# COMPARATIVE NEUROPSYCHIATRIC TOXICITY PROFILE OF DOLUTEGRAVIR VERSUS EFAVIRENZ VERSUS OTHER ANTIRETROVIRAL THIRD DRUGS USED EITHER IN FIRST-LINE OR SWITCH ANTIRETROVIRAL THERAPIES (ART): DATA FROM ICONA FOUNDATION STUDY COHORT

PE 32/10

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## BACKGROUND

- Concerns about an **increased risk of neuropsychiatric adverse events (NPAEs) during exposure to Dolutegravir (DTG)** have been recently raised in observational studies[1-5].
- Historically, **Efavirenz (EFV) was largely associated to a higher risk of NPAEs** with an increased rate of discontinuations for toxicity compared with other antiretrovirals[6].
- **Despite this common toxicity profile, comparisons of NPAEs' risk between DTG and EFV-based regimens are limited.** A large comparative randomized trial showed a lower rate of NPAEs with fewer discontinuations in ART-naïve patients starting DTG compared to those starting EFV[7,8]. **However, direct comparisons in real-life setting are lacking.**

## AIMS

The aim of this study was **to evaluate and compare the risk of discontinuation due to NPAEs among DTG-based, EFV-based and other different antiretroviral regimens currently used as either first-line or switch ART.**

## STUDY DESIGN AND METHODS

### STUDY DESIGN AND POPULATION

- **Prospective, observational, multicentric study** analyzing data from Icona Foundation Study Cohort.
- All consecutive **ART-naïve and virologically-suppressed treatment-experienced (TE) HIV-positive patients**, enrolled in the Icona cohort, **who started or switched for the first time to a regimen including DTG or EFV or other currently used third drugs from January 2006 to December 2018,** were included in the analysis and divided into three groups, according to the third drug started:
  - ✓ **DTG-group**
  - ✓ **EFV-group**
  - ✓ **Other-group** (including patients starting boosted darunavir, atazanavir, rilpivirine or other integrase strand transfer inhibitors [INSTIs] as third drug).

### OUTCOME DEFINITION:

**Treatment discontinuation due to NPAEs (NP-TD): discontinuation of the third drug,** ignoring changes in the backbone**, due to NPAEs** as reported by the treating physician.

### STATISTICAL ANALYSIS

- The probability of NP-TD was estimated and compared among the three treatment groups by Kaplan Meier analysis.
- Cox multivariable analysis were fitted to evaluate the independent risk of NP-TD for the three treatment groups after adjusting for main confounding factors.
- Two sensitivity cox-regression analysis were performed to assess the independent risk of NP-TD: 1) restricting the group "other" only to patients starting a non-DTG INSTI-based regimen in ART-naïve and TE populations 2) restricting the analysis to patients starting ART from 2011 (first year in which DTG was available in Icona database) in ART-naïve population.
- NPAEs leading to discontinuation were characterized and compared among the groups in ART-naïve population.

