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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*

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Final Report

Addendum to the Report on the Frequency of Psychiatric Disorders in Patients Prescribed Antiretroviral Medications-Phase 3

Report Date: August 29, 2017

Previously titled: Addendum to the Report on the Frequency of Neuropsychiatric Events in Patients Prescribed Antiretroviral Medications – Phase 3

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1. EXECUTIVE SUMMARY

Background: Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI), was approved for use in the U.S. in August 2013. The clinical development program for DTG demonstrated a favorable safety profile and high tolerability. [1-5] In contrast, a recent study presented at CROI 2016 (Poster #948, van den Berk et. al.) showed an unexpectedly high rate of intolerance to DTG, including various psychiatric symptoms, in a real-world setting.[6] We sought to evaluate psychiatric disorders (PD) in those using DTG and compare them to individuals using other widely prescribed antiretrovirals (ARV).

Methods: HIV-positive individuals who were prescribed DTG, efavirenz (EFV), raltegravir (RAL), darunavir (DRV), rilpivirine (RPV) or elvitegravir (EVG)-based regimens for the first time by an OPERA caregiver between January 1, 2013 and August 15, 2015 were included for analysis. Patients with exposure to any of the agents before the observation period or who took more than one agent of interest at the same time were excluded. Each was observed from the start of the regimen until discontinuation of the regimen of interest, loss to follow up, death, or data freeze (August 15, 2016). Diagnoses of anxiety, depression, insomnia, or suicidality were the PD endpoints of interest. Additionally, PD diagnoses followed by a discontinuation of the regimen of interest within 14 days were evaluated. Finally, time to PD events was described.

Results: Out of the 70,106 HIV-positive individuals in the OPERA database, 18,241 had been prescribed an ARV regimen of interest (containing DTG, EFV, RAL, DRV, RPV or EVG) during the observation period. Of these 2,401 were excluded because they were prescribed more than one agent of interest. An additional 4,301 patients were excluded because they had previous exposure to any of the regimens of interest prior to the observation window resulting in an analysis population of 11,539 patients. EVG-containing regimens made up the largest proportion of the study population (28.6%), followed by DTG-containing regimens (18.9%). DRV-containing and RPV-containing regimens each made up 15.2% of the study population. The remaining patients took EFV-containing regimens (14.1%) and RAL-containing regimens (7.9%).

Demographic characteristics of the regimens differed significantly at baseline. Prescribing patterns varied by region, treatment guideline approval, and formulations. EFV had the largest proportion of treatment naïve patients (93.6%) compared to the other five regimens (DTG, 57.2%; RAL, 65.5%; DRV, 63.6%; RPV, 83.4%; EVG; 80.9%).

Clinically, patients taking EFV, RPV, and EVG-containing regimens were less likely to have experienced an AIDS defining event at baseline (EFV: 5.1%, RPV: 5.5%, EVG: 6.4%, DTG: 12.2%, RAL: 13.0%, DRV: 13.6%). Patients prescribed DRV-containing regimens had the lowest median CD4 counts (364 cells/uL) and the largest proportion of patients initiating below 50 CD4 cells/uL (9.2%). EVG-containing regimens had the

highest median log viral load at baseline (4.5 log copies/mL) and the highest proportion of patients initiating therapy above 100,000 HIV RNA copies/mL (20.2%). In contrast, RPV-containing regimens had the highest median CD4 counts (504 cells/uL). RAL-containing regimens had the highest proportion of patients who started their regimen with an undetectable viral load.

Psychiatric disorders were common at baseline but not evenly distributed across treatment groups. The groups with larger proportions of treatment-experienced patients (DTG:42.8%, DRV: 36.4%, RAL: 34.5%, EVG: 19.9%, RPV: 16.6%, EFV: 6.4%) had higher proportions of patients with a history of PD at baseline (DTG:39.2%, DRV: 34.0%, RAL: 39.9%, EVG: 30.8%, RPV: 28.4%, EFV: 23.8%). The individual conditions varied. Patients prescribed EFV, DRV, RPV, and EVG were significantly less likely to have had a history of anxiety, depression, or insomnia compared to DTG and RAL. A history of suicidality was rare in all groups and did not differ significantly between groups.

When considering all PD events after baseline regardless of history, depression diagnoses were the most common across treatment groups. Patients prescribed RAL-containing regimens experienced more PD diagnoses over follow up (193, 21.0%) than DTG (384, 17.6%)-containing regimens. The other four regimens did not differ significantly from DTG (EFV: 293, 18.1%; DRV: 321, 18.2%; RPV: 292, 16.6%; EVG: 636, 19.3%). Discontinuations of ARV within 14 days of a PD event were much less frequent. Patients taking EFV, RAL, DRV, and RPV-containing regimens were more likely to discontinue than patients prescribed DTG. Anxiety and depression were most commonly diagnosed in patients prescribed RAL and EVG. Patients taking DTG, EFV, and RAL-containing regimens experienced more insomnia. Discontinuations were higher with EFV and RAL. Diagnoses of suicidality were rare across all groups and only one patient discontinued their regimen for this reason.

The incidence of a new PD, which excluded conditions in individuals who had a history of the disorder at or before baseline, resulted in fewer events for all disorders except suicidality which was rare even without considering past history. New PD diagnoses were similar across regimens (DTG: 278, 12.8%; EFV: 232, 14.3%; RAL: 132, 14.4%; DRV: 205, 11.7%; RPV: 225, 12.8%; EVG: 460, 13.9%). Anxiety was significantly more common with EVG-containing regimens than DTG-containing regimens. Anxiety with discontinuation was more common with EFV, RAL, and EVG use than DTG. Compared to patients taking DTG, a new depression diagnosis occurred more frequently among patients taking EVG, and depression followed by discontinuation was most likely in patients taking EFV, RAL, and RPV-containing regimens. Insomnia was least frequent in the DRV users. Insomnia with discontinuation was highest in the patients prescribed EFV. Suicidality was rare and did not differ between groups with or without discontinuation of medications.

When all prevalent PD diagnoses were considered together in an evaluation of median time to PD event; EFV (156 days), RAL (91 days), and DRV (151 days) reached an event

significantly sooner than DTG (184 days) or RPV (189 days). No differences were seen between groups in time to a PD event with a discontinuation. Individually, few differences in time to PD diagnosis reached statistical significance. Patients taking DRV-containing regimens reached anxiety, depression, and insomnia events sooner than DTG. Patients prescribed EFV also reached insomnia events faster than patients prescribed DTG.

In an evaluation of time to incident new PD diagnoses excluding events in patients with a history of the condition at or before baseline, time to any new PD diagnosis was significantly shorter for EFV (170 days), RAL (110 days), and DRV (175 days)-containing regimens compared to DTG (206 days). There was no difference between DTG, RPV and EVG in time to any new PD event. New PD diagnoses followed by a discontinuation of ARV within 14 days were uncommon. Only RPV was statistically longer than DTG in 43 events (RPV had 36 new events with discontinuation and DTG had 7 events with discontinuation), no other differences reached significance. Individually, few differences in time to diagnosis reached statistical significance. Patients taking DRV-containing regimens reached anxiety and depression events sooner than DTG. Patients prescribed EFV also reached insomnia events faster than patients prescribed DTG.

