Clinical Effectiveness of Guideline-Recommended Antiretroviral Therapy Core Agents in HIV/HCV Coinfected Patients in the OPERA Observational Database

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BACKGROUND

- Effective antiretroviral therapy (ART) can slow HCV progression to a rate comparable to HCV mono-infection
- INSTI trials included very few HIV/HCV co-infected patients, who had a higher incidence of liver biochemistry increases compared to HIV mono-infected patients, although these increases were similar across core agent comparators

OBJECTIVE:

To compare the effectiveness of the guidelines-recommended core agents dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL) and darunavir (DRV) in patients with HIV/HCV co-infection in the U.S.

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 79,883 people living with HIV
- HIV/HCV co-infected patients ≥13 years of age, co-infected on or after first visit in OPERA, initiating DTG, EVG, RAL or DRV between August 12, 2013 (approval date of DTG) and June 30, 2016, with follow-up extending to June 30, 2017
- 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), 3) death, or 4) study end (June 30, 2017)

Exposure

- Any regimen containing DTG, EVG, RAL or DRV, excluding regimens containing >1 core agent of interest

Outcomes

- Viral suppression: first viral load <50 copies/mL within 12 months of core agent initiation
- Grade 3-4 liver enzyme elevation (LEE): alanine aminotransferase (ALT), or aspartate aminotransferase (AST) or alkaline phosphatase (ALK) >5.0 X upper limit of normal (ULN), or bilirubin >2.5 X ULN

Stratification

- ART-naïve: no history of ART prior to core agent of interest initiation and a baseline viral load ≥1,000 copies/mL
- ART-experienced: record of any ART treatment prior to their first core agent of interest initiation or baseline viral load <1,000 copies/mL regardless of ART history

Statistical Analysis

- 12-month suppression probability assessed with Kaplan-Meier methods
- Time to viral suppression assessed with a multivariate Cox proportional hazards model adjusted for baseline age, sex, race, CD4 cell count, HIV RNA and history of AIDS
- Incidence of grade 3-4 liver enzyme elevation (LEE) calculated only among patients with normal baseline liver enzyme levels (AST, ALT, ALK and bilirubin ≤1 X ULN) and who remained HCV treatment naïve throughout follow-up

RESULTS

ART-Naïve Patients

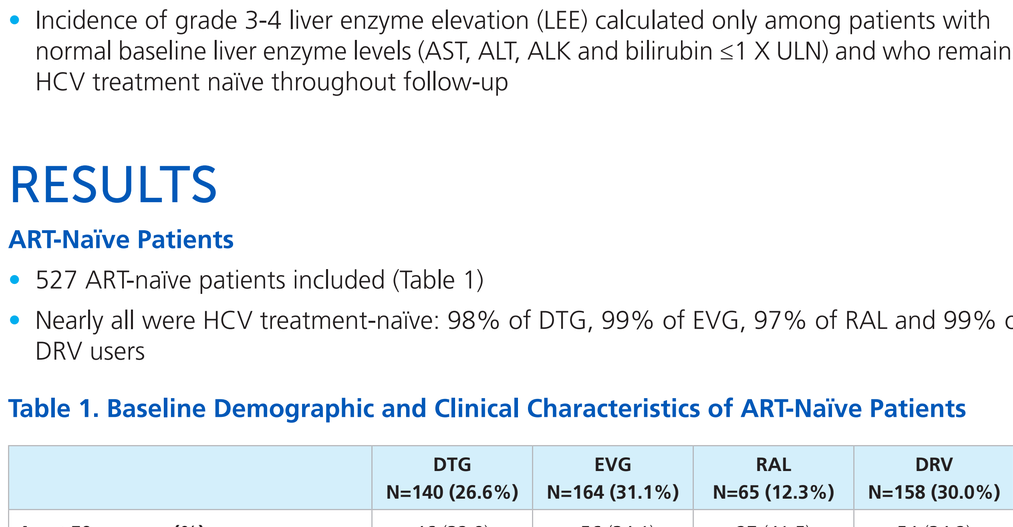
- 527 ART-naïve patients included (Table 1)
- Nearly all were HCV treatment-naïve: 98% of DTG, 99% of EVG, 97% of RAL and 99% of DRV users

