Gastrointestinal Disorders Following Initiation of Dolutegravir, Elvitegravir, Raltegravir or Darunavir

Karam Mounzer[1], Laurence Brunet[2], Jennifer Fusco[2], Ricky Hsu[3], Philip Lackey[4], Vani Vannappagari[5], Leigh Ragone[5], Gregory Fusco[2]

[1]Philadelphia FIGHT, Philadelphia, PA, USA; [2]Epividian, Durham, NC, USA; [3]AIDS Healthcare Foundation, New York, NY, USA; [4]Atrium Health, Charlotte, NC, USA; [5]ViiV Healthcare, Research Triangle Park, NC, USA

OPERA® The Longitudinal Cohort

Contact Information:
Laurence Brunet
4505 Emperor Blvd, Suite 220, Durham, NC 27703
(919) 827-0010
laurence.brunet@epividian.com

Background

- In randomized controlled trials, grade 2-4 gastrointestinal (GI) adverse events were reported in <2% with dolutegravir (DTG), ≤4% with raltegravir (RAL), ≤9% with darunavir (DRV); all grade GI adverse events (mainly grade 1) were reported in ≤16% with elvitegravir (EVG)

OBJECTIVE

To assess the risk of incident gastrointestinal (GI) disorders associated with initiation of antiretroviral therapy (ART) with four common core agents (DTG, EVG, RAL, DRV)

Methods

Study population

- Inclusion criteria
  - HIV positive, ≥13 years of age
  - Start a new regimen with DTG, EVG/c, RAL or DRV between 01AUG2013 and 31DEC2016 (first exposure, only 1 core agent)
  - No diagnosis of selected GI associated comorbidities at baseline (non-HCV viral Hepatitis, liver cirrhosis, NAFLD, NASH, alcoholic liver disease, intestinal parasite, *C. difficile*, *H. pylori*, small intestinal bacterial overgrowth (SIBO), bacterial or viral diarrhea, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), chronic diarrhea, chronic pancreatitis, pancreatic insufficiency, celiac disease, lactose intolerance, GERD, gastritis, gastroenteritis, ulcers, cholecystectomy, gastric bypass, alcohol abuse)
  - Baseline: date of regimen initiation
  - Observation period: from regimen initiation until (1) core agent discontinuation, (2) 12 months after last clinical contact, (3) death, or (4) 31 Dec 2017

GI disorders

- Incident GI disorders: new GI symptom, diagnosis or prescription after baseline, in the absence of any history of GI disorders (Table 1)

Table 1. Definition of historical and incident GI disorders (i.e. symptoms, diagnoses and medications)

		History	Incident
GI symptoms	Diagnosis of nausea, vomiting, diarrhea, abdominal pain, abdominal bloating, gas, flatulence, heartburn, loose stool	≤7 days before baseline	≤8 weeks after baseline
GI diagnoses	Diagnosis of gastritis, peptic ulcer disease, gastrointestinal bleeding, GERD, acid reflux, esophagitis, duodenitis, GI ulcerations	≤6 months before baseline	Any time during follow-up
GI medications	Prescription of anti-diarrheal, antispasmodic, stool softener, acid reducer (PPI, H2 blocker), anti-inflammatory (for IBD), anti-nausea	≤6 months before baseline	≤8 weeks after baseline

Statistical analyses

- Stratified by ART experience, restricted to the first 6 months or all follow-up
- Descriptive statistics: Sidak correction (adjusted alpha level: 0.017)
- Cox Proportional Hazard models adjusted for baseline age, sex, race, nadir CD4 cell count, history of AIDS, opioid use, and NSAID use

