maria Mazzitelli[11], Manuela Colafigli[7], Amedeo Capetti[12], Letizia Oreni[13], Filippo Lagi[5], Stefano Rusconi[13], Simona Di Giambenedetto[1,2]

1 Section of Infectious Diseases, Department of Safety and Bioethics, Catholic University of the Sacred Heart, Rome, Italy

2 Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Infectious Diseases Unit, Rome, Italy.

3 Mater Olbia Hospital, Olbia, Italy

4 Department of Infectious Diseases, Azienda Ospedaliero-Universitaria Policlinico of Modena, Modena, Italy;

5 Division of Tropical and Infectious Diseases, 'Careggi' Hospital, Florence, Italy;

6 Department of Clinical, Surgical and Experimental Sciences, University of Sassari, Sassari, Italy;

7 Infectious Dermatology and Allergology Unit, IFO S. Gallicano Institute (IRCCS), Rome, Italy;

8 Department of Public Health and Infectious Diseases, Azienda Policlinico Umberto I, Rome, Italy;

9 Infectious Diseases Unit, AOU Senese, Siena, Italy;

10 Department of Medical Biotechnologies, University of Siena, Siena, Italy;

11 Department of Health Sciences, Department of Medical and Surgical Sciences, Unit of Infectious and Tropical Diseases, Magna Graecia University, Catanzaro, Italy.

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12 Division of Infectious Diseases, Department of Infectious Diseases, Luigi Sacco University Hospital, Milan, Italy.

13 Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Milan, Italy;

*__Corresponding author__: Dr. Gianmaria Baldin, Istituto di Malattie Infettive, Università Cattolica del Sacro Cuore, Roma, Italy. Tel. 0039 06-30155366. E-mail: gian.baldin@gmail.com

Keywords: HIV, dolutegravir, raltegravir, elvitegravir, durability, integrase inhibitors

Running Head: Overall tolerability of INIs

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Abstract

Background. International guidelines recommend the use of INI-based regimens as first line ARV in both naïve and experienced HIV-infected patients.

Materials and Methods. We analyzed a multicenter cohort of HIV-infected patients, both naïve and experienced, starting a ARV including an INI. Chi-square test and non-parametric tests were used to assess differences in categorical and continuous variables, respectively. Kaplan-Meyer survival analysis were performed to estimate the probability of maintaining the study-drug and Cox-regression analysis to evaluate predictors of discontinuation.

Results. We enrolled 4343 patients: 3143 (72.4%) were males, with a median age of 49 years (IQR 41-55). Naïve patients were 733 (16.9%), of whom 168 (22.9%) AIDS-presenters. Overall, 2282 patients (52.5%) started DTG, 1426 (32.8%) RAL and 635 (14.7%) EVG. During 10032 PYFU, we observed 1278 discontinuations (13 per 100PYFU); 448 of them (35%) due to simplification and 355 (28%) to toxicities (98 for CNS toxicity). Reasons of discontinuation were different between INIs. Estimated probability of maintaining DTG at 3 and 4 years were 81.5% (95%CI 80.5-82.5) and 76.3% (95%CI 73.9-78.7), respectively; RAL 61.6% (95%CI 60.2-63.0) and 54.1% (95%CI 52.7-55.5); EVG 71.6% (95%CI 69.2-74.0) and 68.3% (95%CI 65.3-71.3) (p<0.001). At a multivariable analysis, being on a RAL-based ARV (vs DTG, aHR 2.9, 95%CI 2.3-3.6, p<0.001), a EVG-based ARV (vs DTG, aHR 1.3 95%CI 1.1-1.7, p=0.049) and a peak HIV-RNA>500k cp/mL (aHR 1.3, 95%CI 1.1-1.6, p=0.006) predicted INI discontinuation.

Conclusions. Our data confirm the good tolerability of INIs in clinical practice. Differences emerge between the three drugs in reasons for discontinuation.

Introduction

Integrase strand transfer Inhibitors (INI) have become, in both national and international guidelines [1,2], the first choice for both first line antiretroviral (ARV) regimens and switch regimen in virologically suppressed HIV-infected patients, thanks to their efficacy and favorable tolerability profile compared to other classes [3-5].