Conclusion: In a large observational clinical cohort, many patients initiating modern Arv therapy have a history of PD. Clinicians appear to be prescribing DTG to these patients significantly more often. Prevalence of PD was higher in patients prescribed RAL. Incidence of new PDs did not differ across groups. Time to event of prevalent and incident PD events suggests that patients taking DTG experience these events later than patients prescribed other ARV regimens.

2. BACKGROUND AND STUDY RATIONALE

Dolutegravir, formulated as a once-daily, single agent tablet (Tivicay®) and as a fixed-dose combination, STR (Triumeq®) with ABC/3TC has been recently introduced to the marketplace. Both Tivicay and Triumeq have been reported as generally well-tolerated and efficacious, specifically in comparison to Atripla® and other efavirenz-based regimens.[3,8] Moreover, DTG does not require a boosting agent like STRIBILD® (EVG/c/FTC/TDF) and most of the HIV protease inhibitors. The absence of a boosting agent coupled with its pharmacokinetic properties contribute to minimal drug-drug interactions associated with DTG. These characteristics suggest that DTG could be

easier to take and better tolerated and could, therefore, improve the quality of life for HIV patients now and in the future.[1-5]

Recently, Triumeq® replaced Atripla® as a recommended regimen for HIV-positive patients initiating therapy for the first time in the US Department of Health and Human Services (DHHS) Treatment Guidelines, April 2015.[7] As the latest INSTI to be brought to market and with the recent recommendation by DHHS placing dolutegravir (DTG) as a preferred regimen-component, either as a single agent (Tivicay®) combined with other antiretrovirals or as Triumeq® (a fixed dose combination triple tablet) assessments of the overall tolerability of DTG are beginning to be performed.

The clinical development program for DTG demonstrated a favorable safety profile and high tolerability. Grade 4 psychiatric safety events were rarely seen (<1%) with individual grade 1 or grade 2 events being seen in up to 3% of the patients. Similarly, post-marketing spontaneous adverse event surveillance has reported few psychiatric diagnoses as reported as non-serious adverse events with few being reported as serious.

In contrast, one recent study from CROI 2016 (Poster #948, van den Berk et. al.) showed an unexpectedly high rate of intolerance to DTG, including various psychiatric symptoms, in a real-world setting.[6] Given the results seen in the development programs and the spontaneous reporting databases, a finding of unexpectedly high rates as seen in van den Berk et. al. warrants investigation.

3. METHODS

3.1. Study Population

The study population was limited to HIV-positive patients who have been prescribed DTG-based, efavirenz (EFV)-based, raltegravir (RAL)-based, darunavir (DRV)-based, rilpivirine (RPV)-based and elvitegravir(EVG)-based regimens for the first time by an OPERA caregiver between January 1, 2013 and August 15, 2015. Both treatment-naïve and treatment-experienced patients were included in the analysis.

3.2. Study Design

Study participants were identified from the most recent database build available (August 17, 2016). The observation period was defined as January 1, 2013 (the year DTG was first made available in the U.S.) through August 15, 2016 with study enrollment between 1/1/2013 and 8/15/2015. Patients with exposure to any of the regimens of interest prior to the observation period were excluded.

3.3. Study Endpoints

The study endpoints included the following PD diagnoses of interest (grading/severity not available):

I. Anxiety
   a. Prevalence
   b. Incidence
   c. Anxiety + ARV discontinuation within 14 days
   d. Time to Anxiety
II. Depression
   a. Prevalence
   b. Incidence
   c. Depression + ARV discontinuation with 14 days
   d. Time to Depression
III. Insomnia
   a. Prevalence
   b. Incidence
   c. Depression + ARV discontinuation within 14 days
   d. Time to Insomnia
IV. Suicidality
   a. Prevalence
   b. Incidence
   c. Suicidality + ARV discontinuation within 14 days
   d. Time to Suicidality

3.4. Statistical Analysis

3.4.1. Primary Analysis

Patient demographics and PD diagnoses (baseline and follow-up) among patients taking DTG, EFV, RAL, DRV, RPV, and EFV were described using frequency distributions. Time-to-event was described as median time from start of the regimen of interest to the first occurrence of the diagnosis during follow up. Kaplan-Meier curves were compared using log-rank tests.

3.4.2. Analysis Notes

- Baseline date: The baseline date was defined as the first date of one of the six regimens of interest ever prescribed to a patient.

- Observation period: The observation period began on January 1, 2013 (the year DTG was approved) with study participants identified through August 15, 2015, with follow-up through August 15, 2016. Patients were observed from their baseline date until the first of the following censoring events: 1) discontinuation of the regimen of interest, 2) cessation of continuous clinical activity, 3) death or 4) study end (August 15, 2016). Patients failing to meet the continuous clinical activity requirement were censored 12 months after their last contact.

- Continuous Clinical Activity: Continuous Clinical Contact was defined as a patient who has a telephone contact, visit, lab test, or consultation at least once in every 12-month period after follow-up.

- A medication gap of 45 days or more was considered an independent regimen. A medication gap of less than 45 days was ignored and collapsed across.

- Tenofovir was defined as tenofovir DF or tenofovir AF. “r” stands for boosted with ritonavir; “c” stands for boosted with cobicistat in all tables.

- Pearson’s Chi-Square Test was used to calculate p-values for categorical variables. Fisher’s exact test was used to compare frequencies with few events. Wilcoxon Rank Sum Test was used to calculate p-values for continuous variables. P-values <0.05 are bolded for clarity.

- Prevalent PD diagnoses are all diagnoses that occur for that condition after baseline regardless of whether the patient had the diagnosis prior to baseline.

- Incident PD diagnoses are only new diagnoses of that condition after baseline excluding PD events in patients who had a PD diagnosis prior to baseline. Therefore, incident PD diagnoses are a subset of prevalent PD diagnoses. However, a patient with a history of one PD condition could still have an incident event of another PD condition.

- Patients were counted in both categories when two category names appeared in the diagnosis. For example, "anxiety with depression" was counted in the category of anxiety and in the category of depression.

- If a patient had two diagnoses in one category, they were only counted once.

- Rule out diagnoses were not included in any tables.

- Diagnoses with “history of” or “in remission” in the title in the baseline period or the follow up period were counted in the baseline table only.

- Diagnoses with “recurrent” in the title were counted in the baseline tables and in the prevalence tables but not in the incidence tables even if the diagnosis occurred for the first time in the follow up period.

- Anxiety was defined to include “anxiety” and “anxiety disorder”.

- Depression was defined to include “depression”, “major depression”, “depressed mood”, “depressive symptom”, and “bipolar”.

- Insomnia was defined to include “insomnia”, “initial insomnia”, “middle insomnia” and “terminal insomnia”.

- Suicidality was defined to include “suicide attempt”, “suicide ideation”, “completed suicide”, “intentional self-injury”, and “self-injurious behavior”.

