In February 2013, GlaxoSmithKline (GSK) announced a commitment to further clinical transparency through the public disclosure of GSK Clinical Study Reports (CSRs) on the GSK Clinical Study Register.

The following guiding principles have been applied to the disclosure:

- *Information will be excluded in order to protect the privacy of patients and all named persons associated with the study*
- *Patient data listings will be completely removed* to protect patient privacy. Anonymized data from each patient may be made available subject to an approved research proposal. For further information please see the Patient Level Data section of the* ***GSK Clinical Study Register****.*
- *Aggregate data will be included; with any direct reference to individual patients excluded*

**Complete removal of patient data listings may mean that page numbers are no longer consecutively numbered*

A Comprehensive Assessment of Adverse Events and Overall Safety Profile in HIV Positive Patients Treated with Dolutegravir as Compared to Other Integrase Strand Transfer Inhibitors or Darunavir:

Final Report – Renal Outcomes

Complete data through December 31, 2017

December 4, 2019

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1. Background and Rationale

Background: Clinical guidelines currently recommend the use of the integrase strand transfer inhibitors (INSTI) dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL), or the protease inhibitor (PI) darunavir (DRV) as the core agent in antiretroviral therapy (ART) regimens.[1] Toxicity concerns with multi-agent regimens, and pharmacokinetic interactions with medications for co-morbidities suggest the need for a comprehensive safety evaluation of recommended core agents in a real-world setting. In clinical trials, DTG treatment-related adverse effects (determined by the investigator) were less frequent (1–3%) than comparator drugs. Most adverse events seen in trials of DTG were grade 1–2 (mild-to-moderate in severity), such as headache, diarrhea, nausea, or insomnia.[2-6]

DTG, RAL and cobicistat (boosting agent with EVG) could lead to in the inhibition of tubular creatinine secretion causing rapid non-progressive changes in serum creatinine or estimated glomerular filtration rates (eGFR)[7,8] that do not reflect functional kidney injury.[9] In the absence of kidney injury, a 10-20% decrease in eGFR followed by stabilization can thus occur within the first four weeks of treatment with DTG, RAL or cobicistat.[7]

No renal effects have been reported for either dolutegravir or elvitegravir.[8] However, elvitegravir is available in coformulation with tenofovir (TDF) and cobicistat (STRIBILD®). TDF has been associated with renal impairment due to kidney tubular injury[10-14] and co-administration of cobicistat increases the serum concentration of TDF,[15] which could theoretically enhance the risk for TDF tubular toxicity.[8] Close monitoring is therefore recommended to distinguish TDF-related kidney injury from cobicistat-related tubular secretion inhibition.[8]

Raltegravir has been associated with possible reduction in true GFR, and rhabdomyolysis causing significant acute kidney injury has been reported in case reports.[8] The presence of crystals has been reported in <8% of DRV users, but kidney stones were rare.[7]

Rationale: A comprehensive safety evaluation of DTG and other recommended core agents has not been performed in a real-world setting. As the use of INSTIs increases in various demographic populations and clinical situations, an understanding of the overall safety profile of the members of the class will provide additional information for clinicians as treatment strategies are designed.

Scope of report: This report is limited to renal outcomes and will appear in its entirety in the full report of safety outcomes.

2. Methods

2.1. Study Design

Study population: The study population consisted of HIV-positive patients at least 13 years of age initiating a core agent of interest prescribed by an OPERA caregiver during the eligibility period (August 1, 2013 to December 31, 2016).

Baseline date: The baseline date was defined as the first date of one of the four core agents of interest ever prescribed to a patient

Observation period: The observation period began on August 1, 2013 (the month DTG was approved) with study participants identified through December 31, 2016 on data through December 31, 2017. Patients were observed from their baseline date until the first of the following censoring events: 1) discontinuation of the core agent of interest, 2) cessation of continuous clinical activity, 3) death or 4) study end (December 31, 2017). Patients failing to meet the continuous clinical activity requirement were censored 12 months after their last contact.

Continuous Clinical Activity: Patients with continuous clinical activity were those who had clinical contact at least once in 12 months. Clinical contact was defined as a telephone contact, visit, lab test, or consultation.

Core agent of interest: Core agents of interest consisted of dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), or darunavir (DRV). A regimen was considered discontinued when the core agent of interest was discontinued for 45 days or more.

2.2. Renal Outcomes Definitions

Estimated glomerular filtration rate (eGFR): calculated using the 2009 CKD-EPI equation:

$$eGFR = 141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [1.159\ if\ Black]$$

Where: κ = 0.7 for females and 0.9 for males
α is -0.329 for females and -0.411 for males
min indicates the minimum of Scr /κ or 1
max indicates the maximum of Scr /κ or 1

Renal Disorders consisted of any of the following: (1) Moderate Renal Impairment, (2) Severe Renal Impairment, (3) Renal Failure, or (4) Acute Kidney Injury Diagnosis, defined as:

1. Moderate Renal Impairment: eGFR ≥30 to <60 ml/min per 1.73 m^2
2. Severe Renal Impairment: eGFR ≥15 to <30 ml/min per 1.73 m^2
3. Renal Failure: eGFR <15 ml/min per 1.73 m^2
4. Acute Kidney Injury Diagnosis: Diagnosis of “acute kidney injury”, excluding “traumatic kidney injury”

History of Renal Disorders: history was reported overall, but not for specific disorders. A history of renal disorders was defined as either of the following events occurring at baseline or up to 12 months before baseline:

a) Two consecutive eGFR <60 ml/min per 1.73 m^2, at least 14 days apart
b) One eGFR <30 ml/min per 1.73 m^2
c) Acute Kidney Injury Diagnosis

Prevalent Renal Disorders: defined as the occurrence of moderate renal impairment, severe renal impairment, renal failure, or acute kidney injury diagnosis after baseline, regardless of whether the patient had a history of renal disorders.

Incident Renal Disorders: defined as only a new occurrence of moderate renal impairment, severe renal impairment, renal failure, or acute kidney injury diagnosis after baseline, excluding patients who had any history of renal disorders at baseline. Therefore, incident renal disorders are a subset of prevalent renal disorders. The incidence of any of the disorders excluded patients with a history of any renal disorder (not just the disorder in question) because any one of these events puts a patient at very high risk for future renal events and should not be considered as incident.

Discontinuation (D/C): defined as discontinuation of the core agent of interest within 21 days of the date of a renal disorder. Time to renal disorders with D/C was calculated based on the date of the renal disorders.

2.3. Statistical Analyses

Descriptive analyses of baseline demographic and clinical patient characteristics at baseline, as well as renal outcomes during follow-up were conducted to compare DTG to other core agents of interest. Time to event were presented only for organ systems with >1% disorder history/prevalence/incidence. The Pearson's Chi-Square Test was used to calculate p-values for categorical variables and the Mann-Whitney Test was used to calculate p-values for continuous variables. Fischer Exact Test was used for cells with small numbers (counts of 5 or fewer).

To account for multiple comparisons between DTG and comparator core agents, the Sidak Correction was applied, resulting in an adjusted alpha level for significance of 0.017.

3. Results

3.1. Population Identification

Table 1. Identification of the Study Population

		Patients Included	*%*	*Patients Excluded*	*%*
1	OPERA patients who are HIV+	84,084	.	0	.
2	Patients with HIV-1 infection (excluding HIV-2 infection)	83,999	99.9	85	0.1
3	HIV+ patients prescribed ART	73,215	87.2	10,784	12.8
4	Patients prescribed a regimen of interest (containing DTG, EVG, RAL, or DRV)	47,789	65.3	25,426	34.7
5	Patients prescribed regimen of interest between 08/01/2013 and 12/31/2016	32,394	67.8	15,395	32.2
6	Patients who were 13 years of age or older at first ART regimen of interest	32,393	100.0	1	0.0
7	Patients prescribed a regimen of interest that did not include two or more third agents of interest	29,048	89.7	3,345	10.3
8	Patients whose first ART regimen of interest was not monotherapy	28,336	97.5	712	2.5
9	Patients whose first ART regimen of interest was not prior to date of HIV	28,188	99.5	148	0.5
10	Patients whose regimen of interest was their first experience with DTG, EVG, RAL, or DRV [Study population]	22,674	80.4	5,514	19.6

Table 2. Study Population by ART Core Agent of Interest and Regimen

Core agent of interest	*n(%)*	*Regimens*	*n(%)*
DTG-containing regimens	7,859 (34.7%)	DTG + TDF + FTC	1,524 (19.4%)
		DTG + TAF + FTC	219 (2.8%)
		DTG + ABC + 3TC	4,932 (62.8%)
		DTG + all other agents	1,184 (15.1%)
EVG-containing regimens	9,738 (42.9%)	EVG + r/c + TDF + FTC	5,996 (61.6%)
		EVG + r/c + TAF + FTC	2,987 (30.7%)
		EVG + r/c + all other agents	755 (7.8%)
RAL-containing regimens	1,600 (7.1%)	RAL + TDF + FTC	803 (50.2%)
		RAL + TAF + FTC	14 (0.9%)
		RAL + ABC + 3TC	126 (7.9%)
		RAL + all other agents	657 (41.1%)
DRV-containing regimens	3,477 (15.3%)	DRV + r/c + TDF + FTC	2,481 (71.4%)
		DRV + r/c + TAF + FTC	134 (3.9%)
		DRV + r/c + ABC + 3TC	318 (9.1%)
		DRV + r/c + all other agents	496 (14.3%)
		DRV + TDF + FTC	15 (0.4%)
		DRV + ABC + 3TC	6 (0.2%)
		DRV + all other agents	27 (0.8%)

3.2. Baseline Characteristics

Table 3. Baseline Demographic Characteristics of Patients Taking DTG, EVG, RAL, & DRV Regime

		DTG	*EVG*	*DTG vs. EVG*	*RAL*	*DTG vs. RAL*	*DRV*	*DTG vs. DRV*
		N= 7,859	*N= 9,738*	*p-value*	*N= 1,600*	*p-value*	*N= 3,477*	*p-value*
Age	Median (IQR)	41.1 (29.8, 51.1)	36.9 (28.1, 48.4)	**<.0001**	48.8 (39.8, 55.0)	**<.0001**	43.4 (33.0, 51.1)	**<.0001**
	13-25	1134 (14.4%)	1707 (17.5%)	**<.0001**	72 (4.5%)	**<.0001**	331 (9.5%)	**<.0001**
	26-49	4527 (57.6%)	5993 (61.5%)	**.**	807 (50.4%)	**.**	2159 (62.1%)	**.**
	50+	2198 (28.0%)	2038 (20.9%)	**.**	721 (45.1%)	**.**	987 (28.4%)	**.**
Sex	Male	6670 (84.9%)	8416 (86.4%)	**0.0124**	1273 (79.6%)	**<.0001**	2763 (79.5%)	**<.0001**
	Female	1182 (15.0%)	1314 (13.5%)	**.**	325 (20.3%)	**.**	713 (20.5%)	**.**
	Unknown	7 (0.1%)	8 (0.1%)	**.**	2 (0.1%)	**.**	1 (0.0%)	**.**
Race	African American	3226 (41.0%)	3948 (40.5%)	0.4969	581 (36.3%)	**0.0004**	1661 (47.8%)	**<.0001**
	Not African American	4633 (59.0%)	5790 (59.5%)	.	1019 (63.7%)	**.**	1816 (52.2%)	**.**
Ethnicity	Hispanic	1936 (24.6%)	2496 (25.6%)	0.1297	273 (17.1%)	**<.0001**	720 (20.7%)	**<.0001**
	Not Hispanic	5923 (75.4%)	7242 (74.4%)	.	1327 (82.9%)	**.**	2757 (79.3%)	**.**
Marital Status	Single	5543 (70.5%)	6720 (69.0%)	0.1090	976 (61.0%)	**<.0001**	2302 (66.2%)	**<.0001**
	Married	467 (5.9%)	613 (6.3%)	.	145 (9.1%)	**.**	267 (7.7%)	**.**
	Domestic partnership	258 (3.3%)	293 (3.0%)	.	54 (3.4%)	**.**	116 (3.3%)	**.**
	Widowed	51 (0.6%)	57 (0.6%)	.	21 (1.3%)	**.**	37 (1.1%)	**.**
	Separated/divorced	205 (2.6%)	257 (2.6%)	.	64 (4.0%)	**.**	102 (2.9%)	**.**
	Unknown	1335 (17.0%)	1798 (18.5%)	.	340 (21.3%)	**.**	653 (18.8%)	**.**
Risk of Infection	MSM	4023 (51.2%)	4788 (49.2%)	**0.0077**	589 (36.8%)	**<.0001**	1427 (41.0%)	**<.0001**
	Not MSM	3836 (48.8%)	4950 (50.8%)	**.**	1011 (63.2%)	**.**	2050 (59.0%)	**.**
History of Syphilis	Any	2158 (27.5%)	2817 (28.9%)	0.0315	314 (19.6%)	**<.0001**	830 (23.9%)	**<.0001**
Region	Northeast	674 (8.6%)	809 (8.3%)	**<.0001**	164 (10.3%)	**<.0001**	246 (7.1%)	**<.0001**
	South	4267 (54.3%)	6029 (61.9%)	**.**	1061 (66.3%)	**.**	2174 (62.5%)	**.**
	Midwest	177 (2.3%)	266 (2.7%)	**.**	42 (2.6%)	**.**	65 (1.9%)	**.**
	West	2741 (34.9%)	2634 (27.0%)	**.**	333 (20.8%)	**.**	992 (28.5%)	**.**
Payer	Medicaid	1754 (22.3%)	1557 (16.0%)	**<.0001**	358 (22.4%)	0.9605	839 (24.1%)	0.0342
	Medicare	715 (9.1%)	575 (5.9%)	**<.0001**	309 (19.3%)	**<.0001**	459 (13.2%)	**<.0001**
	Commercial Insurance	2381 (30.3%)	3221 (33.1%)	**<.0001**	506 (31.6%)	0.2929	860 (24.7%)	**<.0001**
	Cash	4420 (56.2%)	5118 (52.6%)	**<.0001**	914 (57.1%)	0.5158	1885 (54.2%)	0.0451

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	ADAP/Ryan White	2820 (35.9%)	3143 (32.3%)	**<.0001**	338 (21.1%)	**<.0001**	1034 (29.7%)	**<.0001**
	Other	36 (0.5%)	33 (0.3%)	0.2259	3 (0.2%)	0.1383	9 (0.3%)	0.1448
	No Payer info	1145 (14.6%)	1934 (19.9%)	**<.0001**	362 (22.6%)	**<.0001**	711 (20.4%)	**<.0001**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 4. General Baseline Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Year of Study Initiation	2013	299 (3.8%)	828 (8.5%)	**<.0001**	344 (21.5%)	**<.0001**	568 (16.3%)	**<.0001**
	2014	1653 (21.0%)	2144 (22.0%)	**.**	631 (39.4%)	**.**	1139 (32.8%)	**.**
	2015	2580 (32.8%)	2435 (25.0%)	**.**	350 (21.9%)	**.**	878 (25.3%)	**.**
	2016	3327 (42.3%)	4331 (44.5%)	**.**	275 (17.2%)	**.**	892 (25.7%)	**.**
Time from first active date to index date	Median (IQR)	2.2 (0.5, 34.7)	1.2 (0.1, 24.0)	**<.0001**	0.2 (0.0, 8.8)	**<.0001**	0.7 (0.0, 19.8)	**<.0001**
Follow-up time between baseline and end of observation	Median (IQR)	18.3 (12.5, 27.5)	17.0 (12.0, 26.0)	**<.0001**	14.5 (9.9, 25.8)	**<.0001**	15.6 (10.8, 25.7)	**<.0001**
Pregnancy	Pregnancy	6 (0.1%)	10 (0.1%)	0.6233	4 (0.3%)	0.0729	11 (0.3%)	**0.0059**
VACS Index†	Median (IQR)	17.0 (7.0, 29.0)	13.0 (7.0, 25.0)	**<.0001**	20.0 (10.0, 35.0)	**<.0001**	22.0 (12.0, 39.0)	**<.0001**
VACS Index† category	0 to <15	2994 (38.1%)	3916 (40.2%)	**<.0001**	374 (23.4%)	**<.0001**	837 (24.1%)	**<.0001**
	>=15 to <30	2038 (25.9%)	2177 (22.4%)	**.**	317 (19.8%)	**.**	809 (23.3%)	**.**
	>=30 to <45	816 (10.4%)	777 (8.0%)	**.**	147 (9.2%)	**.**	381 (11.0%)	**.**
	>= 45	779 (9.9%)	742 (7.6%)	**.**	173 (10.8%)	**.**	528 (15.2%)	**.**
	Missing	1232 (15.7%)	2126 (21.8%)	**.**	589 (36.8%)	**.**	922 (26.5%)	**.**

* VACS Mortality Index: score created by summing pre-assigned points for age, HIV disease (CD4 count and HIV-1 RNA), and general indicators of organ system injury including hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. This score is used to estimate risk of all-cause mortality in the following 5 years. A higher score is associated with a higher risk of mortality.

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 5. Baseline HIV-Related Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimen

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
ART experience at index	ART-naïve	2662 (33.9%)	3452 (35.4%)	0.0290	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	ART-experienced	5197 (66.1%)	6286 (64.6%)	.	1401 (87.6%)	**.**	2499 (71.9%)	**.**
Calendar year of ART initiation	Median (IQR)	2015 (2013, 2016)	2015(2013, 2016)	**<.0001**	2014 (2013, 2015)	**<.0001**	2014 (2013, 2015)	**<.0001**
	Pre-2000	213 (2.7%)	132 (1.4%)	**<.0001**	30 (1.9%)	**<.0001**	55 (1.6%)	**<.0001**
	2000-2004	278 (3.5%)	172 (1.8%)	**.**	34 (2.1%)	**.**	88 (2.5%)	**.**
	2005-2009	620 (7.9%)	548 (5.6%)	**.**	87 (5.4%)	**.**	194 (5.6%)	**.**
	2010-2014	2618 (33.3%)	3852 (39.6%)	**.**	924 (57.8%)	**.**	1706 (49.1%)	**.**
	2015-present	4130 (52.6%)	5034 (51.7%)	**.**	525 (32.8%)	**.**	1434 (41.2%)	**.**
Number of previous ART regimens	Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	**<.0001**	1.0 (1.0, 3.0)	**0.0158**	1.0 (1.0, 2.0)	0.4892
	ART-naïve	2662 (33.9%)	3452 (35.4%)	**<.0001**	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	1-2 previous regimens	2668 (33.9%)	2592 (26.6%)	**.**	281 (17.6%)	**.**	776 (22.3%)	**.**
	3-4 previous regimens	410 (5.2%)	298 (3.1%)	**.**	41 (2.6%)	**.**	103 (3.0%)	**.**
	5 or more previous regimens	266 (3.4%)	208 (2.1%)	**.**	55 (3.4%)	**.**	91 (2.6%)	**.**
	Missing previous regimens	1853 (23.6%)	3188 (32.7%)	**.**	1024 (64.0%)	**.**	1529 (44.0%)	**.**
Previous ART exposure	Naive	2662 (33.9%)	3452 (35.4%)	0.0290	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	NNRTI	2129 (27.1%)	2280 (23.4%)	**<.0001**	200 (12.5%)	**<.0001**	441 (12.7%)	**<.0001**
	PI	1547 (19.7%)	974 (10.0%)	**<.0001**	198 (12.4%)	**<.0001**	587 (16.9%)	**0.0004**
	INSTI	1 (0.0%)	1 (0.0%)	1.0000	0 (0.0%)	1.0000	1 (0.0%)	0.5194
	NRTI	3309 (42.1%)	2988 (30.7%)	**<.0001**	357 (22.3%)	**<.0001**	929 (26.7%)	**<.0001**
	Other	31 (0.4%)	17 (0.2%)	**0.0054**	10 (0.6%)	0.2007	8 (0.2%)	0.1681
	Experienced-ART specifics missing	1853 (23.6%)	3188 (32.7%)	**<.0001**	1024 (64.0%)	**<.0001**	1529 (44.0%)	**<.0001**
Backbone of Regimen of Interest	TDF + FTC	1524 (19.4%)	5996 (61.6%)	**<.0001**	803 (50.2%)	**<.0001**	2496 (71.8%)	**<.0001**
	TAF + FTC	219 (2.8%)	2987 (30.7%)	**.**	14 (0.9%)	**.**	134 (3.9%)	**.**

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	ABC + 3TC	4932 (62.8%)	0 (0.0%)	.	126 (7.9%)	.	324 (9.3%)	.
	All others	1184 (15.1%)	755 (7.8%)	.	657 (41.1%)	.	523 (15.0%)	.
AIDS-defining Illness	AIDS	2040 (26.0%)	2007 (20.6%)	**<.0001**	448 (28.0%)	0.0908	1140 (32.8%)	**<.0001**
	No AIDS	5819 (74.0%)	7731 (79.4%)	.	1152 (72.0%)	.	2337 (67.2%)	.
Baseline viral load	Median (IQR)	460.0 (19.0, 40590.0)	1649.5 (19.0, 45155.0)	0.0424	19.0 (19.0, 820.0)	**<.0001**	1042.0 (19.0, 52360.0)	**<.0001**
Baseline Viral Load log10	Median (IQR)	2.7 (1.3, 4.6)	3.3 (1.3, 4.7)	0.0191	1.3 (1.3, 3.0)	**<.0001**	3.1 (1.3, 4.7)	**<.0001**
Baseline Viral Load category	Suppressed (<50 copies/mL)	2765 (35.2%)	3131 (32.2%)	**<.0001**	617 (38.6%)	**<.0001**	925 (26.6%)	**<.0001**
	Low (>=50 to <10,000 copies/mL)	1288 (16.4%)	1499 (15.4%)	.	224 (14.0%)	.	646 (18.6%)	.
	Moderate (>=10,000 to <100,000 copies/mL)	1708 (21.7%)	2100 (21.6%)	.	136 (8.5%)	.	583 (16.8%)	.
	High (>=100,000 copies/mL)	906 (11.5%)	1110 (11.4%)	.	71 (4.4%)	.	460 (13.2%)	.
	Missing baseline VL	1192 (15.2%)	1898 (19.5%)	.	552 (34.5%)	.	863 (24.8%)	.
Nadir CD4	Median (IQR)	400.0 (237.0, 585.0)	413.0 (253.0, 597.0)	**0.0004**	437.0 (243.0, 659.0)	**0.0001**	318.0 (133.0, 536.0)	**<.0001**
Baseline CD4	Median (IQR)	491.0 (310.0, 706.0)	489.0 (306.0, 697.0)	0.4595	514.0 (303.0, 742.0)	0.1531	384.0 (181.0, 620.5)	**<.0001**
	High (>500 cells/µL)	3242 (41.3%)	3820 (39.2%)	**<.0001**	538 (33.6%)	**<.0001**	950 (27.3%)	**<.0001**
	Moderate (>350 to <=500 cells/µL)	1412 (18.0%)	1669 (17.1%)	.	189 (11.8%)	.	475 (13.7%)	.
	Moderate Low (>200 to <=350 cells/µL)	1054 (13.4%)	1311 (13.5%)	.	173 (10.8%)	.	477 (13.7%)	.
	Low (>50 to <=200 cells/µL)	671 (8.5%)	769 (7.9%)	.	109 (6.8%)	.	424 (12.2%)	.
	Very low (<=50 cells/µL)	293 (3.7%)	319 (3.3%)	.	44 (2.8%)	.	278 (8.0%)	.
	Missing baseline CD4	1187 (15.1%)	1850 (19.0%)	.	547 (34.2%)	.	873 (25.1%)	.