Table 1. Baseline Demographic and Clinical Characteristics of ART-Naïve Patients

	DTG N=140 (26.6%)	EVG N=164 (31.1%)	RAL N=65 (12.3%)	DRV N=158 (30.0%)
Age ≥50 years, n (%)	46 (32.9)	56 (34.1)	27 (41.5)	54 (34.2)
Female sex, n (%)	33 (23.6)	41 (25.0)	16 (24.6)	32 (20.3)
African American, n (%)	43 (30.7)	61 (37.2)	27 (41.5)	67 (42.4)
CD4 cell count ≤200 cells/µl, n (%)	38 (27.1)	33 (20.1)	25 (38.5)	70 (44.3)
HIV RNA ≥100,000 copies/ml, n (%)	40 (28.6)	45 (27.4)	15 (23.1)	60 (38.0)
History of AIDS-defining illness, n (%)	6 (4.3)	12 (7.3)	8 (12.3)	23 (14.6)

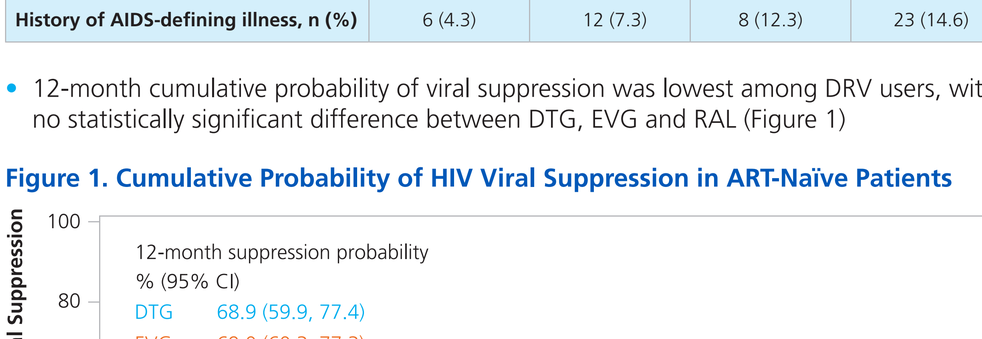
- 12-month cumulative probability of viral suppression was lowest among DRV users, with no statistically significant difference between DTG, EVG and RAL (Figure 1)

Figure 1. Cumulative Probability of HIV Viral Suppression in ART-Naïve Patients



- After adjustment for baseline covariates, only DRV users had a slower time to viral suppression compared to DTG users, with an adjusted hazard ratio (aHR) of 0.49 (95% CI: 0.35, 0.70) (Figure 2)

Figure 2. Association Between Core Agents and Time to Viral Suppression in ART-Naïve Patients



** Adjusted for baseline age, sex, race, CD4 cell count ≤200 cells/µL, HIV RNA ≥100,000 copies/mL and history of AIDS*

ART-Experienced Patients

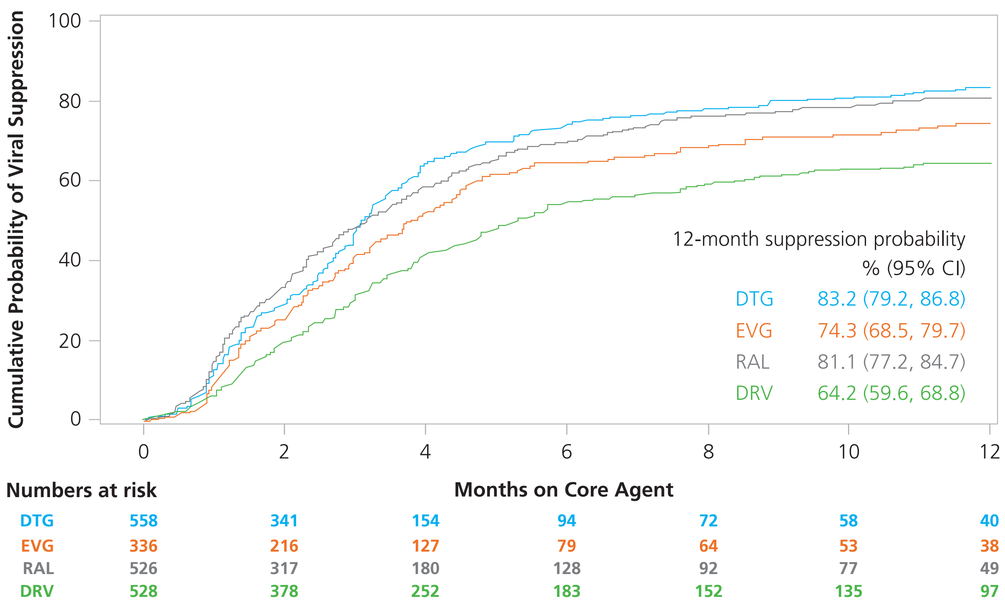
- 1966 ART-experienced patients included (Table 2)
- Most were HCV treatment-naïve: 81% of DTG, 88% of EVG, 83% of RAL and 90% of DRV users