- Time to event was calculated as time from baseline to first occurrence of a PD outcome of interest.

- Searches for PDs utilized text searches of diagnoses provide by ViiV. PD diagnoses identified in the database by condition are provided in Table 6 (PD diagnoses occurring at or before baseline) and in Table 12 (PD diagnoses occurring during follow up).

4. RESULTS

4.1. Study Population & Regimens of Interest

As of August 17, 2016, 707,324 patients were present in the OPERA database of which 70,106 (9.9%) were HIV-positive. Many of these patients had been prescribed an ARV regimens of interest (containing DTG, EFV, RAL, DRV, RPV or EVG) during the observation period without having more than one third agent of interest (15,840). An additional 4,301 patients were excluded because they had previous exposure to the regimen of interest prior to the observation window resulting in an analysis population of 11,539 patients who met the inclusion criteria and did not met the exclusion criteria for the study. (Table 1)

Table 1: Study Population Attrition

	Criteria	Patients Included	%	Patients Excluded	%
1	Patients in OPERA	707,324	.	.	.
2	Patient who are HIV+	70,106	9.9	637,218	90.1
3	HIV+ patients prescribed ART	50,515	72.1	19,591	27.9
4	HIV+ patients prescribed a regimen of interest	42,355	83.8	8,160	16.2
5	HIV+ patients prescribed regimen of interest between 1/1/2013 and 8/15/2015	18,241	43.1	24,114	56.9
6	HIV+ patients prescribed a regimen of interest that did not include two or more third agents of interest	15,840	86.8	2,401	13.2

7	HIV+ patients prescribed a regimen of interest that did not include two or more third agents of interest excluding those with prior exposure to a regimen of interest [study population]	11,539	72.8	4,301	27.2

DTG-containing regimens made up 18.9% of the study population and were most frequently prescribed with ABC and 3TC (1,279; 58.7%). EFV-containing regimens made up 14.1% of the population and were prescribed most frequently with TDF and FTC (1,498, 92.4%). RAL-containing regimens made up 7.9% of the study population and were given with a wide variety of other ART agents. DRV-containing and RPV-containing regimens each made up 15.2% of the study population. DRV was boosted most of the time with either ritonavir or cobicistat. TDF and FTC were the most common backbone given with DRV (72.3%). RPV was not boosted and was also given most frequently with TDF and FTC (93.6%). EVG-containing regimens made up the largest proportion of the study population (3,303; 28.6%) and were given boosted with cobicistat and the TDF and FTC backbone almost exclusively (96.5%). (Table 2a)

Table 2a. Patients by Exposure Group

Third Agents		Regimens of Interest	
	n(%)		n(%)
DTG-containing regimens (not including EFV, RAL, DRV, RPV, or EVG)	2,180 (18.9%)	DTG + TDF + FTC	533 (24.4%)
		DTG + ABC + 3TC	1,279 (58.7%)
		DTG + all other agents	368 (16.8%)

EFV-containing regimens (not including DTG, RAL, DRV**,** RPV, or EVG)	1,622 (14.1%)	EFV + TDF + FTC	1,498 (92.4%)
		EFV + ABC + 3TC	39 (2.4%)
		EFV + all other agents	85 (5.3%)
RAL-containing regimens (not including DTG, EFV, DRV, RPV, or EVG)	917 (7.9%)	RAL + TDF + FTC	475 (51.8%)
		RAL + ABC + 3TC	75 (8.2%)
		RAL + all other agents	367 (40.0%)
DRV-containing regimens (not including DTG, EFV, RAL, RPV, or EVG)	1,759 (15.2%)	DRV + r/c + TDF + FTC	1,260 (71.6%)
		DRV + r/c + ABC + 3TC	179 (10.2%)
		DRV + r/c + all other agents	268 (15.2%)
		DRV + TDF + FTC	12 (0.7%)
		DRV + ABC + 3TC	5 (0.3%)
		DRV + all others	35 (2.0%)
RPV-containing regimens (not including DTG, EFV, RAL, DRV, or EVG)	1,758 (15.2%)	RPV + TDF + FTC	1,645 (93.6%)
		RPV + ABC + 3TC	10 (0.6%)
		RPV + all other agents	103 (5.8%)

EVG-containing regimens (not including DTG, EFV, RAL, DRV, or RPV)	3,303 (28.6%)	EVG + r/c + TDF + FTC	3,189 (96.5%)
		EVG + r/c + ABC + 3TC	0 (0%)
		EVG + r/c + all other agents	114 (3.5%)

The vast majority of DTG was given at 50 mg per day as indicated in the labeling (97.7%). Only 26 (1.2%) patients took a higher dose than 50 mg per day usually as Tivicay BID or Triumeq QD with Tivicay QD. None of the patients were prescribed a lower dose who had dosing information available. A small proportion of patients did not have the dosage noted in the patient's electronic medical record (1.1%). (Table 2b)

Table 2b: Patients by DTG Dosage

Dosage of DTG-containing regimens	Total DTG N=2,180
	n(%)
< 50 mg per day	0 (0%)
50 mg per day	2131 (97.7%)
> 50 mg per day	26 (1.2%)
No dose indicated	23 (1.1%)

EFV, RAL, and DRV were more frequently prescribed in 2013. RPV and EVG were more frequently prescribed in 2014. DTG was prescribed in 2014 and 2015 equally. (Table 2c)

Table 2c. Patients by Year of Initiation

	DTG-containing regimens N= 2180	EFV-containing regimens N= 1622	RAL-containing regimens N= 917	DRV-containing regimens N= 1759	RPV-containing regimens N= 1758	EVG-containing regimens N= 3303
Year of ART initiation	n(%)	n(%)	n(%)	n(%)	N(%)	N(%)
2013	203 (9.3%)	828 (51.0%)	532 (58.0%)	838 (47.6%)	695 (39.5%)	1203 (36.4%)
2014	995 (45.6%)	560 (34.5%)	278 (30.3%)	615 (35.0%)	735 (41.8%)	1278 (38.7%)
2015*	982 (45.0%)	234 (14.4%)	107 (11.7%)	306 (17.4%)	328 (18.7%)	822 (24.9%)

**2015 incomplete year (January through August 15 only)*

4.2. Demographic and Clinical Characteristics at Baseline

Demographic characteristics of the regimens of interest differed significantly at baseline. Patients prescribed RAL-containing regimens were older on average than patients prescribed the five other regimens with the largest proportion of patients 50 year or older (41.8%) in this group. RPV and EVG had the largest proportions of 13-25 year olds; 23.7% and 22.7%, respectively. More men than women received all six regimens of interest. Women made up a larger proportion of DRV, RAL, and RPV-containing regimens; 20.8%, 18.2%, and 19.4%, respectively. African Americans made up a larger proportion of RPV-containing regimens (49.5%) than the other regimens. EVG-containing regimens had the highest proportion of Hispanics; 27.4%. Most patients were single of those with marital status information available. Only EVG and DTG-containing regimens were made up of more men who have sex with men (MSM)s than non-MSMs. All regimens were most frequently prescribed in the South region. DTG had the highest proportion of patients prescribed in the West region. (Table 3a and 3b)