At the time of data collection, licensed INIs in Italy were raltegravir, elvitegravir/cobicistat and dolutegravir: raltegravir (RAL) was the first INI approved (US FDA, October 2007; EMA, January 2008) and as such was prevalently used in experienced, multi-failed patients, elvitegravir (EVG) was then approved, initially (FDA, August 2012; EMA, May 2013) exclusively as a component of a Single Tablet Regimen (STR), while dolutegravir (DTG), although being the most recently approved INI (FDA, August 2013; EMA, November 2013), has now become one of the most used antiretroviral drugs, thanks to its high genetic barrier and convenient dosing [6].

The efficacy of INI has been widely described in different works [7,8], but studies from clinical practice have questioned the optimal tolerability profile of this class of antiretroviral [9-11], showing unexpected high rates of toxicity-related discontinuations. However, data from large cohorts in particular regarding experienced patients are still lacking.

We aimed to compare, in a real-life scenario, the durability of all three INIs in both treatment-naive and experienced HIV-positive patients in our multicenter cohort (the ODOACRE Cohort) [12]. The Clinical centers involved in this study (listed in Table 1) take care of about 15.000 people living with HIV (PLWHIV), more than 10% of the estimated PLWHIV in Italy (130.000). [13] About half of them, at some point, started a INI-based strategy. In this study, we also intend to investigate reasons for INIs discontinuation and differences between them.

Methods

We retrospectively analyzed a cohort of HIV-1 infected adult (age ≥18 years) patients, both treatment-naïve and experienced, from nine Italian clinical centers (the list of Clinical

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Centers is described in Table 1) belonging to the "ODOACRE cohort", starting an INI-based ARV regimen between January 2008 to December 2018. Primary endpoint was the time to treatment discontinuation (TD, defined as the discontinuation of either dolutegravir, raltegravir or elvitegravir, regardless of whether the remaining antiretroviral drugs used in the combination had been stopped or not).

We collected baseline characteristics (age, sex, HIV-risk factor), as well as patients' clinical history and viroimmunological parameters at baseline; reasons for INI discontinuations were also collected. Censor was defined as death, suspension of the INI or the date of the last virological determination.

Chi-square test and non-parametric tests were used to assess differences in categorical and continuous variables, as appropriate. Kaplan-Meyer survival analysis was performed to estimate the probability of maintaining the study-drug and Cox-regression analysis to evaluate predictors of discontinuation. Multi-variable models were adjusted for naïve status, calendar year and for significantly different variables between INIs at baseline.

The study was approved by each local Ethics Committee (protocol number of the promoting center: 5284/15) and all patients signed informed consent for data collection.

Results

We enrolled 4343 patients: 3143 (72.4%) were males, with a median age of 49 years (Interquartile Range [IQR] 41-55). Median peak HIV-RNA was 5.04 $\log_{10}$ copies/mL (IQR 4.50-5.51), while median CD4+ cell nadir was 171 cell/mm3 (IQR 48-304). Treatment-naïve patients were 733 (16.9%), of whom 168 (22.9%) were AIDS-presenters. As to experienced patients, their median time from HIV diagnosis was 16 years (IQR 8-23), with a median time from ARV initiation of 13 years (IQR 4-21); among experienced patients, 2696 (76.2%) had a HIV-RNA ≤50 cp/mL at baseline. Overall, 2282 patients (52.5%) started a DTG-containing regimen, 1426 (33.1%) a regimen containing RAL and 635 (14.7%) EVG. Full patients' characteristics are available in Table 2.

During 10032 Patient Years of Follow-up (PYFU), we observed 1278 discontinuations, with a cumulative rate of 13 per 100 PYFU. Three hundred and thirty-one (14.5%) discontinued

DTG, 812 (56.9%) discontinued RAL while 135 (21.3%) discontinued EVG. Median time to INI discontinuation was 13 months (IQR 4-33). Discontinuations in the first year of follow-up ("early" discontinuations) were 572: 221 in the DTG group (66.7% of group's overall discontinuations), 260 in the RAL group (32.0%) and 91 in the EVG group (66.9%). Difference in discontinuation rate in the first year between the three analyzed groups was statistically significant (p<0.001).