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 6. Baseline Comorbidities of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Any Comorbidity	Any comorbidity	5804 (73.9%)	6455 (66.3%)	**<.0001**	1267 (79.2%)	**<.0001**	2527 (72.7%)	0.1916
Cardiovascular Disease Condition	Any cardiovascular disease	576 (7.3%)	460 (4.7%)	**<.0001**	173 (10.8%)	**<.0001**	224 (6.4%)	0.0891
	Arrhythmia	180 (2.3%)	155 (1.6%)	**0.0007**	36 (2.3%)	0.9215	60 (1.7%)	0.0541
	Myocardial Infarction	52 (0.7%)	31 (0.3%)	**0.0010**	16 (1.0%)	0.1442	17 (0.5%)	0.2756
	Angina	27 (0.3%)	11 (0.1%)	**0.0015**	4 (0.3%)	0.8095	11 (0.3%)	1.0000
	Other/Unspecified CHD	299 (3.8%)	217 (2.2%)	**<.0001**	103 (6.4%)	**<.0001**	119 (3.4%)	0.3195
	Occlusion/stenosis of precerebral arteries	10 (0.1%)	5 (0.1%)	0.1178	2 (0.1%)	1.0000	5 (0.1%)	0.7851
	Stroke	69 (0.9%)	57 (0.6%)	0.0221	29 (1.8%)	**0.0008**	30 (0.9%)	0.9362
	Transient Ischemic Attack	15 (0.2%)	13 (0.1%)	0.3492	3 (0.2%)	1.0000	4 (0.1%)	0.4608
	Other CBV	115 (1.5%)	99 (1.0%)	**0.0072**	38 (2.4%)	**0.0084**	49 (1.4%)	0.8242
	Peripheral Arterial Disease	51 (0.6%)	26 (0.3%)	**0.0001**	12 (0.8%)	0.6505	15 (0.4%)	0.1604
	Abdominal Aortic Aneurysm	3 (0.0%)	3 (0.0%)	1.0000	1 (0.1%)	0.5235	0 (0.0%)	0.5577
Invasive Cancer	Any invasive cancer	425 (5.4%)	369 (3.8%)	**<.0001**	106 (6.6%)	0.0539	189 (5.4%)	0.9517
Endocrine Disorders	Any endocrine disorder	2237 (28.5%)	2140 (22.0%)	**<.0001**	513 (32.1%)	**0.0039**	781 (22.5%)	**<.0001**
	Diabetes Mellitus	558 (7.1%)	480 (4.9%)	**<.0001**	196 (12.3%)	**<.0001**	247 (7.1%)	0.9944
	Hyperlipidemia	1895 (24.1%)	1804 (18.5%)	**<.0001**	381 (23.8%)	0.7980	618 (17.8%)	**<.0001**
	Hyperthyroidism	31 (0.4%)	33 (0.3%)	0.6148	5 (0.3%)	0.8239	9 (0.3%)	0.3056
	Hypothyroidism	168 (2.1%)	163 (1.7%)	0.0244	64 (4.0%)	**<.0001**	53 (1.5%)	0.0294
	Thyroiditis	3 (0.0%)	2 (0.0%)	0.6619	0 (0.0%)	1.0000	2 (0.1%)	0.6457
Mental Health Conditions	Any mental health condition	2064 (26.3%)	2147 (22.0%)	**<.0001**	392 (24.5%)	0.1426	739 (21.3%)	**<.0001**
	Anxiety Disorders	1287 (16.4%)	1457 (15.0%)	**0.0102**	227 (14.2%)	0.0295	412 (11.8%)	**<.0001**
	Bipolar or Manic Disorders	358 (4.6%)	371 (3.8%)	**0.0136**	81 (5.1%)	0.3794	178 (5.1%)	0.1920
	Major Depressive Disorder	699 (8.9%)	554 (5.7%)	**<.0001**	116 (7.3%)	0.0326	208 (6.0%)	**<.0001**
	Schizophrenic Disorder	126 (1.6%)	99 (1.0%)	**0.0006**	18 (1.1%)	0.1544	55 (1.6%)	0.9331
	Dementia	28 (0.4%)	23 (0.2%)	0.1407	7 (0.4%)	0.6257	8 (0.2%)	0.2708
	Suicidality	29 (0.4%)	27 (0.3%)	0.2853	5 (0.3%)	1.0000	8 (0.2%)	0.2853
Liver Diseases	Any liver disease	1186 (15.1%)	1022 (10.5%)	**<.0001**	312 (19.5%)	**<.0001**	572 (16.5%)	0.0651
	Hepatitis B	392 (5.0%)	429 (4.4%)	0.0685	95 (5.9%)	0.1172	246 (7.1%)	**<.0001**

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	Hepatitis C	747 (9.5%)	519 (5.3%)	**<.0001**	208 (13.0%)	**<.0001**	327 (9.4%)	0.8664
	Other chronic liver disease	220 (2.8%)	194 (2.0%)	**0.0004**	52 (3.3%)	0.3255	72 (2.1%)	0.0239
Bone Conditions	Any bone condition	166 (2.1%)	109 (1.1%)	**<.0001**	25 (1.6%)	0.1542	36 (1.0%)	**<.0001**
Peripheral Neuropathy	Any peripheral neuropathy	534 (6.8%)	416 (4.3%)	**<.0001**	150 (9.4%)	**0.0003**	225 (6.5%)	0.5249
Renal Disease	Renal Impairment	3241 (41.2%)	3463 (35.6%)	**<.0001**	655 (40.9%)	0.8231	1282 (36.9%)	**<.0001**
	Moderate/Severe CKD	263 (3.3%)	121 (1.2%)	**<.0001**	56 (3.5%)	0.7565	47 (1.4%)	**<.0001**
	End Stage Renal Disease	78 (1.0%)	149 (1.5%)	**0.0017**	19 (1.2%)	0.4803	35 (1.0%)	0.9444
Hypertension	Any hypertension	1864 (23.7%)	1843 (18.9%)	**<.0001**	514 (32.1%)	**<.0001**	789 (22.7%)	0.2341
Rheumatoid Arthritis	Any rheumatoid arthritis	30 (0.4%)	27 (0.3%)	0.2254	8 (0.5%)	0.4954	9 (0.3%)	0.3028
Substance Abuse	Any substance abuse	1236 (15.7%)	1219 (12.5%)	**<.0001**	160 (10.0%)	<.0001	549 (15.8%)	0.9331
	Alcohol Dependence	278 (3.5%)	276 (2.8%)	**0.0079**	39 (2.4%)	0.0259	121 (3.5%)	0.8786
	Drug Abuse	1192 (15.2%)	1176 (12.1%)	**<.0001**	152 (9.5%)	**<.0001**	529 (15.2%)	0.9488

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 7. Baseline Concomitant Non-ART Medications of Patients Initiating with DTG, EVG, RAL, & DRV-containing regimens

	DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Antibiotics	1041 (13.2%)	1158 (11.9%)	**0.0069**	195 (12.2%)	0.2522	576 (16.6%)	**<.0001**
Direct Acting Antivirals (DAAs)	48 (0.6%)	18 (0.2%)	**<.0001**	8 (0.5%)	0.7219	4 (0.1%)	**0.0001**
Lipid lowering agents	1119 (14.2%)	918 (9.4%)	**<.0001**	305 (19.1%)	**<.0001**	371 (10.7%)	**<.0001**
Non-steroidal Anti-inflammatory Agents (NSAIDS)	517 (6.6%)	477 (4.9%)	**<.0001**	82 (5.1%)	0.0296	221 (6.4%)	0.6581
Antidepressants	1336 (17.0%)	1254 (12.9%)	**<.0001**	372 (23.3%)	**<.0001**	577 (16.6%)	0.5956
Anxiolytics/Hypnotics/Sedatives	875 (11.1%)	866 (8.9%)	**<.0001**	275 (17.2%)	**<.0001**	302 (8.7%)	**<.0001**
Anti-diabetics	359 (4.6%)	277 (2.8%)	**<.0001**	146 (9.1%)	**<.0001**	162 (4.7%)	0.8307
Immune Modulators	588 (7.5%)	559 (5.7%)	**<.0001**	83 (5.2%)	**0.0011**	218 (6.3%)	0.0206

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 8. Baseline eGFR in Patients Taking DTG, EVG, RAL, & DRV Regimens

	DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Median eGFR (IQR)*	101.9 (84.7, 116.9)	105.4 (89.8, 119.6)	**<.0001**	94.1 (74.9, 107.7)	**<.0001**	102.2 (85.5, 118.0)	0.1532
eGFR ≥90, n (%)	4704 (59.9%)	5928 (60.9%)	**<.0001**	577 (36.1%)	**<.0001**	1827 (52.5%)	**<.0001**
eGFR ≥60 to <90, n (%)	1768 (22.5%)	1802 (18.5%)	**.**	324 (20.3%)	**.**	706 (20.3%)	**.**
eGFR ≥30 to <60, n (%)	359 (4.6%)	195 (2.0%)	**.**	92 (5.8%)	**.**	110 (3.2%)	**.**
eGFR ≥15 to <30, n (%)	16 (0.2%)	5 (0.1%)	**.**	13 (0.8%)	**.**	6 (0.2%)	**.**
eGFR <15, n (%)	27 (0.3%)	7 (0.1%)	**.**	32 (2.0%)	**.**	16 (0.5%)	**.**
Missing eGFR, n (%)	985 (12.5%)	1801 (18.5%)	**.**	562 (35.1%)	**.**	812 (23.4%)	**.**

***** eGFR: estimated glomerular filtration rate (ml/min per 1.73 m^2)

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017)

3.3. Assessment of Renal Disorders

Table 9. Characteristics of eGFR Measurements in Patients Taking DT, EVG, RAL or DRV Regimens

		DTG N= 7,859	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
				eGFR Calculated				
Patients with eGFR at baseline	n (%)	6874 (87.5%)	7937 (81.5%)	**<.0001**	1038 (64.9%)	**<.0001**	2665 (76.6%)	**<.0001**
Patients with eGFR during follow-up	n (%)	6593 (83.9%)	7702 (79.1%)	**<.0001**	1140 (71.3%)	**<.0001**	2620 (75.4%)	**<.0001**
Patients with eGFR both at baseline and during follow-up	n (%)	5980 (76.1%)	6673 (68.5%)	**<.0001**	802 (50.1%)	**<.0001**	2141 (61.6%)	**<.0001**
				Population-Level Testing Characteristics				
Number of follow-up eGFR	Total eGFR	31,564	34,830	**<.0001**	5,126	**<.0001**	11,557	**<.0001**
				Patient-Level Testing Characteristics				
Number of follow-up eGFR	Median eGFR (IQR)	3.0 (1.0, 6.0)	3.0 (1.0, 5.0)	**<.0001**	2.0 (0.0, 5.0)	**<.0001**	2.0 (1.0, 5.0)	**<.0001**
Months from baseline to 1st follow-up eGFR	Median months (IQR)	2.2 (1.1, 3.5)	2.2 (1.1, 3.8)	**0.0122**	2.5 (1.1, 3.9)	**0.0063**	2.4 (1.1, 3.9)	**<.0001**
Months from 1st to 2nd follow-up eGFR	Median months (IQR)	3.4 (2.5, 4.5)	3.4 (2.7, 4.6)	**0.0011**	3.4 (2.5, 4.6)	0.4073	3.3 (2.4, 4.6)	0.4504

Table 10. Renal Disorders in Patients Taking DTG, EVG, RAL, & DRV Regimens

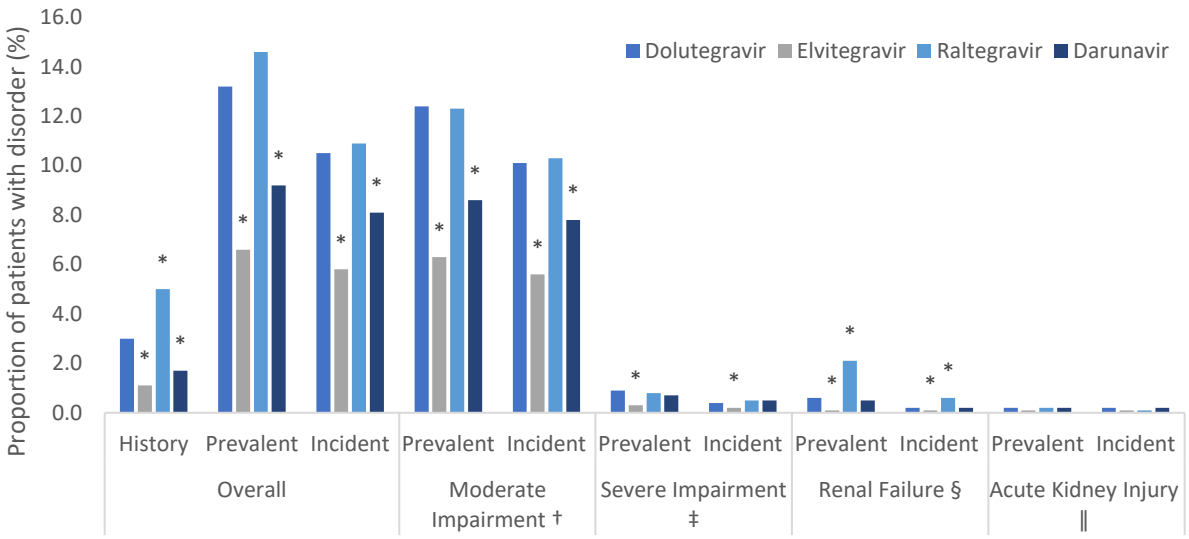
		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
				*Overall Renal Disorders**				
Any Renal Disorders	Any history, n (%)	233 (3.0%)	105 (1.1%)	**<.0001**	80 (5.0%)	**<.0001**	59 (1.7%)	**<.0001**
	Any prevalent event, n (%)	1036 (13.2%)	644 (6.6%)	**<.0001**	233 (14.6%)	0.1398	320 (9.2%)	**<.0001**
	Days to prevalent event, median (IQR)	122.0 (56.0, 279.0)	166.5 (72.5, 351.5)	**<.0001**	100.0 (39.0, 259.0)	0.0320	159.0 (63.0, 423.5)	**0.0004**
	Prevalent event with D/C†, n (%)	34 (0.4%)	45 (0.5%)	0.7712	9 (0.6%)	0.4815	32 (0.9%)	**0.0016**
	Days to prevalent event with D/C, median (IQR)	111.0 (63.0, 270.0)	77.0 (27.0, 162.0)	0.1165	130.0 (89.0, 349.0)	0.3625	120.0 (78.0, 432.0)	0.3760
	Any incident event, n (%)	824 (10.5%)	566 (5.8%)	**<.0001**	175 (10.9%)	0.5912	280 (8.1%)	**<.0001**
	Days to incident event, median (IQR)	153.5 (67.5, 321.0)	194.5 (85.0, 384.0)	**0.0009**	125.0 (42.0, 330.0)	0.1367	186.5 (68.5, 464.5)	**0.0129**
	Incident event with D/C, n (%)	25 (0.3%)	36 (0.4%)	0.5628	8 (0.5%)	0.2607	25 (0.7%)	**0.0030**
	Days to incident event with D/C, median (IQR)	146.0 (83.0, 312.0)	96.5 (27.5, 255.0)	0.1236	185.0 (83.5, 773.5)	0.5424	174.0 (73.0, 541.0)	0.4970
				Specific Renal Disorders				
Moderate Renal Impairment	Prevalent event, n (%)	973 (12.4%)	615 (6.3%)	**<.0001**	197 (12.3%)	0.9398	299 (8.6%)	**<.0001**
	Days to prevalent event, median (IQR)	129.0 (60.0, 294.0)	172.0 (76.0, 362.0)	**0.0001**	106.0 (41.0, 281.0)	0.1397	185.0 (69.0, 447.0)	**<.0001**
	Prevalent event with D/C, n (%)	32 (0.4%)	36 (0.4%)	0.6903	8 (0.5%)	0.6020	28 (0.8%)	**0.0071**
	Days to prevalent event with D/C, median (IQR)	120.5 (66.0, 291.0)	77.0 (27.5, 174.0)	0.1540	185.0 (83.5, 773.5)	0.3185	120.0 (78.0, 432.0)	0.4632
	Incident event, n (%)	794 (10.1%)	543 (5.6%)	**<.0001**	164 (10.3%)	0.8591	271 (7.8%)	**0.0001**
	Days to incident event, median (IQR)	156.0 (70.0, 322.0)	197.0 (87.0, 386.0)	**0.0021**	128.0 (45.0, 343.0)	0.3069	205.0 (69.0, 483.0)	**0.0037**
	Incident event with D/C, n (%)	24 (0.3%)	30 (0.3%)	0.9744	8 (0.5%)	0.2217	24 (0.7%)	**0.0036**
	Days to incident event with D/C, median (IQR)	152.5 (86.0, 330.0)	105.0 (28.0, 252.0)	0.1389	185.0 (83.5, 773.5)	0.5864	170.5 (61.0, 524.0)	0.7105
Severe Renal Impairment	Any prevalent event, n (%)	67 (0.9%)	31 (0.3%)	**<.0001**	13 (0.8%)	0.8734	24 (0.7%)	0.3719
	Prevalent event with D/C, n (%)	1 (0.0%)	7 (0.1%)	0.0828	0 (0.0%)	1.0000	1 (0.0%)	0.5194
	Any incident event, n (%)	34 (0.4%)	18 (0.2%)	**0.0026**	8 (0.5%)	0.7118	16 (0.5%)	0.8383

		DTG *N= 7,859*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	Incident event with D/C, n (%)	0 (0.0%)	5 (0.1%)	0.0696	0 (0.0%)	.	1 (0.0%)	0.3067
Renal Failure	Any prevalent event, n (%)	51 (0.6%)	12 (0.1%)	**<.0001**	34 (2.1%)	**<.0001**	17 (0.5%)	0.3090
	Prevalent event with D/C, n (%)	3 (0.0%)	3 (0.0%)	1.0000	1 (0.1%)	0.5235	5 (0.1%)	0.0633
	Any incident event, n (%)	19 (0.2%)	7 (0.1%)	**0.0035**	10 (0.6%)	**0.0115**	8 (0.2%)	0.9064
	Incident event with D/C, n (%)	2 (0.0%)	1 (0.0%)	0.5897	0 (0.0%)	1.0000	2 (0.1%)	0.5911
Acute Kidney Injury	Any prevalent event, n (%)	19 (0.2%)	14 (0.1%)	0.1611	3 (0.2%)	1.0000	7 (0.2%)	0.8323
	Prevalent event with D/C, n (%)	1 (0.0%)	3 (0.0%)	0.6335	0 (0.0%)	1.0000	1 (0.0%)	0.5194
	Any incident event, n (%)	18 (0.2%)	14 (0.1%)	0.2142	2 (0.1%)	0.5587	7 (0.2%)	1.0000
	Incident event with D/C, n (%)	1 (0.0%)	3 (0.0%)	0.6335	0 (0.0%)	1.0000	1 (0.0%)	0.5194

***** Renal Disorders are defined as (1) Kidney Injury (eGFR < 60 ml/min per 1.73 m^2), (2) Severe Kidney Injury (eGFR < 15 ml/min per 1.73 m^2), or (3) Acute Kidney Injury Diagnosis (diagnosis of "acute kidney injury", excluding "traumatic kidney injury")

[†] D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of a renal disorder

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).



* P-value for the comparison with DTG <0.017
† Moderate Kidney Impairment: eGFR ≥30 to < 60 ml/min per 1.73 m^2
‡ Severe Kidney Impairment: eGFR ≥15 to <30 ml/min per 1.73 m^2
§ Renal Failure: eGFR <15 ml/min per 1.73 m^2
‖ Acute Kidney Injury: diagnosis of "acute kidney injury", excluding "traumatic kidney injury"

Figure 1. Proportion of Patients Taking DTG, EVG, RAL, & DRV Regimens with history, prevalent or incident renal disorders

4. Summary of Findings

Out of 22,674 HIV-infected patients initiating a core agent of interest between August 1st, 2013 and December 31st, 2016 (Table 1), 7,859 (35%) initiated DTG, 89,738 (43%) initiated EVG, 1,600 (7%) initiated RAL and 3,477 (15%) initiated DRV (Table 2). Patients initiating EVG, RAL or DRV were statistically different at baseline from patients initiating DTG for many demographic and clinical characteristics. Of note, TDF is known to be associated with kidney tubular injury causing renal impairment.[10-14] A backbone consisting in a combination of TDF and emtricitabine was used significantly more frequently with EVG (62%), RAL (50%) or DRV (72%) than with DTG (19%), reflecting, to an extent, the composition of available coformulations.

4.1. Elvitegravir vs. Dolutegravir

At baseline, EVG users were younger than DTG users. They were also more likely to be male or receive care in the South, but they were less likely to be MSM or to benefit from ADAP or Ryan White programs (Table 3). EVG users had a shorter average follow-up time (Table 4). There was no difference in the proportion of ART naïve patients, average viral load or average CD4 cell count at baseline (

Table 5).

EVG users were healthier than DTG users, with lower average VACS scores (Table 4). Fewer EVG users had comorbidities at baseline. Liver diseases, including hepatitis C, were least frequent in the EVG group (Table 6)Table 6. All the medications assessed were used less frequently among EVG than DTG users (**Error! Reference source not found.**), including lipid lowering agents, which are known to elevate LFTs. This is likely a result of the boosting agent in EVG-containing regimens which impacts the pharmacokinetics of other medications that are metabolized through the liver.

The distribution of baseline eGFR was statistically higher among EVG users than DTG users. EVG users were less likely to have an eGFR <60 ml/min per 1.73 m^2, but more likely to be missing an eGFR measure at baseline than DTG users (Table 8). Fewer EVG users had eGFR measures available both at baseline and during follow-up (Table 9).

Overall, compared to DTG users, there was a statistically significant lower proportion of EVG users with a history of any renal disorders, defined as either two consecutive eGFR <60 ml/min per 1.73 m^2, at least 14 days apart, or one eGFR <30 ml/min per 1.73 m^2, or a diagnosis of acute kidney injury. EVG users were also statistically less likely have any prevalent or incident renal disorder during follow-up. These events also occurred after a longer exposure to EVG than DTG (Table 10).

Specific renal disorders (moderate renal impairment, severe renal impairment, renal failure and acute kidney injury) are presented in Table 10 and

Figure 1. EVG users were statistically less likely to have prevalent or incident moderate renal impairment, with events occurring after a longer period of exposure than DTG users. Severe renal impairment, renal failure and acute kidney injury were rare during follow-up, occurring in under 1% of patients. EVG users were also statistically less likely to have prevalent or incident severe renal impairment than DTG users. EVG users were also less likely to have prevalent or incident renal failure than DTG users. There was no difference in the frequency of prevalent and incident acute kidney injury events between EVG and DTG users. Core agent discontinuation after a renal disorder was rare (≤0.5%) and there was no statistically significant difference between EVG and DTG for either prevalent or incident events (Table 10).

4.2. Raltegravir vs. Dolutegravir

RAL users were older, less likely to be male, African American or Hispanic, and less likely to be MSM or to benefit from ADAP or Ryan White programs than DTG users. RAL users were however more likely to receive care in the South (Table 3). They also had a shorter average follow-up time (Table 4). Fewer RAL than DTG users were ART naïve. Baseline HIV viral load was lower among RAL users, but baseline CD4 cell count was not statistically different (

Table 5).

At baseline, RAL users were sicker (higher average VACS score, Table 4), and were more likely to have comorbidities than DTG users (Table 6). Liver diseases, including hepatitis C, were more frequent in the RAL groups than the DTG group (Table 6). RAL users were prescribed lipid lowering agents more frequently than DTG users (**Error! Reference source not found.**).

The distribution of baseline eGFR was statistically lower among RAL users than DTG users. RAL users were less likely to have an eGFR ≥90 ml/min per 1.73 m^2 and more likely to have an eGFR <60 ml/min per 1.73 m^2, but also more likely to be missing an eGFR measure at baseline than DTG users (Table 8).

Fewer RAL users had eGFR measures available both at baseline and during follow-up. RAL users also had a lower frequency of eGFR measurement over follow-up, compared to DTG users (Table 9).

Overall, compared to DTG users, there was a statistically significant higher proportion of RAL users with a history of any renal disorders, defined as either two consecutive eGFR <60 ml/min per 1.73 m^2, at least 14 days apart, or one eGFR <30 ml/min per 1.73 m^2, or a diagnosis of acute kidney injury. There was however no difference between RAL and DTG users in prevalent or incident renal disorder during follow-up (Table 10).

Specific renal disorders (moderate renal impairment, severe renal impairment, renal failure and acute kidney injury) are presented in Table 10 and

Figure 1. No difference in prevalent or incident moderate renal impairment was detected between RAL and DTG users. Severe renal impairment, renal failure and acute kidney injury were rare during follow-up, occurring in under 1% of patients. RAL users were more likely to have prevalent or incident renal failure than DTG users. However, there was no difference in the frequency of prevalent and incident severe renal impairment or acute kidney injury events between RAL and DTG users. Core agent discontinuation after a renal disorder was rare (≤0.6%) and there was no statistically significant difference between RAL and DTG for either prevalent or incident events (Table 10).

4.3. Darunavir vs. Dolutegravir

Compared to DTG users, DRV users were older and less likely to be male, Hispanic or MSM, to have a history of syphilis or to benefit from ADAP or Ryan White programs. They were however more likely to be African American or receive care in the South (Table 3). DRV had a shorter average follow-up time than DTG users (Table 4). DRV users were less likely than DTG users to be ART-naïve. Baseline HIV viral load was higher among DRV, but baseline CD4 cell counts were not statistically different (

Table 5).

DRV users were sicker than DTG users at baseline, with higher average VACS scores (Table 4). There was no difference in the proportion of DRV and DTG users with comorbidities at baseline. No differences in liver diseases overall were detected either, although DRV users were more likely than DTG users to have hepatitis B (Table 6). DRV users were less likely than DTG users to use a lipid-lowering agent (**Error! Reference source not found.**Table 7).

DRV users were less likely to have an eGFR ≥90 ml/min per 1.73 m^2, but more likely to be missing an eGFR measure at baseline than DTG users (Table 8). Fewer DRV users had eGFR measures available both at baseline and during follow-up. DRV users also had a lower frequency of eGFR measurement over follow-up, compared to DTG users (Table 9).

Overall, compared to DTG users, there was a statistically significant higher proportion of DRV users with a history of any renal disorders, defined as either two consecutive eGFR <60 ml/min per 1.73 m^2, at least 14 days apart, or one eGFR <30 ml/min per 1.73 m^2, or a diagnosis of acute kidney injury. During follow-up, both prevalent and incident renal disorders were overall less frequent and occurred after a longer follow-up time among DRV users than DTG users (Table 10).

Specific renal disorders (moderate renal impairment, severe renal impairment, renal failure and acute kidney injury) are presented in Table 10 and

Figure 1. Prevalent or incident moderate renal impairment were statistically less frequent, both occurring after a longer follow-up among DRV users than DTG users. Severe renal impairment, renal failure and acute kidney injury were rare during follow-up, occurring in under 1% of patients. There was no difference in the frequency of prevalent and incident severe renal impairment, renal failure or acute kidney injury between DRV and DTG users. Core agent discontinuation after a renal disorder was rare (≤0.9%), but occurred more frequently with DRV use compared to DTG use. (Table 10).

5. Conclusions

Patients using DTG, EVG, RAL or DRV are different in many regards. Some of these differences could be the result of channeling sicker patients away from EVG and towards DTG or RAL. Indeed, compared to DTG users, EVG users were younger and less likely to have existing liver disease, take lipid lowering agents, or have substantial comorbidities than DTG users. EVG users were also less likely than DTG users to have a history of renal disorder. Accordingly, during follow-up, the likelihood of prevalent or incident moderate impairment, severe impairment or renal failure was lower for EVG users than DTG users.

On the contrary, RAL users were older and were more likely to have liver diseases, take lipid lowering agents or have substantial comorbidities, compared to DTG users. RAL users had a greater likelihood of renal disorder history than DTG users, as well as a greater likelihood of prevalent or incident renal failure.

There was no clear evidence of channeling in the case of DRV. DRV users were older and less likely to take lipid lowering agents than DTG users. DRV users were also sicker overall, although there was no difference in the likelihood of comorbidities at baseline. However, DRV users were less likely to have a history or renal disorder. They were also less likely to have prevalent or incident moderate renal impairment or overall renal disorder, compared to DTG users.

Discontinuation following a renal disorder was rare, suggesting that clinicians are willing to tolerate most instances of these disorders. More work would be required to investigate the degree of severity and persistence of disorders required for discontinuation.

While evidence of potential channeling was observed and could have likely played a role in the observed differences in prevalent and incident renal disorders, no adjustment for baseline characteristics were performed. It is therefore impossible to determine from these unadjusted comparisons the impact of channeling on the results presented. In addition, the imbalance in TDF use caused by coformulation availability was not accounted for and could have an important impact on the likelihood of renal disorders.[10-14]

Finally, these analyses rely heavily on eGFR to assess the presence of renal disorders. However, DTG, RAL and cobicistat are known to inhibit secretion of tubular creatinine.[7,8] It is therefore difficult to determine whether low eGFRs are an artefact of tubular creatinine secretion inhibition or reflect true functional kidney injury in this descriptive analysis.

6. References

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A Comprehensive Assessment of Adverse Events and Overall Safety Profile in HIV Positive Patients Treated with Dolutegravir as Compared to Other Integrase Strand Transfer Inhibitors or Darunavir:

Final Report – Gastrointestinal Outcomes

Complete data through December 31, 2017

March 18, 2019

*Sub-report containing only Gastrointestinal Outcomes of the Comprehensive Safety Study.