Table 3a. Baseline Demographic Characteristics of Patients Taking DTG, EFV, RAL, & DRV Regimens

	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
	n(%)	n(%)		n(%)		n(%)	
Age:							
Median (IQR)	42.6 (30.6, 51.6)	41.5 (30.1, 49.6)	**0.0048**	48.1 (38.9, 54.6)	**<.0001**	44.6 (34.3, 51.5)	**<.0001**
13-25	311 (14.3%)	240 (14.8%)	.	44 (4.8%)	**.**	145 (8.2%)	**.**
26-49	1229 (56.4%)	998 (61.5%)	.	493 (53.8%)	**.**	1075 (61.1%)	**.**
50+	640 (29.4%)	384 (23.7%)	**0.0004**	380 (41.4%)	**<.0001**	539 (30.6%)	**<.0001**
Sex:							
Male	1859 (85.3%)	1419 (87.6%)	.	749 (81.8%)	.	1395 (79.4%)	.
Female	320 (14.7%)	201 (12.4%)	**0.0435**	167 (18.2%)	**0.0134**	363 (20.6%)	**<.0001**
Race:							
African American	805 (36.9%)	656 (40.4%)	.	273 (29.8%)	.	737 (41.9%)	.
Not African American	1375 (63.1%)	966 (59.6%)	**0.0274**	644 (70.2%)	**0.0001**	1022 (58.1%)	**0.0015**
Ethnicity:							
Hispanic	539 (24.7%)	335 (20.7%)	.	178 (19.4%)	.	413 (23.5%)	.
Not Hispanic	1641 (75.3%)	1287 (79.3%)	**0.0032**	739 (80.6%)	**0.0014**	1346 (76.5%)	0.3640
Marital Status:							
Single	1496 (68.6%)	1122 (69.2%)	.	610 (66.5%)	.	1193 (67.8%)	.
Married	117 (5.4%)	101 (6.2%)	.	65 (7.1%)	.	123 (7.0%)	.
Domestic partnership	81 (3.7%)	57 (3.5%)	.	32 (3.5%)	.	55 (3.1%)	.
Widowed	16 (0.7%)	13 (0.8%)	.	11 (1.2%)	.	20 (1.1%)	.
Separated/ Divorced	61 (2.8%)	52 (3.2%)	.	33 (3.6%)	.	64 (3.6%)	.
Unknown	409 (18.8%)	277 (17.1%)	0.6414	166 (18.1%)	0.2294	304 (17.3%)	0.0655

Risk of infection							
MSM	1118 (51.3%)	734 (45.3%)	.	392 (42.7%)	**.**	733 (41.7%)	**.**
Not MSM	1062 (48.7%)	888 (54.7%)	**0.0002**	525 (57.3%)	**<.0001**	1026 (58.3%)	**<.0001**
Geographic Region:							
Northeast	170 (7.8%)	148 (9.1%)	.	88 (9.6%)	.	129 (7.3%)	.
South	1214 (55.7%)	1027 (63.3%)	.	571 (62.3%)	.	1074 (61.1%)	.
Midwest	38 (1.7%)	56 (3.5%)	.	26 (2.8%)	.	11 (0.6%)	.
West	758 (34.8%)	391 (24.1%)	**<.0001**	232 (25.3%)	**<.0001**	545 (31.0%)	**0.0003**

Table 3b. Baseline Demographic Characteristics of Patients Taking DTG, RPV, & EVG Regimens

	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**
	n(%)	n(%)		n(%)	
Age:					
Median (IQR)	42.6 (30.6, 51.6)	33.4 (26.4, 45.1)	**<.0001**	34.9 (26.6, 45.8)	**<.0001**
13-25	311 (14.3%)	417 (23.7%)	.	749 (22.7%)	.
26-49	1229 (56.4%)	1082 (61.5%)	.	2051 (62.1%)	.
50+	640 (29.4%)	259 (14.7%)	**<.0001**	503 (15.2%)	**<.0001**
Sex:					
Male	1859 (85.3%)	1415 (80.6%)	.	2861 (86.7%)	.
Female	320 (14.7%)	340 (19.4%)	**<.0001**	439 (13.3%)	0.1471
Race:					
African American	805 (36.9%)	870 (49.5%)	.	1301 (39.4%)	.

Not African American	1375 (63.1%)	888 (50.5%)	**<.0001**	2002 (60.6%)	**0.0666**
Ethnicity:					
Hispanic	539 (24.7%)	388 (22.1%)	.	905 (27.4%)	.
Not Hispanic	1641 (75.3%)	1370 (77.9%)	0.0510	2398 (72.6%)	**0.0278**
Marital Status:					
Single	1496 (68.6%)	1216 (69.2%)	.	2298 (69.6%)	.
Married	117 (5.4%)	94 (5.3%)	.	142 (4.3%)	.
Domestic partnership	81 (3.7%)	59 (3.4%)	.	92 (2.8%)	.
Widowed	16 (0.7%)	12 (0.7%)	.	16 (0.5%)	.
Separated/ Divorced	61 (2.8%)	45 (2.6%)	.	99 (3.0%)	.
Unknown	409 (18.8%)	332 (18.9%)	0.9858	656 (19.9%)	0.0963
Risk of infection					
MSM	1118 (51.3%)	879 (50.0%)	.	1785 (54.0%)	**.**
Not MSM	1062 (48.7%)	879 (50.0%)	0.4229	1518 (46.0%)	**0.0453**
Geographic Region:					
Northeast	170 (7.8%)	155 (8.8%)	.	215 (6.5%)	.
South	1214 (55.7%)	1153 (65.6%)	.	2079 (62.9%)	.
Midwest	38 (1.7%)	31 (1.8%)	.	50 (1.5%)	.
West	758 (34.8%)	419 (23.8%)	**<.0001**	959 (29.0%)	**<.0001**

Prescribing patterns varied by region, treatment guideline approval dates, and formulations. EFV was the first of the regimens of interest to be recommended as therapy for treatment naïve patients by the DHHS HIV/AIDS Treatment Guidelines therefore EFV has the largest proportion of treatment naïve patients (93.6%) compared to the other five regimens (DTG, 57.2%; RAL, 65.5%; DRV, 63.6%; RPV, 83.4%; EVG; 80.9%).[6] The high proportion of treatment naïve patients on EFV, RPV, and EVG meant that there was less time from joining an OPERA caregiver (first active date) to initiation of the regimen of interest than with the other regimens who were proceeded by other ARV regimens a

significant amount of the time. Median follow up time was similar among regimens with significant treatment-experienced use; DTG=16.2 months, DRV=15.7 months, and RAL=14.5 months).

