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

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BACKGROUND

- In the US Department of Health and Human Services clinical guideline, dolutegravir (DTG), elvitegravir (EVG) and raltegravir (RAL) are recommended core agents for initial antiretroviral therapy (ART) and darunavir (DRV) is recommended for patients with a higher risk of resistance
- The efficacy of these commonly used core agents has been evaluated in clinical trials, but longer-term assessments of clinical effectiveness in real world settings are needed

OBJECTIVE:

To assess virologic failure following core agent initiation in ART-naïve patients

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
- Inclusion criteria: ART-naïve HIV-1-infected patients ≥13 years of age, with ≥1 HIV-1 viral load (VL) and ≥1 CD4 test on or up to 90 days prior to initiating DTG, EVG, RAL or DRV between August 12, 2013 and July 31, 2016
- ART-naïve: no history of ART prior to DTG, EVG, RAL or DRV initiation and baseline viral load ≥1,000 copies/mL
- Baseline: date of core agent (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 per year), 3) death, or 4) study end (July 31, 2017)

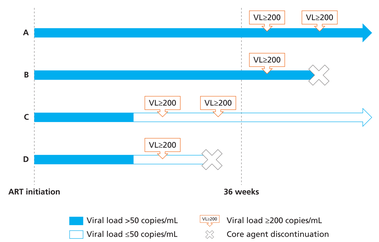
Exposure

- Initiation of DTG, EVG, RAL or DRV

Outcome

- Virologic failure, defined based on time on ART, core agent discontinuation and viral suppression (Figure 1)

Figure 1. Definition of Virologic Failure as either (A) 2 consecutive VL ≥200 copies/mL after 36 weeks of ART, or (B) 1 VL ≥200 with core agent discontinuation after 36 weeks, or (C) 2 consecutive VL ≥200 after suppression (VL ≤50) before 36 weeks, or (D) 1 VL ≥200 with discontinuation after suppression before 36 weeks



Statistical Analyses

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

RESULTS

Patient Characteristics

- Median follow-up time was 18.4 months (IQR: 12.6-27.4)
- EVG vs. DTG: lower baseline mortality index, fewer non-ART prescriptions (Table 1)
- RAL vs. DTG: older, higher mortality index, lower baseline CD4 cell count, more non-ART prescriptions
- DRV vs. DTG: older, higher baseline VL and mortality index, lower baseline CD4 cell count, more non-ART prescriptions

Table 1. Baseline Patient Characteristics by Core Agent

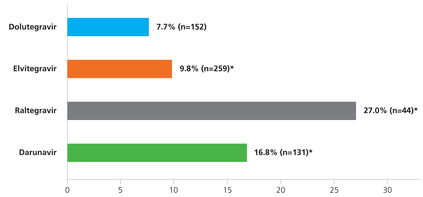
	DOLUTEGRAVIR, N=1970 (35.4%) n (%) or median (IQR)	ELVITEGRAVIR, N=2654 (47.7%) n (%) or median (IQR)	RALTEGRAVIR N=163 (2.9%) n (%) or median (IQR)	DARUNAVIR, N=781 (14.0%) n (%) or median (IQR)
Age (years)	32 (IQR: 25, 42)	31 (IQR: 25, 41)*	42 (IQR: 31, 49)*	38 (IQR: 28, 47)*
Male	1702 (86.4%)	2314 (87.2%)*	111 (68.1%)*	627 (80.3%)*
African American	860 (43.7%)	1199 (45.2%)	88 (54.0%)*	397 (50.8%)*
Hispanic	532 (27.0%)	722 (27.2%)	28 (17.2%)*	174 (22.3%)*
Men who have sex with men	1071 (54.4%)	1411 (53.2%)	64 (39.3%)*	366 (46.9%)*
Receiving care in the southern U.S.	1192 (60.5%)	1714 (64.6%)*	106 (65.0%)*	467 (59.8%)
ADAP, Ryan White, Medicaid or Medicare recipient	1246 (63.2%)	1472 (55.5%)*	111 (68.1%)	517 (66.2%)
Drug abuse	260 (13.2%)	282 (10.6%)	20 (12.3%)	121 (15.5%)
History of syphilis infection	521 (26.4%)	750 (28.3%)	38 (23.3%)	226 (28.9%)
Calendar year of ART initiation				
2013	97 (4.9%)	299 (11.3%)*	46 (28.2%)*	120 (15.4%)*
2014	454 (23.0%)	858 (32.3%)	66 (40.5%)	274 (35.1%)
2015	851 (43.2%)	905 (34.1%)	39 (23.9%)	239 (30.6%)
2016	568 (28.8%)	592 (22.3%)	12 (7.4%)	148 (19.0%)
Baseline Viral Load log10	4.7 (4.2, 5.1)	4.7 (4.2, 5.1)	4.6 (4.3, 5.0)	4.8 (4.3, 5.2)*
Baseline CD4 cell count (cells/µl)	372 (206, 532)	368 (209, 527)	241 (95, 449)*	213 (66, 381)*
VACS Mortality Index Score†	23 (13, 35)	20 (13, 35)*	35 (20, 56)*	35 (20, 54)*
Number of non-ART prescriptions				
0 Non-ART Rx	1216 (61.7%)	1734 (65.3%)*	78 (47.8%)*	410 (52.5%)*
1-2 Non-ART Rx	485 (24.6%)	642 (24.2%)	48 (29.5%)	231 (29.6%)
≥3 Non-ART Rx	269 (13.67%)	278 (10.5%)	37 (22.7%)	140 (17.9%)