Table of Content

1. Background and Rationale

Background: Clinical guidelines currently recommend the use of the integrase strand transfer inhibitors (INSTI) dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL), or the protease inhibitor (PI) darunavir (DRV) as the core agent in antiretroviral therapy (ART) regimens.[1] Toxicity concerns with multi-agent regimens, and pharmacokinetic interactions with medications for co-morbidities suggest the need for a comprehensive safety evaluation of recommended core agents in a real-world setting. In clinical trials, DTG treatment-related adverse effects (determined by the investigator) were less frequent (1–3%) than comparator drugs. Most adverse events seen in trials of DTG were grade 1–2 (mild-to-moderate in severity), such as headache, diarrhea, nausea, or insomnia.[2-6]

Low frequencies of gastrointestinal adverse events were reported in randomized controlled trials for DTG (≤1% grade 2-4 nausea, ≤2% grade 2-4 diarrhea, <2% abdominal pain, abdominal discomfort, flatulence, upper abdominal pain or vomiting),[7] RAL (≤4% moderate/severe nausea, ≥2% mild/moderate/severe abdominal pain, diarrhea, vomiting and decreased appetite).[8] Gastrointestinal adverse events (all grades) were more frequently reported for EVG in randomized controlled trials (11-16% nausea, 7-12% diarrhea , 2% flatulence), although most of these events were of grade 1 severity.[9,10] A higher frequency of Grade 2-4 gastrointestinal adverse reactions was recorded in clinical trials for DRV (9% diarrhea, 6% abdominal pain, 4% nausea, 2% vomiting).[11]

Rationale: A comprehensive safety evaluation of DTG and other recommended core agents has not been performed in a real-world setting. As the use of INSTIs increases in various demographic populations and clinical situations, an understanding of the overall safety profile of the members of the class will provide additional information for clinicians as treatment strategies are designed.

Scope of report: This report is limited to gastrointestinal outcomes and will appear in its entirety in the full report of safety outcomes.

2. Methods

2.1. Study Design

Study population: The study population consisted of HIV-positive patients at least 13 years of age initiating a core agent of interest prescribed by an OPERA caregiver during the eligibility period (August 1, 2013 to December 31, 2016).

Baseline date: The baseline date was defined as the first date of one of the four core agents of interest ever prescribed to a patient.

Observation period: The observation period began on August 1, 2013 (the month DTG was approved) with study participants identified through December 31, 2016 on data through December 31, 2017. Patients were observed from their baseline date until the first of the following censoring events: 1) discontinuation of the core agent of interest, 2) cessation of continuous clinical activity, 3) death or 4) study end (December 31, 2017). Patients failing to meet the continuous clinical activity requirement were censored 12 months after their last contact.

Continuous Clinical Activity: Patients with continuous clinical activity were those who had clinical contact at least once in 12 months. Clinical contact was defined as a telephone contact, visit, lab test, or consultation.

Core agent of interest: Core agents of interest consisted of dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), or darunavir (DRV). A regimen was considered discontinued when the core agent of interest was discontinued for 45 days or more.

2.2. Gastrointestinal Outcomes Definitions

Gastrointestinal Disorders consisted of any of the following: (1) Gastrointestinal intolerance, or (2) Gastrointestinal erosions, defined as:

1. Gastrointestinal intolerance: diagnosis of "nausea", "vomiting", "diarrhea", or "abdominal pain"
2. Gastrointestinal erosions: diagnosis of "gastritis", "gastric erosion", "peptic ulcer disease", or "gastrointestinal bleeding"

History of Gastrointestinal Disorders: defined as a diagnosis of gastrointestinal intolerance or gastrointestinal erosions at or before baseline.

1. Gastrointestinal intolerance: up to 7 days before baseline.
2. Gastrointestinal erosions: up to 12 months before baseline.

Prevalent Gastrointestinal Disorders: defined as a diagnosis of gastrointestinal intolerance or gastrointestinal erosions that occurred after baseline, regardless of whether the patient had a history of gastrointestinal disorders.

1. Gastrointestinal intolerance: within 8 weeks after baseline.
2. Gastrointestinal erosions: any time after baseline.

Incident Gastrointestinal Disorders: defined as only a new diagnosis of gastrointestinal intolerance or gastrointestinal erosions after baseline, excluding patients who had any history of gastrointestinal disorders at baseline. Therefore, incident gastrointestinal disorders are a subset of prevalent gastrointestinal disorders. The incidence of any of the disorders excluded patients with a history of any gastrointestinal disorder (not just the disorder in question) because any one of these events puts a patient at very high risk for future gastrointestinal events and should not be considered as incident.

1. Gastrointestinal intolerance: within 8 weeks after baseline.
2. Gastrointestinal erosions: any time after baseline.

Discontinuation (D/C): defined as discontinuation of the core agent of interest within 21 days of the date of a gastrointestinal disorder. Time to gastrointestinal disorders with D/C was calculated based on the date of the gastrointestinal disorders.

2.3. Statistical Analyses

Descriptive analyses of baseline demographic and clinical patient characteristics at baseline, as well as gastrointestinal outcomes during follow-up were conducted to compare DTG to other core agents of

interest. The Pearson's Chi-Square Test was used to calculate p-values for categorical variables and the Mann-Whitney Test was used to calculate p-values for continuous variables. Fischer Exact Test was used for cells with small numbers (counts of 5 or fewer).

To account for multiple comparisons between DTG and comparator core agents, the Sidak Correction was applied, resulting in an adjusted alpha level for significance of 0.017.

3. Results

3.1. Population Identification

Table 1. Identification of the Study Population

		Patients Included	*%*	*Patients Excluded*	*%*
1	OPERA patients who are HIV+	84,084	.	0	.
2	Patients with HIV-1 infection (excluding HIV-2 infection)	83,999	99.9	85	0.1
3	HIV+ patients prescribed ART	73,223	87.2	10,776	12.8
4	Patients prescribed a regimen of interest (containing DTG, EVG, RAL, or DRV)	47,794	65.3	25,429	34.7
5	Patients prescribed regimen of interest between 08/01/2013 and 12/31/2016	32,398	67.8	15,396	32.2
6	Patients who were 13 years of age or older at first ART regimen of interest	32,394	100.0	4	0.0
7	Patients prescribed a regimen of interest that did not include two or more third agents of interest	29,049	89.7	3,345	10.3
8	Patients whose first ART regimen of interest was not monotherapy	28,337	97.5	712	2.5
9	Patients whose first ART regimen of interest was not prior to date of HIV	28,189	99.5	148	0.5
10	Patients whose regimen of interest was their first experience with DTG, EVG, RAL, or DRV [Study population]	22,675	80.4	5,514	19.6

Table 2. Study Population by ART Core Agent of Interest and Regimen

Core agent of interest	*n(%)*	*Regimens*	*n(%)*
DTG-containing regimens	7,860 (34.7%)	DTG + TDF + FTC	1,524 (19.4%)
		DTG + TAF + FTC	219 (2.8%)
		DTG + ABC + 3TC	4,932 (62.7%)
		DTG + all other agents	1,185 (15.1%)
EVG-containing regimens	9,738 (42.9%)	EVG + r/c + TDF + FTC	5,996 (61.6%)
		EVG + r/c + TAF + FTC	2,987 (30.7%)
		EVG + r/c + all other agents	755 (7.8%)
RAL-containing regimens	1,600 (7.1%)	RAL + TDF + FTC	803 (50.2%)
		RAL + TAF + FTC	14 (0.9%)
		RAL + ABC + 3TC	126 (7.9%)
		RAL + all other agents	657 (41.1%)
DRV-containing regimens	3,477 (15.3%)	DRV + r/c + TDF + FTC	2,481 (71.4%)
		DRV + r/c + TAF + FTC	134 (3.9%)
		DRV + r/c + ABC + 3TC	318 (9.1%)
		DRV + r/c + all other agents	496 (14.3%)
		DRV + TDF + FTC	15 (0.4%)
		DRV + ABC + 3TC	6 (0.2%)
		DRV + all other agents	27 (0.8%)

3.2. Baseline Characteristics

Table 3. Baseline Demographic Characteristics of Patients Taking DTG, EVG, RAL, & DRV Regime

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Age	Median (IQR)	41.1 (29.8, 51.1)	36.9 (28.1, 48.4)	**<.0001**	48.8 (39.8, 55.0)	**<.0001**	43.4 (33.0, 51.1)	**<.0001**
	13-25	1134 (14.4%)	1707 (17.5%)	**<.0001**	72 (4.5%)	**<.0001**	331 (9.5%)	**<.0001**
	26-49	4528 (57.6%)	5993 (61.5%)	**.**	807 (50.4%)	**.**	2159 (62.1%)	**.**
	50+	2198 (28.0%)	2038 (20.9%)	**.**	721 (45.1%)	**.**	987 (28.4%)	**.**
Sex	Male	6671 (84.9%)	8416 (86.4%)	**0.0125**	1273 (79.6%)	**<.0001**	2763 (79.5%)	**<.0001**
	Female	1182 (15.0%)	1314 (13.5%)	**.**	325 (20.3%)	**.**	713 (20.5%)	**.**
	Unknown	7 (0.1%)	8 (0.1%)	**.**	2 (0.1%)	**.**	1 (0.0%)	**.**
Race	African American	3227 (41.1%)	3948 (40.5%)	0.4905	581 (36.3%)	**0.0004**	1661 (47.8%)	**<.0001**
	Not African American	4633 (58.9%)	5790 (59.5%)	.	1019 (63.7%)	**.**	1816 (52.2%)	**.**
Ethnicity	Hispanic	1936 (24.6%)	2496 (25.6%)	0.1285	273 (17.1%)	**<.0001**	720 (20.7%)	**<.0001**
	Not Hispanic	5924 (75.4%)	7242 (74.4%)	.	1327 (82.9%)	**.**	2757 (79.3%)	**.**
Marital Status	Single	5543 (70.5%)	6720 (69.0%)	0.1116	976 (61.0%)	**<.0001**	2302 (66.2%)	**<.0001**
	Married	468 (6.0%)	613 (6.3%)	.	145 (9.1%)	**.**	267 (7.7%)	**.**
	Domestic partnership	258 (3.3%)	293 (3.0%)	.	54 (3.4%)	**.**	116 (3.3%)	**.**
	Widowed	51 (0.6%)	57 (0.6%)	.	21 (1.3%)	**.**	37 (1.1%)	**.**
	Separated/divorced	205 (2.6%)	257 (2.6%)	.	64 (4.0%)	**.**	102 (2.9%)	**.**
	Unknown	1335 (17.0%)	1798 (18.5%)	.	340 (21.3%)	**.**	653 (18.8%)	**.**
Risk of Infection	MSM	4023 (51.2%)	4788 (49.2%)	**0.0079**	589 (36.8%)	**<.0001**	1427 (41.0%)	**<.0001**
	Not MSM	3837 (48.8%)	4950 (50.8%)	**.**	1011 (63.2%)	**.**	2050 (59.0%)	**.**
History of Syphilis	Yes	2158 (27.5%)	2817 (28.9%)	0.0310	314 (19.6%)	**<.0001**	830 (23.9%)	**<.0001**
Region	Northeast	674 (8.6%)	809 (8.3%)	**<.0001**	164 (10.3%)	**<.0001**	246 (7.1%)	**<.0001**
	South	4268 (54.3%)	6029 (61.9%)	**.**	1061 (66.3%)	**.**	2174 (62.5%)	**.**
	Midwest	177 (2.3%)	266 (2.7%)	**.**	42 (2.6%)	**.**	65 (1.9%)	**.**
	West	2741 (34.9%)	2634 (27.0%)	**.**	333 (20.8%)	**.**	992 (28.5%)	**.**
Payer	Medicaid	1754 (22.3%)	1557 (16.0%)	**<.0001**	358 (22.4%)	0.9585	839 (24.1%)	0.0339
	Medicare	715 (9.1%)	575 (5.9%)	**<.0001**	309 (19.3%)	**<.0001**	459 (13.2%)	**<.0001**
	Commercial Insurance	2382 (30.3%)	3221 (33.1%)	**<.0001**	506 (31.6%)	0.2961	860 (24.7%)	**<.0001**
	Cash	4421 (56.2%)	5118 (52.6%)	**<.0001**	914 (57.1%)	0.5185	1885 (54.2%)	0.0445

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	ADAP/Ryan White	2820 (35.9%)	3143 (32.3%)	**<.0001**	338 (21.1%)	**<.0001**	1034 (29.7%)	**<.0001**
	Other	36 (0.5%)	33 (0.3%)	0.2259	3 (0.2%)	0.1383	9 (0.3%)	0.1448
	No Payer info	1145 (14.6%)	1934 (19.9%)	**<.0001**	362 (22.6%)	**<.0001**	711 (20.4%)	**<.0001**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 4. General Baseline Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Year of Study Initiation	2013	299 (3.8%)	828 (8.5%)	**<.0001**	344 (21.5%)	**<.0001**	568 (16.3%)	**<.0001**
	2014	1654 (21.0%)	2144 (22.0%)	.	631 (39.4%)	.	1139 (32.8%)	.
	2015	2580 (32.8%)	2435 (25.0%)	.	350 (21.9%)	.	878 (25.3%)	.
	2016	3327 (42.3%)	4331 (44.5%)	.	275 (17.2%)	.	892 (25.7%)	.
Time from first active date to index date	Median (IQR)	2.2 (0.5, 34.6)	1.2 (0.1, 24.0)	**<.0001**	0.2 (0.0, 8.8)	**<.0001**	0.7 (0.0, 19.8)	**<.0001**
Follow-up time between baseline and end of observation	Median (IQR)	18.3 (12.5, 27.4)	17.0 (12.0, 26.0)	**<.0001**	14.5 (9.9, 25.8)	**<.0001**	15.6 (10.8, 25.7)	**<.0001**
Pregnancy	Pregnancy	6 (0.1%)	10 (0.1%)	0.6233	4 (0.3%)	0.0729	11 (0.3%)	**0.0059**
VACS Index†	Median (IQR)	17.0 (7.0, 29.0)	13.0 (7.0, 25.0)	**<.0001**	20.0 (10.0, 35.0)	**<.0001**	22.0 (12.0, 39.0)	**<.0001**
VACS Index† category	0 to <15	2994 (38.1%)	3916 (40.2%)	**<.0001**	374 (23.4%)	**<.0001**	837 (24.1%)	**<.0001**
	>=15 to <30	2038 (25.9%)	2177 (22.4%)	.	317 (19.8%)	.	809 (23.3%)	.
	>=30 to <45	816 (10.4%)	777 (8.0%)	.	147 (9.2%)	.	381 (11.0%)	.
	>= 45	780 (9.9%)	742 (7.6%)	.	173 (10.8%)	.	528 (15.2%)	.
	Missing	1232 (15.7%)	2126 (21.8%)	.	589 (36.8%)	.	922 (26.5%)	.

† VACS Mortality Index: score created by summing pre-assigned points for age, HIV disease (CD4 count and HIV-1 RNA), and general indicators of organ system injury including hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. This score is used to estimate risk of all-cause mortality in the following 5 years. A higher score is associated with a higher risk of mortality.

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 5. Baseline HIV-Related Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimen

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
ART-naïve at index	ART-naïve	2663 (33.9%)	3452 (35.4%)	0.0298	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	ART-experienced	5197 (66.1%)	6286 (64.6%)	.	1401 (87.6%)	**.**	2499 (71.9%)	**.**
Calendar year of ART initiation	Median (IQR)	2015 (2013, 2016)	2015 (2013, 2016)	**<.0001**	2014 (2013, 2015)	**<.0001**	2014 (2013, 2015)	**<.0001**
	Pre-2000	213 (2.7%)	132 (1.4%)	**<.0001**	30 (1.9%)	**<.0001**	55 (1.6%)	**<.0001**
	2000-2004	278 (3.5%)	172 (1.8%)	**.**	34 (2.1%)	**.**	88 (2.5%)	**.**
	2005-2009	620 (7.9%)	548 (5.6%)	**.**	87 (5.4%)	**.**	194 (5.6%)	**.**
	2010-2014	2619 (33.3%)	3852 (39.6%)	**.**	924 (57.8%)	**.**	1706 (49.1%)	**.**
	2015-present	4130 (52.5%)	5034 (51.7%)	**.**	525 (32.8%)	**.**	1434 (41.2%)	**.**
Number of previous ART regimens	Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	**<.0001**	1.0 (1.0, 3.0)	**0.0158**	1.0 (1.0, 2.0)	0.4892
	ART-naïve	2663 (33.9%)	3452 (35.4%)	**<.0001**	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	1-2 previous regimens	2668 (33.9%)	2592 (26.6%)	**.**	281 (17.6%)	**.**	776 (22.3%)	**.**
	3-4 previous regimens	410 (5.2%)	298 (3.1%)	**.**	41 (2.6%)	**.**	103 (3.0%)	**.**
	5 or more previous regimens	266 (3.4%)	208 (2.1%)	**.**	55 (3.4%)	**.**	91 (2.6%)	**.**
	Missing previous regimens	1853 (23.6%)	3188 (32.7%)	**.**	1024 (64.0%)	**.**	1529 (44.0%)	**.**
Previous ART exposure	Naive	2663 (33.9%)	3452 (35.4%)	0.0298	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	NNRTI	2129 (27.1%)	2280 (23.4%)	**<.0001**	200 (12.5%)	**<.0001**	441 (12.7%)	**<.0001**
	PI	1547 (19.7%)	974 (10.0%)	**<.0001**	198 (12.4%)	**<.0001**	587 (16.9%)	**0.0004**
	INSTI	1 (0.0%)	1 (0.0%)	1.0000	0 (0.0%)	1.0000	1 (0.0%)	0.5193
	NRTI	3309 (42.1%)	2988 (30.7%)	**<.0001**	357 (22.3%)	**<.0001**	929 (26.7%)	**<.0001**
	Other	31 (0.4%)	17 (0.2%)	**0.0054**	10 (0.6%)	0.2006	8 (0.2%)	0.1682
	Experienced-ART specifics missing	1853 (23.6%)	3188 (32.7%)	**<.0001**	1024 (64.0%)	**<.0001**	1529 (44.0%)	**<.0001**
Backbone of Regimen of Interest	TDF + FTC	1524 (19.4%)	5996 (61.6%)	**<.0001**	803 (50.2%)	**<.0001**	2496 (71.8%)	**<.0001**
	TAF + FTC	219 (2.8%)	2987 (30.7%)	**.**	14 (0.9%)	**.**	134 (3.9%)	**.**
	ABC + 3TC	4932 (62.78	0 (0.0%)	**.**	126 (7.9%)	**.**	324 (9.3%)	**.**

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	All others	1185 (15.1%)	755 (7.8%)	.	657 (41.1%)	.	523 (15.0%)	.
AIDS-defining Illness	AIDS	2040 (26.0%)	2007 (20.6%)	**<.0001**	448 (28.0%)	0.0902	1140 (32.8%)	**<.0001**
	No AIDS	5820 (74.0%)	7731 (79.4%)	.	1152 (72.0%)	.	2337 (67.2%)	.
Baseline viral load	Median (IQR)	460.0 (19.0, 40580.0)	1649.5 (19.0, 45155.0)	0.0426	19.0 (19.0, 820.0)	**<.0001**	1042.0 (19.0, 52360.0)	**<.0001**
Baseline Viral Load log10	Median (IQR)	2.7 (1.3, 4.6)	3.3 (1.3, 4.7)	0.0192	1.3 (1.3, 3.0)	**<.0001**	3.1 (1.3, 4.7)	**<.0001**
Baseline Viral Load category	Suppressed (<50 copies/mL)	2765 (35.2%)	3131 (32.2%)	**<.0001**	617 (38.6%)	**<.0001**	925 (26.6%)	**<.0001**
	Low (>=50 to <10,000 copies/mL)	1289 (16.4%)	1499 (15.4%)	.	224 (14.0%)	.	646 (18.6%)	.
	Moderate (>=10,000 to <100,000 copies/mL)	1708 (21.7%)	2100 (21.6%)	.	136 (8.5%)	.	583 (16.8%)	.
	High (>=100,000 copies/mL)	906 (11.5%)	1110 (11.4%)	.	71 (4.4%)	.	460 (13.2%)	.
	Missing baseline VL	1192 (15.2%)	1898 (19.5%)	.	552 (34.5%)	.	863 (24.8%)	.
Nadir CD4	Median (IQR)	400.0 (237.0, 585.0)	413.0 (253.0, 597.0)	**0.0004**	437.0 (243.0, 659.0)	**0.0001**	318.0 (133.0, 536.0)	**<.0001**
Baseline CD4	Median (IQR)	491.0 (310.0, 706.0)	489.0 (306.0, 697.0)	0.4656	514.0 (303.0, 742.0)	0.1517	384.0 (181.0, 620.5)	**<.0001**
	High (>500 cells/µL)	3242 (41.2%)	3820 (39.2%)	**<.0001**	538 (33.6%)	**<.0001**	950 (27.3%)	**<.0001**
	Moderate (>350 to <=500 cells/µL)	1412 (18.0%)	1669 (17.1%)	.	189 (11.8%)	.	475 (13.7%)	.
	Moderate Low (>200 to <=350 cells/µL)	1055 (13.4%)	1311 (13.5%)	.	173 (10.8%)	.	477 (13.7%)	.
	Low (>50 to <=200 cells/µL)	671 (8.5%)	769 (7.9%)	.	109 (6.8%)	.	424 (12.2%)	.
	Very low (<=50 cells/µL)	293 (3.7%)	319 (3.3%)	.	44 (2.8%)	.	278 (8.0%)	.
	Missing baseline CD4	1187 (15.1%)	1850 (19.0%)	.	547 (34.2%)	.	873 (25.1%)	.

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 6. Baseline Comorbidities of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Any Comorbidity at baseline	Any comorbidity	5805 (73.9%)	6455 (66.3%)	**<.0001**	1267 (79.2%)	**<.0001**	2527 (72.7%)	0.1903
Cardiovascular Disease Condition	Any cardiovascular disease	576 (7.3%)	460 (4.7%)	**<.0001**	173 (10.8%)	**<.0001**	224 (6.4%)	0.0894
	Arrhythmia	180 (2.3%)	155 (1.6%)	**0.0008**	36 (2.3%)	0.9221	60 (1.7%)	0.0542
	Myocardial Infarction	52 (0.7%)	31 (0.3%)	**0.0010**	16 (1.0%)	0.1441	17 (0.5%)	0.2758
	Angina	27 (0.3%)	11 (0.1%)	**0.0015**	4 (0.3%)	0.8095	11 (0.3%)	1.0000
	Other/Unspecified CHD	299 (3.8%)	217 (2.2%)	**<.0001**	103 (6.4%)	**<.0001**	119 (3.4%)	0.3201
	Occlusion/stenosis of precerebral arteries	10 (0.1%)	5 (0.1%)	0.1178	2 (0.1%)	1.0000	5 (0.1%)	0.7850
	Stroke	69 (0.9%)	57 (0.6%)	0.0221	29 (1.8%)	**0.0008**	30 (0.9%)	0.9367
	Transient Ischemic Attack	15 (0.2%)	13 (0.1%)	0.3492	3 (0.2%)	1.0000	4 (0.1%)	0.4609
	Other CBV	115 (1.5%)	99 (1.0%)	**0.0072**	38 (2.4%)	**0.0084**	49 (1.4%)	0.8248
	Peripheral Arterial Disease	51 (0.6%)	26 (0.3%)	**0.0001**	12 (0.8%)	0.6502	15 (0.4%)	0.1605
	Abdominal Aortic Aneurysm	3 (0.0%)	3 (0.0%)	1.0000	1 (0.1%)	0.5235	0 (0.0%)	0.5577
Invasive Cancer	Any invasive cancer	425 (5.4%)	369 (3.8%)	**<.0001**	106 (6.6%)	0.0537	189 (5.4%)	0.9505
Endocrine Disorders	Any endocrine disorder	2237 (28.5%)	2140 (22.0%)	**<.0001**	513 (32.1%)	0.0038	781 (22.5%)	**<.0001**
	Diabetes Mellitus	558 (7.1%)	480 (4.9%)	**<.0001**	196 (12.3%)	**<.0001**	247 (7.1%)	0.9930
	Hyperlipidemia	1895 (24.1%)	1804 (18.5%)	**<.0001**	381 (23.8%)	0.8001	618 (17.8%)	**<.0001**
	Hyperthyroidism	31 (0.4%)	33 (0.3%)	0.6148	5 (0.3%)	0.8239	9 (0.3%)	0.3056
	Hypothyroidism	168 (2.1%)	163 (1.7%)	0.0244	64 (4.0%)	**<.0001**	53 (1.5%)	0.0295
	Thyroiditis	3 (0.0%)	2 (0.0%)	0.6619	0 (0.0%)	1.0000	2 (0.1%)	0.6457
Mental Health Conditions	Any mental health condition	2064 (26.3%)	2147 (22.0%)	**<.0001**	392 (24.5%)	0.1434	739 (21.3%)	**<.0001**
	Anxiety Disorders	1287 (16.4%)	1457 (15.0%)	**0.0103**	227 (14.2%)	0.0297	412 (11.8%)	**<.0001**
	Bipolar or Manic Disorders	358 (4.6%)	371 (3.8%)	**0.0137**	81 (5.1%)	0.3788	178 (5.1%)	0.1915
	Major Depressive Disorder	699 (8.9%)	554 (5.7%)	**<.0001**	116 (7.3%)	0.0327	208 (6.0%)	**<.0001**
	Schizophrenic Disorder	126 (1.6%)	99 (1.0%)	**0.0006**	18 (1.1%)	0.1546	55 (1.6%)	0.9337
	Dementia	28 (0.4%)	23 (0.2%)	0.1408	7 (0.4%)	0.6255	8 (0.2%)	0.2709
	Suicidality	29 (0.4%)	27 (0.3%)	0.2854	5 (0.3%)	1.0000	8 (0.2%)	0.2853
Liver Diseases	Any liver disease	1186 (15.1%)	1022 (10.5%)	**<.0001**	312 (19.5%)	**<.0001**	572 (16.5%)	0.0647