Clinically, the EFV, RPV, and EVG-containing regimens were made up of far fewer patients who had already experienced an AIDS defining event at baseline; 5.1%, 5.5%, and 6.4%, respectively. Patients prescribed DRV-containing regimens had the lowest median CD4 counts (364 cells/uL) and the largest proportion of patients initiating below 50 CD4 cells/uL (9.2%). EVG-containing regimens had the highest median log viral load at baseline (4.5 log copies/mL) and the highest proportion of patients initiating therapy above 100,000 HIV RNA copies/mL (20.2%). In contrast, RPV-containing regimens had the highest median CD4 counts (504 cells/uL). RAL-containing regimens had the highest proportion of patients who started their regimen with an undetectable viral load. RAL was the first of the INSTIs to be released and many treatment-experienced patients on challenging (many drugs) and complex (injectables) salvage ARV regimens were waiting for this new class of medicines to simplify their ARV regimens. (Tables 4a and 4b)

Table 2a: Baseline Clinical Characteristics of Patients Taking DTG, EFV, RAL, & DRV Regimens

	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
	n(%)	n(%)		n(%)		n(%)	
Backbone of Regimen:							
ABC + 3TC only	1279 (58.7%)	39 (2.4%)	.	75 (8.2%)	.	184 (10.5%)	.
TDF + FTC only	533 (24.4%)	1498 (92.4%)	.	475 (51.8%)	.	1272 (72.3%)	.
AZT + 3TC only	3 (0.1%)	16 (1.0%)	.	5 (0.5%)	.	2 (0.1%)	.
All others	365 (16.7%)	69 (4.3%)	**<.0001**	362 (39.5%)	**<.0001**	301 (17.1%)	**<.0001**
ARV Exposure:							
Naive	1247 (57.2%)	1519 (93.6%)	.	601 (65.5%)	.	1119 (63.6%)	.
Experienced	933 (42.8%)	103 (6.4%)	**<.0001**	316 (34.5%)	**<.0001**	640 (36.4%)	**<.0001**

Time between first active date and baseline							
Median months (IQR)	4.0 (0.9, 37.2)	1.6 (0.7, 11.1)	**<.0001**	3.7 (0.8, 30.4)	**0.0344**	3.5 (0.7, 45.3)	**0.0470**
Follow-up time between baseline and end of follow up							
Median months (IQR)	16.2 (12.1, 21.6)	15.2 (9.5, 25.1)	**0.0077**	14.5 (8.7, 25.3)	**0.0064**	15.7 (11.1, 26.2)	0.7793
AIDS (clinical dx only):							
Yes	267 (12.2%)	82 (5.1%)	**<.0001**	119 (13.0%)	0.5748	240 (13.6%)	0.1932
Baseline viral load:							
Median log copies/mL (IQR)	3.9 (1.3, 4.8)	4.0 (1.3, 4.9)	0.9848	1.8 (1.3, 4.4)	**<.0001**	4.1 (1.6, 5.0)	**0.0002**
Undetectable	515 (23.6%)	323 (19.9%)	.	246 (26.8%)	.	308 (17.5%)	.
Low (detectable to <10,000 copies/mL)	425 (19.5%)	186 (11.5%)	.	140 (15.3%)	.	322 (18.3%)	.
Moderate (≥10,000 to <100,000 copies/mL)	566 (26.0%)	253 (15.6%)	.	91 (9.9%)	.	305 (17.3%)	.
High (≥100,000 copies/mL)	335 (15.4%)	184 (11.3%)	.	81 (8.8%)	.	314 (17.9%)	.
Missing baseline VL	339 (15.6%)	676 (41.7%)	**<.0001**	359 (39.1%)	**<.0001**	510 (29.0%)	**<.0001**
Baseline CD4:							
Median cells/ µL (IQR)	452.0 (274.0, 650.0)	459.0 (294.0, 674.0)	0.2082	480.5 (266.0, 680.0)	0.2771	364.0 (152.0, 587.0)	**<.0001**
High (>500 cells/µL)	789 (36.2%)	421 (26.0%)	.	264 (28.8%)	.	421 (23.9%)	.
Med High (>350 to ≤500 cells/µL)	395 (18.1%)	221 (13.6%)	.	112 (12.2%)	.	214 (12.2%)	.
Medium (>200 to ≤350 cells/µL)	336 (15.4%)	168 (10.4%)	.	96 (10.5%)	.	219 (12.5%)	.
Med Low (>50 to ≤200 cells/µL)	215 (9.9%)	100 (6.2%)	.	69 (7.5%)	.	216 (12.3%)	.

Low (≤50 cells/µL)	96 (4.4%)	43 (2.7%)	.	33 (3.6%)	.	161 (9.2%)	.
Missing baseline CD4	349 (16.0%)	669 (41.2%)	**<.0001**	343 (37.4%)	**<.0001**	528 (30.0%)	**<.0001**

Table 4b: Baseline Clinical Characteristics of Patients Taking DTG, RPV, and EVG Regimens

	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**
	n(%)	n(%)		n(%)	
Backbone of Regimen:					
ABC + 3TC only	1279 (58.7%)	10 (0.6%)	.	0 (0%)	.
TDF + FTC only	533 (24.4%)	1645 (93.6%)	.	3189 (96.5%)	.
AZT + 3TC only	3 (0.1%)	1 (0.1%)	.	0 (0%)	.
All others	365 (16.7%)	102 (5.8%)	**<.0001**	114 (3.5%)	**<.0001**
ARV Exposure:					
Naive	1247 (57.2%)	1466 (83.4%)	.	2672 (80.9%)	.
Experienced	933 (42.8%)	292 (16.6%)	**<.0001**	631 (19.1%)	**<.0001**
Time between first active date and baseline					
Median months (IQR)	4.0 (0.9, 37.2)	1.6 (0.8, 10.6)	**<.0001**	1.5 (0.7, 13.6)	**<.0001**
Follow-up time between baseline and end of follow up					
Median months (IQR)	16.2 (12.1, 21.6)	18.9 (12.0, 27.1)	**<.0001**	18.3 (12.0, 27.1)	**<.0001**
AIDS (clinical dx only):					
Yes	267 (12.2%)	96 (5.5%)	**<.0001**	211 (6.4%)	**<.0001**

Baseline viral load:					
Median log copies/mL (IQR)	3.9 (1.3, 4.8)	4.0 (2.5, 4.5)	0.4522	4.5 (3.4, 5.0)	**<.0001**
Undetectable	515 (23.6%)	247 (14.1%)	.	342 (10.4%)	.
Low (detectable to <10,000 copies/mL)	425 (19.5%)	466 (26.5%)	.	594 (18.0%)	.
Moderate (≥10,000 to <100,000 copies/mL)	566 (26.0%)	631 (35.9%)	.	1044 (31.6%)	.
High (≥100,000 copies/mL)	335 (15.4%)	48 (2.7%)	.	668 (20.2%)	.
Missing baseline VL	339 (15.6%)	366 (20.8%)	**<.0001**	655 (19.8%)	**<.0001**
Baseline CD4:					
Median cells/ µL (IQR)	452.0 (274.0, 650.0)	504.0 (360.0, 677.0)	**<.0001**	414.0 (259.0, 590.0)	**<.0001**
High (>500 cells/µL)	789 (36.2%)	696 (39.6%)	.	968 (29.3%)	.
Med High (>350 to ≤500 cells/µL)	395 (18.1%)	367 (20.9%)	.	659 (20.0%)	.
Medium (>200 to ≤350 cells/µL)	336 (15.4%)	236 (13.4%)	.	535 (16.2%)	.
Med Low (>50 to ≤200 cells/µL)	215 (9.9%)	76 (4.3%)	.	357 (10.8%)	.
Low (≤50 cells/µL)	96 (4.4%)	10 (0.6%)	.	119 (3.6%)	.
Missing baseline CD4	349 (16.0%)	373 (21.2%)	**<.0001**	665 (20.1%)	**<.0001**