Table 2. Baseline Demographic and Clinical Characteristics of ART-Experienced Patients

	DTG N=567 (28.8%)	EVG N=340 (17.3%)	RAL N=530 (27.0%)	DRV N=529 (26.9%)
Age ≥50 years, n (%)	310 (54.7)	177 (52.1)	267 (50.4)	217 (41.0)
Female sex, n (%)	103 (18.2)	65 (19.1)	125 (23.6)	119 (22.5)
African American, n (%)	219 (38.6)	121 (35.6)	176 (33.2)	189 (35.7)
CD4 cell count ≤200 cells/µl, n (%)	52 (9.2)	38 (11.2)	83 (15.7)	128 (24.2)
HIV RNA ≥100,000 copies/ml, n (%)	21 (3.7)	13 (3.8)	24 (4.5)	43 (8.1)
History of AIDS-defining illness, n (%)	117 (20.6)	53 (15.6)	154 (29.1)	156 (29.5)

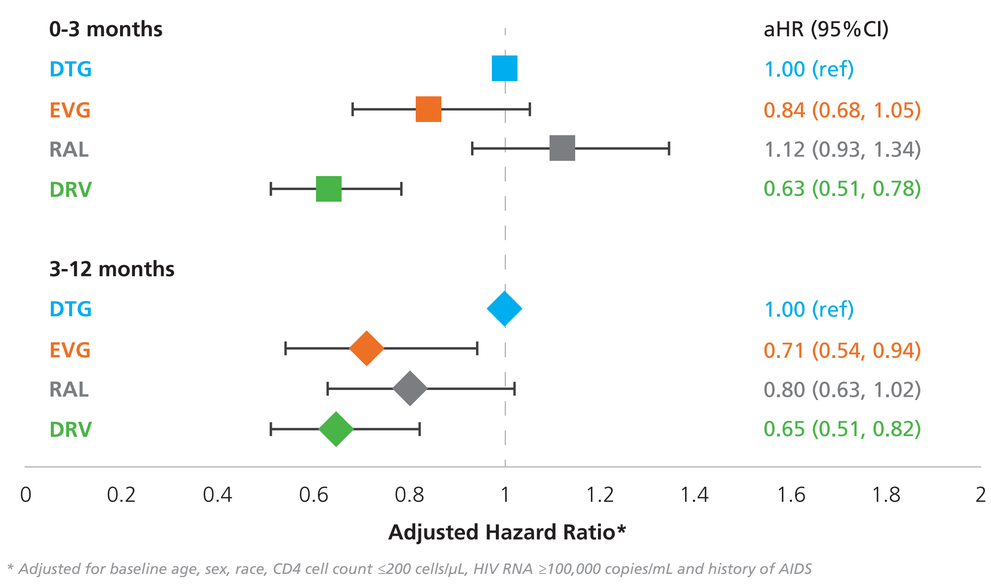
- DRV and EVG users had the lowest cumulative probability of viral suppression after 12 months of ART, but confidence intervals overlapped across core agent groups (Figure 3)