As to the reasons for INI discontinuations: 448 (35.0% of total discontinuations) were due to simplification, 355 (27.8%) to toxicities (98 of which were due to neuropsychiatric events), 145 (11.3%) to virological failure, 69 (5.4%) to death, 35 (2.7%) to drug-drug interactions and 227 (17.7%) to other/unknown causes. Reasons of discontinuation were different between INIs, as shown in Table 3.

Estimated probabilities of maintaining DTG at 2, 3 and 4 years were 84.7% (95%CI 83.9-85.5), 81.5% (95%CI 80.5-82.5) and 76.3% (95%CI 73.9-78.7), respectively; for RAL they were 69.2% (95%CI 67.9-70.5), 61.6% (95%CI 60.2-63.0) and 54.1% (95%CI 52.7-55.5), while for EVG were 77.2% (95%CI 75.8-78.6), 71.6% (95%CI 69.2-74.0) and 68.3% (95%CI 65.3-71.3) [Figure 1]. Differences between groups were statistically significant (Log-Rank p<0.001). At a multivariable analysis, being on a RAL-based regimen (compared with DTG, aHR 2.9, 95%CI 2.3-3.6, p<0.001), a EVG-based one (vs DTG, aHR 1.3 95%CI 1.1-1.7, p=0.049) and a peak HIV-RNA over 500.000 copies/mL (aHR 1.3, 95%CI 1.1-1.6, p=0.006) predicted INI discontinuation, after adjusting for calendar year, naïve status, age, sex, HIV risk factor, time of virological suppression, years of HIV and CD4+ cell nadir.

Considering only treatment-naive patients, probability of maintaining DTG was 78.7 (95%CI 76.2-81.2) at 2 years, 77.1% (95%CI 74.4-79.8) at 3 years and 72.6% (95%CI 67.5-78.1) at 4 years. Probabilities for RAL were 54.1% (95%CI 50.4-57.8), 45.6% (95%CI 41.8-49.4) and 40.4% (95%CI 36.3-44.2), while for EVG they were 73.3% (95%CI 69.1-77.5), 65.6% (95%CI 60.6-70.6) and 58.5% (95%CI 52.0-65.0), respectively. In this sub-analysis, starting a first-line RAL-based regimen (compared with DTG, aHR 3.32, 95%CI 2.1-5.2, p<0.001) and a concomitant AIDS-defining event (aHR 1.65, 95%CI 1.01-2.71, p=0.045) resulted predictors of INI discontinuation.

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Evaluating discontinuations due only to toxicities, we did not find a significant difference between INIs using Kaplan-Meyer survival analysis and Cox regression analysis (Log-Rank p=0.064, Figure 2); in this specific analysis, male sex (vs female, aHR 0.65, 95%CI 0.44-0.96, p=0.030) was reversely associated with drug discontinuation. Reasons for stopping study INI were significantly different between males and females (p<0.001); in particular, among women, 8.7% of the total discontinuations were due to GI toxicity, 2.3% to renal toxicity and 6.7% to neuropsychiatric events. Meanwhile, among males, the observed percentages were 5.4%, 3.5% and 8.2%, respectively.

A specific sub-analysis on discontinuation due only to neuropsychiatric toxicity, found significant differences between groups (Log-rank p<0.001); a previous INI exposure (aHR 1.9, 95%CI 1.1-3.3, p=0.017) was associated with the event, while being on a RAL-based regimen (vs DTG, aHR 0.1, 95%CI 0.1-0.5, p=0.004) or on a EVG-based one (vs DTG, aHR 0.4, 95%CI 0.2-0.9, p=0.035) was inversely associated.

We also observed significant differences between groups in estimated probabilities of INI discontinuations due to drug-drug interactions (Log-rank p<0.001) and simplification (Log-rank p<0.001). In our cohort, being on a EVG-based regimen (vs DTG, aHR 8.4, 95%CI 3.0-23.0, p<0.001) independently predicted discontinuation due to drug-drug interaction. Discontinuation of study INI due to simplification, meanwhile, was predicted by being on a RAL-based regimen (vs DTG, aHR 20.0, 95%CI 11.3-35.2, p<0.001) or a EVG-based one (vs DTG, aHR 2.4, 95%CI 1.1-5.7, p=0.042) while it was inversely associated with time of ARV exposure (aHR 0.96, 95%CI 0.92-0.98, p=0.024). As to patients discontinuing RAL due to simplification, 258 of them (65.0%) started a ARV regimen containing another INI (177 with DTG).

