Adverse reactions to dolutegravir reported to the National HIV & TB Health Care Worker Hotline in South Africa

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BACKGROUND

- The National HIV and TB Health Care Worker Hotline in South Africa provides advice to health care workers on the management of HIV and TB, including adverse drug reactions (ADRs).
- In December 2019, dolutegravir (DTG) was included in preferred first- and second-line regimens in the South African antiretroviral treatment (ART) guidelines[1].
- Commonly reported side effects of DTG include diarrhoea, nausea, vomiting, headache, dizziness, sleep disturbance and pruritis/rash[2,3,4]. Liver injury is an uncommon but potentially serious ADR[2] . DTG increases serum creatinine through renal transporter inhibition[2]. This may complicate assessment of suspected renal toxicity in patients taking potentially nephrotoxic antiretrovirals (e.g. tenofovir disoproxil fumarate).

OBJECTIVE

- To describe adverse reactions to DTG reported through queries to the HIV & TB Health Care Worker Hotline during the first year of DTG rollout (January-December 2020).

METHODS

- All Hotline queries were prospectively captured in an Access database.
- For this case series, we reviewed all queries received by the Hotline between 1 January 2020 and 31 December 2020 about suspected ADRs, in which the patient was taking DTG.
- We used World Health Organization Uppsala Monitoring Centre (WHO-UMC) criteria for causality assessment[5].

RESULTS

- There were 694 queries regarding suspected ADRs due to ART and/or antituberculosis medicines during 2020.
- 104 of these queries involved patients on DTG-containing ART:
  - In 40 queries in 40 patients, we identified 46 adverse reactions to DTG (26 possible, 20 probable) (Table 1):
    - In 33 of 40 patients (83%), DTG was stopped or advised to be stopped due to the ADR:
      - 5 of 33 had already discontinued DTG.
      - 27 of 33 were advised by the Hotline to stop DTG and switch to an alternative regimen.
      - 1 of 33 (a drug-induced liver injury due to DTG or isoniazid) was advised to stop and rechallenge DTG after resolution of the liver injury, as isoniazid was thought to be the more likely cause. We have no further information on outcomes after rechallenge.
  - 14 queries involved serum creatinine and/or estimated Glomerular Filtration Rate (eGFR) changes, 10 in adults and 4 in adolescents (Table 2):
    - In 9 of 10 adults, tenofovir disoproxil fumarate (TDF) was implicated (all assessed as probable adverse reactions to TDF). In 1 of 10 adults, both TDF and rifampicin were potentially implicated (both possible ADRs). DTG may have contributed to the change in renal function observed in all 10 cases, through its effect on renal secretion of creatinine. We did not, however, classify these cases as adverse reactions to DTG, as the DTG tubular effect does not reflect renal damage.
    - TDF was stopped or advised to be stopped and switched to abacavir in all 10 adults.
    - In the four adolescents, all had normal baseline renal function and eGFR > 90 mL/min/1.73m² after switching to TLD, and the Hotline recommended continuing TLD. None were classified as ADRs:
      - In one, TDF was substituted with abacavir despite a preserved eGFR and advice from the Hotline not to switch because the clinician making the query remained concerned about the 111% increase in creatinine.
      - In all four adolescents, creatinine had stabilised on follow up.

Table 1: ADRs to DTG reported to the South African National HIV & TB Health Care Worker Hotline

Description of ADR	n	DTG discontinued (%)
Dermatological (n=14)		
Rash only	8	8 (100)
Rash with associated angioedema	3	3 (100)
Rash with mucosal involvement	1	1 (100)
Angioedema with no rash	2	2 (100)
Neuropsychiatric (n=13)		
Insomnia	7	5 (71)
Psychosis	2	2 (100)
Depression	1	1 (100)
Headache	1	1 (100)
Fatigue	1	0 (0)
Dizziness	1	0 (0)
Liver Injury (n=7)	7*	6 (86)
GI Symptoms (n=5)		
Nausea	1	0 (0)
Diarrhoea	1	1 (100)
Constipation	1	1 (100)
Nausea, vomiting and diarrhoea	1	1 (100)
Left upper quadrant pain	1	1 (100)
Other (n=7)		
Weight gain	3	1 (33)
Musculoskeletal pain	1	1 (100)
Rhabdomyolysis	1	1 (100)
Erectile dysfunction	1	1 (100)
Lower back pain & Paraesthesia	1	1 (100)

* 6 of 7 were taking other potentially hepatotoxic drugs.

Table 2: Renal ADR queries in patients on DTG-containing ART

	Adults (10)	Adolescents (4)
ART Experienced or Naïve		
New on TLD	4	0
Switched from TEE to TLD	5	1
Switched from other regimen to TLD	0	3
Unknown	1	0
Drug discontinuations		
TDF stopped	10	0
DTG stopped	1*	1

*Reason for discontinuation: there was no available DTG outside of fixed-dose combination
Abbreviations: ADR adverse drug reaction, ART antiretroviral therapy, TLD tenofovir disoproxil fumarate plus lamivudine plus dolutegravir, TEE tenofovir disoproxil fumarate plus emtricitabine plus dolutegravir, TDF tenofovir disoproxil fumarate, DTG dolutegravir

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LIMITATIONS

- This is a case series identified from queries made to The National HIV & TB Health Care Worker Hotline. There is no denominator data and therefore we cannot determine the incidence or prevalence of DTG-related ADRs.

CONCLUSIONS

In the first year of DTG rollout in South Africa, 15% of ADR queries received by the Hotline concerned patients taking DTG, in 38% of which we confirmed an adverse reaction to DTG. The most commonly reported adverse reactions to DTG were insomnia, rash, and liver injury. Diagnosis and management of these ADRs should be included in health care worker training.

13% of ADR queries in patients taking DTG concerned changes in renal function. DTG may increase serum creatinine, complicating assessment of changes in renal function in patients taking TDF with DTG. Health care workers in resource-limited settings require training and support regarding investigation and management of serum creatinine increases in patients receiving TDF with DTG.

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