Figure 3. Cumulative Probability of HIV Viral Suppression in ART-Experienced Patients



- Kaplan-Meier curves for DTG and RAL crossed at 3 months of follow-up: violation of the proportional hazards assumption (Figure 3). Cox Proportional Hazards model stratified at 3 months to accommodate the changing hazards over time
- 0-3 months of follow up: only DRV users had a slower time to viral suppression compared to DTG users, with an adjusted hazard ratio (aHR) of 0.63 (95% CI: 0.51, 0.78) (Figure 4)
- 3-12 months of follow-up: both EVG and DRV had a slower time to viral suppression compared to DTG users, with an aHR of 0.71 (95% CI: 0.54, 0.94) for EVG and 0.65 (95% CI: 0.51, 0.82) for DRV (Figure 4)

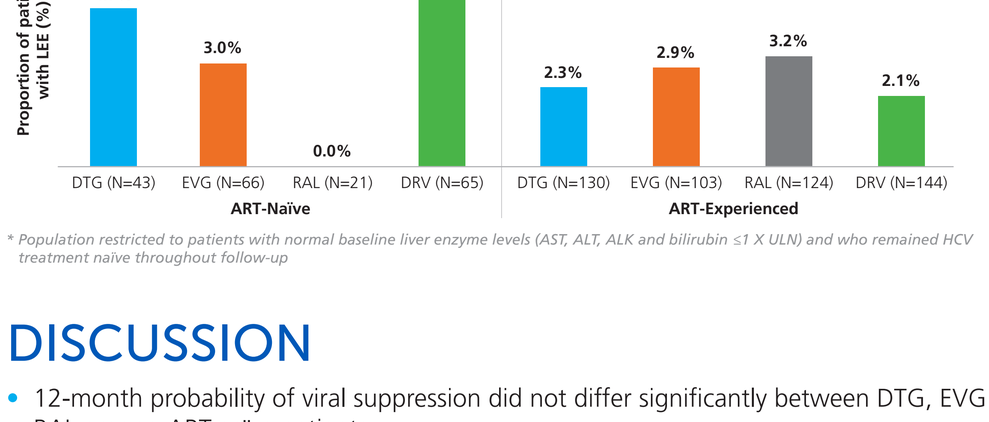
Figure 4. Association Between Core Agents and Time To Viral Suppression in ART-Experienced Patients



** Adjusted for baseline age, sex, race, CD4 cell count ≤200 cells/µL, HIV RNA ≥100,000 copies/mL and history of AIDS*

- Grade 3-4 LEE was rare among patients who remained HCV-treatment naïve throughout follow-up and had normal baseline liver enzyme levels, with no statistically significant difference in incidence across core agent used, regardless of ART experience (Figure 5)

Figure 5. Incidence of Liver Enzyme Elevation Among ART-Naïve and ART-Experienced Patients



** Population restricted to patients with normal baseline liver enzyme levels (AST, ALT, ALK and bilirubin ≤1 X ULN) and who remained HCV treatment naïve throughout follow-up*

DISCUSSION

- 12-month probability of viral suppression did not differ significantly between DTG, EVG and RAL among ART-naïve patients
- 12-month probability of viral suppression did not differ significantly across core agent groups among ART-experienced patients
- Only DRV was associated with a slower time to suppression compared to DTG among ART-naïve patients and over the first 3 months of core agent use among ART-experienced patients
- With 3-12 months of core agent use, both EVG and DRV were associated with a slower time to suppression compared to DTG among ART-experienced patients
- LEE were rare among ART-naïve and ART-experienced patients with normal baseline liver enzyme levels without HCV treatment. All core agents investigated were comparable, although the small number of events was a limiting factor

KEY FINDINGS:

Among ART-naïve HIV/HCV co-infected patients, INSTIs (DTG, EVG, RAL) performed as well in terms of viral suppression, while DRV use resulted in poorer outcomes. Among ART-experienced HIV/HCV co-infected patients, DRV use resulted in a slower viral suppression throughout follow-up, while both EVG and DRV resulted in a slower viral suppression beyond 3 months of use.

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