* p-value <0.05 for the comparison with dolutegravir
† 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.

Virologic Failure

- The proportion of patients experiencing virologic failure was highest among RAL (27.0%) and DRV users (16.8%), lower among EVG users (9.8%) and lowest among DTG users (7.7%) (Figure 2)

Figure 2. Frequency of Virologic Failure Over Follow-Up



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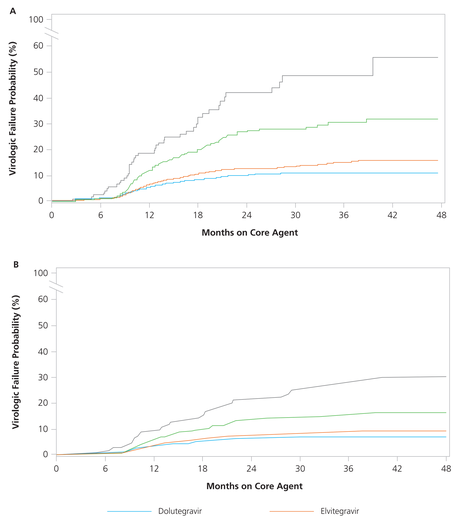
- Throughout follow-up, unadjusted cumulative probability of virologic failure remained highest with RAL use, followed by DRV use, and was the lowest with EVG or DTG use (Figure 3A)
- After adjustment for baseline covariates, patterns of cumulative probability of virologic failure remained unchanged, although the magnitude was reduced (Figure 3B)

Figure 3. (A) Unadjusted and (B) Adjusted* Cumulative Probability of Virologic Failure

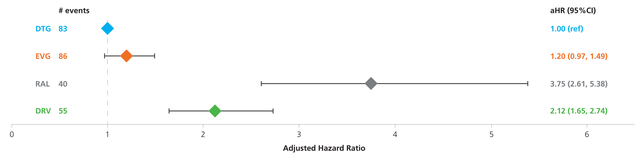


* Adjusted for age, sex, race, CD4 cell count ≤200 cells/µL, HIV RNA ≥100,000 copies/mL, history of AIDS, VACS score (15-29, 30-44 or ≥45 vs. <15), number of non-ART prescriptions (1-2 or ≥3 vs. 0), drug abuse, history of syphilis infection, calendar year of ART initiation, men who have sex with men, and type of health coverage (ADAP, Ryan White, Medicaid or Medicare vs. other), at baseline

Time to Virologic Failure

- After adjustment for baseline covariates*, RAL and DRV users experienced virologic failure statistically significantly faster than DTG users (Figure 4)
  - RAL vs. DTG: HR = 3.75 (95% CI: 2.61, 5.38)
  - DRV vs. DTG : HR = 2.12 (95% CI: 1.65, 2.74)
- There was no statistically significant difference in time to virologic failure between EVG and DTG users (Figure 4)
  - EVG vs. DTG: HR = 1.20 (95% CI: 0.97, 1.49)

Figure 4. Association Between Core Agent and Time to Virologic Failure Estimated with a Multivariate* Cox Proportional Hazards Model



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DISCUSSION

- Overall, EVG users had more favorable baseline clinical characteristics than DTG users, while RAL and DRV users had less favorable baseline clinical characteristics than DTG users (Table 1)
- The frequency and cumulative probability of virologic failure was 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 and DRV use were associated with a statistically significant faster time to virologic failure than DTG use. EVG use was associated with a marginally faster time to virologic failure than DTG use (Figure 4)
- These associations remained after adjusting for important clinical characteristics

KEY FINDINGS

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

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