BACKGROUND

- Concerns about an increased risk of neuropsychiatric adverse events (NPAs) during exposure to Dolutegravir (DTG) have been recently reported in observational studies[1].
- Historically, Efavirenz (EFV) was largely associated to a higher risk of NPAs with an increased rate of discontinuations for toxicity compared with other antiretrovirals[2].
- Despite this common toxicity profile, comparisons of NPAs' risk between DTG and EFV-based regimens are limited. A large comparative randomised trial has shown a discontinuation rate of NPAs with fewer discontinuations in ART-naive patients starting DTG compared to those starting EFV[3]. However, direct comparisons in real-life setting are lacking.

AIMS

The aim of the study was to evaluate the risk of discontinuation due to comparing the effect of DTG-based, EFV-based and other 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 and other Italian centres.
  - All consecutive ART-naive and virologically-suppressed-treated-experience (TE) HIV-positive patients, enrolled in the icona cohort, who started or switched for the first time to a regimen containing 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: 2006-2010 (1st group), 2011-2015 (2nd group), 2016-2018 (3rd group).
- **EFV** group (including patients starting boosted darunavir, atazanavir, rilpivirine or other integrase strand transfer inhibitors (INSTIs) as third drug).
- **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 NPAs (NP-TD): discontinuation of the third drug, ignoring changes in the backbone, due to NPAs 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 the main confounding factors.
- Two sensitivity co-regression analysis were performed to assess the independent risk of NP-TD: 1) restricting the “other” group only to patients starting a non-DTG INSTI-based regimen in ART-naive and TE populations, 2) restricting the analysis to patients starting ART from 2011 (first year in which DTG was available in Italian database) in ART-naive population.
- NPAs leading to discontinuation were characterized and compared among the groups in ART-naive population.

**CONCLUSIONS**

- Overall, 7,854 ART-naive 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 were similar between the three groups.
- At survival analysis, patients on EFV-based ART were more likely to stop third drug due to NPAs compared to patients on DTG-based or other ART both in ART-naive (p<0.001) and in TE (p=0.001) population (Fig.1a,1b).
- At multivariable analysis, after adjusting for 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-naive and TE populations (Table2A). In ART-naive 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 switchstrategy from an INSTI-based ART (Table2B) Conversely, in TE population, the risk of NP-TD did not significantly differ between patients treated with DTG versus other INSTI-based ART (Table2B).
- In ART-naive patients, NPAs leading to discontinuation were mostly sleep disturbances (insomnia and abnormal dreams), dizziness and impaired concentration, while those leading to DTG stop were mainly insomnia and mood disturbance (Table2).

References

- De Rienzo F et al., AIDS 2016.
- Menzaghi B et al., AIDS 2017.
- Rabinetti et al., JACLT 2017, Elsi et al., AIDS 2017.
- Wolinsky S et al., NEJM 2017.
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Table 1 - Baseline characteristics according to treatment history and third drug started

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

Table 2B - Adjusted** Relative Hazards (RHR) of discontinuing third drug due to NPAs from fitting Cox regression models

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

Acknowledgments — Icona Foundation Study Group


**All the data were collected from the patients’ medical records and were anonymously coded.

**AIDS-related conditions**

- **AIDS**
- **AIDS-related dementia**
- **AIDS dementia complex**
- **AIDS wasting**
- **AIDS-related complex**
- **AIDS-related complex**

**ART**

- **ART-related**
- **ART-related**

**Avoided treatments**

- **Avoided treatments**
- **Avoided treatments**

**Clinical governance**

- **Clinical governance**
- **Clinical governance**

**Funding**

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**Figure 2 - NPAs leading to treatment discontinuation according to third drug in ART-naive population**

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