Discussion

In our multicenter cohort we found differences in durability of the three integrase inhibitors available in Italy at the time of data analysis. Overall, the probability of maintaining DTG was higher compared with those of RAL and EVG both in treatment experienced and naïve patients, a finding in line with previous studies [14,15]. However, no difference was found regarding discontinuations due to toxicity between groups,

confirming the good tolerability of the whole integrase inhibitors drug class observed in other cohort studies [16].

Central nervous system toxicity was a particular concern, not only for patients taking dolutegravir [17], but also for those on other INIs [11]. In our cohort, we found that patients taking DTG-based regimens were more prone to discontinue following neuropsychiatric events compared with the other INIs, a finding that confirms results from other cohorts [18,19]. CNS toxicity was the leading cause of DTG interruption in our cohort.

However, as recently pointed out by Llibre et al. [20], there is the possibility that Clinicians' awareness, following initial reports on the association between DTG and neuropsychiatric events, had a significant biasing effect. On the other hand, the favorable dosing and the high efficacy shown as part of 2DR [21,22], make DTG the drug less likely to be stopped due to simplification.

The higher probability of stopping EVG due to drug-drug interaction could be explained by the need of a pharmacokinetic booster.

Early (≤1 year) discontinuations were lower in the RAL group compared with the other two. This finding could be explained by the different use that was made of raltegravir when it was first approved; being the first INI available, in fact, led clinicians in using RAL prevalently in heavily experienced patients, while DTG and EVG in our cohort were started mainly because of simplification or dyslipidemia.

Strengths of our study include the size of the population, one of the largest described, representing different clinical experiences, as well as the length of follow-up; these features make it possible to best reflect clinical practice. As to the main limitations, the most important is the high number of discontinuations due to unknown reasons. In addition, the three groups are very different, mainly due to the fact that the three molecules were introduced into the clinical practice in different time points and were used often in the context of different ARV strategies, although during analysis we tried to correct this bias, by adjusting for differences between groups. Finally, other limitations are

the retrospective design of the study and the fact that adverse events not leading to drug discontinuations were not collected.

In conclusion, our data confirm the good tolerability of INIs in clinical practice, with some differences between the three analyzed drugs regarding reasons for discontinuation.

Acknowledgment

Collaborators in ODOACRE group: Alberto Borghetti, Roberto Cauda, Luigi Celani, Alex Dusina, Silvia Lamonica, Francesca Lombardi, Claudio Maria Mastroianni, Davide Moschese, Enrica Tamburrini (Roma), Arianna Emiliozzi, Barbara Rossetti (Siena), Cristina Mussini (Modena), Sergio Babudieri, Andrea De Vito (Sassari), Carlo Torti, Enrico Maria Trecarichi (Catanzaro), Maria Vittoria Cossu, Massimo Galli, Andrea Giacomelli, Giuliano Rizzardini (Milano)

Author Contribution statement

ACi, GB and SDG contributed to the conception and design of the study. ACi and GB contributed to the draft of the paper. VB, GS, GM, ALat, GdE, Alan, MM, MC, Aca, LO, FL and SR contributed to the acquisition of the data. ACi, GB and SDG contributed to the analysis and interpretation of data. GS, GM, SR and SDG contributed to the critical revision of the paper for important intellectual content. All Authors approved the final version of the paper.

Transparency declaration

GB received travel grant from Gilead Sciences. GS has received funds for speaking by Gilead, Merk, Janssen, Abbvie, ViiV. GM reports personal fees from Gilead Sciences, Janssen-Cilag,Merck Sharp & Dohme, ViiV Healthcare, outside the submitted work. ACa has received a personal grant from AB, Gilead and ViiV. SR received research grants to his Institution from ViiV Heathcare, Gilead Sciences and Janssen, outside the submitted work; he was also a paid consultant for ViiV Heathcare, Gilead Sciences, Merck Sharp and Dohme, Bristol-Myers Squibb and Janssen. SDG was a paid consultant or member of advisory boards for Gilead, ViiV Healthcare, Janssen-Cilag, Merck Sharp & Dohme and

Bristol-Myers Squibb. All other authors (ACi, VB, GdE, AL, MM, MC, LO, FL): none to declare.

