811

Dolutegravir, Body Mass Index, and Metabolic Syndrome in the IeDEA Sentinel Research Network

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BACKGROUND

- Dolutegravir (DTG) use has been associated with increased body mass index (BMI) compared to efavirenz.
- We hypothesized that weight gain from DTG use is also associated with higher risk for metabolic syndrome (MetS), a predictor of incident cardiovascular disease.

METHODS

Study Design and Population

- Associations between DTG use and the two primary outcomes of (1) BMI and (2) MetS were examined.
- Baseline data from the IeDEA Sentinel Research Network (SRN) prospective cohort study were used.
- The SRN collected data from people with HIV (PWH) from low- and middle-income sites worldwide.
- All participants were ≥ 40 years and had been on 3-drug antiretroviral therapy (ART) for at least six months prior to enrollment.

Definitions

- MetS was defined using the International Diabetes Federation definition:
  - BMI >30 kg/m^2 OR increased country/ethnic specific values for waist circumference, PLUS two of the following:
    - Triglycerides ≥150 mg/dL (1.7 mmol/L) or treatment for this lipid abnormality
    - High-density lipoprotein cholesterol <40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females or treatment for this lipid abnormality
    - Systolic BP ≥130 or diastolic BP ≥85 mmHg or treatment for known hypertension
    - Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus

Statistical Analysis

- Multivariable linear and logistic regression models were constructed to identify independent predictors of BMI and MetS, respectively.
  - Independent variables include DTG use vs. non-use at enrollment, age, sex, country, smoking status (ever vs. never), and HIV RNA level (<200 vs. ≥200 copies/mL).
  - CD4 cell count was not included as it was unavailable in some countries.
  - DTG use, sex, and country interactions were also assessed.

In this global analysis of LMIC study participants, DTG use was modestly associated with higher BMI but not with MetS. However, both BMI and MetS were dependent on sex and country.

RESULTS

- A total of 1446 participants were included in these analyses.
  - 212 Brazil; 298 Côte d'Ivoire, 188 India, 77 Kenya, 193 Mexico, 244 Togo, 100 Uganda, 134 Zambia
  - Overall: 54% female, 94% HIV-1 RNA <200 c/mL, 53% using DTG (78% for >6 mos)
  - Median age 50.5 years, median BMI 25.3 kg/m^2, 35% had MetS
- Associations of independent variables with BMI and MetS shown in the Table.
- There were significant interactions between sex and country for both BMI (Figure) and MetS:
  - Compared to males, females had higher odds [adjusted OR (95% CI)] of MetS in Zambia [20.75 (2.71,158.97)], Uganda [15.17 (4.69,49.11)], Kenya [12.53 (2.55,61.69)], Togo [4.31 (1.98,9.36)], Côte d'Ivoire [3.21 (1.80,5.74)], and Mexico [3.02 (1.18,7.72)], but not in Brazil or India.
- No other interactions involving DTG use, sex, and country were associated with BMI or MetS.

Table. Multivariable models of body mass index and metabolic syndrome in the IeDEA SRN.

Body Mass Index (kg/m^2)			Metabolic Syndrome		
Variable	Estimate (95% CI)	P-value	Variable	Odds Ratio (95% CI)	P-value
DTG use (yes vs. no)	0.773 (0.089, 1.456)	0.0267	DTG use (yes vs. no)	1.197 (0.884, 1.620)	0.2450
Age, years	-0.041 (-0.074, -0.008)	0.0163	Age <52 (vs. ≥52), years	0.620 (0.489, 0.786)	<.0001
Smoking status (ever vs. never)	-0.086 (-0.769, 0.597)	0.80	Smoking status (ever vs. never)	1.273 (0.930, 1.742)	0.1318
HIV RNA level (≥200 vs. <200 c/mL)	-0.707 (-1.814, 0.400)	0.21	HIV RNA level (≥200 vs. <200 c/mL)	0.884 (0.538, 1.451)	0.6249
Sex*country interaction	See text	<0.0001	Sex*country interaction	See text	<.0001

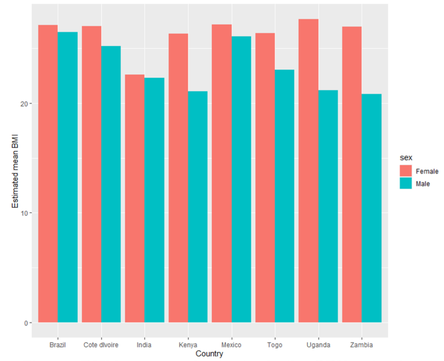

Figure. BMI by sex and country in the SRN cohort.

CONCLUSIONS

- In this large, global cohort of PWH in LMIC, DTG use was significantly associated with modestly higher BMI, which did not translate to a significantly higher risk for MetS.
  - The small increase in BMI may not necessarily lead to increased cardiometabolic risk.
  - It is possible that DTG use would have been associated with MetS if duration of use was longer.
- Greater age was significantly associated with *lower* BMI but *higher* risk for MetS.
- BMI and MetS were significantly dependent on interactions between sex and country, suggesting local factors may play a role weight and cardiometabolic risk.
- We cannot determine if the association between DTG and BMI was causally related or due to the comparator ART being relatively anorexigenic.
- These findings were limited by not having CD4 count data uniformly available in the cohort at baseline.
- Follow-up evaluations of the SRN cohort may provide insights on longer-term ART-related cardiometabolic risk in people with HIV in LMIC.

ADDITIONAL KEY INFORMATION

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