Virologic Outcomes among Treatment-Naïve HIV+ Patients Initiating Common First Antiretroviral Therapy Core Agents in the OPERA Observational Database

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BACKGROUND

- The treatment landscape in human immunodeficiency virus (HIV) is changing rapidly. In 2018 alone, the FDA approved nine new ART agents. The explosion in new therapies adds to the clinician's arsenal but also substantially complicates clinical decision making.
- The long term effectiveness of commonly used core agents to treat ART-naïve patients with HIV type 1 (HIV-1) infection in real world settings is poorly understood.

OBJECTIVE

To compare rates of virologic failure following core agent initiation among ART naïve patients initiating on one of four US Department of Health and Human Services guideline-recommended core agents: dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), and darunavir (DRV).

METHODS

Study Population

- Data source: OPERA® database: prospective electronic health record data from 85 HIV out-patient clinics in 18 US states following 94,145 people living with HIV
- Inclusion criteria:
  - HIV-1-positive, ≥13 years of age
  - ART-naïve prior to initiating DTG, EVG, RAL or DRV between August 12, 2013 and July 31, 2017
  - ≥1 HIV-1 viral load (VL) and ≥1 CD4 test ≤90 days prior to initiation
- ART-naïve: no history of ART prior to initiation and baseline VL ≥1,000 copies/mL
- Index date: date of core agent initiation
- Censoring events: 1) discontinuation of the core agent (gap ≥45 days), 2) cessation of continuous clinical activity (<1 clinic visit or telephone contact per year), 3) death, or 4) study end (July 31, 2018).

Exposure

- Initiation of DTG, EVG, RAL or DRV

Outcome

- Virologic failure was defined as any of the following:
  - (i) 2 consecutive HIV viral load (VL) ≥200 copies/mL after 36 weeks of ART
  - (ii) 1 VL ≥200 copies/mL with core agent discontinuation after 36 weeks
  - (iii) 2 consecutive VL ≥200 copies/mL after suppression (VL ≤50 copies/mL) before 36 weeks
  - (iv) 1 VL ≥200 copies/mL with discontinuation after suppression before 36 weeks

Analyses

- Unadjusted and adjusted cumulative virologic failure probability
- Kaplan Meier methods, multivariate Cox Proportional Hazards model
- Adjustment set: baseline age, sex, race, CD4 cell count, HIV RNA VL, history of AIDS, VACS score, number of non- ART prescriptions, drug abuse, history of syphilis infection, calendar year of ART initiation, route of infection and type of health coverage

RESULTS

Patient Characteristics

- Median follow-up time was 19.4 months (IQR: 12.8-30.0).
- Table 1 profiles demographic and clinical characteristics.

Table 1. Baseline Patient Characteristics by Core Agent

	Dolutegravir N=2238 (35.9%)	Elvitegravir N=3013 (48.3%)	Darunavir N=818 (13.1%)	Raltegravir N=164 (2.6%)
	n (%) or median (IQR)			
Age (years)	31 (25, 41)	31 (25, 41)	36 (28, 46)*	42 (31, 51)*
Male	1,970 (88.0%)	2,660 (88.3%)	683 (83.5%)*	115 (70.1%)*
African American	999 (44.6%)	1,431 (47.5%)*	445 (54.4%)*	88 (53.7%)*
Hispanic	619 (27.7%)	798 (26.5%)	179 (21.9%)*	29 (17.7%)*
MSM	1,086 (48.5%)	1,354 (44.9%)*	361 (44.1%)*	55 (33.5%)*
Southern US	1,293 (57.8%)	1,978 (65.6%)*	517 (63.2%)	107 (65.2%)*
Drug Abuse	260 (11.6%)	307 (10.2%)	107 (13.1%)	18 (11.0%)
History of Syphilis	613 (27.4%)	881 (29.2%)	262 (32.0%)*	37 (22.6%)
Government Payer	1,331 (59.5%)	1,530 (50.8%)*	516 (63.1%)	106 (64.6%)
Hx AIDS Dx	376 (16.8%)	462 (15.3%)	266 (32.5%)*	44 (26.8%)*
Year of ART Initiation				
2013	78 (3.5%)	263 (8.7%)*	95 (11.6%)*	37 (22.6%)*
2014	352 (15.7%)	640 (21.2%)	209 (25.6%)	49 (29.9%)
2015	602 (26.9%)	648 (21.5%)	178 (21.8%)	40 (24.4%)
2016	773 (34.5%)	828 (27.5%)	189 (23.1%)	20 (12.2%)
2017	433 (19.3%)	634 (21.0%)	147 (18.0%)	18 (11.0%)
Baseline VL (log_{10})	4.7 (4.2, 5.1)	4.7 (4.2, 5.1)*	4.8 (4.2, 5.3)*	4.7 (4.2, 5.1)
Baseline CD4 (cells/μL)	371 (209, 529)	367 (211, 532)	228 (78, 407)*	292 (133, 451)*
VACS Mortality Score†	20 (13, 35)	20 (13, 34)	30 (19, 53)*	35 (23, 52)*
Number of non-Art Rx				
0	1,440 (64.3%)	2,033 (67.8%)*	478 (58.4%)*	82 (50.0%)*
1-2	715 (32.0%)	901 (29.9%)	296 (36.2%)	66 (40.2%)
≥3	83 (3.7%)	79 (2.6%)	44 (5.4%)	16 (9.8%)