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
	Hepatitis B	392 (5.0%)	429 (4.4%)	0.0688	95 (5.9%)	0.1169	246 (7.1%)	**<.0001**
	Hepatitis C	747 (9.5%)	519 (5.3%)	**<.0001**	208 (13.0%)	**<.0001**	327 (9.4%)	0.8680
	Other chronic liver disease	220 (2.8%)	194 (2.0%)	**0.0004**	52 (3.3%)	0.3251	72 (2.1%)	0.0240
Bone Conditions	Any bone condition	166 (2.1%)	109 (1.1%)	**<.0001**	25 (1.6%)	0.1543	36 (1.0%)	**<.0001**
Peripheral Neuropathy	Any peripheral neuropathy	534 (6.8%)	416 (4.3%)	**<.0001**	150 (9.4%)	**0.0003**	225 (6.5%)	0.5260
Renal Disease	Renal Impairment	3242 (41.2%)	3463 (35.6%)	**<.0001**	655 (40.9%)	0.8188	1282 (36.9%)	**<.0001**
	Moderate/Severe CKD	263 (3.3%)	121 (1.2%)	**<.0001**	56 (3.5%)	0.7558	47 (1.4%)	**<.0001**
	End Stage Renal Disease	78 (1.0%)	149 (1.5%)	**0.0017**	19 (1.2%)	0.4800	35 (1.0%)	0.9439
Hypertension	Any hypertension	1865 (23.7%)	1843 (18.9%)	**<.0001**	514 (32.1%)	**<.0001**	789 (22.7%)	0.2298
Rheumatoid Arthritis	Any rheumatoid arthritis	30 (0.4%)	27 (0.3%)	0.2255	8 (0.5%)	0.4952	9 (0.3%)	0.3030
Substance Abuse	Any substance abuse	1236 (15.7%)	1219 (12.5%)	**<.0001**	160 (10.0%)	**<.0001**	549 (15.8%)	0.9309
	Alcohol Dependence	278 (3.5%)	276 (2.8%)	**0.0080**	39 (2.4%)	0.0259	121 (3.5%)	0.8795
	Drug Abuse	1192 (15.2%)	1176 (12.1%)	**<.0001**	152 (9.5%)	**<.0001**	529 (15.2%)	0.9467

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 7. Baseline Concomitant Non-ART Medications of Patients Initiating with DTG, EVG, RAL, & DRV-containing regimens

	DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,477*	*DTG vs. DRV p-value*
Antibiotics	1041 (13.2%)	1158 (11.9%)	**0.0070**	195 (12.2%)	0.2529	576 (16.6%)	**<.0001**
Direct Acting Antivirals (DAAs)	48 (0.6%)	18 (0.2%)	**<.0001**	8 (0.5%)	0.7219	4 (0.1%)	**0.0001**
Lipid lowering agents	1119 (14.2%)	918 (9.4%)	**<.0001**	305 (19.1%)	**<.0001**	371 (10.7%)	**<.0001**
Non-steroidal Anti-inflammatory Agents (NSAIDS)	517 (6.6%)	477 (4.9%)	**<.0001**	82 (5.1%)	0.0296	221 (6.4%)	0.6593
Antidepressants	1336 (17.0%)	1254 (12.9%)	**<.0001**	372 (23.3%)	**<.0001**	577 (16.6%)	0.5976
Anxiolytics/Hypnotics/Sedatives	875 (11.1%)	866 (8.9%)	**<.0001**	275 (17.2%)	**<.0001**	302 (8.7%)	**<.0001**
Anti-diabetics	359 (4.6%)	277 (2.8%)	**<.0001**	146 (9.1%)	**<.0001**	162 (4.7%)	0.8296
Immune Modulators	588 (7.5%)	559 (5.7%)	**<.0001**	83 (5.2%)	**0.0011**	218 (6.3%)	0.0207

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

3.3. Assessment of Gastrointestinal Disorders

Table 8. Gastrointestinal Disorders in Patients Taking DTG, EVG, RAL, & DRV Reg

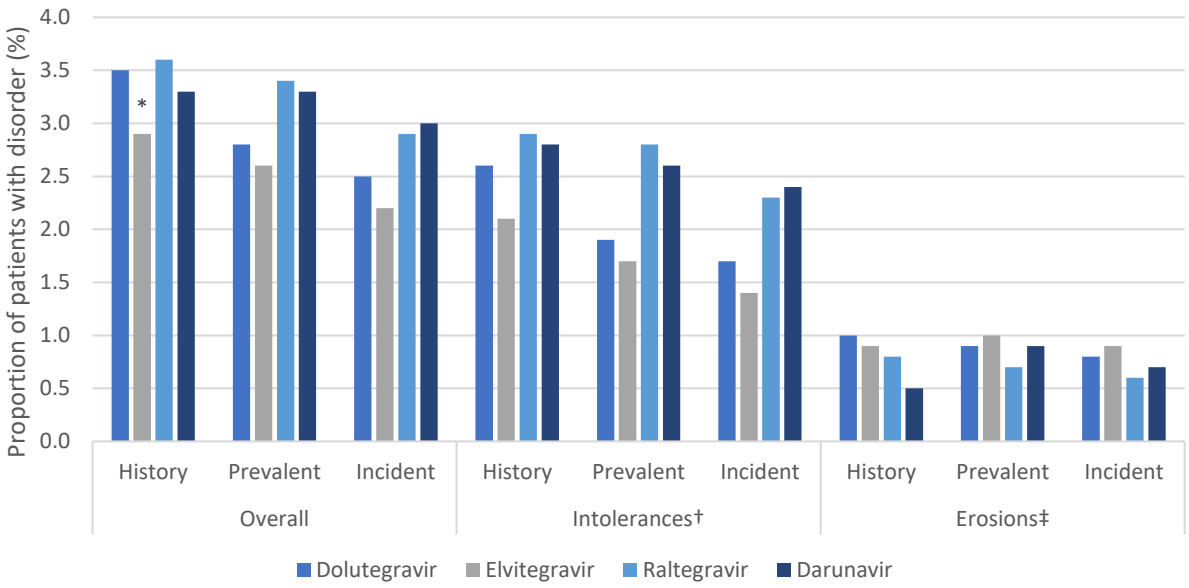
		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG* *p-value*	*RAL* *N= 1,600*	*DTG vs. RAL* *p-value*	*DRV* *N= 3,347*	*DTG vs. DRV* *p-value*
				*Overall Gastrointestinal Disorders**				
Any Gastrointestinal Disorders	Any history, n (%)	278 (3.5%)	282 (2.9%)	**0.0160**	58 (3.6%)	0.8622	114 (3.3%)	0.4878
	Any prevalent event, n (%)	220 (2.8%)	252 (2.6%)	0.3887	54 (3.4%)	0.2105	116 (3.3%)	0.1199
	Days to prevalent event, median (IQR)	35.0 (26.5, 117.5)	39.0 (20.0, 120.5)	0.7898	28.0 (14.0, 42.0)	**0.0121**	28.0 (16.5, 46.5)	**0.0021**
	Prevalent event with D/C†, n (%)	11 (0.1%)	15 (0.2%)	0.8089	6 (0.4%)	0.0430	16 (0.5%)	**0.0013**
	Days to prevalent event with D/C, median (IQR)	35.0 (19.0, 451.0)	27.0 (11.0, 37.0)	0.1192	30.0 (14.0, 54.0)	0.3146	23.0 (16.5, 45.5)	0.1905
	Any incident event, n (%)	198 (2.5%)	216 (2.2%)	0.1903	47 (2.9%)	0.3368	105 (3.0%)	0.1274
	Days to incident event, median (IQR)	38.0 (27.0, 122.0)	41.5 (20.5, 130.5)	0.8707	29.0 (18.0, 52.0)	0.0232	30.0 (17.0, 48.0)	**0.0036**
	Incident event with D/C, n (%)	10 (0.1%)	12 (0.1%)	0.9405	6 (0.4%)	0.0279	14 (0.4%)	**0.0033**
	Days to incident event with D/C, median (IQR)	45.5 (27.0, 451.0)	27.0 (11.0, 33.0)	0.0376	30.0 (14.0, 54.0)	0.1927	23.0 (17.0, 56.0)	0.1069
				Specific Gastrointestinal Disorders				
Gastrointestinal Intolerance	Any history, n (%)	207 (2.6%)	204 (2.1%)	0.0187	46 (2.9%)	0.5854	97 (2.8%)	0.6350
	Any prevalent event, n (%)	151 (1.9%)	161 (1.7%)	0.1808	44 (2.8%)	0.0334	90 (2.6%)	0.0231
	Days to prevalent event, median (IQR)	29.0 (16.0, 41.0)	27.0 (14.0, 42.0)	0.3717	26.0 (14.0, 35.0)	0.1864	27.0 (16.0, 35.0)	0.2085
	Prevalent event with D/C, n (%)	7 (0.1%)	14 (0.1%)	0.2960	6 (0.4%)	**0.0049**	12 (0.3%)	**0.0021**
	Days to prevalent event with D/C, median (IQR)	27.0 (17.0, 35.0)	27.0 (11.0, 32.0)	0.7368	30.0 (14.0, 54.0)	0.8862	19.0 (16.5, 30.0)	0.5251
	Any incident event, n (%)	137 (1.7%)	137 (1.4%)	0.0734	37 (2.3%)	0.1223	83 (2.4%)	0.0219

		DTG *N= 7,860*	*EVG* *N= 9,738*	*DTG vs. EVG p-value*	*RAL* *N= 1,600*	*DTG vs. RAL p-value*	*DRV* *N= 3,347*	*DTG vs. DRV p-value*
	Days to incident event, median (IQR)	30.0 (18.0, 42.0)	27.0 (14.0, 42.0)	0.3233	26.0 (14.0, 35.0)	0.2115	27.0 (16.0, 36.0)	0.1881
	Incident event with D/C, n (%)	6 (0.1%)	12 (0.1%)	0.3333	6 (0.4%)	**0.0022**	11 (0.3%)	**0.0023**
	Days to incident event with D/C, median (IQR)	30.0 (19.0, 35.0)	27.0 (11.0, 33.0)	0.4815	30.0 (14.0, 54.0)	1.0000	18.0 (16.0, 32.0)	0.1733
Gastrointestinal Erosions	Any history, n (%)	77 (1.0%)	84 (0.9%)	0.4175	12 (0.8%)	0.3858	19 (0.5%)	0.0203
	Any prevalent event, n (%)	72 (0.9%)	98 (1.0%)	0.5425	11 (0.7%)	0.3716	30 (0.9%)	0.7820
	Days to prevalent event, median (IQR)	213.5 (124.5, 496.5)	192.5 (77.0, 406.0)	0.3604	247.0 (59.0, 611.0)	0.8614	272.0 (27.0, 427.0)	0.3702
	Prevalent event with D/C, n (%)	4 (0.1%)	1 (0.0%)	0.1797	0 (0.0%)	1.0000	4 (0.1%)	0.2597
	Days to prevalent event with D/C, median (IQR)	463.5 (260.5, 524.5)	153.0 (153.0, 153.0)	0.7237		.	294.0 (103.5, 436.5)	0.4705
	Any incident event, n (%)	64 (0.8%)	86 (0.9%)	0.6212	10 (0.6%)	0.4335	24 (0.7%)	0.4879
	Days to incident event, median (IQR)	225.5 (134.5, 523.5)	231.0 (91.0, 426.0)	0.4000	287.0 (59.0, 611.0)	0.8557	305.0 (86.0, 437.5)	0.8148
	Incident event with D/C, n (%)	4 (0.1%)	0 (0.0%)	0.0398	0 (0.0%)	1.0000	3 (0.1%)	0.4451
	Days to incident event with D/C, median (IQR)	463.5 (260.5, 524.5)		.		.	391.0 (197.0, 482.0)	0.8597

***** Gastrointestinal Disorders are defined as (1) gastrointestinal intolerance (diagnosis of “nausea”, “vomiting”, “diarrhea”, or “abdominal pain”), or (2) gastrointestinal erosions (diagnosis of “gastritis”, “gastric erosion”, “peptic ulcer disease”, or “gastrointestinal bleeding”)

[†] D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of a gastrointestinal disorder

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).



* P-value for the comparison with DTG <0.017
† Gastrointestinal Intolerance: diagnosis of "nausea", "vomiting", "diarrhea", or "abdominal pain")
‡ Gastrointestinal erosions: diagnosis of "gastritis", "gastric erosion", "peptic ulcer disease", or "gastrointestinal bleeding"

Figure 1. Proportion of Patients Taking DTG, EVG, RAL, & DRV Regimens with history, prevalent or incident gastrointestinal disorders

4. Summary of Findings

Out of 22,675 HIV-infected patients initiating a core agent of interest between August 1st, 2013 and December 31st, 2016 (Table 1), 7,860 (35%) initiated DTG, 89,738 (43%) initiated EVG, 1,600 (7%) initiated RAL and 3,477 (15%) initiated DRV (Table 2). Patients initiating EVG, RAL or DRV were statistically different at baseline from patients initiating DTG for many demographic and clinical characteristics.

4.1. Elvitegravir vs. Dolutegravir

At baseline, EVG users were younger than DTG users. They were also more likely to be male or receive care in the South, but they were less likely to be MSM or to benefit from ADAP or Ryan White programs (Table 3). EVG users had a shorter average follow-up time (Table 4). There was no difference in the proportion of ART naïve patients, average viral load or average CD4 cell count at baseline (Table 5).

EVG users were healthier than DTG users, with lower average VACS scores (Table 4). Fewer EVG users had comorbidities at baseline. Liver diseases, including hepatitis C, were least frequent in the EVG group (Table 6)Table 6. All the concomitant medications assessed were used less frequently among EVG than DTG users (**Error! Reference source not found.**), including lipid lowering agents, which are known to

elevate LFTs. This is likely a result of the boosting agent in EVG-containing regimens which impacts the pharmacokinetics of other medications that are metabolized through the liver.

Overall, EVG users had a statistically significant lower proportion of patients with a history of any gastrointestinal disorders than DTG users (Table 8). There was however no statistically significant difference in prevalent or incident gastrointestinal disorders between EVG and DTG users. Specific gastrointestinal disorders are presented in Table 8 and Figure 1. There was no difference in history, prevalence or incidence of either gastrointestinal intolerance or gastrointestinal erosions between EVG and DTG users. Core agent discontinuation was rare (≤0.2%) and there was no statistically significant difference between groups after a prevalent or incident gastrointestinal disorder event (Table 8).

4.2. Raltegravir vs. Dolutegravir

RAL users were older, less likely to be male, African American or Hispanic, and less likely to be MSM or to benefit from ADAP or Ryan White programs than DTG users. RAL users were however more likely to receive care in the South (Table 3). They also had a shorter average follow-up time (Table 4). Fewer RAL than DTG users were ART naïve. Baseline HIV viral load was lower among RAL users, but baseline CD4 cell count was not statistically different (Table 5).

At baseline, RAL users were sicker (higher average VACS score, Table 4), and were more likely to have comorbidities than DTG users (Table 6). Liver diseases, including hepatitis C, were more frequent in the RAL groups than the DTG group (Table 6). RAL users were prescribed lipid lowering agents more frequently than DTG users (**Error! Reference source not found.**).

Overall, there was no statistically significant difference in history, prevalence or incidence of any gastrointestinal disorders. However, prevalent gastrointestinal disorders occurred earlier on average among RAL than DTG users (Table 8). Gastrointestinal events are broken down into intolerance or erosions in Table 8 and Figure 1. There was no statistically significant difference in history, prevalence or incidence of gastrointestinal intolerances or erosion between RAL and DTG users. Discontinuations were rare, occurring in ≤0.4% of prevalent and incident events. However, both prevalent and incident gastrointestinal intolerance with discontinuation occurred more frequently in RAL than DTG users.

4.3. Darunavir vs. Dolutegravir

Compared to DTG users, DRV users were older and less likely to be male, Hispanic or MSM, to have a history of syphilis or to benefit from ADAP or Ryan White programs. They were however more likely to be African American and receive care in the South (Table 3). DRV had a shorter average follow-up time than DTG users (Table 4) and were more likely to be ART-experienced with a history of AIDS. Baseline HIV viral load was higher among DRV, but baseline CD4 cell counts were not statistically different (Table 5).

DRV users were sicker than DTG users at baseline, with higher average VACS scores (Table 4). There was no difference in the proportion of DRV and DTG users with comorbidities at baseline. No differences in liver diseases overall were detected either,

*although DRV users were more likely than DTG users to have hepatitis B (Table 6). DRV users were less likely than DTG users to use a lipid-lowering agent (**Error! Reference source not found.***

Table 7).

Overall, there was no statistically significant difference in the proportion of patients with history, prevalence or incidence of any gastrointestinal disorders between DRV and DTG users (Table 8). However, DRV users experienced a shorter time to prevalent events than DTG users. DRV users were also more likely to discontinue the core agent after a prevalent or incident gastrointestinal disorder, compared to DTG users (Table 8). Specific gastrointestinal disorders (intolerance and erosions) are detailed in Table 8 and Figure 1. For gastrointestinal intolerances, there was no difference in the proportion of patients with a history, prevalent or incident events, although discontinuation following a prevalent or incident event was more likely among DRV users than DTG users. There was no difference in gastrointestinal erosions between groups.

5. Conclusions

Patients using DTG, EVG, RAL or DRV are different in many regards. Some of these differences could be the result of channeling sicker patients away from EVG and towards DTG or RAL. Indeed, compared to DTG users, EVG users were younger and less likely to have existing liver disease, take lipid lowering agents, or have substantial comorbidities than DTG users. During follow-up, however, the likelihood of prevalent or incident gastrointestinal intolerance and/or erosion was observed to be no different between EVG and DTG users, with or without discontinuation of core agent.

On the contrary, RAL users were older and were more likely to be female, have liver diseases, take lipid lowering agents or have substantial comorbidities, compared to DTG users. This did not translate into differences in the history, prevalence or incidence of overall gastrointestinal disorder, gastrointestinal intolerance, or gastrointestinal erosion. However, discontinuation following a prevalent or incident intolerance occurred statistically more frequently in RAL than DTG users.

DRV users were more likely to be female, African American, have had AIDS, and be ART-experienced with higher VACS scores. Although DRV users were sicker with the worst 5-year mortality probability, there was no difference in the likelihood of comorbidities at baseline suggesting that their HIV indicators were driving their poor overall health. The INSTIs had a greater number of patients initiating virologically suppressed. No statistical difference in prevalent or incident gastrointestinal disorders were detected between DRV and DTG users. Only discontinuation following a prevalent or incident gastrointestinal intolerance was more likely among DRV users than DTG users.

Discontinuation following a gastrointestinal disorder was rare, suggesting that clinicians are willing to tolerate most instances of these disorders. More work would be required to investigate the degree of severity and persistence of disorders required for discontinuation.

Of note, several gastrointestinal intolerance events were excluded from this analysis due to the long lag time between core agent initiation and symptom onset. While these symptoms often manifest within days of initiation, a switch is usually considered after 4-6 weeks if the symptoms persist. Therefore, a window of 8 weeks was selected to allow for delays in drug initiation and clinical contact. It is however

possible that some intolerance symptoms were not captured. It is also possible that some of the intolerances capture within that window were not related to the medication use, as gastrointestinal intolerance symptoms are associated with many common illnesses.

While evidence of potential channeling was observed and could have likely played a role in the observed differences of discontinuations following prevalent or incident gastrointestinal disorders, no adjustment for baseline characteristics were performed. It is therefore impossible to determine from these unadjusted comparisons the impact of channeling on the results presented.

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A Comprehensive Assessment of Adverse Events and Overall Safety Profile in HIV Positive Patients Treated with Dolutegravir as Compared to Other Integrase Strand Transfer Inhibitors or Darunavir:

Final Report – Systems with Rare Events (Body Fat Redistribution/Accumulation, Pancreatic Disorders, Musculoskeletal Disorders, IRIS, Severe Systemic Rash, Hypersensitivity Reactions and Dofetilide Co-administration)

Complete data through December 31, 2017

April 4, 2018

Table of Content

1. Background and Rationale

Background: Clinical guidelines currently recommend the use of the integrase strand transfer inhibitors (INSTI) dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL), or the protease inhibitor (PI) darunavir (DRV) as the core agent in antiretroviral therapy (ART) regimens.[1] Toxicity concerns with multi-agent regimens, and pharmacokinetic interactions with medications for co-morbidities suggest the need for a comprehensive safety evaluation of recommended core agents in a real-world setting. In clinical trials, DTG treatment-related adverse effects (determined by the investigator) were less frequent (1–3%) than comparator drugs. Most adverse events seen in trials of DTG were grade 1–2 (mild-to-moderate in severity), such as headache, diarrhea, nausea, or insomnia.[2-6]

Rationale: A comprehensive safety evaluation of DTG and other recommended core agents has not been performed in a real-world setting. As the use of INSTIs increases in various demographic populations and clinical situations, an understanding of the overall safety profile of the members of the class will provide additional information for clinicians as treatment strategies are designed.

Scope of report: This report is limited to systems with rare events (body fat redistribution/accumulation, pancreatic disorders, musculoskeletal disorders, IRIS, severe systemic rash, hypersensitivity reaction, dofetilide co-administration). It will appear in its entirety in the full report of safety outcomes.

2. Methods

2.1. Study Design

Study population: The study population consisted of HIV-positive patients at least 13 years of age initiating a core agent of interest prescribed by an OPERA caregiver during the eligibility period (August 1, 2013 to December 31, 2016).

Baseline date: The baseline date was defined as the first date of one of the four core agents of interest ever prescribed to a patient

Observation period: The observation period began on August 1, 2013 (the month DTG was approved) with study participants identified through December 31, 2016 on data through December 31, 2017. Patients were observed from their baseline date until the first of the following censoring events: 1) discontinuation of the core agent of interest, 2) cessation of continuous clinical activity, 3) death or 4) study end (December 31, 2017). Patients failing to meet the continuous clinical activity requirement were censored 12 months after their last contact.

Continuous Clinical Activity: Patients with continuous clinical activity were those who had clinical contact at least once in 12 months. Clinical contact was defined as a telephone contact, visit, lab test, or consultation.

Core agent of interest: Core agents of interest consisted of dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), or darunavir (DRV). A regimen was considered discontinued when the core agent of interest was discontinued for 45 days or more.

2.2. Outcomes Definitions

2.2.1. Disorder Groups

Body Fat Redistribution/Accumulation consisted of a diagnosis of "lipohypertrophy", "lipoaccumulation", "hyperadiposity", "lipoatrophy", or "lipodystrophy"

Pancreatic Disorders consisted of (1) Pancreatitis or (2) Pancreatic Adverse Elevations, defined as:

1. Pancreatitis: diagnosis of "pancreatitis"
2. Pancreatic Adverse Elevation: Grade 3 or 4 lipase elevation (lipase >3X ULN)

Musculoskeletal Disorders consisted of (1) Rhabdomyolysis or (2) Musculoskeletal Adverse Elevations, defined as:

1. Rhabdomyolysis: diagnosis of "Rhabdomyolysis "
2. Musculoskeletal Adverse Elevations: Grade 3 or 4 creatinine phosphokinase (creatinine kinase) elevation (CPK ≥10X ULN)

IRIS consisted of a diagnosis of "Immune Reconstitution Inflammatory Syndrome" (IRIS), "Immune Restoration Disease" (IRD), "Immune Reconstitution Syndrome" (IRS), or "Paradoxical Reactions"

Severe systemic rash consisted of a diagnosis of "Blistering rash", "Open skin ulcers", "Serious rash", "Severe rash", "Systemic rash", "Stevens-Johnson syndrome", or "Toxic Epidermal Necrolysis (TEN)". Only incident severe systematic rash were reported.

Hypersensitivity Reaction (HSR) consisted of a diagnosis of "hypersensitivity reaction", "anaphylaxis", "anaphylactic shock", or "immunologic reaction" during follow-up. Only incident HSR were reported, stratified by concurrent ABC use.

Dofetilide Co-Administration: Any use of dofetilide was assessed in the entire OPERA cohort, among HIV+ patients in the OPERA cohort and among the Comprehensive Safety Study population.

2.2.1. History, Prevalence and Incidence Definition

History of Disorder: defined as an event occurring at baseline or up to 12 months before baseline.

Prevalent Disorder: defined as an event occurring after baseline, regardless of whether the patient had a history of that disorder group.

Incident Disorder: defined as only a new event occurring after baseline, excluding patients who had any history of that disorder group. Therefore, incident disorders are a subset of prevalent disorders. The incidence of any of the specific disorder within a group excluded patients with a history of disorder for that group (not just the specific disorder in question) because any one of these events puts a patient at very high risk for future events for that disorder group and should not be considered as incident.

Discontinuation (D/C): defined as discontinuation of the core agent of interest within 21 days of the date of a disorder. Time to disorders with D/C was calculated based on the date of the disorder.

2.3. Statistical Analyses

Descriptive analyses of baseline demographic and clinical patient characteristics at baseline, as well as rare disorders outcomes during follow-up were conducted to compare DTG to other core agents of interest. The Pearson's Chi-Square Test was used to calculate p-values for categorical variables and the Mann-Whitney Test was used to calculate p-values for continuous variables. Fischer Exact Test was used for cells with small numbers (counts of 5 or fewer).

To account for multiple comparisons between DTG and comparator core agents, the Sidak Correction was applied, resulting in an adjusted alpha level for significance of 0.017.

