A 3-year adverse drug reactions analysis on dolutegravir-containing regimens in Ethiopia

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Background

- Dolutegravir (DTG) is designated as a preferred first-line antiretroviral (ARV) in the Ethiopian national treatment guidelines since 2018.
- DTG is preferred over other regimens because of:
  - rapid and higher viral suppression
  - higher genetic barrier against drug resistance
  - lower risk of toxicity and drug interactions
  - availability as fixed-dose and loose formulations
- However, there are potential side effects associated with DTG, including:
  - ✔ hypersensitivity reactions, weight gain, hyperglycemia, insomnia, and abnormal liver function in patients with hepatitis

Background cont'd

- Even though DTG has relatively fewer side effects than previously used regimens, large-group post-marketing data is limited.
- WHO recommends enhanced monitoring and surveillance of toxicity during any transition to new antiretroviral (ARV) drugs.
- In addition, unless closely monitored and managed, adverse drug reactions (ADRs) could lead to nonadherence, drug discontinuation, and affect viral suppression and quality of life.
- ADRs had not been consistently reported to the regulatory authority.

Background cont'd

- The Ethiopian Food and Drug Authority (EFDA) is responsible for monitoring an adverse events reporting system for all medicines, including ARVs like DTG.
- Since July 2019, the USAID Global Health Supply Chain Program-Procurement and Supply Management (GHSC-PSM) project began supporting EFDA, regional health bureaus, and ARV treatment (ART) sites to improve monitoring and reporting ADRs for DTG through building the capacity of providers and ART clinics and pharmacies:
  - Developed and delivered a national pharmacovigilance training course
  - Printed and distributed user-friendly ADR reporting and screening tools
  - Held face-to-face discussions and supportive supervision visits
- This support allowed ART sites to collect ADR data between 2019 to 2021.

Background cont'd

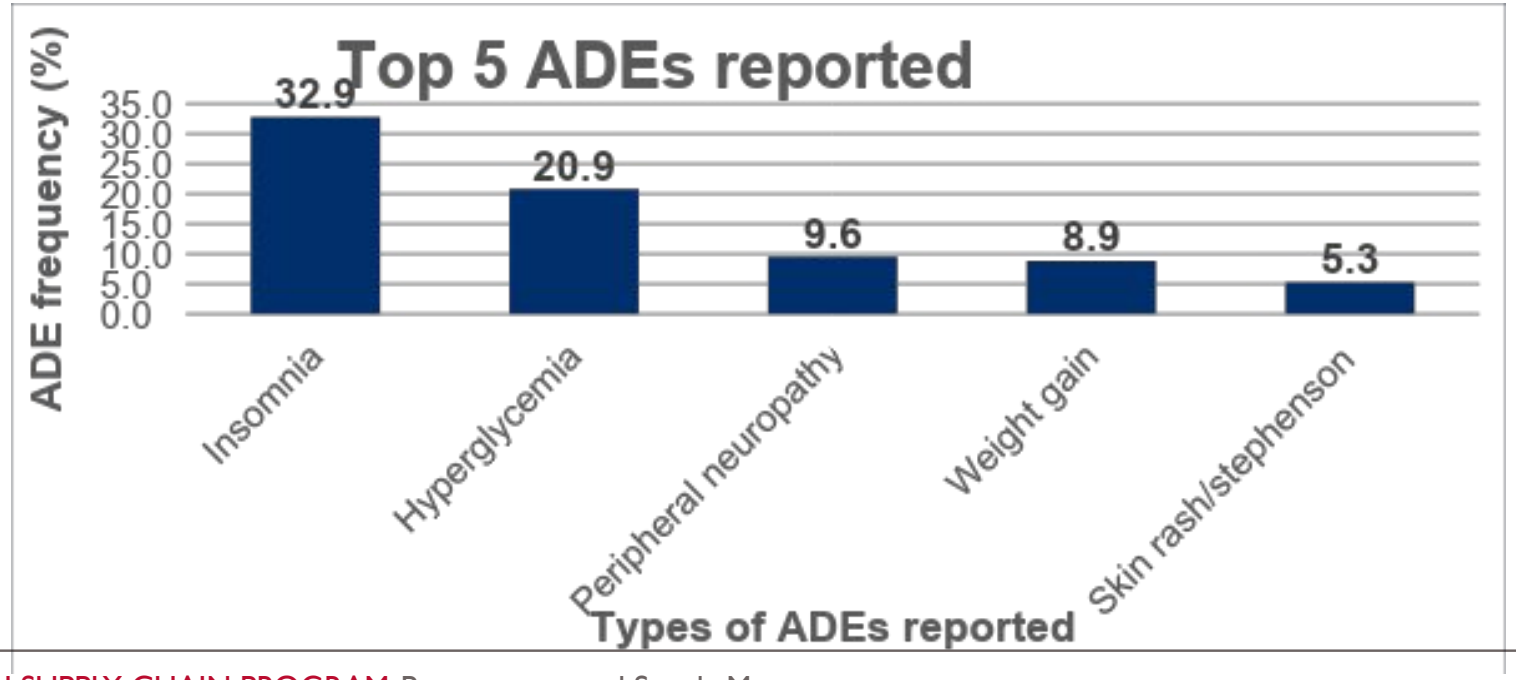
- Due to concerted efforts by GHSC-PSM and other stakeholders, the ADE reporting rate increased.
- However, national ADR data was not comprehensively aggregated and analyzed to generate information for decision making.
- After increasing sites' capacity to collect data on ADRs, GHSC-PSM supported EFDA to aggregate and analyze ADR reports to identify:
  - Common adverse events (AEs) and serious AEs
  - Regimens/drugs suspected to cause the ADRs
  - Factors contributing to the occurrence of ADRs
- The support was provided to make this data more useful for national and regional health program decision-making.