4.3. Psychiatric Disorder Diagnoses at Baseline

PD diagnoses were common at baseline and not evenly distributed across groups. The groups with larger proportions of treatment-experienced patients had higher proportions of PDs at baseline (DTG, 39.2%; RAL, 39.9%

and DRV, 34.0%). The individual PD conditions varied. Patients prescribed EFV, DRV, RPV, and EVG were significantly less likely to have had a history of anxiety, depression, or insomnia compared to DTG or RAL. A history of suicidality was rare in all groups and did not differ between groups significantly. (Tables 5a and 5b)

Table 3a: Prevalence of PD Diagnoses at Baseline for Patients Taking DTG, EFT, RAL and DRV Regimens

	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
	n(%)	n(%)		n(%)		n(%)	
History of Any PD Diagnosis	854 (39.2%)	386 (23.8%)	**<.0001**	366 (39.9%)	0.7010	598 (34.0%)	**0.0008**
Anxiety	356 (16.3%)	142 (8.8%)	**<.0001**	136 (14.8%)	0.2974	215 (12.2%)	**0.0003**
Depression	649 (29.8%)	260 (16.0%)	**<.0001**	269 (29.3%)	0.8084	461 (26.2%)	**0.0135**
Insomnia	278 (12.8%)	120 (7.4%)	**<.0001**	127 (13.8%)	0.4083	167 (9.5%)	**0.0013**
Suicidality	12 (0.6%)	3 (0.2%)	0.1141	5 (0.5%)	1.0000	8 (0.5%)	0.8226

Table 4b: Prevalence of PD Diagnoses at Baseline for Patients Taking DTG, RPV and EVG Regimens

	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**

	n(%)	n(%)		n(%)	
History of Any PD Diagnosis	854 (39.2%)	500 (28.4%)	**<.0001**	1017 (30.8%)	**<.0001**
Anxiety	356 (16.3%)	188 (10.7%)	**<.0001**	461 (14.0%)	**0.0157**
Depression	649 (29.8%)	368 (20.9%)	**<.0001**	709 (21.5%)	**<.0001**
Insomnia	278 (12.8%)	113 (6.4%)	**<.0001**	289 (8.7%)	**<.0001**
Suicidality	12 (0.6%)	8 (0.5%)	0.8226	11 (0.3%)	0.2856

4.4. Listings of Diagnoses Included in Psychiatric Disorders at Baseline

Table 6: Listing of Diagnoses Included in Each PD Category on or prior to Baseline
[See separate document]

Table 7: Listing of Diagnoses NOT Included in Any Condition Category on or prior to Baseline
[Omitted due to length in excess of 50 pages]

4.5. Prevalence of Psychiatric Disorder Diagnoses During Follow-up

When considering all psychiatric disorders after baseline regardless of previous history, depression diagnoses were the most common. Patients prescribed RAL-containing regimens experienced more PD diagnoses over follow up (193, 21.0%) than DTG (384, 17.6%)-containing regimens. The other four regimens did not differ significantly from DTG (EFV: 293, 18.1%; DRV: 321, 18.2%; RPV: 292, 16.6%; EVG: 636, 19.3%). Discontinuations of ARV within 14 days of a PD event were much less frequent. Those taking EFV, RAL, DRV, and RPV-containing regimens experienced a significantly higher proportion of patients discontinuing than patients prescribed DTG. Anxiety and depression were highest in patients

prescribed RAL and EVG. DTG, EFV, and RAL-containing regimens experienced higher proportions of insomnia. Discontinuations were higher with EFV and RAL. Diagnoses of suicidality were rare across all groups. Only one patient discontinued their regimen after this diagnosis. (Tables 8a and 8b)

Table 8a. Prevalence of PD Diagnoses During Follow-up of Patients Taking DTG, EFV, RAL and DRV Regimens

	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
	n(%)	n(%)		n(%)		n(%)	
Any Prevalent PD Diagnoses	384 (17.6%)	293 (18.1%)	0.7201	193 (21.0%)	**0.0251**	321 (18.2%)	0.6056
Any Prevalent PDc Diagnoses + DC	17 (0.8%)	48 (3.0%)	**<.0001**	34 (3.7%)	**<.0001**	35 (2.0%)	**0.0009**
Anxiety	148 (6.8%)	106 (6.5%)	0.7565	86 (9.4%)	**0.0128**	132 (7.5%)	0.3851
Anxiety + DC	6 (0.3%)	13 (0.8%)	**0.0229**	14 (1.5%)	**<.0001**	16 (0.9%)	**0.0079**
Depression	210 (9.6%)	149 (9.2%)	0.6412	119 (13.0%)	**0.0058**	202 (11.5%)	0.0592
Depression + DC	9 (0.4%)	23 (1.4%)	**0.0008**	22 (2.4%)	**<.0001**	18 (1.0%)	**0.0210**
Insomnia	156 (7.2%)	133 (8.2%)	0.2297	76 (8.3%)	0.2746	93 (5.3%)	**0.0166**
Insomnia + DC	7 (0.3%)	18 (1.1%)	**0.0038**	10 (1.1%)	**0.0138**	9 (0.5%)	0.4514
Suicidality	2 (0.1%)	2 (0.1%)	1.0000	2 (0.2%)	0.5867	1 (0.1%)	1.0000
Suicidality + DC	0 (0%)	1 (0.1%)	0.4266	0 (0%)	.	0 (0%)	.

DC=ARV of interest discontinued within 14 days of PD diagnosis

Table 8b. Prevalence of PD Diagnoses During Follow-up of Patients Taking DTG, RPV and EVG Regimens

	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**
	n(%)	n(%)		n(%)	
Any Prevalent PD Diagnosis	384 (17.6%)	292 (16.6%)	0.4058	636 (19.3%)	0.1266
Any Prevalent PD Diagnosis + DC	17 (0.8%)	26 (1.5%)	**0.0358**	41 (1.2%)	0.1021
Anxiety	148 (6.8%)	110 (6.3%)	0.5025	292 (8.8%)	**0.0062**
Anxiety + DC	6 (0.3%)	6 (0.3%)	0.7085	18 (0.5%)	0.1387
Depression	210 (9.6%)	182 (10.4%)	0.4533	374 (11.3%)	**0.0471**
Depression + DC	9 (0.4%)	17 (1.0%)	**0.0328**	22 (0.7%)	0.2210
Insomnia	156 (7.2%)	96 (5.5%)	**0.0307**	195 (5.9%)	0.0638
Insomnia + DC	7 (0.3%)	5 (0.3%)	1.0000	14 (0.4%)	0.6579
Suicidality	2 (0.1%)	5 (0.3%)	0.2538	6 (0.2%)	0.4901
Suicidality + DC	0 (0%)	0 (0%)	.	0 (0%)	.

