Discontinuation of dolutegravir containing regimens due to adverse reactions: real world data

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Background

- We have observed a number of people living with HIV (PLWH) discontinuing dolutegravir (DTG) containing regimens due to adverse drug reactions (ADRs)
- Rates of discontinuation in phase III trials were low (2%) [1,2] but post-marketing data show higher rates, particularly due to central nervous system (CNS) effects [3]
- A previous cohort study [4] has found CNS ADRs to be more frequent in females, older patients and when DTG is co-administered with abacavir
- We present real world data of DTG use in our large, urban cohort of 10,371 patients

Objectives

To assess:

- ADR-related discontinuation rates
- Nature of ADRs
- Influence of NRTI backbone
- Whether stopping DTG led to resolution of symptoms

Methods

- All PLWH ever prescribed DTG from Apr 2011 to Sept 2018 were identified using electronic patient records
- Data was extracted as follows: basic demographics, ARV combination details including start and end dates, time to discontinuation
- Retrospective case note review was carried out to identify reason for switch and whether symptoms resolved following DTG cessation
- Chi-squared tests were performed to look at associations between: discontinuation of DTG and type of DTG regimen, discontinuation of DTG and gender

Results

- 2543 patients were prescribed a DTG-containing regimen over the 7.5 year period

Figure 1: Baseline demographics (n=2543)

Median age	% male (n)	% White	Median CD4 at time of starting (cells/mm³)
44	91	75	651

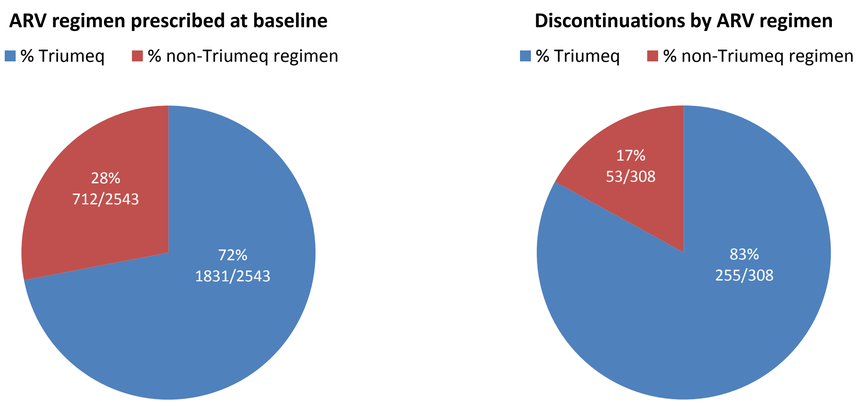
Figure 2: Demographics of PLWH who discontinued DTG (n=308)

Median age	% male	% White	Median CD4 at time of discontinuation (cells/mm³)
44	89	79	674

- 308 patients discontinued DTG due to ADRs
- Overall ADR related discontinuation rate = **12% (308)**
- 69 patients stopped DTG due to other reasons and were thus excluded from the analysis
- Median time to discontinuation was 132 days (4.4 months)

- There was an association between DTG discontinuation and type of DTG regimen prescribed
- Discontinuation rate: Triumeq (Abacavir/Lamivudine/Dolutegravir) 13.9% (255/1831) vs. other DTG containing regimens 7.4% (53/712); p-value <0.001