3. Results

3.1. Population Identification

Table 1. Identification of the Study Population

		Patients Included	*%*	*Patients Excluded*	*%*
1	OPERA patients who are HIV+	84,084	.	0	.
2	Patients with HIV-1 infection (excluding HIV-2 infection)	83,999	99.9	85	0.1
3	HIV+ patients prescribed ART	73,223	87.2	10,776	12.8
4	Patients prescribed a regimen of interest (containing DTG, EVG, RAL, or DRV)	47,794	65.3	25,429	34.7
5	Patients prescribed regimen of interest between 08/01/2013 and 12/31/2016	32,398	67.8	15,396	32.2
6	Patients who were 13 years of age or older at first ART regimen of interest	32,394	100.0	4	0.0
7	Patients prescribed a regimen of interest that did not include two or more third agents of interest	29,049	89.7	3,345	10.3
8	Patients whose first ART regimen of interest was not monotherapy	28,337	97.5	712	2.5
9	Patients whose first ART regimen of interest was not prior to date of HIV	28,189	99.5	148	0.5
10	Patients whose regimen of interest was their first experience with DTG, EVG, RAL, or DRV [Study population]	22,675	80.4	5,514	19.6

Table 2. Study Population by ART Core Agent of Interest and Regimen

Core agent of interest	*n(%)*	*Regimens*	*n(%)*
DTG-containing regimens	7,860 (34.7%)	DTG + TDF + FTC	1,524 (19.4%)
		DTG + TAF + FTC	219 (2.8%)
		DTG + ABC + 3TC	4,932 (62.7%)
		DTG + all other agents	1,185 (15.1%)
EVG-containing regimens	9,738 (42.9%)	EVG + r/c + TDF + FTC	5,996 (61.6%)
		EVG + r/c + TAF + FTC	2,987 (30.7%)
		EVG + r/c + all other agents	755 (7.8%)
RAL-containing regimens	1,600 (7.1%)	RAL + TDF + FTC	803 (50.2%)
		RAL + TAF + FTC	14 (0.9%)
		RAL + ABC + 3TC	126 (7.9%)
		RAL + all other agents	657 (41.1%)
DRV-containing regimens	3,477 (15.3%)	DRV + r/c + TDF + FTC	2,481 (71.4%)
		DRV + r/c + TAF + FTC	134 (3.9%)
		DRV + r/c + ABC + 3TC	318 (9.1%)
		DRV + r/c + all other agents	496 (14.3%)
		DRV + TDF + FTC	15 (0.4%)
		DRV + ABC + 3TC	6 (0.2%)
		DRV + all other agents	27 (0.8%)

3.2. Baseline Characteristics

Table 3. Baseline Demographic Characteristics of Patients Taking DTG, EVG, RAL, & DRV Regime

		DTG *N= 7,315*	*EVG* *N= 9,035*	*DTG vs. EVG p-value*	*RAL* *N= 1,551*	*DTG vs. RAL p-value*	*DRV* *N= 3,350*	*DTG vs. DRV p-value*
Age	Median (IQR)	41.1 (29.8, 51.1)	36.9 (28.1, 48.4)	**<.0001**	48.8 (39.8, 55.0)	**<.0001**	43.4 (33.0, 51.1)	**<.0001**
	13-25	1134 (14.4%)	1707 (17.5%)	**<.0001**	72 (4.5%)	**<.0001**	331 (9.5%)	**<.0001**
	26-49	4528 (57.6%)	5993 (61.5%)	**.**	807 (50.4%)	**.**	2159 (62.1%)	**.**
	50+	2198 (28.0%)	2038 (20.9%)	**.**	721 (45.1%)	**.**	987 (28.4%)	**.**
Sex	Male	6671 (84.9%)	8416 (86.4%)	**0.0125**	1273 (79.6%)	**<.0001**	2763 (79.5%)	**<.0001**
	Female	1182 (15.0%)	1314 (13.5%)	**.**	325 (20.3%)	**.**	713 (20.5%)	**.**
	Unknown	7 (0.1%)	8 (0.1%)	**.**	2 (0.1%)	**.**	1 (0.0%)	**.**
Race	African American	3227 (41.1%)	3948 (40.5%)	0.4905	581 (36.3%)	**0.0004**	1661 (47.8%)	**<.0001**
	Not African American	4633 (58.9%)	5790 (59.5%)	.	1019 (63.7%)	**.**	1816 (52.2%)	**.**
Ethnicity	Hispanic	1936 (24.6%)	2496 (25.6%)	0.1285	273 (17.1%)	**<.0001**	720 (20.7%)	**<.0001**
	Not Hispanic	5924 (75.4%)	7242 (74.4%)	.	1327 (82.9%)	**.**	2757 (79.3%)	**.**
Marital Status	Single	5543 (70.5%)	6720 (69.0%)	0.1116	976 (61.0%)	**<.0001**	2302 (66.2%)	**<.0001**
	Married	468 (6.0%)	613 (6.3%)	.	145 (9.1%)	**.**	267 (7.7%)	**.**
	Domestic partnership	258 (3.3%)	293 (3.0%)	.	54 (3.4%)	**.**	116 (3.3%)	**.**
	Widowed	51 (0.6%)	57 (0.6%)	.	21 (1.3%)	**.**	37 (1.1%)	**.**
	Separated/divorced	205 (2.6%)	257 (2.6%)	.	64 (4.0%)	**.**	102 (2.9%)	**.**
	Unknown	1335 (17.0%)	1798 (18.5%)	.	340 (21.3%)	**.**	653 (18.8%)	**.**
Risk of Infection	MSM	4023 (51.2%)	4788 (49.2%)	**0.0079**	589 (36.8%)	**<.0001**	1427 (41.0%)	**<.0001**
	Not MSM	3837 (48.8%)	4950 (50.8%)	**.**	1011 (63.2%)	**.**	2050 (59.0%)	**.**
History of Syphilis	Yes	2158 (27.5%)	2817 (28.9%)	0.0310	314 (19.6%)	**<.0001**	830 (23.9%)	**<.0001**
Region	Northeast	674 (8.6%)	809 (8.3%)	**<.0001**	164 (10.3%)	**<.0001**	246 (7.1%)	**<.0001**
	South	4268 (54.3%)	6029 (61.9%)	**.**	1061 (66.3%)	**.**	2174 (62.5%)	**.**
	Midwest	177 (2.3%)	266 (2.7%)	**.**	42 (2.6%)	**.**	65 (1.9%)	**.**
	West	2741 (34.9%)	2634 (27.0%)	**.**	333 (20.8%)	**.**	992 (28.5%)	**.**
Payer	Medicaid	1754 (22.3%)	1557 (16.0%)	**<.0001**	358 (22.4%)	0.9585	839 (24.1%)	0.0339
	Medicare	715 (9.1%)	575 (5.9%)	**<.0001**	309 (19.3%)	**<.0001**	459 (13.2%)	**<.0001**
	Commercial Insurance	2382 (30.3%)	3221 (33.1%)	**<.0001**	506 (31.6%)	0.2961	860 (24.7%)	**<.0001**

		DTG *N= 7,315*	*EVG* *N= 9,035*	*DTG vs. EVG p-value*	*RAL* *N= 1,551*	*DTG vs. RAL p-value*	*DRV* *N= 3,350*	*DTG vs. DRV p-value*
	Cash	4421 (56.2%)	5118 (52.6%)	**<.0001**	914 (57.1%)	0.5185	1885 (54.2%)	0.0445
	ADAP/Ryan White	2820 (35.9%)	3143 (32.3%)	**<.0001**	338 (21.1%)	**<.0001**	1034 (29.7%)	**<.0001**
	Other	36 (0.5%)	33 (0.3%)	0.2259	3 (0.2%)	0.1383	9 (0.3%)	0.1448
	No Payer info	1145 (14.6%)	1934 (19.9%)	**<.0001**	362 (22.6%)	**<.0001**	711 (20.4%)	**<.0001**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 4. General Baseline Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Year of Study Initiation	2013	299 (3.8%)	828 (8.5%)	**<.0001**	344 (21.5%)	**<.0001**	568 (16.3%)	**<.0001**
	2014	1654 (21.0%)	2144 (22.0%)	**.**	631 (39.4%)	**.**	1139 (32.8%)	**.**
	2015	2580 (32.8%)	2435 (25.0%)	**.**	350 (21.9%)	**.**	878 (25.3%)	**.**
	2016	3327 (42.3%)	4331 (44.5%)	**.**	275 (17.2%)	**.**	892 (25.7%)	**.**
Time from first active date to index date	Median (IQR)	2.2 (0.5, 34.6)	1.2 (0.1, 24.0)	**<.0001**	0.2 (0.0, 8.8)	**<.0001**	0.7 (0.0, 19.8)	**<.0001**
Follow-up time between baseline and end of observation	Median (IQR)	18.3 (12.5, 27.4)	17.0 (12.0, 26.0)	**<.0001**	14.5 (9.9, 25.8)	**<.0001**	15.6 (10.8, 25.7)	**<.0001**
Pregnancy	Pregnancy	6 (0.1%)	10 (0.1%)	0.6233	4 (0.3%)	0.0729	11 (0.3%)	**0.0059**
*VACS Index**	Median (IQR)	17.0 (7.0, 29.0)	13.0 (7.0, 25.0)	**<.0001**	20.0 (10.0, 35.0)	**<.0001**	22.0 (12.0, 39.0)	**<.0001**
VACS Index category	0 to <15	2994 (38.1%)	3916 (40.2%)	**<.0001**	374 (23.4%)	**<.0001**	837 (24.1%)	**<.0001**
	>=15 to <30	2038 (25.9%)	2177 (22.4%)	**.**	317 (19.8%)	**.**	809 (23.3%)	**.**
	>=30 to <45	816 (10.4%)	777 (8.0%)	**.**	147 (9.2%)	**.**	381 (11.0%)	**.**
	>= 45	780 (9.9%)	742 (7.6%)	**.**	173 (10.8%)	**.**	528 (15.2%)	**.**
	Missing	1232 (15.7%)	2126 (21.8%)	**.**	589 (36.8%)	**.**	922 (26.5%)	**.**

* VACS Mortality Index: score created by summing pre-assigned points for age, HIV disease (CD4 count and HIV-1 RNA), and general indicators of organ system injury including hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. This score is used to estimate risk of all-cause mortality in the following 5 years. A higher score is associated with a higher risk of mortality.

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 5. Baseline HIV-Related Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimen

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
ART-naïve at index	ART-naïve	2663 (33.9%)	3452 (35.4%)	0.0298	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	ART-experienced	5197 (66.1%)	6286 (64.6%)	.	1401 (87.6%)	**.**	2499 (71.9%)	**.**
Calendar year of ART initiation	Median (IQR)	2015 (2013, 2016)	2015 (2013, 2016)	**<.0001**	2014 (2013, 2015)	**<.0001**	2014 (2013, 2015)	**<.0001**
	Pre-2000	213 (2.7%)	132 (1.4%)	**<.0001**	30 (1.9%)	**<.0001**	55 (1.6%)	**<.0001**
	2000-2004	278 (3.5%)	172 (1.8%)	**.**	34 (2.1%)	**.**	88 (2.5%)	**.**
	2005-2009	620 (7.9%)	548 (5.6%)	**.**	87 (5.4%)	**.**	194 (5.6%)	**.**
	2010-2014	2619 (33.3%)	3852 (39.6%)	**.**	924 (57.8%)	**.**	1706 (49.1%)	**.**
	2015-present	4130 (52.5%)	5034 (51.7%)	**.**	525 (32.8%)	**.**	1434 (41.2%)	**.**
Number of previous ART regimens	Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	**<.0001**	1.0 (1.0, 3.0)	**0.0158**	1.0 (1.0, 2.0)	0.4892
Number of previous ART regimens category	ART-naïve	2663 (33.9%)	3452 (35.4%)	**<.0001**	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	1-2 previous regimens	2668 (33.9%)	2592 (26.6%)	**.**	281 (17.6%)	**.**	776 (22.3%)	**.**
	3-4 previous regimens	410 (5.2%)	298 (3.1%)	**.**	41 (2.6%)	**.**	103 (3.0%)	**.**
	5 or more previous regimens	266 (3.4%)	208 (2.1%)	**.**	55 (3.4%)	**.**	91 (2.6%)	**.**
	Missing previous regimens	1853 (23.6%)	3188 (32.7%)	**.**	1024 (64.0%)	**.**	1529 (44.0%)	**.**
Previous ART exposure	Naive	2663 (33.9%)	3452 (35.4%)	0.0298	199 (12.4%)	**<.0001**	978 (28.1%)	**<.0001**
	NNRTI	2129 (27.1%)	2280 (23.4%)	**<.0001**	200 (12.5%)	**<.0001**	441 (12.7%)	**<.0001**
	PI	1547 (19.7%)	974 (10.0%)	**<.0001**	198 (12.4%)	**<.0001**	587 (16.9%)	**0.0004**
	INSTI	1 (0.0%)	1 (0.0%)	1.0000	0 (0.0%)	1.0000	1 (0.0%)	0.5193
	NRTI	3309 (42.1%)	2988 (30.7%)	**<.0001**	357 (22.3%)	**<.0001**	929 (26.7%)	**<.0001**
	Other	31 (0.4%)	17 (0.2%)	0.0054	10 (0.6%)	0.2006	8 (0.2%)	0.1682
	Unknown	1853 (23.6%)	3188 (32.7%)	**<.0001**	1024 (64.0%)	**<.0001**	1529 (44.0%)	**<.0001**
Backbone of Regimen of Interest	TDF + FTC	1524 (19.4%)	5996 (61.6%)	**<.0001**	803 (50.2%)	**<.0001**	2496 (71.8%)	**<.0001**
	TAF + FTC	219 (2.8%)	2987 (30.7%)	**.**	14 (0.9%)	**.**	134 (3.9%)	**.**
	ABC + 3TC	4932 (62.7%)	0 (0.0%)	**.**	126 (7.9%)	**.**	324 (9.3%)	**.**
	All others	1185 (15.1%)	755 (7.8%)	**.**	657 (41.1%)	**.**	523 (15.0%)	**.**

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
AIDS-defining Illness	AIDS	2040 (26.0%)	2007 (20.6%)	**<.0001**	448 (28.0%)	0.0902	1140 (32.8%)	**<.0001**
	No AIDS	5820 (74.0%)	7731 (79.4%)	**.**	1152 (72.0%)	.	2337 (67.2%)	**.**
Baseline viral load	Median (IQR)	460.0 (19.0, 40580.0)	1649.5 (19.0, 45155.0)	0.0426	19.0 (19.0, 820.0)	**<.0001**	1042.0 (19.0, 52360.0)	**<.0001**
Baseline Viral Load log10	Median (IQR)	2.7 (1.3, 4.6)	3.3 (1.3, 4.7)	0.0192	1.3 (1.3, 3.0)	**<.0001**	3.1 (1.3, 4.7)	**<.0001**
Baseline Viral Load category	Suppressed (<50 copies/mL)	2765 (35.2%)	3131 (32.2%)	**<.0001**	617 (38.6%)	**<.0001**	925 (26.6%)	**<.0001**
	Low (>=50 to <10,000 copies/mL)	1289 (16.4%)	1499 (15.4%)	**.**	224 (14.0%)	**.**	646 (18.6%)	**.**
	Moderate (>=10,000 to <100,000 copies/mL)	1708 (21.7%)	2100 (21.6%)	**.**	136 (8.5%)	**.**	583 (16.8%)	**.**
	High (>=100,000 copies/mL)	906 (11.5%)	1110 (11.4%)	**.**	71 (4.4%)	**.**	460 (13.2%)	**.**
	Missing baseline VL	1192 (15.2%)	1898 (19.5%)	**.**	552 (34.5%)	**.**	863 (24.8%)	**.**
Nadir CD4	Median (IQR)	400.0 (237.0, 585.0)	413.0 (253.0, 597.0)	**0.0004**	437.0 (243.0, 659.0)	0.0001	318.0 (133.0, 536.0)	<.0001
Baseline CD4	Median (IQR)	491.0 (310.0, 706.0)	489.0 (306.0, 697.0)	0.4656	514.0 (303.0, 742.0)	0.1517	384.0 (181.0, 620.5)	<.0001
Baseline CD4 category	High (>500 cells/µL)	3242 (41.2%)	3820 (39.2%)	**<.0001**	538 (33.6%)	**<.0001**	950 (27.3%)	**<.0001**
	Moderate (>350 to <=500 cells/µL)	1412 (18.0%)	1669 (17.1%)	**.**	189 (11.8%)	**.**	475 (13.7%)	**.**
	Moderate Low (>200 to <=350 cells/µL)	1055 (13.4%)	1311 (13.5%)	**.**	173 (10.8%)	**.**	477 (13.7%)	**.**
	Low (>50 to <=200 cells/µL)	671 (8.5%)	769 (7.9%)	**.**	109 (6.8%)	**.**	424 (12.2%)	**.**
	Very low (<=50 cells/µL)	293 (3.7%)	319 (3.3%)	**.**	44 (2.8%)	**.**	278 (8.0%)	**.**
	Missing baseline CD4	1187 (15.1%)	1850 (19.0%)	**.**	547 (34.2%)	**.**	873 (25.1%)	**.**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 6. Baseline Comorbidities of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Any Comorbidity at baseline	Any comorbidity	5805 (73.9%)	6455 (66.3%)	**<.0001**	1267 (79.2%)	**<.0001**	2527 (72.7%)	0.1903
Cardiovascular Disease Condition	Any cardiovascular disease	576 (7.3%)	460 (4.7%)	**<.0001**	173 (10.8%)	**<.0001**	224 (6.4%)	0.0894
	Arrhythmia	180 (2.3%)	155 (1.6%)	**0.0008**	36 (2.3%)	0.9221	60 (1.7%)	0.0542
	Myocardial Infarction	52 (0.7%)	31 (0.3%)	**0.0010**	16 (1.0%)	0.1441	17 (0.5%)	0.2758
	Angina	27 (0.3%)	11 (0.1%)	**0.0015**	4 (0.3%)	0.8095	11 (0.3%)	1.0000
	Other/Unspecified CHD	299 (3.8%)	217 (2.2%)	**<.0001**	103 (6.4%)	**<.0001**	119 (3.4%)	0.3201
	Occlusion/stenosis of precerebral arteries	10 (0.1%)	5 (0.1%)	0.1178	2 (0.1%)	1.0000	5 (0.1%)	0.7850
	Stroke	69 (0.9%)	57 (0.6%)	0.0221	29 (1.8%)	**0.0008**	30 (0.9%)	0.9367
	Transient Ischemic Attack	15 (0.2%)	13 (0.1%)	0.3492	3 (0.2%)	1.0000	4 (0.1%)	0.4609
	Other CBV	115 (1.5%)	99 (1.0%)	**0.0072**	38 (2.4%)	0.0084	49 (1.4%)	0.8248
	Peripheral Arterial Disease	51 (0.6%)	26 (0.3%)	**0.0001**	12 (0.8%)	0.6502	15 (0.4%)	0.1605
	Abdominal Aortic Aneurysm	3 (0.0%)	3 (0.0%)	1.0000	1 (0.1%)	0.5235	0 (0.0%)	0.5577
Invasive Cancer	Any invasive cancer	425 (5.4%)	369 (3.8%)	**<.0001**	106 (6.6%)	0.0537	189 (5.4%)	0.9505
Endocrine Disorders	Any endocrine disorder	2237 (28.5%)	2140 (22.0%)	**<.0001**	513 (32.1%)	**0.0038**	781 (22.5%)	**<.0001**
	Diabetes Mellitus	558 (7.1%)	480 (4.9%)	**<.0001**	196 (12.3%)	**<.0001**	247 (7.1%)	0.9930
	Hyperlipidemia	1895 (24.1%)	1804 (18.5%)	**<.0001**	381 (23.8%)	0.8001	618 (17.8%)	**<.0001**
	Hyperthyroidism	31 (0.4%)	33 (0.3%)	0.6148	5 (0.3%)	0.8239	9 (0.3%)	0.3056
	Hypothyroidism	168 (2.1%)	163 (1.7%)	0.0244	64 (4.0%)	**<.0001**	53 (1.5%)	0.0295
	Thyroiditis	3 (0.0%)	2 (0.0%)	0.6619	0 (0.0%)	1.0000	2 (0.1%)	0.6457
Mental Health Conditions	Any mental health condition	2064 (26.3%)	2147 (22.0%)	**<.0001**	392 (24.5%)	0.1434	739 (21.3%)	**<.0001**
	Anxiety Disorders	1287 (16.4%)	1457 (15.0%)	**0.0103**	227 (14.2%)	0.0297	412 (11.8%)	**<.0001**
	Bipolar or Manic Disorders	358 (4.6%)	371 (3.8%)	**0.0137**	81 (5.1%)	0.3788	178 (5.1%)	0.1915
	Major Depressive Disorder	699 (8.9%)	554 (5.7%)	**<.0001**	116 (7.3%)	0.0327	208 (6.0%)	**<.0001**
	Schizophrenic Disorder	126 (1.6%)	99 (1.0%)	**0.0006**	18 (1.1%)	0.1546	55 (1.6%)	0.9337
	Dementia	28 (0.4%)	23 (0.2%)	0.1408	7 (0.4%)	0.6255	8 (0.2%)	0.2709
	Suicidality	29 (0.4%)	27 (0.3%)	0.2854	5 (0.3%)	1.0000	8 (0.2%)	0.2853
Liver Diseases	Any liver disease	1186 (15.1%)	1022 (10.5%)	**<.0001**	312 (19.5%)	**<.0001**	572 (16.5%)	0.0647
	Hepatitis B	392 (5.0%)	429 (4.4%)	0.0688	95 (5.9%)	0.1169	246 (7.1%)	**<.0001**

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
	Hepatitis C	747 (9.5%)	519 (5.3%)	**<.0001**	208 (13.0%)	**<.0001**	327 (9.4%)	0.8680
	Other chronic liver disease	220 (2.8%)	194 (2.0%)	**0.0004**	52 (3.3%)	0.3251	72 (2.1%)	0.0240
Bone Conditions	Any bone condition	166 (2.1%)	109 (1.1%)	**<.0001**	25 (1.6%)	0.1543	36 (1.0%)	<.0001
Peripheral Neuropathy	Any peripheral neuropathy	534 (6.8%)	416 (4.3%)	**<.0001**	150 (9.4%)	**0.0003**	225 (6.5%)	0.5260
Renal Disease	Renal Impairment	3242 (41.2%)	3463 (35.6%)	**<.0001**	655 (40.9%)	0.8188	1282 (36.9%)	**<.0001**
	Moderate/Severe CKD	263 (3.3%)	121 (1.2%)	**<.0001**	56 (3.5%)	0.7558	47 (1.4%)	**<.0001**
	End Stage Renal Disease	78 (1.0%)	149 (1.5%)	**0.0017**	19 (1.2%)	0.4800	35 (1.0%)	0.9439
Hypertension	Any hypertension	1865 (23.7%)	1843 (18.9%)	**<.0001**	514 (32.1%)	**<.0001**	789 (22.7%)	0.2298
Rheumatoid Arthritis	Any rheumatoid arthritis	30 (0.4%)	27 (0.3%)	0.2255	8 (0.5%)	0.4952	9 (0.3%)	0.3030
Substance Abuse	Any substance abuse	1236 (15.7%)	1219 (12.5%)	**<.0001**	160 (10.0%)	**<.0001**	549 (15.8%)	0.9309
	Alcohol Dependence	278 (3.5%)	276 (2.8%)	**0.0080**	39 (2.4%)	0.0259	121 (3.5%)	0.8795
	Drug Abuse	1192 (15.2%)	1176 (12.1%)	**<.0001**	152 (9.5%)	**<.0001**	529 (15.2%)	0.9467

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 7. Baseline Concomitant Non-ART Medications of Patients Initiating with DTG, EVG, RAL, & DRV-containing regimens

	DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Antibiotics	1041 (13.2%)	1158 (11.9%)	**0.0070**	**195 (12.2%)**	0.2529	576 (16.6%)	**<.0001**
Direct Acting Antivirals (DAAs)	48 (0.6%)	18 (0.2%)	**<.0001**	**8 (0.5%)**	0.7219	4 (0.1%)	**0.0001**
Lipid lowering agents	1119 (14.2%)	918 (9.4%)	**<.0001**	**305 (19.1%)**	**<.0001**	371 (10.7%)	**<.0001**
Non-steroidal Anti-inflammatory Agents (NSAIDS)	517 (6.6%)	477 (4.9%)	**<.0001**	**82 (5.1%)**	0.0296	221 (6.4%)	0.6593
Antidepressants	1336 (17.0%)	1254 (12.9%)	**<.0001**	**372 (23.3%)**	**<.0001**	577 (16.6%)	0.5976
Anxiolytics/Hypnotics/Sedatives	875 (11.1%)	866 (8.9%)	**<.0001**	**275 (17.2%)**	**<.0001**	302 (8.7%)	**<.0001**
Anti-diabetics	359 (4.6%)	277 (2.8%)	**<.0001**	**146 (9.1%)**	**<.0001**	162 (4.7%)	0.8296
Immune Modulators	588 (7.5%)	559 (5.7%)	**<.0001**	**83 (5.2%)**	**0.0011**	218 (6.3%)	0.0207

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

3.3. Assessment of Disorders

Table 8. Body Fat Redistribution/Accumulation in Patients Taking DTG, EVG, RAL, & DRV Regimens*

	DTG N= 7,860	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
Any history, n (%)	92 (1.2%)	75 (0.8%)	**0.0065**	37 (2.3%)	**0.0003**	29 (0.8%)	0.1079
Any prevalent event, n (%)	77 (1.0%)	55 (0.6%)	**0.0015**	22 (1.4%)	0.1566	29 (0.8%)	0.4576
Days to prevalent event, median (IQR)	210.0 (47.0, 526.0)	234.0 (104.0, 485.0)	0.6745	141.0 (57.0, 403.0)	0.6986	209.0 (85.0, 553.0)	0.4212
Prevalent event with D/C†, n (%)	4 (0.1%)	1 (0.0%)	0.1797	1 (0.1%)	1.0000	4 (0.1%)	0.2597
Days to prevalent event with D/C, median (IQR)	274.0 (107.5, 572.0)	229.0 (229.0, 229.0)	1.0000	62.0 (62.0, 62.0)	0.7237	347.0 (195.5, 547.0)	0.8852
Any incident event, n (%)	53 (0.7%)	47 (0.5%)	0.0927	15 (0.9%)	0.2560	25 (0.7%)	0.7906
Days to incident event, median (IQR)	223.0 (58.0, 790.0)	247.0 (113.0, 485.0)	0.7612	220.0 (57.0, 403.0)	0.7281	306.0 (91.0, 637.0)	0.5102
Incident event with D/C, n (%)	3 (0.0%)	1 (0.0%)	0.3307	0 (0.0%)	1.0000	3 (0.1%)	0.3791
Days to incident event with D/C, median (IQR)	210.0 (5.0, 338.0)	229.0 (229.0, 229.0)	1.0000		.	388.0 (306.0, 706.0)	0.1904

* Body Fat Redistribution/Accumulation defined as a diagnosis of “lipohypertrophy”, “lipoaccumulation”, “hyperadiposity”, “lipoatrophy”, or “lipodystrophy”
† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of an event
Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 9: Pancreatic Disorders in Patients Taking DTG, EVG, RAL, & DRV Regimens

		DTG N= 7,860	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
				*Overall Pancreatic Disorders**				
Any Pancreatic Disorders	Any history, n (%)	36 (0.5%)	23 (0.2%)	**0.0125**	13 (0.8%)	0.0838	5 (0.1%)	**0.0099**
	Any prevalent event, n (%)	35 (0.4%)	36 (0.4%)	0.4315	11 (0.7%)	0.2043	9 (0.3%)	0.1409
	Prevalent event with D/C†, n (%)	4 (0.1%)	0 (0.0%)	0.0398	0 (0.0%)	1.0000	2 (0.1%)	1.0000
	Any incident event, n (%)	32 (0.4%)	33 (0.3%)	0.4581	10 (0.6%)	0.2321	9 (0.3%)	0.2252
	Incident event with D/C, n (%)	4 (0.1%)	0 (0.0%)	0.0398	0 (0.0%)	1.0000	2 (0.1%)	1.0000
				Specific Pancreatic Disorders				
Pancreatitis	Any history, n (%)	28 (0.4%)	16 (0.2%)	**0.0144**	12 (0.8%)	0.0342	4 (0.1%)	0.0325
	Prevalent event, n (%)	26 (0.3%)	17 (0.2%)	0.0369	10 (0.6%)	0.0815	6 (0.2%)	0.1431
	Prevalent event with D/C, n (%)	3 (0.0%)	0 (0.0%)	0.0891	0 (0.0%)	1.0000	2 (0.1%)	0.6457
	Incident event, n (%)	24 (0.3%)	15 (0.2%)	0.0338	9 (0.6%)	0.1118	6 (0.2%)	0.2044
	Incident event with D/C, n (%)	3 (0.0%)	0 (0.0%)	0.0891	0 (0.0%)	1.0000	2 (0.1%)	0.6457
Pancreatic Adverse Elevation	Any history, n (%)	10 (0.1%)	9 (0.1%)	0.4983	2 (0.1%)	1.0000	1 (0.0%)	0.1902
	Any prevalent event, n (%)	11 (0.1%)	22 (0.2%)	0.2217	1 (0.1%)	0.7038	3 (0.1%)	0.5714
	Prevalent event with D/C, n (%)	2 (0.0%)	0 (0.0%)	0.1995	0 (0.0%)	1.0000	0 (0.0%)	1.0000
	Any incident event, n (%)	10 (0.1%)	21 (0.2%)	0.2059	1 (0.1%)	0.7029	3 (0.1%)	0.7657
	Incident event with D/C, n (%)	2 (0.0%)	0 (0.0%)	0.1995	0 (0.0%)	1.0000	0 (0.0%)	1.0000