## RESULTS

**Table 1 – Baseline characteristics according to treatment history and third-drug started**

| | ART-naive (N=7,854) | | | | Treatment-Experienced (N=3,300) | | | |
|---|---|---|---|---|---|---|---|---|
| | DTG group (N=1,322) | EFV group (N=1,542) | Other group (N=4,990) | p-value | DTG group (N=1,014) | EFV group (N=515) | Other group (N=1,771) | p-value |
| Female gender* | 223 (16.9) | 230 (14.9) | 1016 (20.4) | **<0.001** | 228 (22.5) | 126 (24.5) | 437 (24.7) | 0.411 |
| Age, years** | 40 (31-49) | 39 (32-46) | 39 (31-47) | **0.051** | 48 (39-56) | 41 (35-47) | 45 (38-52) | **<0.001** |
| Non-Italian born* | 556 (42.1) | 289 (18.7) | 1351 (27.1) | **<0.001** | 124 (12.2) | 46 (8.9) | 225 (12.7) | 0.065 |
| Risk Factor for HIV* | | | | **<0.001** | | | | **<0.001** |
| -MSM | 703 (53.7) | 701 (45.9) | 2293 (46.4) | | 421 (41.6) | 165 (32.1) | 610 (34.6) | |
| -Heterosexual | 442 (33.4) | 599 (38.8) | 1948.(39.0) | | 412 (40.6) | 212 (41.2) | 746 (42.1) | |
| -IDU | 62 (4.7) | 121 (7.9) | 381. (7.7) | | 122 (12.1) | 114 (22.2) | 307 (17.4) | |
| -Other/Unknown | 102 (7.8) | 107 (7.0) | 322 (6.5) | | 56 (5.5) | 23 (4.5) | 102 (5.8) | |
| AIDS diagnosis* | 163 (12.3) | 136 (8.8) | 486 (9.7) | **0.005** | 164 (16.2) | 105 (20.4) | 276 (15.6) | **0.033** |
| HCV-Ab Positive* | 69 (5.2) | 151 (9.8) | 416 (8.3) | **<0.001** | 151 (14.9) | 139 (27.0) | 366 (20.7) | **<0.001** |
| CD4 count nadir, cells/mm3** | 333 (129-526) | 307 (213-399) | 337 (191-480) | **<0.001** | 271 (141-384) | 236 (109-334) | 258 (132-361) | **<0.001** |
| BL calendar year** | 2016 (2016-2017) | 2011 (2009-2012) | 2014 (2012-2016) | **<0.001** | 2016 (2016-2017) | 2007 (2003-2011) | 2014 (2010-2016) | **<0.001** |
| Months from HIV diagnosis to ART** | 1 (1-3) | 11 (2-39) | 3 (1-24) | **<0.001** | 71 (32, 171) | 61 (28, 124) | 92 (42, 172) | **<0.001** |
| BL CD4 count, cell/mm3** | 349 (139-562) | 324 (226-420) | 351 (199-503) | **<0.001** | 658 (463-882) | 500 (355-720) | 616 (442-821) | **<0.001** |
| BL HIV-RNA, $log_{10}$ copies/mL** | 4.62 (4.10-5.24) | 4.75 (4.23-5.14) | 4.57 (4.00-5.04) | **<0.001** | - | - | - | - |
| Third Drug non-EFV Non-DTG* | | | | - | | | | - |
| - RPV | - | - | 1230 (24.7) | | - | - | 640 (36.1) | |
| - ATV/r | - | - | 1131 (22.6) | | - | - | 533 (30.1) | |
| - DRV/r | - | - | 1271 (25.5) | | - | - | 182 (10.3) | |
| - RAL | - | - | 469 (9.4) | | - | - | 221 (12.5) | |
| - EVG/c | | | 889 (17.8) | | | | 195 (11.0) | |
| Follow-up, months** | 11 (4-19) | 8 (3-27) | 21 (9-38) | **<0.001** | 19 (11-29) | 28 (9-60) | 45 (23-75) | **<0.001** |

*= n (%); **= median (IQR)

- Overall, **7,854 ART-naïve patients** (starting ART based on DTG in 17%, EFV in 20% and non-EFV non-DTG in 63%) and **3,300 TE patients** (switching to regimens based on DTG in 31%, EFV in 15% and non-EFV non-DTG in 54%) were included. Main BL characteristics are shown in Table 1.
- At survival analysis, **patients on EFV-based ART were more likely to stop third drug due to NPAEs compared to patients on DTG-based or other ART both in ART-naïve (p<.001) and in TE (p<.001) population** [Fig.1a,1b]
- At multivariable analysis, after adjusting for main confounders, **DTG was associated with a risk of NP-TD significantly lower than EFV but higher than non-DTG non-EFV drugs in both ART-naïve and TE patients** [Table2A]. **In ART-naïve population, these data were confirmed** also restricting the analysis to **patients starting ART after 2011** [Table2A] and **including in the "other" group only people who started a elvitegravir- or raltegravir-based ART** [Table2B]. Conversely, **in TE patients, the risk of NP-TD did not significantly differ between patients treated with DTG *versus* other INSTI-based ART** [Table2B].
- In ART-naïve patients, NPAEs leading to EFV discontinuation were mostly sleep disturbances (insomnia and abnormal dreams), dizziness and impaired concentration while those leading to DTG stop were mainly insomnia and mood disorders [Fig2].