DC=ARV of interest discontinued within 14 days of PD diagnosis

4.6. Incidence of New Psychiatric Disorder Diagnoses During Follow up

The incidence of new PD diagnoses which excluded conditions in individuals who had a history of the condition at or before baseline resulted in fewer events for all conditions except suicidality which was rare even without considering past history. New diagnoses were similar across regimens (DTG: 278, 12.8%; EFV: 232, 14.3%; RAL: 132, 14.4%; DRV: 205, 11.7%; RPV: 225, 12.8%; EVG: 460, 13.9%) Anxiety was higher with EVG-containing regimens than DTG-containing regimens. Anxiety with discontinuation was higher with EFV, RAL, and EVG use than DTG. Depression was higher with EVG use. Depression with discontinuation was higher in EFV, RAL and RPV-containing regimens than DTG. Insomnia was least frequent in the DRV users with remaining other regimens not significantly different from one another. Insomnia with discontinuation was highest in the patients prescribed EFV. Suicidality was rare and did not differ between groups with or without discontinuation of medications. (Table 9a and 9b)

Table 9a. Incidence of New PD Diagnoses During Follow-up of DTG, EFV, RAL, and DRV Regimens

	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
	n(%)	n(%)		n(%)		n(%)	
Any Incident PD Diagnosis	278 (12.8%)	232 (14.3%)	0.1652	132 (14.4%)	0.2182	205 (11.7%)	0.2963
Any Incident PD Diagnosis + DC	7 (0.3%)	36 (2.2%)	**<.0001**	16 (1.7%)	**<.0001**	18 (1.0%)	**0.0058**
Anxiety	110 (5.0%)	87 (5.4%)	0.6619	56 (6.1%)	0.2314	91 (5.2%)	0.8565
Anxiety + DC	2 (0.1%)	10 (0.6%)	**0.0061**	7 (0.8%)	**0.0039**	8 (0.5%)	0.0502
Depression	115 (5.3%)	96 (5.9%)	0.3914	57 (6.2%)	0.2967	100 (5.7%)	0.5735

Depression + DC	2 (0.1%)	15 (0.9%)	**0.0002**	6 (0.7%)	**0.0104**	8 (0.5%)	0.0502
Insomnia	113 (5.2%)	106 (6.5%)	0.0769	52 (5.7%)	0.5815	68 (3.9%)	**0.0496**
Insomnia + DC	5 (0.2%)	13 (0.8%)	**0.0151**	6 (0.7%)	0.0944	6 (0.3%)	0.5550
Suicidality	2 (0.1%)	2 (0.1%)	1.0000	2 (0.2%)	0.5867	1 (0.1%)	1.0000
Suicidality + DC	0 (0%)	1 (0.1%)	0.4266	0 (0%)	.	0 (0%)	.

Table 9b. Incidence of New PD Diagnoses During Follow-up of DTG, RPV, and EVG Regimens

	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**
	n(%)	n(%)		n(%)	
Any Incident PD Diagnosis	278 (12.8%)	225 (12.8%)	0.9655	460 (13.9%)	0.2124
Any Incident PD Diagnosis + DC	7 (0.3%)	18 (1.0%)	**0.0058**	25 (0.8%)	**0.0381**
Anxiety	110 (5.0%)	87 (4.9%)	0.8895	214 (6.5%)	**0.0276**
Anxiety + DC	2 (0.1%)	3 (0.2%)	0.6617	13 (0.4%)	**0.0369**
Depression	115 (5.3%)	118 (6.7%)	0.0574	232 (7.0%)	**0.0092**
Depression + DC	2 (0.1%)	11 (0.6%)	**0.0042**	11 (0.3%)	0.0903
Insomnia	113 (5.2%)	73 (4.2%)	0.1295	149 (4.5%)	0.2533
Insomnia + DC	5 (0.2%)	4 (0.2%)	1.0000	6 (0.2%)	0.7624

Suicidality	2 (0.1%)	5 (0.3%)	0.2538	5 (0.2%)	0.7101
Suicidality + DC	0 (0%)	0 (0%)	.	0 (0%)	.

4.7. Time to Prevalent Psychiatric Disorder Diagnoses

When all prevalent diagnoses were considered together, EFV, RAL, and DRV reached an event significantly sooner than DTG or RPV. No differences were seen between groups in time to an event with a discontinuation. Individually, few differences in time to diagnosis reached statistical significance. Patients taking DRV-containing regimens reached anxiety, depression, and insomnia events sooner than DTG. Patients prescribed EFV also reached insomnia events faster than patients prescribed DTG. (Table 10a and 10b)

Table 10a. Time to Prevalent PD Diagnoses during Follow-up of DTG, EFV, RAL, and DRV Regimens

	Time to Event (days) Median (IQR)						
	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
Any Prevalent PD Diagnosis	184.5 (84.5, 364.0)	156.0 (45.0, 322.0)	**0.0168**	91.0 (22.0, 280.0)	**<.0001**	151.0 (45.0, 371.0)	**0.0343**
Any Prevalent PD Diagnosis + DC	364.0 (172.0, 438.0)	301.5 (130.0, 562.5)	0.6489	300.0 (84.0, 530.0)	0.5623	199.0 (71.0, 383.0)	0.1186
Anxiety	204.5 (92.0, 362.5)	171.0 (57.0, 365.0)	0.5183	101.0 (30.0, 240.0)	**0.0010**	161.0 (51.0, 473.0)	0.5818
Anxiety + DC	294.5 (172.0, 398.0)	352.0 (120.0, 626.0)	0.8608	285.5 (127.0, 599.0)	0.8690	146.5 (28.0, 369.5)	0.1306

Depression	204.0 (94.0, 369.0)	178.0 (64.0, 358.0)	0.2400	106.0 (22.0, 376.0)	**0.0016**	140.5 (42.0, 385.0)	0.0595
Depression + DC	398.0 (182.0, 519.0)	198.0 (120.0, 507.0)	0.2322	350.5 (70.0, 599.0)	0.6321	199.0 (82.0, 383.0)	0.1358
Insomnia	228.0 (97.0, 409.5)	131.0 (35.0, 252.0)	**<.0001**	95.0 (20.5, 283.0)	**0.0003**	158.0 (45.0, 258.0)	**0.0093**
Insomnia + DC	381.0 (237.0, 438.0)	327.0 (149.0, 640.0)	1.0000	323.5 (241.0, 599.0)	1.0000	216.0 (171.0, 868.0)	0.6338
Suicidality	293.5 (111.0, 476.0)	291.0 (224.0, 358.0)	1.0000	124.0 (4.0, 244.0)	0.4386	314.0 (314.0, 314.0)	1.0000
Suicidality + DC	0 (0%)	224.0 (224.0, 224.0)	.	0 (0%)	.	0 (0%)	.