* Pancreatic Disorders defined as (1) Pancreatitis (diagnosis of "pancreatitis") or (2) Pancreatic Adverse Elevations (lipase >3X ULN)

† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of an event

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 10. Musculoskeletal Disorders in Patients Taking DTG, EVG, RAL, & DRV Regimens

		DTG N= 7,860	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
				*Overall Musculoskeletal Disorders**				
Any Musculoskeletal Disorders	Any history, n (%)	6 (0.1%)	8 (0.1%)	1.0000	2 (0.1%)	0.6300	1 (0.0%)	0.6835
	Any prevalent event, n (%)	9 (0.1%)	8 (0.1%)	0.6269	3 (0.2%)	0.4394	1 (0.0%)	0.3009
	Prevalent event with D/C†, n (%)	2 (0.0%)	0 (0.0%)	0.1995	0 (0.0%)	1.0000	0 (0.0%)	1.0000
	Any incident event, n (%)	9 (0.1%)	7 (0.1%)	0.4521	3 (0.2%)	0.4394	1 (0.0%)	0.3009
	Incident event with D/C, n (%)	2 (0.0%)	0 (0.0%)	0.1995	0 (0.0%)	1.0000	0 (0.0%)	1.0000
				Specific Musculoskeletal Disorders				
Rhabdomyolysis	Any history, n (%)	1 (0.0%)	3 (0.0%)	0.6335	1 (0.1%)	0.3097	1 (0.0%)	0.5193
	Prevalent event, n (%)	3 (0.0%)	6 (0.1%)	0.7398	1 (0.1%)	0.5235	1 (0.0%)	1.0000
	Prevalent event with D/C, n (%)	0	0	.	0	.	0	.
	Incident event, n (%)	3 (0.0%)	5 (0.1%)	0.7388	1 (0.1%)	0.5235	1 (0.0%)	1.0000
	Incident event with D/C, n (%)	0	0	.	0	.	0	.
Musculoskeletal Adverse Elevation	Any history, n (%)	5 (0.1%)	6 (0.1%)	1.0000	1 (0.1%)	1.0000	0 (0.0%)	0.3321
	Any prevalent event, n (%)	6 (0.1%)	2 (0.0%)	0.1508	2 (0.1%)	0.6300	0 (0.0%)	0.1869
	Prevalent event with D/C, n (%)	2 (0.0%)	0 (0.0%)	0.1995	0 (0.0%)	1.0000	0 (0.0%)	1.0000
	Any incident event, n (%)	6 (0.1%)	2 (0.0%)	0.1508	2 (0.1%)	0.6300	0 (0.0%)	0.1869
	Incident event with D/C, n (%)	2 (0.0%)	0 (0.0%)	0.1995	0 (0.0%)	1.0000	0 (0.0%)	1.0000

* Musculoskeletal Disorders defined as (1) Rhabdomyolysis (diagnosis of "Rhabdomyolysis ") or (2) Musculoskeletal Adverse Elevations (CPK ≥10X ULN)
† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of an event
Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 11. IRIS in Patients Taking DTG, EVG, RAL, & DRV Regimens*

	DTG N= 7,860	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
Any history, n (%)	1 (0.0%)	0 (0.0%)	0.4466	0 (0.0%)	1.0000	0 (0.0%)	1.0000
Any prevalent event, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	1 (0.0%)	0.3067
Prevalent event with D/C†, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	0 (0.0%)	.
Any incident event, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	1 (0.0%)	0.3067
Incident event with D/C, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	0 (0.0%)	.

* IRIS defined as a diagnosis of "Immune Reconstitution Inflammatory Syndrome" (IRIS), "Immune Restoration Disease" (IRD), "Immune Reconstitution Syndrome" (IRS), or "Paradoxical Reactions"
† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of an event
Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 12. Severe Systemic Rash in Patients Taking DTG, EVG, RAL, & DRV Regimens*

	DTG N= 7,860	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
Any incident event, n (%)	1 (0.0%)	0 (0.0%)	0.4466	0 (0.0%)	1.0000	1 (0.0%)	0.5193
Incident event with D/C, n (%)	1 (0.0%)	0 (0.0%)	0.4466	0 (0.0%)	1.0000	0 (0.0%)	1.0000

* Severe Systemic Rash defined as a diagnosis of "Blistering rash", "Open skin ulcers", "Serious rash", "Severe rash", "Systemic rash", "Stevens-Johnson syndrome", or "Toxic Epidermal Necrolysis (TEN)"
† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of an event
Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

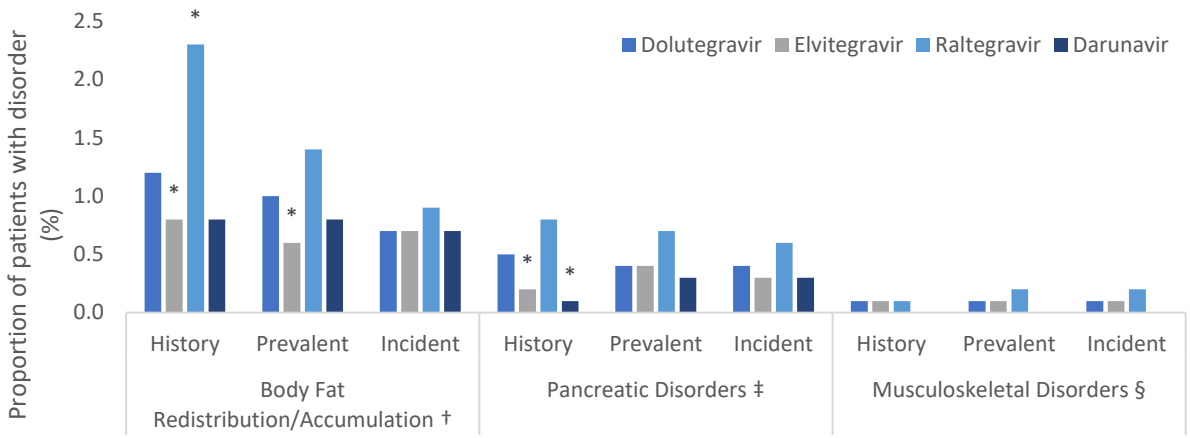
Table 13. Hypersensitivity Reaction in Patients Taking DTG, EVG, RAL, & DRV Regimens

		DTG N= 7,860	*EVG N= 9,738*	*DTG vs. EVG p-value*	*RAL N= 1,600*	*DTG vs. RAL p-value*	*DRV N= 3,477*	*DTG vs. DRV p-value*
ABC use	Any HSR diagnosis, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	1 (0.0%)	0.3067
	HSR diagnosis with D/C†, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	0 (0.0%)	.
No ABC use	Any HSR diagnosis, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	1 (0.0%)	0.3067
	HSR diagnosis with D/C, n (%)	0 (0.0%)	2 (0.0%)	0.5057	0 (0.0%)	.	0 (0.0%)	.

* Hypersensitivity reaction (HSR) defined as a diagnosis of hypersensitivity reaction", "anaphylaxis", "anaphylactic shock", or "immunologic reaction"
† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of an event
Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 14. Dofetilide Exposure

	Total Number of Patients	*Patients with any Dofetilide use*
OPERA population	855,495	13
HIV+ OPERA population	84,079	5
Comprehensive Safety Study population	22,675	0



* P-value for the comparison with DTG <0.017
† Body Fat Redistribution/Accumulation: diagnosis of "lipohypertrophy", "lipoaccumulation", "hyperadiposity", "lipoatrophy", or "lipodystrophy"
‡ Pancreatic Disorders: diagnosis of "pancreatitis" or pancreatic adverse elevation (lipase >3X ULN)
§ Musculoskeletal Disorders: diagnosis of "Rhabdomyolysis" or musculoskeletal adverse elevations (CPK ≥10X ULN)

Figure 1. Proportion of Patients Taking DTG, EVG, RAL, & DRV Regimens with history, prevalent or incident rare disorders

4. Summary of Findings

*Out of 22,675 HIV-infected patients initiating a core agent of interest between August 1st, 2013 and December 31st, 2016 (Table 1), 7,860 (35%) initiated DTG, 89,738 (43%) initiated EVG, 1,600 (7%) initiated RAL and 3,477 (15%) initiated DRV (**Error! Reference source not found.**). Dofetilide use was rare: only 13 patients received a prescription in the OPERA cohort, including 5 patients with HIV; none were included in the Comprehensive Safety Study population (Table 14). IRIS (Table 11), severe systemic rash (Table 12) and HSR (Table 13) occurred in no more than 2 patients per core agent group, with no difference detected between groups. Body fat redistribution (Table 8), pancreatic disorders (Table 9) and musculoskeletal disorders (*

Table 10) were also rare, occurring in no more than 2.3 % of patients (Figure 1).

4.1. Elvitegravir vs. Dolutegravir

At baseline, EVG users were younger than DTG users. They were also more likely to be male or receive care in the South, but they were less likely to be MSM or to benefit from ADAP or Ryan White programs (Table 3). EVG users had a shorter average follow-up time (Table 4). There was no difference in the proportion of ART naïve patients, average viral load or average CD4 cell count at baseline (Table 5).

EVG users were healthier than DTG users, with lower average VACS scores (Table 4). Fewer EVG users had comorbidities at baseline. Liver diseases, including hepatitis C, were least frequent in the EVG group (Table 6)Table 6. All the medications assessed were used less frequently among EVG than DTG users (**Error! Reference source not found.**), including lipid lowering agents, which are known to elevate LFTs.

This is likely a result of the boosting agent in EVG-containing regimens which impacts the pharmacokinetics of other medications that are metabolized through the liver.

EVG users were less likely than DTG users to have a history or prevalent body fat redistribution/accumulation, although no difference was detected in incident body fat redistribution/accumulation (Table 8). EVG were less likely than DTG users to have a history of any pancreatic disorders or pancreatitis, but not pancreatic adverse elevation. No difference was detected for prevalence or incidence of any of the pancreatic disorders assessed (Table 9). There was no difference between EVG and DTG users in terms of any musculoskeletal disorders, rhabdomyolysis or musculoskeletal adverse elevations (

Table 10).

4.2. Raltegravir vs. Dolutegravir

RAL users were older, less likely to be male, African American or Hispanic, and less likely to be MSM or to benefit from ADAP or Ryan White programs than DTG users. RAL users were however more likely to receive care in the South (Table 3). They also had a shorter average follow-up time (Table 4). Fewer RAL than DTG users were ART naïve. Baseline HIV viral load was lower among RAL users, but baseline CD4 cell count was not statistically different (Table 5).

At baseline, RAL users were sicker (higher average VACS score, Table 4), and were more likely to have comorbidities than DTG users (Table 6). Liver diseases, including hepatitis C, were more frequent in the RAL groups than the DTG group (Table 6). RAL users were prescribed lipid lowering agents more frequently than DTG users (**Error! Reference source not found.**).

While RAL users were more likely than DTG users to have a history of any body fat redistribution/accumulation, their likelihood of any prevalent or incident events was not different (Table 8). No difference was detected between RAL and DTG users in terms of history, prevalence or incidence of any pancreatic disorders, pancreatitis or pancreatic adverse elevation (Table 9). Finally, no difference was detected between RAL and EVG in the history, prevalence and incidence of any musculoskeletal disorders, rhabdomyolysis or musculoskeletal adverse elevation (

Table 10).

4.3. Darunavir vs. Dolutegravir

Compared to DTG users, DRV users were older and less likely to be male, Hispanic or MSM, to have a history of syphilis or to benefit from ADAP or Ryan White programs. They were however more likely to be African American or receive care in the South (Table 3). DRV had a shorter average follow-up time than DTG users (Table 4). DRV users were less likely than DTG users to be ART-naïve. Baseline HIV viral load was higher among DRV, but baseline CD4 cell counts were not statistically different (Table 5).

DRV users were sicker than DTG users at baseline, with higher average VACS scores (Table 4). There was no difference in the proportion of DRV and DTG users with comorbidities at baseline. No differences in liver diseases overall were detected either, although DRV users were more likely than DTG users to have hepatitis B (Table 6). DRV users were less likely than DTG users to use a lipid-lowering agent (**Error! Reference source not found.**Table 7).

There was no difference in the proportion of DRV and DTG users with a history, prevalent or incident body fat redistribution/accumulation (Table 8). A history of any pancreatic disorder occurred less frequently among DRV than DTG users, but there was no difference in prevalent and incidence events. No difference in history, prevalence or incidence of specific pancreatic disorders (pancreatitis or pancreatic adverse elevation) was detected (Table 9). The proportion of DRV users with a history, prevalent or incident musculoskeletal disorder (any disorder, rhabdomyolysis or musculoskeletal adverse elevation) was not different from the proportion of DTG users experiencing these events (

Table 10).

5. Conclusions

All events assessed in this report were rare across all core agent groups, occurring at most in 2.3% of patients, but often to as few as 0 or 1 patient per group. Patients initiating DTG, EVG, RAL or DRV are different in many regards. Some of these differences could be the result of channeling sicker patients away from EVG and towards DTG and RAL.

Compared to DTG users, EVG users were younger and less likely to have existing liver disease, take lipid lowering agents, or have substantial comorbidities than DTG users. EVG users were also less likely than DTG users to have a history of body fat redistribution/accumulation or any pancreatic disorder. During follow-up, however, only the likelihood of prevalent body fat redistribution/accumulation was lower for EVG users than DTG users.

On the contrary, RAL users were older and were more likely to have liver diseases, take lipid lowering agents or have substantial comorbidities, compared to DTG users. RAL users only had a greater likelihood of body fat redistribution/accumulation history compared to DTG users.

There was no clear evidence of channeling in the case of DRV. DRV users were older and less likely to take lipid lowering agents than DTG users. DRV users were also sicker overall, although there was no difference in the likelihood of comorbidities at baseline. However, DRV users were less likely to have any history of any pancreatic disorders compare to DTG users.

While evidence of potential channeling was observed, body fat redistribution/accumulation, pancreatic disorders, musculoskeletal disorders, IRIS, severe systemic rash and HSR were too rare to detect statistically significant differences in their occurrence following different core agent initiation. They very low frequency observed however indicates that these rare outcomes are not a major safety concern of DTG, EVG, RAL and DRV.

6. References

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A Comprehensive Assessment of Adverse Events and Overall Safety Profile in HIV Positive Patients Treated with Dolutegravir as Compared to Other Integrase Strand Transfer Inhibitors or Darunavir:

Final Report – Hepatobiliary Outcomes

Data through October 31, 2017 only

January 15, 2018

Table of Content

1. Background and Rationale

Background: Clinical guidelines currently recommend the use of the integrase strand transfer inhibitors (INSTI) dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL), or the protease inhibitor (PI) darunavir (DRV) as the core agent in antiretroviral therapy (ART) regimens. Toxicity concerns with multi-agent regimens, and pharmacokinetic interactions with medications for co-morbidities suggest the need for a comprehensive safety evaluation of recommended core agents in a real-world setting. In clinical trials, DTG treatment-related adverse effects (determined by the investigator) were less frequent (1–3%) than comparator drugs. Most adverse events seen in trials of DTG were grade 1–2 (mild-to-moderate in severity), such as headache, diarrhea, nausea, or insomnia.[1-5] Low frequencies of liver chemistry elevations (LCE) were reported in randomized controlled trials for DTG (≤5% Grade 2 and ≤3% Grade 3-4 ALT, AST or bilirubin elevations),[6] EVG (≤3% Grade 3-4 ALT or AST elevations),[7,8] or RAL (≤11% Grade 2, ≤4% Grade 3 and ≤2% Grade 4 ALT, AST, alkaline phosphatase or bilirubin elevations).[9] Drug-induced hepatitis (e.g., acute hepatitis, cytolytic hepatitis) has been reported with DRV/ritonavir, although low frequencies of LCE were reported in randomized controlled trials (≤9% Grade 2, ≤4% Grade 3 and ≤1% Grade 4 ALT, AST, alkaline phosphatase or bilirubin elevations).[10]

Rationale: A comprehensive safety evaluation of DTG and other recommended core agents has not been performed in a real-world setting. As the use of INSTIs increases in various demographic populations and clinical situations, an understanding of the overall safety profile of the members of the class will provide additional information for clinicians as treatment strategies are designed.

Scope of report: This report is limited to hepatobiliary outcomes and will appear in its entirety in the full report of safety outcomes through December 31, 2017 when the data become available.

2. Methods

2.1. Study Design

Study population: The study population consisted of HIV-positive patients at least 13 years of age initiating a core agent of interest prescribed by an OPERA caregiver during the eligibility period (August 1, 2013 to October 31, 2016).

Baseline date: The baseline date was defined as the first date of one of the four core agents of interest ever prescribed to a patient

Observation period: The observation period began on August 1, 2013 (the month DTG was approved) with study participants identified through October 31, 2016 on data through October 31, 2017. Patients were observed from their baseline date until the first of the following censoring events: 1) discontinuation of the core agent of interest, 2) cessation of continuous clinical activity, 3) death or 4) study end (October 31, 2017). Patients failing to meet the continuous clinical activity requirement were censored 12 months after their last contact.

Continuous Clinical Activity: Patients with continuous clinical activity were those who had clinical contact at least once in 12 months. Clinical contact was defined as a telephone contact, visit, lab test, or consultation.

Core agent of interest: Core agents of interest consisted of dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL), or darunavir (DRV). A regimen was considered discontinued when the core agent of interest was discontinued for 45 days or more.

2.2. Hepatobiliary Outcomes Definitions

Hepatobiliary Disorders consisted of any of the following: (1) DILI, (2) moderate liver chemistry elevation (LCE), or (3) severe LCE, defined as:

1. DILI: diagnosis of DILI, drug-induced liver injury, or drug-induced hepatotoxicity
2. Moderate LCE (DAIDS Grade 2):
    - ALT ≥2.5 to <5x ULN,
    - AST ≥2.5 to <5x ULN
    - Alkaline phosphatase ≥2.5 to <5x ULN
    - Bilirubin ≥1.6 to <2.6x ULN
3. Severe LCE (DAIDS Grade 3-4):
    - ALT ≥5x ULN
    - AST ≥5x ULN
    - Alkaline phosphatase ≥5x ULN
    - Bilirubin ≥2.6x ULN

History of Hepatobiliary Disorders: defined as a diagnosis of DILI, moderate LCE, or severe LCE at baseline or up to 12 months before baseline.

History of Hepatobiliary Disorders or Advanced Liver Fibrosis: defined as a diagnosis of DILI, moderate LCE, severe LCE, or advanced liver fibrosis (i.e. Fib-4 Index >3.25) at baseline or up to 12 months before baseline.

Prevalent Hepatobiliary Disorders: defined as a diagnosis of DILI, moderate LCE, severe LCE, or advanced fibrosis that occurred after baseline, regardless of whether the patient had a history of hepatobiliary disorders or advanced liver fibrosis.

Incident Hepatobiliary Disorders: defined as only a new diagnosis of DILI, moderate LCE, severe LCE, or advanced fibrosis after baseline, excluding patients who had any history of hepatobiliary disorders or advanced liver fibrosis at baseline. Therefore, incident hepatobiliary disorders are a subset of prevalent hepatobiliary disorders. The incidence of any of the disorders excluded patients with a history of any hepatobiliary disorder or liver fibrosis (not just the disorder in question) because any one of these events put a patient at very high risk for future hepatobiliary events and should not be considered as incident.

Discontinuation (D/C): defined as discontinuation of the core agent of interest within 21 days of the date of a hepatobiliary disorder. Time to hepatobiliary disorders with D/C was calculated based on the date of the hepatobiliary disorders.

2.3. Statistical Analyses

Descriptive analyses of baseline patient characteristics as well as hepatobiliary conditions at baseline and during follow-up were conducted to compare DTG to other core agents of interest. The Pearson's Chi-Square Test was used to calculate p-values for categorical variables and the Mann-Whitney Test was used to calculate p-values for continuous variables. Fischer Exact Test was used for cells with small numbers (counts of 5 or fewer).

To account for multiple comparisons between DTG and comparator core agents, the Sidak Correction was applied, resulting in an adjusted alpha level for significance of 0.017.

3. Results

3.1. Population Identification

Table 1. Identification of the Study Population

		Patients Included	*%*	*Patients Excluded*	*%*
1	OPERA patients who are HIV+	82,283	.	0	.
2	Patients with HIV-1 infection (excluding HIV-2 infection)	82,198	99.9	85	0.1
3	HIV+ patients prescribed ART	71,630	87.1	10,568	12.9
4	Patients prescribed a regimen of interest (containing DTG, EVG, RAL, or DRV)	46,349	64.7	25,281	35.3
5	Patients prescribed regimen of interest between 08/01/2013 and 10/31/2016	30,488	65.8	15,861	34.2
6	Patients who were 13 years of age or older at first ART regimen of interest	30,485	100.0	3	0.0
7	Patients prescribed a regimen of interest that did not include two or more third agents of interest	27,311	89.6	3,174	10.4
8	Patients whose first ART regimen of interest was not monotherapy	26,601	97.4	710	2.6
9	Patients whose first ART regimen of interest was not prior to date of HIV	26,394	99.2	207	0.8
10	Patients whose regimen of interest was their first experience with DTG, EVG, RAL, or DRV [Study population]	21,046	79.7	5,348	20.3

Table 2. Study Population by ART Core Agent of Interest and Regimen

Core agent of interest	*n(%)*	*Regimens*	*n(%)*
DTG-containing regimens	7,245 (34.4%)	DTG + TDF + FTC	1,452 (20.0%)
		DTG + TAF + FTC	121 (1.7%)
		DTG + ABC + 3TC	4,560 (62.9%)
		DTG + all other agents	1,112 (15.3%)
EVG-containing regimens	8,943 (42.5%)	EVG + r/c + TDF + FTC	5,823 (65.1%)
		EVG + r/c + TAF + FTC	2,452 (27.4%)
		EVG + r/c + all other agents	668 (7.5%)
RAL-containing regimens	1,531 (7.3%)	RAL + TDF + FTC	768 (50.2%)
		RAL + TAF + FTC	7 (0.5%)
		RAL + ABC + 3TC	122 (8.0%)
		RAL + all other agents	634 (41.4%)
DRV-containing regimens	3,327 (15.8%)	DRV + r/c + TDF + FTC	2,406 (72.3%)
		DRV + r/c + TAF + FTC	98 (2.9%)
		DRV + r/c + ABC + 3TC	303 (9.1%)
		DRV + r/c + all other agents	472 (14.2%)
		DRV + TDF + FTC	15 (0.5%)
		DRV + ABC + 3TC	6 (0.2%)
		DRV + all other agents	27 (0.8%)

3.2. Baseline Characteristics

Table 3. Baseline Demographic Characteristics of Patients Taking DTG, EVG, RAL, & DRV Regime

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Age	Median (IQR)	41.4 (29.9, 51.1)	**36.8 (28.0, 48.3)**	**<.0001**	**48.7 (39.7, 54.9)**	**<.0001**	**43.4 (33.0, 51.1)**	**<.0001**
	13-25	1043 (14.4%)	**1578 (17.6%)**	**<.0001**	**75 (4.9%)**	**<.0001**	**319 (9.6%)**	**<.0001**
	26-49	4168 (57.5%)	**5530 (61.8%)**	**.**	**773 (50.5%)**	**.**	**2068 (62.2%)**	**.**
	50+	2034 (28.1%)	**1835 (20.5%)**	**.**	**683 (44.6%)**	**.**	**940 (28.3%)**	**.**
Sex	Male	6150 (84.9%)	7720 (86.3%)	0.0292	**1222 (79.8%)**	**<.0001**	**2639 (79.3%)**	**<.0001**
	Female	1088 (15.0%)	1213 (13.6%)	.	**307 (20.1%)**	**.**	**687 (20.6%)**	**.**
	Unknown	7 (0.1%)	10 (0.1%)	.	**2 (0.1%)**	**.**	**1 (0.0%)**	**.**
Race	African American	2961 (40.9%)	3586 (40.1%)	0.3202	**554 (36.2%)**	**0.0007**	**1575 (47.3%)**	**<.0001**
	Not African American	4284 (59.1%)	5357 (59.9%)	.	**977 (63.8%)**	**.**	**1752 (52.7%)**	**.**
Ethnicity	Hispanic	1792 (24.7%)	2307 (25.8%)	0.1222	**267 (17.4%)**	**<.0001**	**691 (20.8%)**	**<.0001**
	Not Hispanic	5453 (75.3%)	6636 (74.2%)	.	**1264 (82.6%)**	**.**	**2636 (79.2%)**	**.**
Marital Status	Single	5066 (69.9%)	6123 (68.5%)	0.1666	**926 (60.5%)**	**<.0001**	**2190 (65.8%)**	**0.0001**
	Married	423 (5.8%)	559 (6.3%)	.	**140 (9.1%)**	**.**	**252 (7.6%)**	**.**
	Domestic partnership	244 (3.4%)	273 (3.1%)	.	**51 (3.3%)**	**.**	**114 (3.4%)**	**.**
	Widowed	48 (0.7%)	54 (0.6%)	.	**21 (1.4%)**	**.**	**35 (1.1%)**	**.**
	Separated/divorced	187 (2.6%)	238 (2.7%)	.	**59 (3.9%)**	**.**	**101 (3.0%)**	**.**
	Unknown	1277 (17.6%)	1696 (19.0%)	.	**334 (21.8%)**	**.**	**635 (19.1%)**	**.**
Risk of Infection	MSM	3757 (51.9%)	**4461 (49.9%)**	**0.0125**	**573 (37.4%)**	**<.0001**	**1375 (41.3%)**	**<.0001**
	Not MSM	3488 (48.1%)	**4482 (50.1%)**	**.**	**958 (62.6%)**	**.**	**1952 (58.7%)**	**.**
History of Syphilis	Yes	1997 (27.6%)	2591 (29.0%)	0.0480	**308 (20.1%)**	**<.0001**	**795 (23.9%)**	**<.0001**
Region	Northeast	630 (8.7%)	**715 (8.0%)**	**<.0001**	**155 (10.1%)**	**<.0001**	**238 (7.2%)**	**<.0001**
	South	3943 (54.4%)	**5510 (61.6%)**	**.**	**1014 (66.2%)**	**.**	**2065 (62.1%)**	**.**
	Midwest	118 (1.6%)	**213 (2.4%)**	**.**	**34 (2.2%)**	**.**	**51 (1.5%)**	**.**
	West	2554 (35.3%)	**2505 (28.0%)**	**.**	**328 (21.4%)**	**.**	**973 (29.2%)**	**.**
Payer	Medicaid	1844 (25.5%)	**1518 (17.0%)**	**<.0001**	353 (23.1%)	0.0493	852 (25.6%)	0.8638
	Medicare	645 (8.9%)	**523 (5.8%)**	**<.0001**	**286 (18.7%)**	**<.0001**	**431 (13.0%)**	**<.0001**
	Commercial Insurance	2493 (34.4%)	**3384 (37.8%)**	**<.0001**	543 (35.5%)	0.4295	**916 (27.5%)**	**<.0001**

