A Comprehensive Assessment of Hepatobiliary Disorders in HIV-Infected Patients Treated with Dolutegravir, Elvitegravir, Raltegravir or Darunavir in the OPERA Database

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BACKGROUND

- Low frequencies of liver chemistry elevations (LCE) were reported for dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), and darunavir (DRV) in randomized controlled trials
- Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with DRV/ritonavir
- As the use of INSTIs increases in various demographic populations and clinical situations, an understanding of the overall hepatic safety profile of the most commonly used core agent will provide additional information for clinicians as treatment strategies are designed

OBJECTIVE:

To assess the occurrence of hepatobiliary disorders before and after prescription of regimens based on DTG, EVG, RAL, or DRV

METHODS

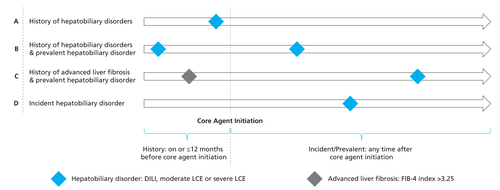
Study Population

- Observational Pharmaco-Epidemiology Research & Analysis (OPERA®) observational database: prospective electronic health record data from 79 HIV out-patient clinics in 15 U.S. states following 84,084 people living with HIV
- Inclusion criteria: HIV-positive patients ≥13 years of age initiating a DTG, EVG, RAL or DRV regimen; 21,046 patients met these criteria
- Baseline: date of DTG, EVG, RAL or DRV initiation
- Censoring events: 1) discontinuation of the core agent (gap ≥45 days), 2) cessation of continuous clinical activity (≥1 clinic visit or telephone contact in 12 months), 3) death, or 4) study end (31Oct2017)
- Population restricted to patients with liver function tests (LFT) available both in the 12-month period preceding initiation of core agents and over follow-up; 16,026 patients had LFTs both before and after baseline (study population)

Exposures & Outcomes

- Exposures: Initiation of DTG, EVG, RAL or DRV
- Outcomes: Hepatobiliary disorders
  1. DILI: diagnosis of drug-induced liver injury or drug-induced hepatotoxicity
  2. Moderate LCE (DAIDS Grade 2):
     - ALT or AST or alkaline phosphatase (ALP) ≥2.5 to <5x ULN, or
     - Bilirubin ≥1.6 to <2.6x ULN
  3. Severe LCE (DAIDS Grade 3-4):
     - ALT or AST or ALP ≥5x ULN, or
     - Bilirubin ≥2.6x ULN
- Timing of hepatobiliary disorders: history, prevalent or incident disorders (Figure 1)
- Discontinuation (D/C): discontinuation of the core agent within 21 days of the date of a hepatobiliary disorder

Figure 1. Examples of Hepatobiliary Disorder Classification



Statistical Analyses

- Comparisons between DTG and other core agents: Pearson's chi-square test (categorical variables), Fischer exact test (counts ≤5), Mann-Whitney test (continuous variables)
- Sidak Correction applied to account for multiple comparisons between DTG and other core agents; adjusted alpha level for significance: 0.017

RESULTS

Patient Characteristics at Baseline

- Core agent groups differed on many demographic and clinical baseline characteristics (Table 1)
- Patients prescribed EVG were less likely to have elevated liver chemistries at baseline compared to patients prescribed DTG (Figure 2)

Table 1. Baseline Patient Characteristics by Core Agent

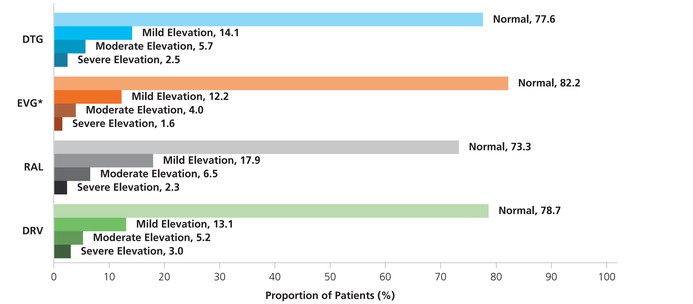
	DTG	EVG	RAL	DRV
N(%)	6102 (38.1%)	6899 (43.1%)	827 (5.2%)	2196 (13.7%)
Socio-demographic characteristics				
Age, median years (IQR)†	41 (29, 51)	36 (27, 48)*	48 (39, 54)*	43 (33, 51)*
Male, n (%)	5221 (85.6%)	5965 (86.5%)	659 (79.7%)*	1730 (78.8%)*
African American, n (%)	2479 (40.6%)	2866 (41.5%)	299 (36.2%)*	1056 (48.1%)*
Medicaid, n (%)	1407 (23.1%)	1159 (16.8%)*	202 (24.4%)	547 (24.9%)
ADAP/Ryan White, n (%)	2374 (38.9%)	2564 (37.2%)	244 (29.5%)*	788 (35.9%)*
HIV-related characteristics				
ART-naïve, n (%)	2236 (36.6%)	2858 (41.4%)*	143 (17.3%)*	715 (32.6%)*
Baseline viral load log10, median (IQR)	2.6 (1.3, 4.6)	3.3 (1.3, 4.7)*	1.3 (1.3, 3.0)*	3.0 (1.3, 4.7)*
Baseline CD4 cell count, median cells/µl (IQR)	494 (311, 710)	489 (306, 698)	516 (310, 741)	387 (187, 631)*
Baseline regimen contains a core agent other than DTG, EVG, RAL or DRV	780 (12.8%)	455 (6.6%)*	292 (35.3%)*	207 (9.4%)*
Clinical characteristics				
VACS mortality index score‡, median (IQR)	17 (7, 29)	13 (7, 25)*	20 (10, 34)*	22 (12, 39)*
Any comorbidities, n (%)	4643 (76.1%)	4739 (68.7%)*	704 (85.1%)*	1664 (75.8%)
Liver diseases, n (%)	928 (15.2%)	744 (10.8%)*	184 (22.2%)*	369 (16.8%)
Lipid lowering agent use, n (%)	935 (15.3%)	694 (10.1%)*	165 (20.0%)*	247 (11.2%)*