Funding

This study was conducted during our routine clinical activity

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Table 1. List of Clinical Centers involved in the study

Catholic University of the Sacred Heart, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome
Azienda Ospedaliero Universitaria di Modena, Clinica Malattie Infettive e Tropicali, Modena
Division of Tropical and Infectious Diseases, 'Careggi' Hospital, Florence
Department of Clinical, Surgical and Experimental Sciences, University of Sassari, Sassari
Infectious Dermatology and Allergology Unit, IFO S. Gallicano Institute (IRCCS), Rome
Department of Public Health and Infectious Diseases, Azienda Policlinico Umberto I, Rome
Infectious Diseases Unit, AOU Senese, Siena
Department of Health Sciences, Department of Medical and Surgical Sciences, Unit of Infectious and Tropical Diseases, Magna Graecia University, Catanzaro
Division of Infectious Diseases, Department of Infectious Diseases, Luigi Sacco University Hospital, Milan

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Table 2. Characteristics of the study population.

Variables	Overall n=4343	Dolutegravir n=2282	Raltegravir n=1426	Elvitegravir n=635	p
Males, n (%)	3143 (72.4%)	1698 (74.4)	961 (67.4)	484 (76.2)	<0.001
Age, Years, Median (IQR)	48.9 (41.2-54.8)	50.0 (41.3-55.7)	48.0 (42.3-53.7)	47.2 (36.8-54.2)	<0.001
Risk factors, n (%)					<0.001
Heterosexual	1684 (38.8)	898 (39.4)	555 (38.9)	231 (36.4)	
MSM	1540 (35.5)	856 (37.5)	395 (27.7)	289 (45.5)	
IDU	771 (17.8)	314 (13.8)	387 (27.1)	70 (11.0)	
Others/Unknown	348 (8.0)	214 (9.4)	89 (6.2)	45 (7.1)	
HCV Ab positive, n (%)	733 (18.9)	295 (14.3)	378 (30.6)	60 (10.5)	<0.001
HBsAg positive, n (%)	122 (3.2)	50 (2.5)	42 (3.4)	30 (5.4)	0.002
CDC stage C, n (%)	1244 (28.9)	619 (27.6)	462 (32.4)	163 (25.7)	0.001
Years from HIV diagnosis, Median (IQR)	13.5 (3.8-21.4)	13.2 (3.9-21.6)	15.1 (5.5-21.9)	9.9 (1.5-19.6)	<0.001
Zenith HIV-RNA, log_{10} cp/ml, Median (IQR)	5.04 (4.50-5.51)	5.05 (4.49-5.51)	5.03 (4.51-5.51)	5.07 (4.52-5.52)	0.894
Nadir CD4+, cells/mmc, Median (IQR)	171 (48-304)	181 (48-316)	154 (46-272)	189 (58-327)	<0.001
Baseline CD4+, cells/mmc, Median (IQR)	550 (329-788)	610 (396-840)	469 (270-699)	520 (320-752)	<0.001
Reasons for starting study drug, n (%)					<0.001
Naive	734 (16.9)	378 (16.6)	213 (14.9)	143 (22.5)	
Treatment failure	515 (11.9)	214 (9.4)	257 (18.0)	44 (6.9)	