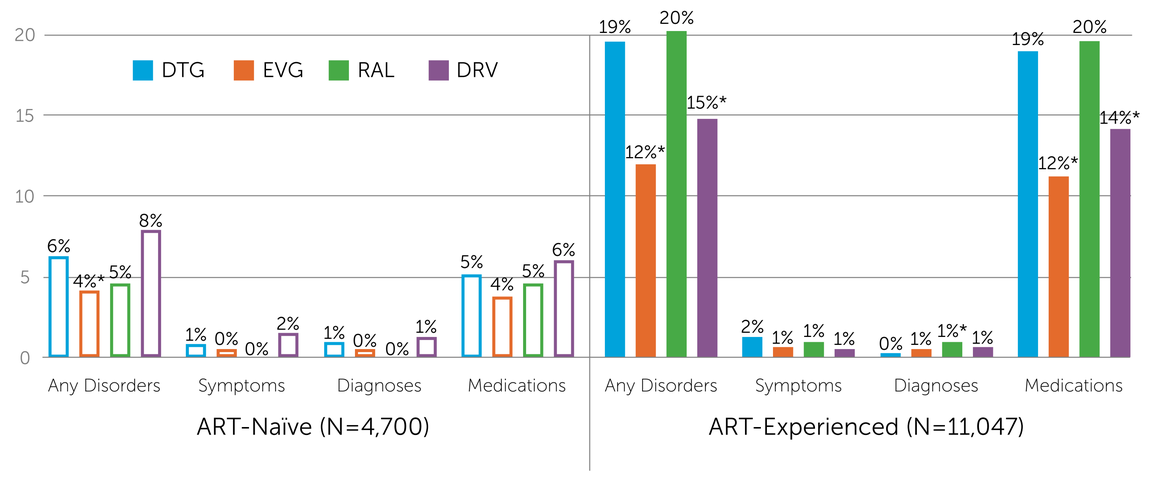
Results

Table 2. Baseline characteristics

	ART-naïve (N=4,700)				ART-experienced (N=11,047)			
	DTG (n=1,653)	EVG (n=2,288)	RAL (n=109)	DRV (n=650)	DTG (n=3,958)	EVG (n=4,916)	RAL (n=549)	DRV (n=1,624)
Age, median (IQR)	30 (25, 40)	30 (25, 41)	39 (29, 50)*	36 (28, 46)*	43 (32, 52)	38 (29, 49)*	48 (37, 54)*	44 (34, 52)
Female	199 (12.0%)	267 (11.7%)	28 (25.7%)*	113 (17.4%)*	591 (14.9%)	692 (14.1%)	107 (19.5%)*	379 (23.3%)*
African-American	750 (45.4%)	1053 (46.0%)	54 (49.5%)	346 (53.2%)*	1606 (40.6%)	1968 (40.0%)	192 (35.0%)*	771 (47.5%)*
Nadir CD4 (cells/µL), med (IQR)	376 (224, 524)	364 (214, 523)	319 (140, 456)*	220 (78, 381)*	416 (251, 609)	446 (277, 635)*	510 (299, 716)*	365 (178, 584)*
Hx of AIDS	248 (15.0%)	339 (14.8%)	26 (23.9%)	223 (34.3%)*	1112 (28.1%)	1090 (22.2%)*	147 (26.8%)	515 (31.7%)*
Opioid Use	42 (2.5%)	45 (2.0%)	6 (5.5%)	28 (4.3%)	295 (7.5%)	245 (5.0%)*	46 (8.4%)	114 (7.0%)
NSAID Use	53 (3.2%)	63 (2.8%)	2 (1.8%)	33 (5.1%)	306 (7.7%)	298 (6.1%)*	40 (7.3%)	125 (7.7%)

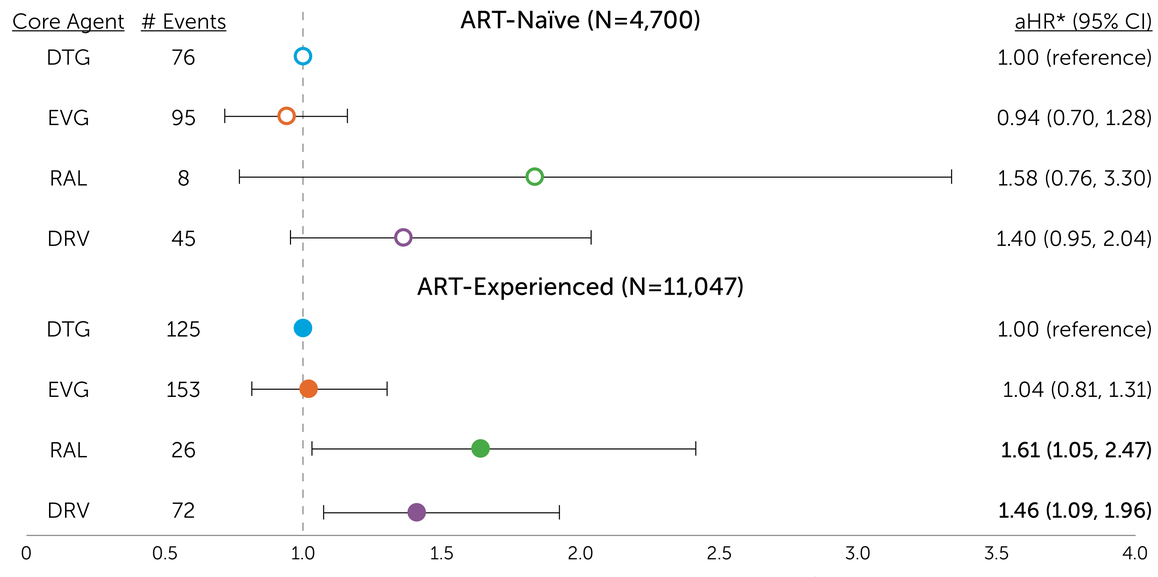
* p-value <0.017 for the comparison with DTG