Methods

- The ADR data were collected using spontaneous reporting and as a routine service data through program support from AA and regions.
- The ADR reports collected were entered to MS excel and analysis was performed using SPSS statistical software version 25.
- The analyzed data were taken from documented ADRs experienced by patients taking DTG-based ART from 2019-2021.
- Simple descriptive statistics were used to present the data.

Results

- The national overall ADR reports rate per year doubled during this period of support.
- A total of 417 ADRs (357 patients) taking DTG were used in the analysis*.
  - 127 ADE reports were received from 17 facilities throughout the country
  - 290 ADE reports were received from 30 ART sites in Addis Ababa

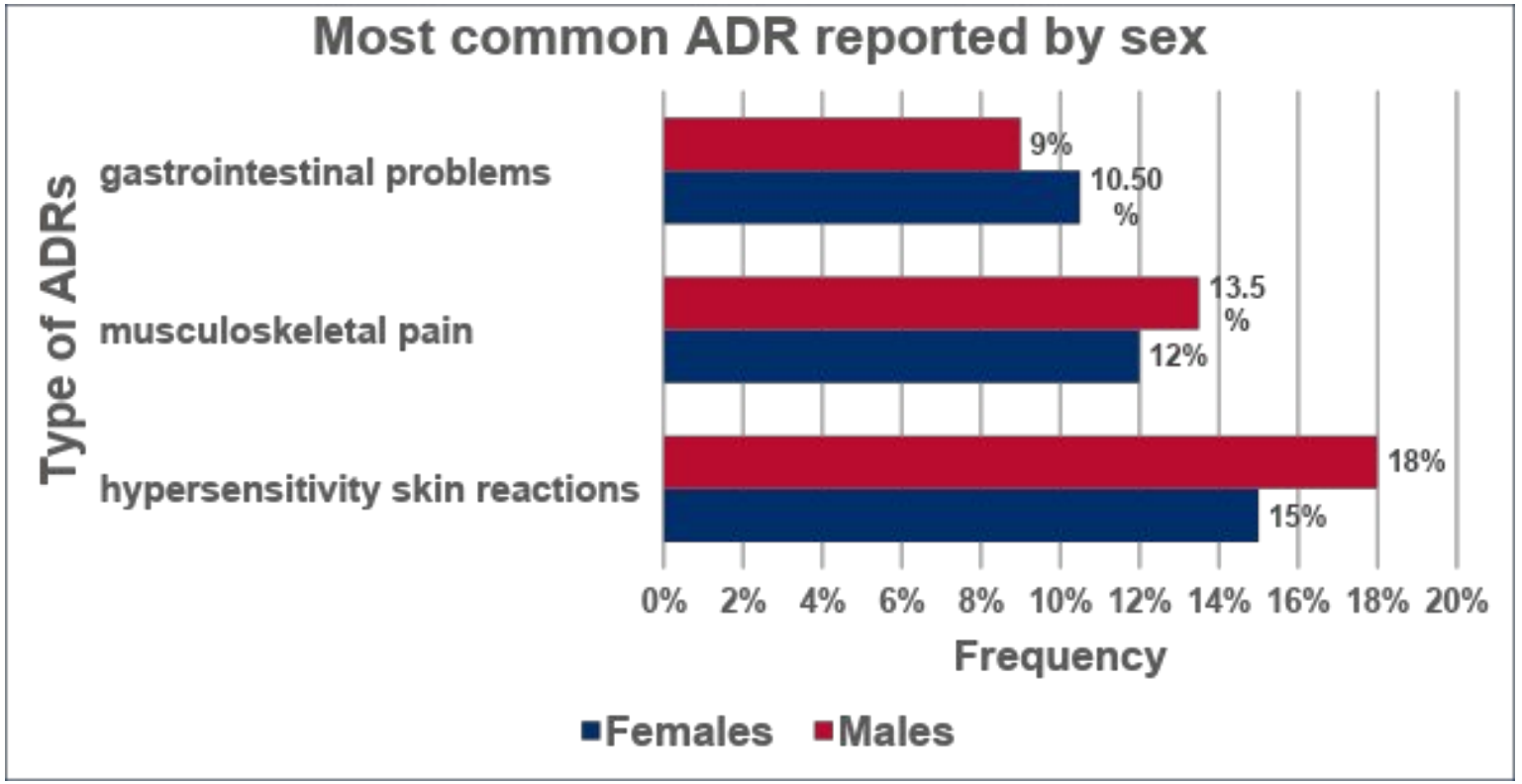


Results cont'd

- Of the ADRs reported by patients taking DTG-based regimen, DTG was suspected to be responsible for the occurrence of the reported ADR in 92.5%.
- Most patients (57.1%) were between 31 and 45 years of age.
- In 68.8% of the cases, ADRs were noted within 15 days of starting DTG.
  - Exceptions include:
    - weight loss occurred from 15 days to 1 month after
    - hyperglycemia occurred after 3 months
- The use of other concomitant drugs reported in 19.4% of the patients, including cotrimoxazole (4.5%) and metronidazole (3%).
- Presence of comorbidities reported in 6% of the patients, including CNS toxoplasmosis, disseminated TB, and type 2 diabetes mellitus.

Results cont'd

- Most ADR findings were comparable between sexes (male vs female).
- However, slight variations occur on the following ADRs between sexes.



Results cont'd

- Most of the ADR reports came from Addis Ababa; and pharmacists were the top ADE reporters (45%) compared to other health professionals.
- Although for most of the patients the ART regimen was continued with reassurance and symptomatic managements the ADRs such as use of antihistamines, analgesic, antiemetic and antidiarrheal
  - TLD was changed to TLE in 19.5% of the patients
- Nearly 12% of the patients experienced serious* ADRs which resulted in hospitalization/prolonged hospitalization.