**Table 2-Relative hazards (RH) of discontinuing third drug due to NPAEs from fitting Cox regression models**

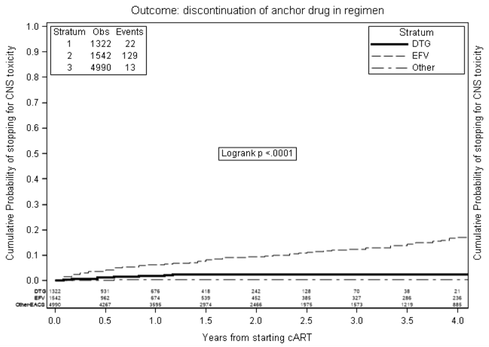
| TABLE 2A | Adjusted* RH (95% CI) of NP-TD in ART-naïve population | p-value | Adjusted* RH (95% CI) of NP-TD in ART-naïve population# | p-value | Adjusted* RH (95% CI) of NP-TD in TE population | p-value |
|---|---|---|---|---|---|---|
| DTG-based regimens | 1.00 | | 1.00 | | 1.00 | |
| EFV-based regimens | 7.02 (2.98-16.58) | **<0.001** | 6.29 (2.28-17.34) | **<0.001** | 5.09 (1.62, 15.98) | **0.005** |
| Other regimens | 0.10 (0.03-0.30) | **<0.001** | 0.08 (0.02-0.27) | **<0.001** | 0.24 (0.09-0.66) | **0.006** |

| TABLE 2B | Adjusted* RH (95% CI) of NP-TD in ART-naïve population | p-value | Adjusted* RH (95% CI) of NP-TD in TE population | p-value |
|---|---|---|---|---|
| DTG-based regimens | 1.00 | | 1.00 | |
| EFV-based regimens | 6.98 (2.95-16.51) | **<0.001** | 8.00 (2.53-25.31) | **<0.001** |
| Other INSTI-based regimens | 0.08 (0.01-0.68) | **0.021** | 0.72 (0.26-1.97) | 0.519 |

** Adjusted for: gender, age, mode of HIV transmission, nationality, calendar year of starting ART, AIDS diagnosis, BMI (only for ART-naïve patients), STR (yes vs no), backbone, CD4 count nadir, highest level of education, employment and NPS symptoms at baseline. # sensitivity analysis on patients starting ART from 2011.*

**Figure 1- Probability of discontinuing third drug due to NPAEs according to treatment history and third drug started**

**1a) ART-naïve population**




**1b) Treatment-experienced population**

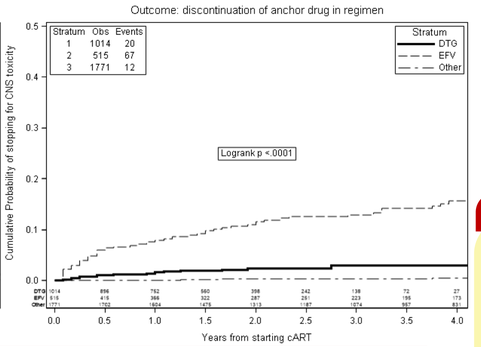
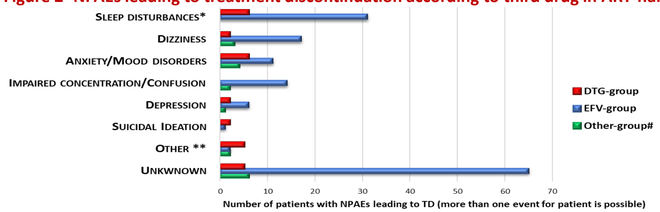



**Figure 2- NPAEs leading to treatment discontinuation according to third drug in ART-naïve population**




*# Regimens of patients in the group «other» who experienced NP-TD were based on: RPV (6); ATV/r (3): EVG/C (3); RAL (2).*
**Abnormal dreams were reported only in EFV-group;*
*** Other NPAEs includes:*
- *paraesthesia, anosmia, paranoid ideation, hallucinations and headache (DTG group);*
- *hallucinations, acouphene (EFV-group)*
- *hands shacking and hallucinations (other-group).*

## CONCLUSIONS

- In this large cohort, **both ART-naïve and TE patients on DTG-based regimens showed a risk of experiencing treatment-limiting NPAES significantly lower than patients on EFV-based regimens but higher than people on non-EFV non-DTG-based ART**.
- The **slightly higher risk of discontinuation due to neuropsychiatric toxicity of DTG- *versus* non-EFV non-DTG-based regimens was confirmed, in ART-naïve population, also specifically comparing DTG- to other INSTI-based ART**. Conversely, in **TE patients, the risk of stopping treatment among different INSTI-based ART did not significantly differ.**
- The **neuropsychiatric toxicity profile of DTG and EFV, assessed in ART-naïve population, seems to be only partially comparable**. However, this finding should be interpreted cautiously due to the lack of characterization of most EFV-related NPAEs.

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