*p-value for comparison to dolutegravir <0.05

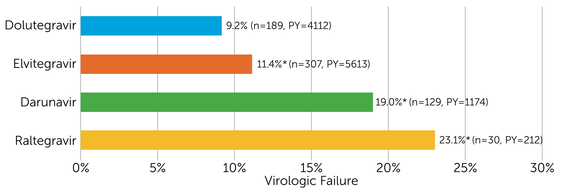
†Scored by summing pre-assigned points for age, CD4 count, HIV-1 RNA, hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. A higher score is associated with a higher risk of 5-year all-cause mortality.

RESULTS, cont.

Virologic Failure

- The proportion of patients experiencing virologic failure was highest among RAL (23.1%) and DRV users (19.0%), lower among EVG users (11.4%) and lowest among DTG users (9.2%) (Figure 1).

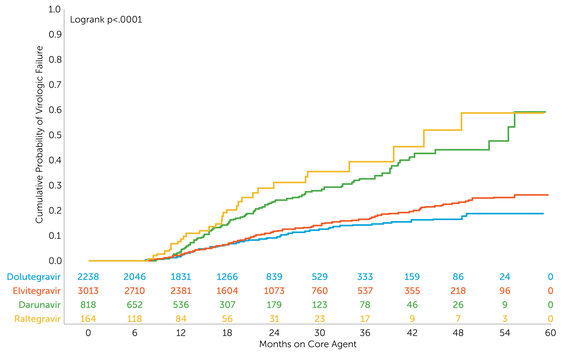
Figure 1. Frequency of Virologic Failure Over Follow-Up



*p-value for comparison to dolutegravir <0.05
PY = person-years

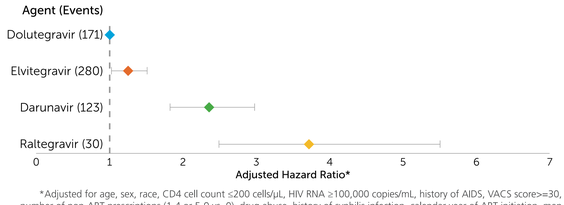
- Throughout follow-up, unadjusted cumulative probability of virologic failure remained highest with RAL use, followed by DRV, EVG and DTG (Figure 2).

Figure 2. Unadjusted Cumulative Probability of Virologic Failure



- After adjustment for baseline covariates, EVG, RAL and DRV users experienced virologic failure statistically significantly faster than DTG users (Figure 3).
  - RAL vs. DTG: HR = 3.63 (95% CI: 2.42, 5.43)
  - DRV vs. DTG: HR = 2.35 (95% CI: 1.84, 2.99)
  - EVG vs. DTG: HR = 1.23 (95% CI: 1.02, 1.50)

Figure 3. Association Between Core Agent and Time to Virologic Failure Estimated with a Multivariate* Cox Proportional Hazards Model



*Adjusted for age, sex, race, CD4 cell count ≤200 cells/μL, HIV RNA ≥100,000 copies/mL, history of AIDS, VACS score>=30, number of non-ART prescriptions (1-4 or 5-9 vs. 0), drug abuse, history of syphilis infection, calendar year of ART initiation, men who have sex with men, and type of health coverage (ADAP, Ryan White, Medicaid or Medicare vs. other)

DISCUSSION

- DTG and EVG users were similar at baseline, while RAL and DRV users had less favorable characteristics than DTG users (Table 1).
- The frequency and cumulative probability of virologic failure were highest among RAL users, followed by DRV users. Both the frequency and cumulative probability were slightly higher in EVG users than DTG users (Figures 2-3). RAL, DRV and EVG use were associated with a statistically significant faster time to virologic failure than DTG use. These associations remained after adjusting for important clinical characteristics.
- This analysis may be limited by residual confounding as the small number of RAL initiators, and their complex medical presentation, may have constrained our ability to account for observed channeling bias in multivariable modeling.

KEY FINDING

In this assessment of ART-naïve patients in a real-world clinical setting, DTG users were significantly less likely to experience virologic failure compared to RAL, DRV and EVG users.

ACKNOWLEDGMENTS

This research would not be possible without the generosity of the OPERA HIV caregivers and their patients. Additionally, we are grateful for the following individuals: Lito Torres (SAS programming), Jeff Briney (QA), Ted Ising (Database Arch & Mgmt), Bernie Stooks (Database Mgmt), Judy Johnson (Medical Terminology Classification), Rodney Mood (Site Support & Data Analyst).

SUPPORT

This research was funded by ViiV Healthcare.

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ISPOR 2019, New Orleans, LA, 18-22 May 2019