† IQR=interquartile range

‡ VACS Mortality Index: Scored by summing pre-assigned points for age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. A higher score is associated with a higher risk of 5-year all-cause mortality

* p-value <0.017 for the comparison with dolutegravir

Figure 2. Distribution of Liver Chemistry† at Baseline

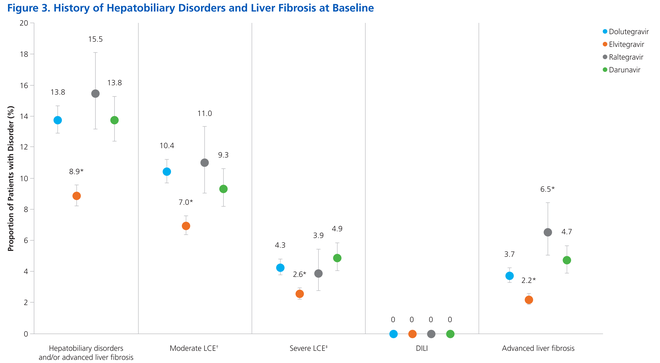


* p-value <0.017 for the comparison with dolutegravir, computed using Pearson's Chi-Square Test

† Normal: AST/ALT /ALP <1.25x ULN and bilirubin <1.1x ULN; Mild Elevation: AST, ALT or ALP ≥1.25 to <2.5x ULN or bilirubin ≥1.1 to <1.6x ULN; Moderate Elevation: AST, ALT or ALP ≥2.5 to <5x ULN or bilirubin ≥1.6 to <2.6x ULN; Severe Elevation: AST, ALT or ALP ≥5x ULN or bilirubin ≥2.6x ULN

- EVG users were less likely than DTG users to have a history of elevated liver chemistries or advanced liver fibrosis (Figure 3)
- RAL users were more likely than DTG users to have a history of advanced liver fibrosis (Figure 3)

Figure 3. History of Hepatobiliary Disorders and Liver Fibrosis at Baseline

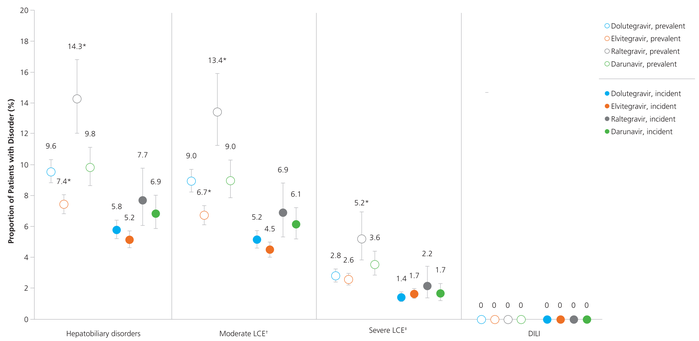


* p-value <0.017 for the comparison with dolutegravir

Hepatobiliary Disorders Over Follow-Up

- EVG users were less likely than DTG users to have prevalent moderate LCE (Figure 4)
- RAL users were more likely than DTG users to have prevalent hepatobiliary disorders and moderate/severe LCE (Figure 4)
- There were no differences in any incident hepatobiliary disorders (Figure 4)
- Discontinuation following hepatobiliary disorders was rare and did not differ significantly across groups for prevalent disorders (DTG: 0.6%, EVG: 0.4%, RAL: 0.7%, DRV: 0.9%) and incident disorders (DTG: 0.3%, EVG: 0.2%, RAL: 0.2%, DRV: 0.7%)

Figure 4. Prevalent and Incident Hepatobiliary Disorders Over Follow-Up



* p-value <0.017 for the comparison with dolutegravir

DISCUSSION

Poster Summary

- ART-naïve patients may be less prone to hepatotoxicity than ART-experienced patients; RAL users were less likely to be naïve (17%) than DRV (33%), DTG (37%) or EVG users (41%) (Table 1)
- RAL users were more likely to be on a regimen with ≥2 core agents (35%) than DTG (13%), DRV (9%) and EVG (7%) (Table 1)
- Despite statistically significant differences in history (Figure 3) and prevalence of hepatobiliary disorders (Figure 4), incident disorders did not differ significantly between core agents (Figure 4)
- No cases of DILI (Figure 4) were observed and discontinuation following a hepatobiliary disorder was rare, underscoring the hepatic safety of the core agents most commonly prescribed

Comparison to Abstract Results

- Study period extended, but population restricted to patients with LFTs, resulting in a smaller population (16,024 vs. 21,046)
- EVG or DRV vs. DTG: no changes for prevalent or incident disorders
- RAL vs. DTG: no changes for prevalent disorders; incident hepatobiliary disorders and incident moderate LCE no longer significantly higher

KEY FINDINGS

The incidence of moderate or severe liver chemistry elevation following core agent initiation did not differ between DTG and EVG, RAL and DRV. No DILI events were observed and discontinuation following a hepatobiliary disorder occurred in <1% of patients.

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