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
	Cash	4409 (60.9%)	**5133 (57.4%)**	**<.0001**	925 (60.4%)	0.7499	**1882 (56.6%)**	**<.0001**
	ADAP/Ryan White	2590 (35.7%)	**2841 (31.8%)**	**<.0001**	**321 (21.0%)**	**<.0001**	**974 (29.3%)**	**<.0001**
	Other	34 (0.5%)	28 (0.3%)	0.1247	3 (0.2%)	0.1898	9 (0.3%)	0.1868
	No Payer info	751 (10.4%)	**1444 (16.1%)**	**<.0001**	**301 (19.7%)**	**<.0001**	**600 (18.0%)**	**<.0001**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 4. General Baseline Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Year of Study Initiation	2013	298 (4.1%)	**826 (9.2%)**	**<.0001**	**343 (22.4%)**	**<.0001**	**566 (17.0%)**	**<.0001**
	2014	1650 (22.8%)	**2144 (24.0%)**	**.**	**626 (40.9%)**	**.**	**1140 (34.3%)**	**.**
	2015	2563 (35.4%)	**2419 (27.0%)**	**.**	**348 (22.7%)**	**.**	**874 (26.3%)**	**.**
	2016	2734 (37.7%)	**3554 (39.7%)**	**.**	**214 (14.0%)**	**.**	**747 (22.5%)**	**.**
Time from first active date to index date	Median (IQR)	2.5 (0.5, 36.0)	**1.3 (0.2, 24.8)**	**<.0001**	**0.3 (0.0, 9.4)**	**<.0001**	**0.8 (0.0, 21.6)**	**<.0001**
Follow-up time between baseline and end of observation	Median (IQR)	17.8 (12.4, 26.9)	**16.7 (12.0, 25.9)**	**<.0001**	**14.4 (10.0, 26.0)**	**<.0001**	**15.5 (11.1, 25.5)**	**<.0001**
Pregnancy	Pregnancy	6 (0.1%)	8 (0.1%)	1.0000	3 (0.2%)	0.1968	**10 (0.3%)**	**0.0126**
VACS Index†	Median (IQR)	17.0 (7.0, 29.0)	**13.0 (7.0, 25.0)**	**<.0001**	**20.0 (10.0, 35.0)**	**<.0001**	**22.0 (12.0, 40.0)**	**<.0001**
VACS Index† category	0 to <15	2758 (38.1%)	**3592 (40.2%)**	**<.0001**	**358 (23.4%)**	**<.0001**	**792 (23.8%)**	**<.0001**
	>=15 to <30	1917 (26.5%)	**2026 (22.7%)**	**.**	**303 (19.8%)**	**.**	**771 (23.2%)**	**.**
	>=30 to <45	754 (10.4%)	**717 (8.0%)**	**.**	**137 (8.9%)**	**.**	**373 (11.2%)**	**.**
	>= 45	735 (10.1%)	**687 (7.7%)**	**.**	**169 (11.0%)**	**.**	**507 (15.2%)**	**.**
	Missing	1081 (14.9%)	**1921 (21.5%)**	**.**	**564 (36.8%)**	**.**	**884 (26.6%)**	**.**

† VACS Mortality Index: score created by summing pre-assigned points for age, HIV disease (CD4 count and HIV-1 RNA), and general indicators of organ system injury including hemoglobin, platelets, aspartate and alanine transaminase, creatinine, and viral hepatitis C infection. This score is used to estimate risk of all-cause mortality in the following 5 years. A higher score is associated with a higher risk of mortality.

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 5. Baseline HIV-Related Clinical Characteristics of Patients Initiating with DTG, EVG, RAL, & DRV Regimen

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
ART-naïve at index	ART-naïve	2449 (33.8%)	**3194 (35.7%)**	**0.0111**	**193 (12.6%)**	**<.0001**	**933 (28.0%)**	**<.0001**
	ART-experienced	4796 (66.2%)	**5749 (64.3%)**	**.**	**1338 (87.4%)**	**.**	**2394 (72.0%)**	**.**
Calendar year of ART initiation	Median (IQR)	2015 (2012, 2016)	**2014 (2013, 2016)**	**<.0001**	**2014 (2013, 2015)**	**<.0001**	**2014 (2013, 2015)**	**<.0001**
	Pre-2000	207 (2.9%)	**126 (1.4%)**	**<.0001**	**30 (2.0%)**	**<.0001**	**55 (1.7%)**	**<.0001**
	2000-2004	272 (3.8%)	**161 (1.8%)**	**.**	**34 (2.2%)**	**.**	**86 (2.6%)**	**.**
	2005-2009	597 (8.2%)	**507 (5.7%)**	**.**	**85 (5.6%)**	**.**	**192 (5.8%)**	**.**
	2010-2014	2539 (35.0%)	**3768 (42.1%)**	**.**	**916 (59.8%)**	**.**	**1690 (50.8%)**	**.**
	2015-present	3630 (50.1%)	**4381 (49.0%)**	**.**	**466 (30.4%)**	**.**	**1304 (39.2%)**	**.**
Number of previous ART regimens	Median (IQR)	1.0 (1.0, 2.0)	**1.0 (1.0, 2.0)**	**<.0001**	1.0 (1.0, 3.0)	0.0221	1.0 (1.0, 2.0)	0.4865
	ART-naïve	2449 (33.8%)	**3194 (35.7%)**	**<.0001**	**193 (12.6%)**	**<.0001**	**933 (28.0%)**	**<.0001**
	1-2 previous regimens	2518 (34.8%)	**2421 (27.1%)**	**.**	**271 (17.7%)**	**.**	**745 (22.4%)**	**.**
	3-4 previous regimens	391 (5.4%)	**286 (3.2%)**	**.**	**40 (2.6%)**	**.**	**102 (3.1%)**	**.**
	5 or more previous regimens	259 (3.6%)	**195 (2.2%)**	**.**	**55 (3.6%)**	**.**	**89 (2.7%)**	**.**
	Missing previous regimens	1628 (22.5%)	**2847 (31.8%)**	**.**	**972 (63.5%)**	**.**	**1458 (43.8%)**	**.**
Previous ART exposure	Naive	2449 (33.8%)	**3194 (35.7%)**	**0.0111**	**193 (12.6%)**	**<.0001**	**933 (28.0%)**	**<.0001**
	NNRTI	2016 (27.8%)	**2124 (23.8%)**	**<.0001**	**194 (12.7%)**	**<.0001**	**427 (12.8%)**	**<.0001**
	PI	1483 (20.5%)	**926 (10.4%)**	**<.0001**	**195 (12.7%)**	**<.0001**	**568 (17.1%)**	**<.0001**
	INSTI	0 (0.0%)	1 (0.0%)	1.0000	0 (0.0%)	.	1 (0.0%)	0.3147
	NRTI	3139 (43.3%)	**2798 (31.3%)**	**<.0001**	**346 (22.6%)**	**<.0001**	**897 (27.0%)**	**<.0001**
	Other	30 (0.4%)	**17 (0.2%)**	**0.0084**	9 (0.6%)	0.3530	7 (0.2%)	0.0996
	Experienced-ART specifics missing	1628 (22.5%)	**2847 (31.8%)**	**<.0001**	**972 (63.5%)**	**<.0001**	**1458 (43.8%)**	**<.0001**
Backbone of Regimen of Interest	TDF + FTC	1452 (20.0%)	**5823 (65.1%)**	**<.0001**	**768 (50.2%)**	**<.0001**	**2421 (72.8%)**	**<.0001**
	TAF + FTC	121 (1.7%)	**2452 (27.4%)**	**.**	**7 (0.5%)**	**.**	**98 (2.9%)**	**.**

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
	ABC + 3TC	4560 (62.9%)	**0 (0.0%)**	**.**	**122 (8.0%)**	**.**	**309 (9.3%)**	**.**
	All others	1112 (15.3%)	**668 (7.5%)**	**.**	**634 (41.4%)**	**.**	**499 (15.0%)**	**.**
AIDS-defining Illness	AIDS	845 (11.7%)	**824 (9.2%)**	**<.0001**	202 (13.2%)	0.0932	**449 (13.5%)**	**0.0076**
	No AIDS	6400 (88.3%)	**8119 (90.8%)**	**.**	1329 (86.8%)	.	**2878 (86.5%)**	**.**
Baseline viral load	Median (IQR)	500.0 (19.0, 40640.0)	**2090.0 (19.0, 45900.0)**	**0.0088**	**19.0 (19.0, 940.0)**	**<.0001**	**1100.0 (19.0, 52360.0)**	**<.0001**
Baseline Viral Load log10	Median (IQR)	2.7 (1.3, 4.6)	**3.4 (1.3, 4.7)**	**0.0033**	**1.3 (1.3, 3.0)**	**<.0001**	**3.1 (1.3, 4.7)**	**<.0001**
Baseline Viral Load category	Suppressed (<50 copies/mL)	2546 (35.1%)	**2820 (31.5%)**	**<.0001**	**591 (38.6%)**	**<.0001**	**870 (26.1%)**	**<.0001**
	Low (>=50 to <10,000 copies/mL)	1191 (16.4%)	**1389 (15.5%)**	**.**	**211 (13.8%)**	**.**	**622 (18.7%)**	**.**
	Moderate (>=10,000 to <100,000 copies/mL)	1587 (21.9%)	**1965 (22.0%)**	**.**	**133 (8.7%)**	**.**	**560 (16.8%)**	**.**
	High (>=100,000 copies/mL)	837 (11.6%)	**1017 (11.4%)**	**.**	**68 (4.4%)**	**.**	**439 (13.2%)**	**.**
	Missing baseline VL	1084 (15.0%)	**1752 (19.6%)**	**.**	**528 (34.5%)**	**.**	**836 (25.1%)**	**.**
Nadir CD4	Median (IQR)	396.0 (235.0, 579.0)	**410.0 (253.0, 594.0)**	**0.0002**	**435.5 (240.0, 658.0)**	**0.0001**	**313.0 (132.0, 529.0)**	**<.0001**
Baseline CD4	Median (IQR)	490.0 (308.5, 705.5)	487.0 (302.0, 694.0)	0.3688	511.0 (299.0, 739.0)	0.1972	**383.0 (178.0, 615.0)**	**<.0001**
	High (>500 cells/µL)	2990 (41.3%)	**3489 (39.0%)**	**<.0001**	**516 (33.7%)**	**<.0001**	**896 (26.9%)**	**<.0001**
	Moderate (>350 to <=500 cells/µL)	1312 (18.1%)	**1531 (17.1%)**	**.**	**181 (11.8%)**	**.**	**455 (13.7%)**	**.**
	Moderate Low (>200 to <=350 cells/µL)	978 (13.5%)	**1216 (13.6%)**	**.**	**168 (11.0%)**	**.**	**457 (13.7%)**	**.**
	Low (>50 to <=200 cells/µL)	633 (8.7%)	**718 (8.0%)**	**.**	**105 (6.9%)**	**.**	**407 (12.2%)**	**.**
	Very low (<=50 cells/µL)	267 (3.7%)	**294 (3.3%)**	**.**	**44 (2.9%)**	**.**	**272 (8.2%)**	**.**
	Missing baseline CD4	1065 (14.7%)	**1695 (19.0%)**	**.**	**517 (33.8%)**	**.**	**840 (25.2%)**	**.**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 6. Baseline Liver Chemistry Testing of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Any Liver Chemistry	All Normal	5056 (69.8%)	**6221 (69.6%)**	**<.0001**	**754 (49.2%)**	**<.0001**	**2047 (61.5%)**	**<.0001**
	Any Mild Elevation	901 (12.4%)	**926 (10.4%)**	**.**	**186 (12.1%)**	**.**	**346 (10.4%)**	**.**
	Any Moderate Elevation	382 (5.3%)	**304 (3.4%)**	**.**	**70 (4.6%)**	**.**	**142 (4.3%)**	**.**
	Any Severe Elevation	168 (2.3%)	**114 (1.3%)**	**.**	**22 (1.4%)**	**.**	**81 (2.4%)**	**.**
	All Missing	738 (10.2%)	**1378 (15.4%)**	**.**	**499 (32.6%)**	**.**	**711 (21.4%)**	**.**
ALT	Median (IQR)	24.0 (17.0, 36.0)	**23.0 (16.0, 34.0)**	**0.0164**	25.0 (17.0, 39.0)	0.0363	**22.0 (15.0, 34.0)**	**<.0001**
	Normal (<1.25x ULN)	5762 (79.5%)	**6765 (75.6%)**	**<.0001**	**872 (57.0%)**	**<.0001**	**2312 (69.5%)**	**<.0001**
	Mild Elevation (≥1.25 to <2.5x ULN)	550 (7.6%)	**596 (6.7%)**	**.**	**111 (7.3%)**	**.**	**203 (6.1%)**	**.**
	Moderate Elevation (≥2.5 to <5x ULN)	139 (1.9%)	**158 (1.8%)**	**.**	**39 (2.5%)**	**.**	**82 (2.5%)**	**.**
	Severe Elevation (≥5x ULN)	54 (0.7%)	**43 (0.5%)**	**.**	**10 (0.7%)**	**.**	**19 (0.6%)**	**.**
	Missing	740 (10.2%)	**1381 (15.4%)**	**.**	**499 (32.6%)**	**.**	**711 (21.4%)**	**.**
AST	Median (IQR)	24.0 (19.0, 33.0)	**24.0 (19.0, 31.0)**	**0.0037**	**25.0 (20.0, 36.0)**	**0.0003**	24.0 (19.0, 33.0)	0.7838
	Normal (<1.25x ULN)	5863 (80.9%)	**6914 (77.3%)**	**<.0001**	**887 (57.9%)**	**<.0001**	**2309 (69.4%)**	**<.0001**
	Mild Elevation (≥1.25 to <2.5x ULN)	460 (6.3%)	**484 (5.4%)**	**.**	**103 (6.7%)**	**.**	**222 (6.7%)**	**.**
	Moderate Elevation (≥2.5 to <5x ULN)	144 (2.0%)	**122 (1.4%)**	**.**	**32 (2.1%)**	**.**	**65 (2.0%)**	**.**
	Severe Elevation (≥5x ULN)	37 (0.5%)	**38 (0.4%)**	**.**	**9 (0.6%)**	**.**	**17 (0.5%)**	**.**
	Missing	741 (10.2%)	**1385 (15.5%)**	**.**	**500 (32.7%)**	**.**	**714 (21.5%)**	**.**
Alkaline Phosphatase	Median (IQR)	76.0 (64.0, 94.0)	76.0 (63.0, 93.0)	0.0367	78.0 (63.0, 99.0)	0.0496	**78.0 (65.0, 97.0)**	**0.0002**
	Normal (<1.25x ULN)	6171 (85.2%)	**7221 (80.7%)**	**<.0001**	**949 (62.0%)**	**<.0001**	**2448 (73.6%)**	**<.0001**
	Mild Elevation (≥1.25 to <2.5x ULN)	199 (2.7%)	**187 (2.1%)**	**.**	**59 (3.9%)**	**.**	**103 (3.1%)**	**.**
	Moderate Elevation (≥2.5 to <5x ULN)	22 (0.3%)	**19 (0.2%)**	**.**	**9 (0.6%)**	**.**	**8 (0.2%)**	**.**
	Severe Elevation (≥5x ULN)	9 (0.1%)	**5 (0.1%)**	**.**	**2 (0.1%)**	**.**	**5 (0.2%)**	**.**
	Missing	844 (11.6%)	**1511 (16.9%)**	**.**	**512 (33.4%)**	**.**	**763 (22.9%)**	**.**

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Bilirubin	Median (IQR)	0.4 (0.3, 0.6)	**0.4 (0.3, 0.6)**	**0.0038**	**0.4 (0.3, 0.6)**	**0.0030**	0.4 (0.3, 0.6)	0.7949
	Normal (<1.1x ULN)	5971 (82.4%)	**7161 (80.1%)**	**<.0001**	**956 (62.4%)**	**<.0001**	**2413 (72.5%)**	**<.0001**
	Mild Elevation (≥1.1 to <1.6x ULN)	201 (2.8%)	**142 (1.6%)**	**.**	**31 (2.0%)**	**.**	**57 (1.7%)**	**.**
	Moderate Elevation (≥1.6 to <2.6x ULN)	178 (2.5%)	**105 (1.2%)**	**.**	**22 (1.4%)**	**.**	**42 (1.3%)**	**.**
	Severe Elevation (≥2.6x ULN)	102 (1.4%)	**51 (0.6%)**	**.**	**10 (0.7%)**	**.**	**53 (1.6%)**	**.**
	Missing	793 (10.9%)	**1484 (16.6%)**	**.**	**512 (33.4%)**	**.**	**762 (22.9%)**	**.**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 7. Baseline Comorbidities of Patients Initiating with DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Any Comorbidity at baseline	Any comorbidity	5469 (75.5%)	**6000 (67.1%)**	**<.0001**	**1219 (79.6%)**	**0.0006**	**2428 (73.0%)**	**0.0059**
Cardiovascular Disease Condition	Any cardiovascular disease	526 (7.3%)	**410 (4.6%)**	**<.0001**	**162 (10.6%)**	**<.0001**	202 (6.1%)	0.0250
	Arrhythmia	170 (2.3%)	**141 (1.6%)**	**0.0004**	34 (2.2%)	0.7668	55 (1.7%)	0.0218
	Myocardial Infarction	43 (0.6%)	**25 (0.3%)**	**0.0021**	15 (1.0%)	0.0901	17 (0.5%)	0.5998
	Angina	23 (0.3%)	**10 (0.1%)**	**0.0046**	4 (0.3%)	1.0000	9 (0.3%)	0.8491
	Other/Unspecified CHD	271 (3.7%)	**194 (2.2%)**	**<.0001**	**95 (6.2%)**	**<.0001**	111 (3.3%)	0.3011
	Occlusion/stenosis of precerebral arteries	10 (0.1%)	5 (0.1%)	0.1181	2 (0.1%)	1.0000	3 (0.1%)	0.7661
	Stroke	61 (0.8%)	54 (0.6%)	0.0728	**28 (1.8%)**	**0.0005**	28 (0.8%)	0.9985
	Transient Ischemic Attack	13 (0.2%)	11 (0.1%)	0.4134	2 (0.1%)	1.0000	3 (0.1%)	0.4193
	Other CBV	95 (1.3%)	**81 (0.9%)**	**0.0134**	**36 (2.4%)**	**0.0023**	44 (1.3%)	0.9623
	Peripheral Arterial Disease	47 (0.6%)	**26 (0.3%)**	**0.0007**	12 (0.8%)	0.5568	**9 (0.3%)**	**0.0128**
	Abdominal Aortic Aneurysm	3 (0.0%)	1 (0.0%)	0.3313	1 (0.1%)	0.5356	0 (0.0%)	0.5566
Invasive Cancer	Any invasive cancer	404 (5.6%)	**336 (3.8%)**	**<.0001**	98 (6.4%)	0.2067	182 (5.5%)	0.8252

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
Endocrine Disorders	Any endocrine disorder	2091 (28.9%)	**1987 (22.2%)**	**<.0001**	486 (31.7%)	0.0244	**727 (21.9%)**	**<.0001**
	Diabetes Mellitus	521 (7.2%)	**440 (4.9%)**	**<.0001**	**188 (12.3%)**	**<.0001**	234 (7.0%)	0.7698
	Hyperlipidemia	1767 (24.4%)	**1674 (18.7%)**	**<.0001**	360 (23.5%)	0.4678	571 (17.2%)	<.0001
	Hyperthyroidism	31 (0.4%)	30 (0.3%)	0.3678	5 (0.3%)	0.8251	6 (0.2%)	0.0505
	Hypothyroidism	158 (2.2%)	**149 (1.7%)**	**0.0170**	**60 (3.9%)**	**<.0001**	**49 (1.5%)**	**0.0147**
	Thyroiditis	3 (0.0%)	2 (0.0%)	0.6622	0 (0.0%)	1.0000	2 (0.1%)	0.6529
Mental Health Conditions	Any mental health condition	1910 (26.4%)	**1950 (21.8%)**	**<.0001**	369 (24.1%)	0.0667	**673 (20.2%)**	**<.0001**
	Anxiety Disorders	1187 (16.4%)	**1327 (14.8%)**	**0.0070**	**207 (13.5%)**	**0.0054**	**365 (11.0%)**	**<.0001**
	Bipolar or Manic Disorders	330 (4.6%)	342 (3.8%)	0.0205	78 (5.1%)	0.3620	165 (5.0%)	0.3605
	Major Depressive Disorder	648 (8.9%)	**491 (5.5%)**	**<.0001**	115 (7.5%)	0.0706	**198 (6.0%)**	**<.0001**
	Schizophrenic Disorder	116 (1.6%)	**89 (1.0%)**	**0.0006**	17 (1.1%)	0.1533	52 (1.6%)	0.8842
	Dementia	26 (0.4%)	18 (0.2%)	0.0555	7 (0.5%)	0.5678	8 (0.2%)	0.3180
	Suicidality	29 (0.4%)	25 (0.3%)	0.2173	4 (0.3%)	0.6441	8 (0.2%)	0.2190
Liver Diseases	Any liver disease	1420 (19.6%)	**1187 (13.3%)**	**<.0001**	338 (22.1%)	0.0278	655 (19.7%)	0.9160
	Hepatitis B	732 (10.1%)	**687 (7.7%)**	**<.0001**	141 (9.2%)	0.2884	369 (11.1%)	0.1226
	Hepatitis C	690 (9.5%)	**455 (5.1%)**	**<.0001**	**197 (12.9%)**	**<.0001**	309 (9.3%)	0.6999
	Other chronic liver disease	203 (2.8%)	**178 (2.0%)**	**0.0007**	51 (3.3%)	0.2617	70 (2.1%)	0.0356
Bone Conditions	Any bone condition	162 (2.2%)	**103 (1.2%)**	**<.0001**	22 (1.4%)	0.0474	**32 (1.0%)**	**<.0001**
Peripheral Neuropathy	Any peripheral neuropathy	499 (6.9%)	**366 (4.1%)**	**<.0001**	**143 (9.3%)**	**0.0008**	198 (6.0%)	0.0716
Renal Disease	Renal Impairment	3026 (41.8%)	**3206 (35.8%)**	**<.0001**	630 (41.1%)	0.6563	**1232 (37.0%)**	**<.0001**
	Moderate/Severe CKD	253 (3.5%)	**116 (1.3%)**	**<.0001**	53 (3.5%)	0.9532	**45 (1.4%)**	**<.0001**
	End Stage Renal Disease	72 (1.0%)	**141 (1.6%)**	**0.0012**	19 (1.2%)	0.3856	38 (1.1%)	0.4850
Hypertension	Any hypertension	1705 (23.5%)	**1621 (18.1%)**	**<.0001**	**476 (31.1%)**	**<.0001**	721 (21.7%)	0.0345
Rheumatoid Arthritis	Any rheumatoid arthritis	26 (0.4%)	27 (0.3%)	0.5282	8 (0.5%)	0.3489	9 (0.3%)	0.4627
Substance Abuse	Any substance abuse	1133 (15.6%)	**1100 (12.3%)**	**<.0001**	**154 (10.1%)**	**<.0001**	506 (15.2%)	0.5710
	Alcohol Dependence	260 (3.6%)	**239 (2.7%)**	**0.0008**	38 (2.5%)	0.0298	111 (3.3%)	0.5126
	Drug Abuse	1094 (15.1%)	**1060 (11.9%)**	**<.0001**	**146 (9.5%)**	**<.0001**	489 (14.7%)	0.5905

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 8. Baseline Concomitant Non-ART Medications of Patients Initiating with DTG, EVG, RAL, & DRV-containing regimens

	DTG	*EVG*	*DTG vs. EVG*	*RAL*	*DTG vs. RAL*	*DRV*	*DTG vs. DRV*
	N= 7,245	*N= 8,943*	*p-value*	*N= 1,531*	*p-value*	*N= 3,327*	*p-value*
Antibiotics	974 (13.4%)	**1076 (12.0%)**	**0.0072**	191 (12.5%)	0.3103	**555 (16.7%)**	**<.0001**
Direct Acting Antivirals (DAAs)	48 (0.7%)	**18 (0.2%)**	**<.0001**	8 (0.5%)	0.7231	**4 (0.1%)**	**<.0001**
Lipid lowering agents	1054 (14.5%)	**838 (9.4%)**	**<.0001**	**294 (19.2%)**	**<.0001**	**357 (10.7%)**	**<.0001**
Non-steroidal Anti-inflammatory Agents (NSAIDS)	491 (6.8%)	**444 (5.0%)**	**<.0001**	79 (5.2%)	0.0197	212 (6.4%)	0.4377
Antidepressants	1261 (17.4%)	**1182 (13.2%)**	**<.0001**	**357 (23.3%)**	**<.0001**	558 (16.8%)	0.4231
Anxiolytics/Hypnotics/Sedatives	836 (11.5%)	**804 (9.0%)**	**<.0001**	**270 (17.6%)**	**<.0001**	**290 (8.7%)**	**<.0001**
Anti-diabetics	338 (4.7%)	**259 (2.9%)**	**<.0001**	**143 (9.3%)**	**<.0001**	157 (4.7%)	0.9034
Immune Modulators	554 (7.6%)	**520 (5.8%)**	**<.0001**	**81 (5.3%)**	**0.0012**	**210 (6.3%)**	**0.0138**

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

3.3. Assessment of Hepatobiliary Disorders

Table 9. Hepatobiliary Disorders in Patients Taking DTG, EVG, RAL, & DRV Reg

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
				Overall Hepatobiliary Disorders				
Any Hepatobiliary Disorders or Advanced Liver Fibrosis†*	Any history, n (%)	907 (12.5%)	674 (7.5%)	<.0001	158 (10.3%)	0.0167	370 (11.1%)	0.0405
*Any Hepatobiliary Disorders**	Any history, n (%)	798 (11.0%)	**574 (6.4%)**	**<.0001**	**127 (8.3%)**	**0.0016**	**303 (9.1%)**	**0.0029**
	Any prevalent event, n (%)	586 (8.1%)	**538 (6.0%)**	**<.0001**	**161 (10.5%)**	**0.0020**	251 (7.5%)	0.3360
	Days to prevalent event, median (IQR)	132.0 (54.0, 325.0)	**183.5 (77.0, 407.0)**	**<.0001**	119.0 (53.0, 329.0)	0.6145	182.0 (60.0, 385.0)	0.0321
	Prevalent event with D/C‡, n (%)	35 (0.5%)	26 (0.3%)	0.0470	7 (0.5%)	0.8940	21 (0.6%)	0.3299
	Days to prevalent event with D/C†, median (IQR)	104.0 (35.0, 204.0)	**337.0 (106.0, 578.0)**	**0.0016**	113.0 (1.0, 388.0)	0.6731	139.0 (61.0, 427.0)	0.0769
	Any incident event, n (%)	373 (5.1%)	396 (4.4%)	0.0322	108 (7.1%)	0.0029	189 (5.7%)	0.2571
	Days to incident event, median (IQR)	204.0 (87.0, 409.0)	234.5 (94.0, 436.0)	0.0796	184.5 (80.0, 415.0)	0.6349	223.0 (96.0, 482.0)	0.2818
	Incident event with D/C, n (%)	20 (0.3%)	19 (0.2%)	0.4246	3 (0.2%)	0.7849	17 (0.5%)	0.0745
	Days to incident event with D/C, median (IQR)	140.5 (72.0, 213.5)	**391.0 (106.0, 720.0)**	**0.0140**	113.0 (1.0, 377.0)	0.8911	182.0 (107.0, 661.0)	0.1750
				Specific Hepatobiliary Disorders				
DILI	Any history, n (%)	0	0	.	0	.	0	.
	Any prevalent event, n (%)	0	0	.	0	.	0	.
	Prevalent event with D/C, n (%)	0	0	.	0	.	0	.
	Any incident event, n (%)	0	0	.	0	.	0	.