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Simplification	1259 (29.0)	839 (36.8)	195 (13.7)	225 (35.4)	
GI/hepatic toxicity	218 (5.0)	97 (4.3)	92 (6.5)	29 (4.6)	
Dyslipidemia	301 (6.9)	203 (8.9)	77 (5.4)	21 (3.3)	
Renal toxicity	163 (3.8)	74 (3.2)	77 (5.4)	12 (1.9)	
CNS toxicity	102 (2.3)	28 (1.2)	34 (2.4)	40 (6.3)	
Rash/hypersensitivity	100 (2.3)	14 (0.6)	78 (5.5)	8 (1.3)	
Osteoporosis	65 (1.5)	39 (1.7)	18 (1.3)	8 (1.3)	
Other toxicities	75 (1.7)	36 (1.6)	26 (1.8)	13 (2.0)	
Drug-drug interactions	225 (5.2)	104 (4.6)	113 (7.9)	8 (1.3)	
Restart after interruption	68 (1.6)	24 (1.1)	38 (2.7)	6 (0.9)	
Cardiovascular disease	25 (0.6)	11 (0.5)	11 (0.8)	3 (0.5)	
Other/Unknown	493 (11.3)	221 (9.7)	197 (13.8)	75 (11.8)	
Months of follow-up, Median (IQR)	22.9 (10.2-36.9)	21.9 (10.1-31.8)	32.7 (11.1-63.2)	18.4 (9.4-28.6)	<0.001
Years on ARV (for TE), Median (IQR)	12.6 (5.7-18.3)	13.3 (6.0-19.1)	12.8 (6.0-17.0)	10.3 (3.8-18.1)	<0.001
Virologically suppressed patients at baseline (for TE), n (%)	2696 (76.2)	1551 (82.5)	773 (65.9)	372 (77.0)	<0.001
Months of virological suppression (for TE), Median (IQR)	43.0 (5.8-97.6)	63.2 (13.2-114.8)	28.1 (2.0-70.2)	29.5 (3.7-95.7)	<0.001
Previous virological failure (for TE), n (%)	1680 (48.0)	835 (46.4)	656 (54.1)	189 (38.4)	<0.001

Therapies before switch (for TE)					<0.001
2NRTI + PI	1218 (33.9)	554 (29.2)	514 (42.7)	150 (30.5)	
2NRTI + NNRTI	874 (24.3)	469 (24.7)	259 (21.5)	146 (29.7)	
2NRTI + INI	405 (11.3)	246 (13.0)	51 (4.2)	108 (22.0)	
Mono/Dual	712 (19.8)	448 (23.6)	208 (17.3)	56 (11.4)	
Others	382 (10.6)	180 (9.5)	171 (14.2)	31 (6.3)	
Previous INI exposure (for TE), n (%)	1017 (28.4)	703 (37.6)	129 (10.6)	185 (37.6)	<0.001

TE: Treatment experienced patients

P values were evaluated between the three groups

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Table 3. Reasons for INI discontinuation

	Overall (n=1278)	Dolutegravir (n=331)	Raltegravir (n=812)	Elvitegravir (n=135)	p
					<0.001
Treatment failure	145 (11.3)	22 (6.6)	108 (13.3)	15 (11.0)	
Simplification	448 (35.0)	32 (9.7)	397 (48.9)	19 (14.0)	
GI/hepatic toxicity	82 (6.4)	42 (12.7)	27 (3.3)	13 (9.6)	
Dyslipidemia	21 (1.6)	3 (0.9)	14 (1.7)	4 (2.9)	
Renal toxicity	40 (3.1)	12 (3.6)	18 (2.2)	10 (7.4)	
CNS toxicity	98 (7.7)	76 (23.0)	10 (1.2)	12 (9.6)	
Rash/hypersensitivity	41 (3.2)	21 (6.3)	13 (1.6)	7 (5.1)	
Osteoporosis	9 (0.7)	1 (0.3)	6 (0.7)	2 (1.5)	
Other toxicities	63 (4.9)	22 (6.6)	36 (4.4)	5 (3.7)	
Drug-drug interactions	35 (2.7)	9 (2.7)	8 (1.0)	18 (13.2)	
Pregnancy	7 (0.5)	4 (1.2)	2 (0.2)	1 (0.7)	
Cardiovascular disease	3 (0.2)	2 (0.6)	1 (0.1)	0	
Death	69 (5.4)	23 (6.9)	43 (5.3)	3 (2.2)	
Other/Unknown	217 (17.0)	62 (18.7)	129 (15.9)	26 (19.1)	