Figure 1. History of GI disorders



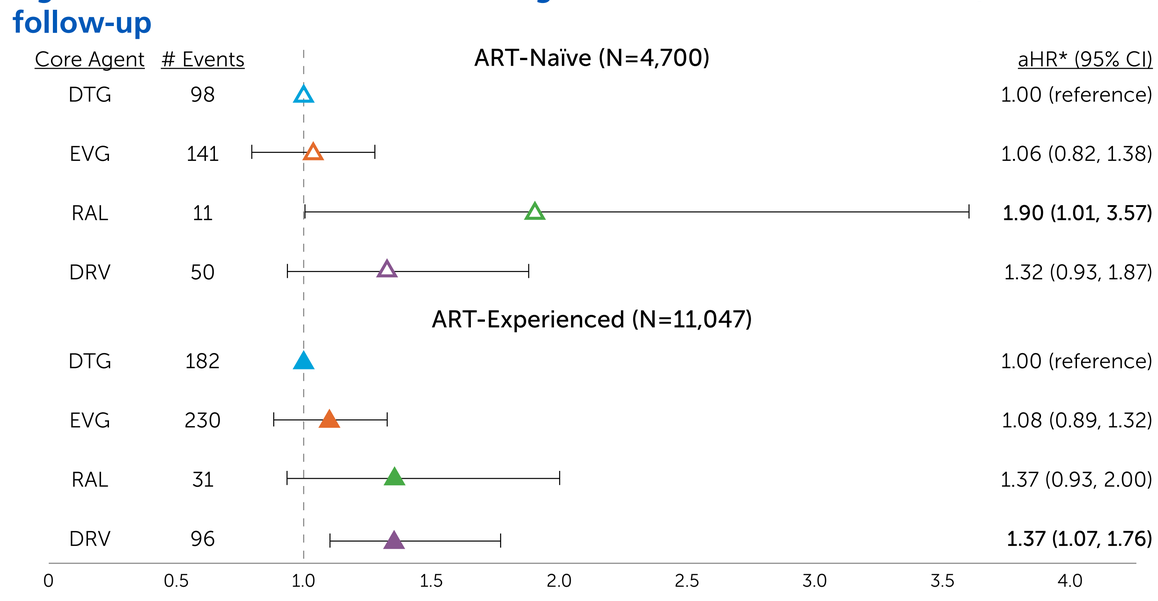
* p-value <0.017 for the comparison with DTG

Figure 2. Association between core agents and incident GI disorders, first 6 months of follow-up



* Cox proportional hazards models adjusted for baseline age, sex, race, nadir CD4 cell count, history of AIDS-defining illnesses, opioid use and NSAID use

Figure 3. Association between core agents and incident GI disorders, all follow-up



* Cox proportional hazards models adjusted for baseline age, sex, race, nadir CD4 cell count, history of AIDS-defining illnesses, opioid use and NSAID use

Discussion

- Six-month follow-up informed by a clinical understanding that most incident cases of GI disorders occur shortly (within 2 months) after initiation of a new regimen
  - Allowed for most early incident GI disorders to be recorded in the EMR at a follow-up appointment
- Over the first 6 months of treatment:
  - Incident GI disorders were infrequent in both ART-naïve (4.5% overall) and ART-experienced patients up (3.4% overall)
  - Switching to RAL or DRV was associated with an increased risk of incident GI disorders, compared to DTG (ART-experienced)
- Limitations: few RAL initiators; key differences in demographic and clinical characteristics with RAL and DRV compared to DTG; no adjustments for ART backbone

KEY FINDINGS

- ART-naïve: compared to DTG, initiating EVG, RAL or DRV was not associated with an increased risk of incident GI disorders in the first 6 months
- ART-experienced: compared to DTG, switching to RAL and DRV may be associated with an increased risk of incident GI disorders in the first 6 months

Support

This research was sponsored by ViiV Healthcare.

Acknowledgements

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: Robin Beckerman (SAS programming), Jeff Briney (QA), Ted Ising (Database Arch & Mgmt), Bernie Stooks (Database Mgmt), Redemptor Perez (Database Mgmt), Judy Johnson (Med Terminology Classification), Rodney Mood (Site Support), Antonin Fusco (Poster design).

ViiV Healthcare

10th IAS Conference on HIV Science, Mexico City, Mexico, 21-24 July 2019

Epividian®