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LABOR LADEMANNBOGEN
MEDICAL EXPERTISE

CNS Toxicity of Dolutegravir Is Not Associated with Psychiatric Conditions or Higher Plasma Exposure

ICH STUDY CENTER

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BACKGROUND

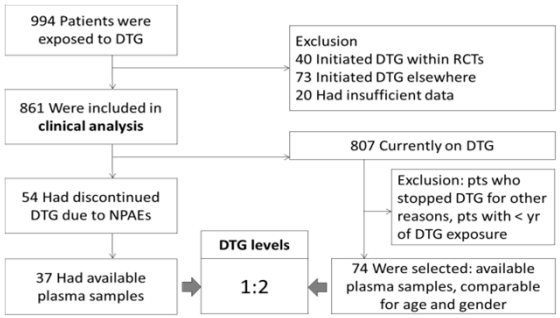
- Reported rates of neuropsychiatric adverse events (NPAEs) leading to dolutegravir (DTG) discontinuation in clinical routine have been markedly higher than seen in randomized trials, in particular in female and in older patients (pts).[1,2]
- It has been speculated that this may be due to higher background rates of psychiatric conditions in HIV+ pts and/or elevated plasma drug levels in specific populations.[3,4]

METHODS

- Retrospective single center study, evaluating all HIV+ pts initiating DTG in clinical routine during 2014-2017.
- Time on DTG and all reasons for discontinuation were extracted from the electronic database, as well as covariables, including preexisting depressive disorders or other neuropsychiatric diagnoses (ICD-10-CM, Diagnosis Codes F01-F99).
- DTG plasma levels from frozen samples of pts discontinuing DTG due to NPAEs (for definition see Fig. 3) were measured by liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS).
- Levels were compared with those of a control group comparable in age (±5 yrs) and gender who had tolerated various DTG-containing regimens (QD) for > 12 months without reporting NPAEs.

PATIENT DISPOSITION

Figure 1. Patient disposition/selection



RESULTS

In total, 861 pts (768 males, median age 47.1 years) had initiated DTG outside RCTs since 2014, among them 151 ART-naïve and 710 ART-experienced pts. There were 155 pts (18.0%) with preexisting depressive disorders and 55 pts (6.4%) with other neuropsychiatric diagnoses.

Figure 2. Time on DTG (months), discontinuation due to NPAEs (all other events censored), n=861. Stratfied for gender, age, abacavir use (simultaneous initiation), preexisting psychiatric conditions

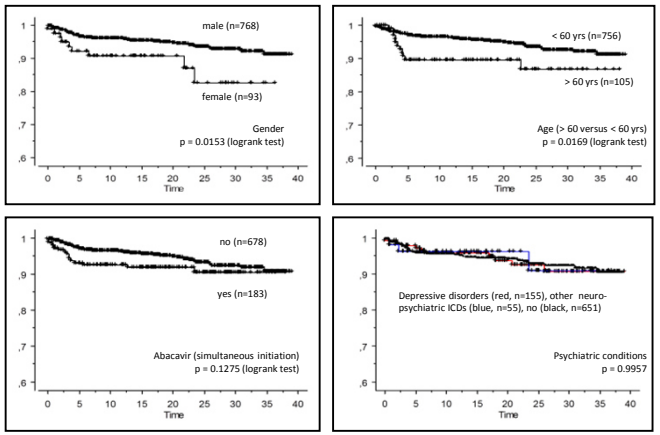


Table 1: Adjusted Relative Hazards (RH) for the covariables of interest, using the Cox model.

Risk factors for NPAEs leading to DTG discontinuation	RH	95 % CI	p
Female, versus male gender	2.31	1.12-4.74	0.03
Older age (> 60 years), versus younger age	2.14	1.10-4.18	0.025
Depressive disorders, versus no	1.00	0.54-1.88	0.952
Other neuropsychiatric diagnoses, versus no	0.93	0.29-3.00	0.896

Figure 3. Reasons (%) for discontinuing DTG, n=54 (mean of 2.9 symptoms/NPAEs were reported)

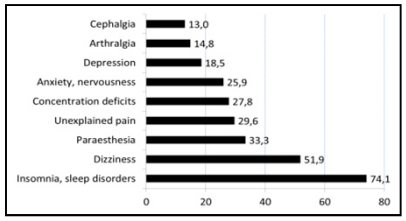


Figure 4. Pts discontinuing DTG, time on subsequent ART regimen (n=53, 1 pt lost to FU)

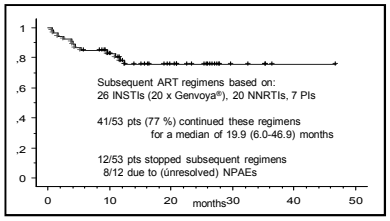
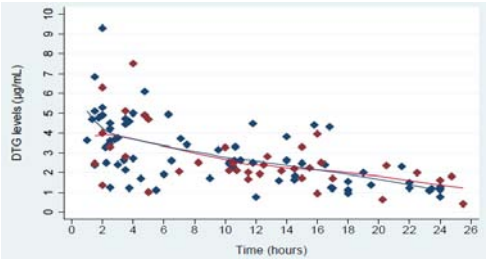


Figure 5. DTG plasma levels in pts discontinuing DTG due to NPAEs (n=37, red dots) and in 71 controls (blue dots), comparable for age and gender. Time after drug intake



Regression lines based on locally weighted scatterplot smoothing ('lowess') using least squares, STATA/SE 13.1

CONCLUSIONS

- In this large cohort of HIV+ pts exposed to DTG in clinical routine, discontinuation due to NPAEs was around 6 %.
- DTG discontinuation was not associated with a pre-existing or prevalent depression or with other neuro-psychiatric diagnoses, but with female sex and older age.
- The majority of pts discontinuing DTG due to NPAEs had no tolerability problems with subsequent ART regimens.
- We found no association between DTG plasma levels and risk of discontinuation due to NPAEs.
- Thus, the notion that neuropsychiatric comorbidity or higher DTG plasma exposure may explain these findings is not supported by these data. Other factors impacting on brain exposure should be investigated.

REFERENCES

1. de Boer MG et al. Intolerance of dolutegravir-containing combination antiretroviral therapy regimens in real-life clinical practice. AIDS 2016, 30:2831-2834.
2. Hoffmann C et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med 2017, 18:56-63.
3. Fettiplace A et al. Psychiatric symptoms in patients receiving dolutegravir. J AIDS 2017, 74: 423-431.
4. Yagura H et al. Impact of UGT1A1 gene polymorphisms on plasma dolutegravir trough concentrations and neuropsychiatric adverse events in Japanese individuals infected with HIV-1. BMC Infect Dis 2017, 17:622.

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