- **Figure 3:** Discontinuations by ARV regimen



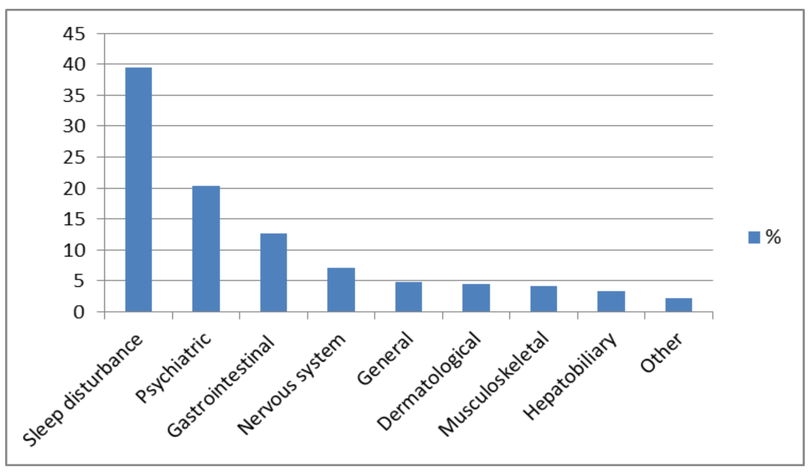
- Higher discontinuation rates were noted in the following groups:
  - Women compared to men: 15.7% (34/217) vs. 11.7% (273/2326); p-value= 0.075
  - Women > 60 years old compared to women < 60: 23% (6/26) vs. 14.7% (28/191)

- CNS related ADRs led to 52% (161/308) of all discontinuations – 70% of these were sleep related
- The frequency of other ADRs were: GI (13%), nervous system (7%), general (5%), dermatological (4.5%), musculoskeletal (4%)

Results (continued)

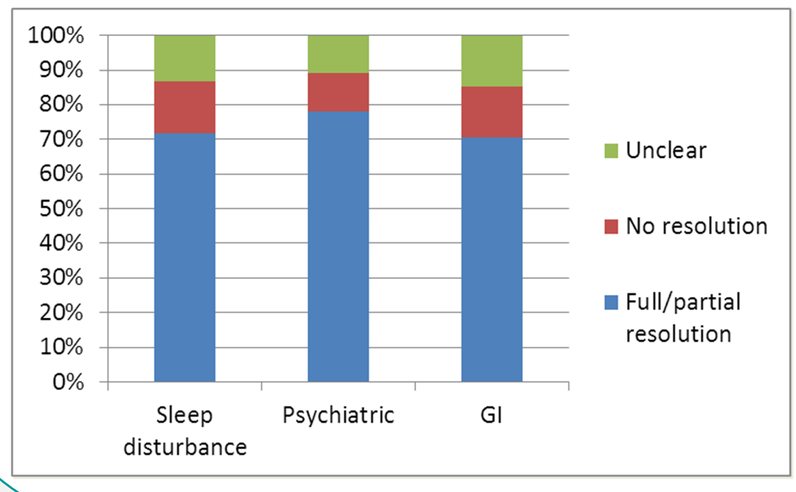
- There were also 9 cases of discontinuation due to transaminitis

Figure 4: Primary reason for discontinuation of DTG



- 69% of PLWH who switched off DTG showed full or partial improvement of symptoms at follow up

Figure 5: Resolution of ADR following DTG cessation



Discussion

- We observed considerably higher rates of ADR-related discontinuation than those reported in several RCTs [1,2]
- This could be due to higher rates of mental health issues and recreational drug use in real-world cohorts
- The higher rate of discontinuation in women, especially if older, has been demonstrated in a previous study [4]
- This requires further work to assess significance, and analysis of DTG pharmacokinetics in these patient groups
- Our data reinforces the need for inclusion of underrepresented populations in clinical trials
- As Triumeq was associated with higher rates of discontinuation compared with other regimens, further work is needed to directly compare tolerability of DTG when coupled with different NRTI backbones

Limitations

- The study did not capture patients who experienced side effects but persevered with treatment
- Resolution of symptoms post-switch was difficult to assess as patients switching off DTG may also have switched other agents in their ARV regimen
- Due to retrospective design, it was not possible to account for confounding factors (e.g. persisting CNS effects in patients switching off efavirenz, psychiatric history, co-medications)

References

1. Raffi F et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013; https://www.ncbi.nlm.nih.gov/pubmed/23306000
2. Molina JM et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. Lancet 2015.
3. Van den Berk G et al. Unexpectedlyhigh rate of intolerance for dolutegravir in real life setting. Abstract 948, CROI 2016.
4. Hoffman C et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med 2017.