- Regarding the outcomes after experiencing ADRs, nearly 18% of the patients recovered **without** sequalae, 2% recovered **with** sequalae and the remaining had unknown status.

Actions taken

During our support:

- Through site-level support, timely communications, and facilitating consultation with clinicians
  - The time of ARV administration was changed, and adjusted concomitant medicines and regimens that caused insomnia, weight loss, and hyperglycemia.

After the analysis:

- The project used the results to recommend:
  - A national DTG toxicity study to further assess ADRs and inform the program (ongoing by MOH).
  - Cohort Event Monitoring (CEM) on DTG-based ART regimens in 3,000 patients for 1 year in AA in 24 ART sites (ongoing by EFDA and GHSC-PSM).

Challenges and limitations

- While supporting the Ethiopian public health system to improve ADR reporting and analysis, GHSC-PSM found several challenges:
  - Limited human resource capacity at all levels
  - Poor information system and weak data management
  - Weak systems of communication and feedback
  - Inadequate collaboration with public health programs
  - Incomplete ADR reports both from spontaneous reports and service data

Conclusion

- Overall, the extent of ADR report on DTG is limited.
- The top five ADRs reported in this analysis were also reported during clinical trials and/or post marketing findings.
- Overall, insomnia, hyperglycemia, peripheral neuropathy, weight gain and hypersensitivity skin reactions were the top five ADRs reported.
- The difference in ADRs by sex is nearly indistinguishable.
- Most of the ADRs were observed within 15 days of starting DTG.
- Most of the ADRs observed in patients 31- 45 years.

Recommendations

- Following this activity, GHSC-PSM recommended that EFDA:
  - Conduct further assessment and ADR analysis to better inform the HIV program
  - Improve existing collaboration with HIV program and stakeholders
  - Strengthen online ADR reporting system
  - Strengthen active surveillance on DTG
  - Scale up the capacity-building activity
  - Decentralize the pharmacovigilance system
  - Increase appropriate response to reported ADEs

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THANK YOU.

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