GI=Gastrointestinal

CNS=Central Nervous System

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Figure Legends

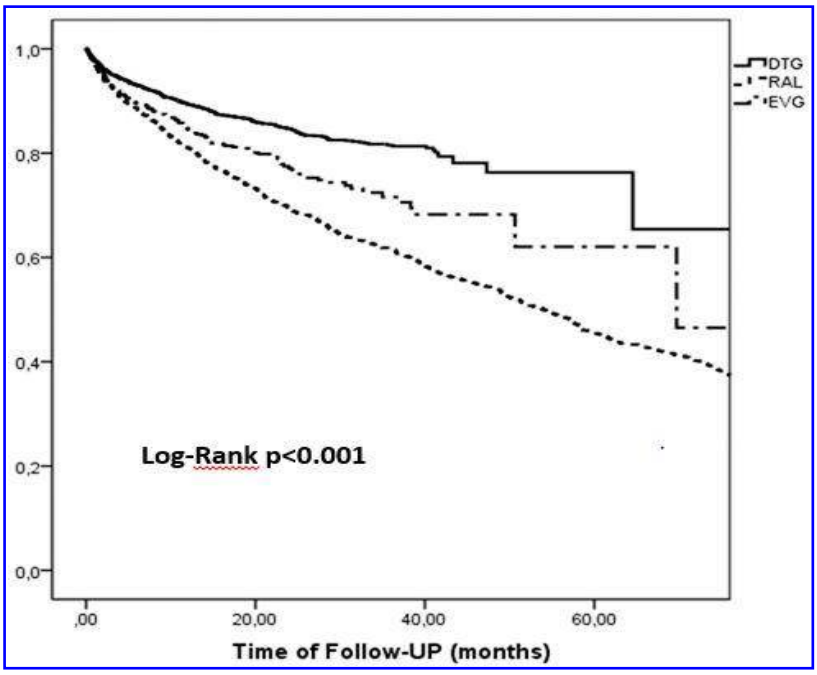

Figure 1. Estimated probability of maintaining study drug (Overall population)

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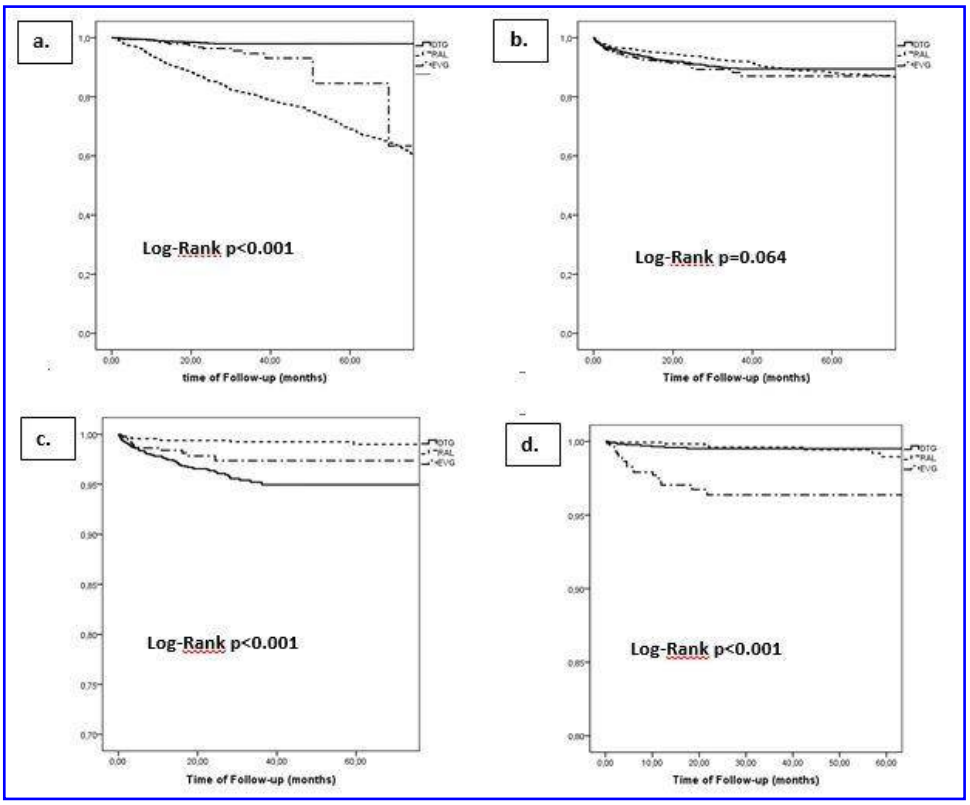

Figure 2. Estimated probabilities of maintatining study drugs (Sub-analysis): a. discontinuations due to treatment simplification. b. discontinuations due to overall toxicity. c. discontinutions due to neuropsychiatric events. d. discontinuations due to drug-drug interactions.

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