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
	Incident event with D/C, n (%)	0	0	.	0	.	0	.
Moderate liver chemistry elevations	Any history, n (%)	686 (9.5%)	**513 (5.7%)**	**<.0001**	**113 (7.4%)**	**0.0099**	**248 (7.5%)**	**0.0007**
	Any prevalent event, n (%)	545 (7.5%)	**487 (5.4%)**	**<.0001**	**153 (10.0%)**	**0.0012**	231 (6.9%)	0.2889
	Days to prevalent event, median (IQR)	143.0 (60.0, 336.0)	**193.0 (80.0, 412.0)**	**0.0002**	125.0 (55.0, 321.0)	0.4738	185.0 (70.0, 405.0)	0.0259
	Prevalent events with D/C, n (%)	34 (0.5%)	**22 (0.2%)**	**0.0161**	6 (0.4%)	0.6829	20 (0.6%)	0.3771
	Days to prevalent event with D/C, median (IQR)	107.5 (42.0, 204.0)	**381.0 (107.0, 578.0)**	**0.0025**	240.5 (1.0, 388.0)	0.7048	145.5 (76.0, 414.0)	0.0732
	Any incident event, n (%)	329 (4.5%)	347 (3.9%)	0.0366	**100 (6.5%)**	**0.0010**	171 (5.1%)	0.1781
	Days to incident event, median (IQR)	211.0 (86.0, 416.0)	240.0 (95.0, 478.0)	0.0677	211.5 (82.0, 415.0)	0.7109	207.0 (91.0, 482.0)	0.5540
	Incident event with D/C, n (%)	20 (0.3%)	17 (0.2%)	0.3207	2 (0.1%)	0.4069	14 (0.4%)	0.2663
	Days to incident event with D/C, median (IQR)	140.5 (75.0, 213.5)	395.0 (107.0, 720.0)	0.0232	189.0 (1.0, 377.0)	0.9545	145.5 (96.0, 427.0)	0.5875
Severe Liver chemistry elevations	Any history, n (%)	284 (3.9%)	**185 (2.1%)**	**<.0001**	**36 (2.4%)**	**0.0029**	128 (3.8%)	0.8578
	Any prevalent event, n (%)	177 (2.4%)	187 (2.1%)	0.1330	53 (3.5%)	0.0234	91 (2.7%)	0.3748
	Days to prevalent event, median (IQR)	156.0 (59.0, 362.0)	205.0 (86.0, 415.0)	0.0487	**307.0 (91.0, 525.0)**	**0.0155**	179.0 (58.0, 423.0)	0.3988
	Prevalent event with D/C, n (%)	13 (0.2%)	12 (0.1%)	0.5475	4 (0.3%)	0.5198	6 (0.2%)	1.0000
	Days to prevalent event with D/C, median (IQR)	42.0 (21.0, 265.0)	239.0 (102.5, 496.5)	0.1654	309.0 (57.0, 851.5)	0.4617	388.5 (70.0, 661.0)	0.1248
	Any incident event, n (%)	97 (1.3%)	128 (1.4%)	0.6174	29 (1.9%)	0.0970	53 (1.6%)	0.3048
	Days to incident event, median (IQR)	258.0 (124.0, 474.0)	245.0 (105.5, 434.5)	0.9695	446.0 (149.0, 714.0)	0.0675	259.0 (74.0, 599.0)	0.8503
	Incident event with D/C, n (%)	4 (0.1%)	7 (0.1%)	0.7641	2 (0.1%)	0.2821	2 (0.1%)	1.0000

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
	Days to incident event with D/C, median (IQR)	268.0 (121.0, 520.5)	258.0 (107.0, 519.0)	0.9247	655.5 (113.0, 1198.0)	0.8170	789.0 (661.0, 917.0)	0.2472

***** Hepatobiliary Disorders are defined as (1) DILI (diagnosis of "DILI", or "drug-induced liver injury", or "drug-induced hepatotoxicity") or (2) Moderate liver chemistry elevations (ALT ≥2.5 to <5x ULN, AST ≥2.5 to <5x ULN, Alkaline phosphatase ≥2.5 to <5x ULN, Bilirubin ≥1.6 to <2.6x ULN) or (3) Severe liver chemistry elevations (ALT ≥5x ULN, AST ≥5x ULN, Alkaline phosphatase ≥5x ULN, Bilirubin ≥2.6x ULN)

† Advanced Liver Fibrosis defined as Fib-4 Index >3.25

‡ D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of a hepatobiliary disorder

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

Table 10. Specific Liver Chemistry Elevations in Patients Taking DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
*Moderate ALT elevation**	Any history, n (%)	220 (3.0%)	234 (2.6%)	0.1075	56 (3.7%)	0.2058	96 (2.9%)	0.6718
	Any prevalent event, n (%)	303 (4.2%)	**280 (3.1%)**	**0.0004**	85 (5.6%)	0.0178	134 (4.0%)	0.7109
	Prevalent events with D/C††, n (%)	14 (0.2%)	9 (0.1%)	0.1429	5 (0.3%)	0.3577	11 (0.3%)	0.1969
	Any incident event, n (%)	192 (2.7%)	192 (2.1%)	0.0365	53 (3.5%)	0.0798	103 (3.1%)	0.1962
	Incident event with D/C, n (%)	8 (0.1%)	7 (0.1%)	0.6062	3 (0.2%)	0.4195	7 (0.2%)	0.2641
Severe ALT elevation†	Any history, n (%)	97 (1.3%)	**71 (0.8%)**	**0.0007**	17 (1.1%)	0.4732	32 (1.0%)	0.1010
	Any prevalent event, n (%)	99 (1.4%)	118 (1.3%)	0.7960	27 (1.8%)	0.2353	54 (1.6%)	0.3049
	Prevalent events with D/C, n (%)	8 (0.1%)	8 (0.1%)	0.8027	3 (0.2%)	0.4195	5 (0.2%)	0.5624
	Any incident event, n (%)	58 (0.8%)	79 (0.9%)	0.5673	16 (1.0%)	0.3418	33 (1.0%)	0.3227
	Incident event with D/C, n (%)	3 (0.0%)	5 (0.1%)	0.7383	1 (0.1%)	0.5356	2 (0.1%)	0.6529

		DTG N= 7,245	*EVG N= 8,943*	*DTG vs. EVG p-value*	*RAL N= 1,531*	*DTG vs. RAL p-value*	*DRV N= 3,327*	*DTG vs. DRV p-value*
Moderate AST elevation‡	Any history, n (%)	208 (2.9%)	**187 (2.1%)**	**0.0014**	54 (3.5%)	0.1705	86 (2.6%)	0.4062
	Any prevalent event, n (%)	260 (3.6%)	281 (3.1%)	0.1160	68 (4.4%)	0.1099	126 (3.8%)	0.6133
	Prevalent events with D/C, n (%)	14 (0.2%)	14 (0.2%)	0.5754	2 (0.1%)	1.0000	15 (0.5%)	0.0261
	Any incident event, n (%)	152 (2.1%)	199 (2.2%)	0.5806	40 (2.6%)	0.2110	83 (2.5%)	0.1988
	Incident event with D/C, n (%)	10 (0.1%)	11 (0.1%)	0.8288	1 (0.1%)	0.7017	9 (0.3%)	0.1432
Severe AST elevation§	Any history, n (%)	70 (1.0%)	66 (0.7%)	0.1137	13 (0.8%)	0.6672	28 (0.8%)	0.5348
	Any prevalent event, n (%)	86 (1.2%)	99 (1.1%)	0.6339	21 (1.4%)	0.5498	50 (1.5%)	0.1808
	Prevalent events with D/C n (%)	7 (0.1%)	6 (0.1%)	0.5828	3 (0.2%)	0.3936	3 (0.1%)	1.0000
	Any incident event, n (%)	55 (0.8%)	68 (0.8%)	0.9929	13 (0.8%)	0.7153	28 (0.8%)	0.6555
	Incident event with D/C, n (%)	4 (0.1%)	4 (0.0%)	1.0000	1 (0.1%)	1.0000	1 (0.0%)	1.0000
Moderate Alkaline phosphatase elevation‖	Any history, n (%)	31 (0.4%)	26 (0.3%)	0.1430	10 (0.7%)	0.2402	11 (0.3%)	0.4604
	Any prevalent event, n (%)	38 (0.5%)	31 (0.3%)	0.0841	11 (0.7%)	0.3547	**31 (0.9%)**	**0.0157**
	Prevalent events with D/C, n (%)	4 (0.1%)	2 (0.0%)	0.4178	1 (0.1%)	1.0000	4 (0.1%)	0.2701
	Any incident event, n (%)	24 (0.3%)	18 (0.2%)	0.1060	6 (0.4%)	0.7119	**23 (0.7%)**	**0.0098**
	Incident event with D/C, n (%)	2 (0.0%)	2 (0.0%)	1.0000	0 (0.0%)	1.0000	4 (0.1%)	0.0827
Severe Alkaline phosphatase elevation¶	Any history, n (%)	10 (0.1%)	7 (0.1%)	0.3295	2 (0.1%)	1.0000	7 (0.2%)	0.4349
	Any prevalent event, n (%)	18 (0.2%)	18 (0.2%)	0.6154	1 (0.1%)	0.2293	10 (0.3%)	0.6843
	Prevalent events with D/C, n (%)	1 (0.0%)	5 (0.1%)	0.2341	0 (0.0%)	1.0000	0 (0.0%)	1.0000
	Any incident event, n (%)	8 (0.1%)	11 (0.1%)	1.0000	1 (0.1%)	1.0000	7 (0.2%)	0.2641
	Incident event with D/C, n (%)	0 (0.0%)	2 (0.0%)	0.5055	0 (0.0%)	.	0 (0.0%)	.
	Any history, n (%)	362 (5.0%)	**191 (2.1%)**	**<.0001**	**38 (2.5%)**	**<.0001**	**110 (3.3%)**	**<.0001**

		DTG N= 7,245	*EVG N= 8,943*	*DTG vs. EVG p-value*	*RAL N= 1,531*	*DTG vs. RAL p-value*	*DRV N= 3,327*	*DTG vs. DRV p-value*
Moderate Bilirubin elevation#	Any prevalent event, n (%)	116 (1.6%)	**47 (0.5%)**	**<.0001**	**49 (3.2%)**	**<.0001**	**26 (0.8%)**	**0.0007**
	Prevalent events with D/C, n (%)	7 (0.1%)	3 (0.0%)	0.1232	1 (0.1%)	1.0000	2 (0.1%)	0.7287
	Any incident event, n (%)	56 (0.8%)	**31 (0.3%)**	**0.0002**	**29 (1.9%)**	**<.0001**	13 (0.4%)	0.0234
	Incident event with D/C, n (%)	5 (0.1%)	2 (0.0%)	0.2544	0 (0.0%)	0.5947	0 (0.0%)	0.3341
*Severe Bilirubin elevation***	Any history, n (%)	181 (2.5%)	**90 (1.0%)**	**<.0001**	**19 (1.2%)**	**0.0027**	82 (2.5%)	0.9180
	Any prevalent event, n (%)	46 (0.6%)	**25 (0.3%)**	**0.0007**	**24 (1.6%)**	**0.0002**	17 (0.5%)	0.4419
	Prevalent events with D/C, n (%)	8 (0.1%)	**1 (0.0%)**	**0.0135**	2 (0.1%)	0.6892	4 (0.1%)	1.0000
	Any incident event, n (%)	15 (0.2%)	16 (0.2%)	0.6840	**10 (0.7%)**	**0.0029**	7 (0.2%)	0.9719
	Incident event with D/C, n (%)	2 (0.0%)	1 (0.0%)	0.5902	1 (0.1%)	0.4374	2 (0.1%)	0.5948

***** Moderate ALT elevation: ALT ≥2.5 to <5x ULN
† Severe ALT chemistry elevation: ALT ≥5x ULN
‡ Moderate AST chemistry elevation: AST ≥2.5 to <5x ULN
§ Severe AST chemistry elevation: AST ≥5x ULN
‖ Moderate alkaline phosphatase elevation: alkaline phosphatase ≥2.5 to <5x ULN
¶ Severe alkaline phosphatase chemistry elevation: alkaline phosphatase ≥5x ULN
# Moderate bilirubin elevation: bilirubin ≥1.6 to <2.6x ULN
** Severe bilirubin chemistry elevation: bilirubin ≥2.6x ULN
†† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of a hepatobiliary disorder
Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).

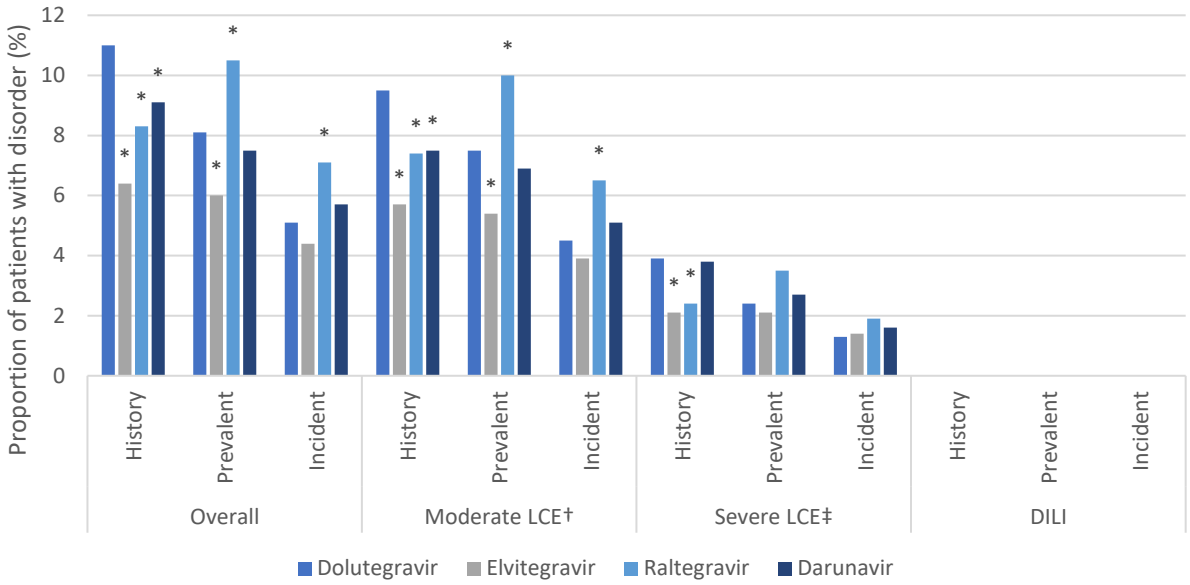
Table 11. Advanced Liver Fibrosis in Patients Taking DTG, EVG, RAL, & DRV Regimens

		DTG *N= 7,245*	*EVG* *N= 8,943*	*DTG vs. EVG p-value*	*RAL* *N= 1,531*	*DTG vs. RAL p-value*	*DRV* *N= 3,327*	*DTG vs. DRV p-value*
*Advanced Liver Fibrosis**	Any history, n (%)	243 (3.4%)	**186 (2.1%)**	**<.0001**	64 (4.2%)	0.1099	129 (3.9%)	0.1750
	Any prevalent event, n (%)	243 (3.4%)	**215 (2.4%)**	**0.0003**	**102 (6.7%)**	**<.0001**	**161 (4.8%)**	**0.0002**
	Prevalent events with D/C†, n (%)	8 (0.1%)	8 (0.1%)	0.6729	**7 (0.5%)**	**0.0028**	**15 (0.5%)**	**0.0005**
	Any incident event, n (%)	113 (1.6%)	129 (1.4%)	0.5411	**61 (4.0%)**	**<.0001**	**98 (2.9%)**	**<.0001**
	Incident event with D/C, n (%)	3 (0.0%)	6 (0.1%)	0.7398	**5 (0.3%)**	**0.0056**	**10 (0.3%)**	

***** Advanced Liver Fibrosis defined as Fib-4 Index >3.25

† D/C: Discontinuation, defined as discontinuation of the core agent of interest within 21 days of the date of a hepatobiliary disorder

Significant comparisons to DTG bolded. To account for multiple comparisons, the Sidak Correction was applied (adjusted alpha level: 0.017).



* P-value for the comparison with DTG <0.017
† Moderate liver chemistry elevations (LCE): ALT ≥2.5 to <5x ULN, AST ≥2.5 to <5x ULN, alkaline phosphatase ≥2.5 to <5x ULN, or bilirubin ≥1.6 to <2.6x ULN
‡ Severe liver chemistry elevations (LCE): ALT ≥5x ULN, AST ≥5x ULN, alkaline phosphatase ≥5x ULN, or bilirubin ≥2.6x ULN

Figure 1. Proportion of Patients Taking DTG, EVG, RAL, & DRV Regimens with history, prevalent or incident hepatobiliary disorders

4. Summary of Findings

Out of 21,046 HIV-infected patients initiating a core agent of interest between August 1st, 2013 and October 31st, 2016 (Table 1), 7,245 (34%) initiated DTG, 8,943 (42%) initiated EVG, 1,531 (7%) initiated RAL and 3,327 (16%) initiated DRV (Table 2). Patients initiating EVG, RAL or DRV were statistically different at baseline than patients initiating DTG for many demographic and clinical characteristics.

4.1. Elvitegravir vs. Dolutegravir

At baseline, EVG users were younger than DTG users. They were also more likely to be MSM or receive care in the South, but they were less likely to benefit from ADAP or Ryan White programs (Table 3). EVG users had a shorter average follow-up time (Table 4). They had been on ART for a shorter time before core agent initiation. More EVG users were ART naïve than DTG users. Their baseline HIV viral load was higher and a lower proportion had baseline CD4 cell counts >500 cells/µL among EVG users than DTG users (Table 5).

EVG users were healthier than DTG users, with lower average VACS score (Table 4). Fewer EVG users had comorbidities at baseline and liver diseases including viral hepatitis were least frequent in the EVG group (Table 7). EVG users had a greater

proportion of missing liver chemistry testing within 12 months of core agent initiation, but a similar proportion of patients with normal tests, compared to DTG users (

Table 6). All the medications assessed were used less frequently among EVG than DTG users (

Table 8), including lipid lowering agents, which are known to elevate LFTs. This is likely a result of the boosting agent in EVG-containing regimens which impact the pharmacokinetics of other medications that are metabolized through the liver.

4.2. Overall, EVG users had a statistically significant lower proportion of patients with a history of any hepatobiliary disorder or advanced liver fibrosis than DTG users (

Table 9). EVG users also had a statistically significant lower proportion of any prevalent hepatobiliary disorders during follow-up. These events occurred after a longer exposure to EVG than to DTG. However, there was no difference in incident events between EVG and DTG users.

4.3. Specific hepatobiliary disorders are presented in

Table 9 and Figure 1. There were no cases of DILI in either group. Both history and prevalent moderate LCE occurred less frequently among EVG than DTG users, while there were no differences in incident moderate LCE. Moderate bilirubin elevations seem to have been driving the difference in history and prevalent LCE (Table 10). Only a history of severe LCE was less frequent among EVG users than DTG users, while there was no difference in prevalent or incident severe LCE during follow-up. Compared to DTG users, a smaller proportion of EVG users had a history of advanced fibrosis or prevalent fibrosis during follow-up, but there was no difference in incident fibrosis events (Table 11).

4.4. Core agent discontinuation (

Table 9) was rare and there was no statistically significant difference between groups after a prevalent (0.5% DTG, 0.3% EVG) or incident hepatobiliary disorder event (0.3% DTG, 0.2% EVG). Events leading to discontinuation generally occurred after a longer exposure time with EVG than DTG. However, discontinuation occurred less frequently after a prevalent moderate liver chemistry elevation in EVG users, compared to DTG users.

4.5. Raltegravir vs. Dolutegravir

RAL users were older and less likely to be male, African American or Hispanic or to benefit from ADAP or Ryan White programs than DTG users, but more likely to be MSM or receive care in the South (Table 3). They also had a shorter average follow-up time (Table 4). RAL users had been on ART for a shorter time than DTG users before core agent initiation and; fewer were ART naïve. Baseline HIV viral load was lower among RAL users and a smaller proportion had baseline CD4 cell counts >500 cells/µL, compared to DTG users (Table 5).

At baseline, RAL users were sicker (higher average VACS score, Table 4), and were more likely to have comorbidities than DTG users (Table 7). Liver diseases, including viral hepatitis, were marginally more frequent in the RAL groups than the DTG group (Table 7). RAL users were prescribed lipid lowering agents more frequently than DTG users (

Table 8).

4.6. Overall, RAL users had a statistically significant lower proportion of patients with a history of any hepatobiliary disorders than DTG users (

4.7. Table 9). RAL users had a statistically significant higher proportion of any prevalent hepatobiliary disorders than DTG users. However, no difference in time to events was detected (

Table 9).

4.8. Hepatobiliary events are broken down into specific disorders in

Table 9 and Figure 1. There were no cases of DILI reported. In terms of moderate LCE, a history was less frequent among RAL users, but both prevalent and incident events were more frequent among RAL than DTG users, with no difference in time to events. While a history of severe LCE was less frequent among RAL users than DTG users, there were no differences in prevalent and incident LCE during follow-up. However, prevalent severe LCE occurred after a statistically longer exposure to RAL than DTG. As for advanced liver fibrosis, while there was no difference between groups for history of fibrosis, prevalent events (with or without discontinuation and incident events (with or without discontinuation) were more likely among RAL than DTG users (Table 11). Discontinuations were however rare, occurring in <1% of prevalent and incident events. Only bilirubin elevations contributed in the differences observed in moderate and severe LCE between RAL and DTG users (Table 10).

4.9. Darunavir vs. Dolutegravir

Compared to DTG users, DRV users were older and less likely to be male, African American or Hispanic, or to benefit from ADAP or Ryan White programs, but more likely to be MSM or receive care in the South (Table 3). DRV had a shorter average follow-up time than DTG users (Table 4). They had been on ART for a shorter time before core agent initiation, and fewer DRV users were ART naïve than DTG users. Baseline HIV viral load was higher among DRV users and a smaller proportion had baseline CD4 cell counts >500 cells/µL than DTG users (Table 5).

DRV users were sicker than DTG users at baseline, with higher average VACS score (Table 4). They were however less likely to have comorbidities at baseline, although no differences in liver diseases were detected (Table 7). DRV users were less likely than DTG users to have a lipid-lowering agent prescription (

Table 8).

4.10. Overall, DRV users had a statistically significant lower proportion of patients with a history of any hepatobiliary disorders than DTG users, although no difference was detected for prevalent or incident hepatobiliary disorders (

4.11. Table 9). No differences between DRV and DTG were detected for history of hepatobiliary disorders or advanced liver fibrosis(

Table 9).

4.12. Specific hepatobiliary events are detailed in

Table 9 and Figure 1. There were no cases of DILI among either DRV or DTG users. A history of moderate LCE was less frequent among DRV users than DTG users, which was driven by differences in history of moderate bilirubin elevations (Table 10). However, there was no difference in prevalent or incident moderate LCE during follow-up. This might be due to a higher frequency of prevalent and incident moderate alkaline phosphatase elevation, but a lower frequency of prevalent moderate bilirubin elevations among DRV, compared to DTG users (Table 10). No difference in history of severe LCE, or prevalent or incident severe LCE were detected between groups. In terms of advanced liver fibrosis, there was no difference in history of events, although both prevalent and incident fibrosis were more frequent among DRV users than DTG users (Table 11).

5. Conclusions

The patient populations using DTG, EVG, RAL or DRV are different in many regards. Some of these differences could be the result of channeling sicker patients away from EVG and towards DTG or RAL. Indeed, compared to DTG users, EVG users were younger and less likely to have existing liver disease, take lipid lowering agents, or have substantial comorbidities than DTG users. During follow-up, EVG users were statistically less likely to have prevalent hepatobiliary disorders or moderate LCE compared to DTG, although no differences were noted for prevalent severe LCE or any incident events.

On the contrary, RAL users were older and were more likely to have liver diseases, take lipid lowering agents or have substantial comorbidities. RAL users were indeed statistically more likely than DTG users to develop prevalent and incident hepatobiliary disorders, more specifically moderate LCE.

There was no clear evidence of channeling in the case of DRV. While DRV users were older and less likely to take lipid lowering agents than DTG users, they were overall sicker, although they were less likely to have comorbidities, without any difference in terms of liver disease specifically. No statistical difference in any prevalent or incident hepatobiliary disorders were detected between DRV and DTG users.

While channeling likely played a role in the differences of prevalent and incident hepatobiliary disorders observed, no adjustment for baseline characteristics were performed. It is therefore impossible to determine from these unadjusted comparisons the impact of channeling on the results presented.

Discontinuation following a hepatobiliary disorder was rare, suggesting that clinicians are willing to tolerate most of the hepatobiliary disorders observed. More work would be required to investigate the degree of severity and persistence of disorders required for discontinuation.

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