Table 10b. Time to Prevalent PD Diagnoses during Follow-up of DTG, RPV and EVG Regimens

	Time to Event (days) Median (IQR)				
	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**
Any Prevalent PD Diagnosis	184.5 (84.5, 364.0)	189.5 (75.5, 405.0)	0.5325	168.0 (48.5, 392.5)	0.3653
Any Prevalent PD Diagnosis + DC	364.0 (172.0, 438.0)	517.5 (282.0, 733.0)	0.2008	282.0 (130.0, 607.0)	0.9251
Anxiety	204.5 (92.0, 362.5)	264.5 (91.0, 492.0)	0.0602	175.0 (56.0, 412.0)	0.6485
Anxiety + DC	294.5 (172.0, 398.0)	644.0 (423.0, 888.0)	0.0782	296.5 (121.0, 665.0)	0.9468

Depression	204.0 (94.0, 369.0)	184.0 (68.0, 377.0)	0.5531	202.5 (61.0, 455.0)	0.4022
Depression + DC	398.0 (182.0, 519.0)	530.0 (97.0, 764.0)	0.7669	310.0 (127.0, 435.0)	0.4862
Insomnia	228.0 (97.0, 409.5)	216.5 (104.0, 429.5)	0.4849	164.0 (42.0, 398.0)	0.0820
Insomnia + DC	381.0 (237.0, 438.0)	445.0 (363.0, 505.0)	0.2232	368.0 (185.0, 1010.0)	0.6544
Suicidality	293.5 (111.0, 476.0)	244.0 (98.0, 488.0)	1.0000	346.0 (226.0, 455.0)	0.7389
Suicidality + DC	0 (0%)	0 (0%)	.	0 (0%)	.

4.8. Time to Incident New Psychiatric Disorder Diagnoses

Incident new PD diagnoses excluding events in patients with a history of the condition at or before baseline were not as common across groups. Time to any new PD diagnosis was significantly shorter for EFV, RAL, and DRV-containing regimens compared to DTG. There was no difference between DTG, RPV and EVG in median time to any new PD event. New PD diagnoses followed by a discontinuation of ARV within 14 days were uncommon. Only RPV was statistically longer in median time to event than DTG based on 43 events (RPV had 36 events with discontinuation and DTG had 7 events with discontinuation), no other differences reached significance. Individually, few differences in time to a PD diagnosis reached statistical significance. Patients taking DRV-containing regimens reached anxiety and depression events sooner than DTG. Patients prescribed EFV also reached insomnia events faster than patients prescribed DTG. (Table 11a and 11b) When depicted as Kaplan Meier curves, differences existed across regimens with EFV and RAL reaching a new PD event soonest. (Figure 1) When considering time to a new PD event with discontinuation of the regimen of interest, DTG took significantly ($p<.0001$) longer to reach an event. (Figure 2)

Table 11a. Time to Incident New PD Diagnoses during Follow-up of DTG, EFV, RAL, and DRV Regimens

	Time to Event (days) Median (IQR)						
	DTG-containing regimens N=2,180	EFV-containing regimens N=1,622	**p-value EFV vs. DTG**	RAL-containing regimens N=917	**p-value RAL vs. DTG**	DRV-containing regimens N=1,759	**p-value DRV vs. DTG**
Any New PD Diagnosis	206.0 (88.0, 378.0)	170.5 (56.5, 352.5)	**0.0417**	110.5 (29.5, 349.0)	**0.0006**	175.0 (70.0, 477.0)	0.9692
Any New PD Diagnosis + DC	237.0 (153.0, 398.0)	248.5 (128.0, 423.5)	0.9738	283.0 (56.5, 437.5)	0.9467	155.5 (71.0, 374.0)	0.3035
Anxiety	237.5 (94.0, 372.0)	183.0 (62.0, 379.0)	0.5543	120.0 (36.0, 242.0)	**0.0039**	181.0 (62.0, 512.0)	0.8047
Anxiety + DC	275.5 (153.0, 398.0)	344.0 (28.0, 626.0)	1.0000	315.0 (140.0, 599.0)	0.7697	88.0 (19.5, 382.0)	0.2963
Depression	224.0 (106.0, 389.0)	201.5 (74.5, 361.5)	0.2604	82.0 (20.0, 473.0)	**0.0317**	223.5 (63.5, 488.0)	0.9588
Depression + DC	290.0 (182.0, 398.0)	198.0 (73.0, 429.0)	0.6545	207.5 (43.0, 599.0)	0.7389	115.0 (44.5, 364.5)	0.2963
Insomnia	196.0 (85.0, 378.0)	145.5 (49.0, 274.0)	**0.0160**	130.5 (30.5, 323.5)	0.0850	167.0 (72.5, 258.5)	0.1065
Insomnia + DC	280.0 (237.0, 398.0)	190.0 (135.0, 356.0)	0.4597	323.5 (241.0, 345.0)	0.8551	193.5 (80.0, 337.0)	0.3613
Suicidality	293.5 (111.0, 476.0)	291.0 (224.0, 358.0)	1.0000	124.0 (4.0, 244.0)	0.4386	314.0 (314.0, 314.0)	1.0000
Suicidality + DC	0 (0%)	224.0 (224.0, 224.0)	.	0 (0%)	.	0 (0%)	.

Table 11b. Time to Incident New PD Diagnoses during Follow-up of DTG, RPV and EVG Regimens

	Time to Event (days) Median (IQR)				
	DTG-containing regimens N= 2,180	RPV-containing regimens N= 1,758	**p-value RPV vs. DTG**	EVG-containing regimens N= 3,303	**p-value EVG vs. DTG**
Any Prevalent PD Diagnosis	206.0 (88.0, 378.0)	238.0 (99.0, 437.0)	0.0731	200.0 (67.0, 427.5)	0.8803
Any Prevalent PD Diagnosis + DC	237.0 (153.0, 398.0)	577.5 (337.0, 733.0)	**0.0458**	429.0 (208.0, 700.0)	0.1787
Anxiety	237.5 (94.0, 372.0)	341.0 (131.0, 534.0)	**0.0052**	209.5 (70.0, 435.0)	0.9247
Anxiety + DC	275.5 (153.0, 398.0)	721.0 (567.0, 888.0)	0.0833	338.0 (127.0, 461.0)	0.8651
Depression	224.0 (106.0, 389.0)	224.0 (83.0, 442.0)	0.8292	246.5 (97.0, 466.0)	0.1946
Depression + DC	290.0 (182.0, 398.0)	730.0 (69.0, 764.0)	0.5532	429.0 (338.0, 574.0)	0.3237
Insomnia	196.0 (85.0, 378.0)	312.0 (132.0, 445.0)	0.0509	211.0 (54.0, 383.0)	0.4749
Insomnia + DC	280.0 (237.0, 398.0)	475.0 (391.0, 546.5)	0.0500	808.5 (270.0, 1023.0)	0.2012
Suicidality	293.5 (111.0, 476.0)	244.0 (98.0, 488.0)	1.0000	434.0 (226.0, 455.0)	0.6985
Suicidality + DC	0 (0%)	0 (0%)	.	0 (0%)	.

Figure 1: Time to First Incident Psychiatric Disorder

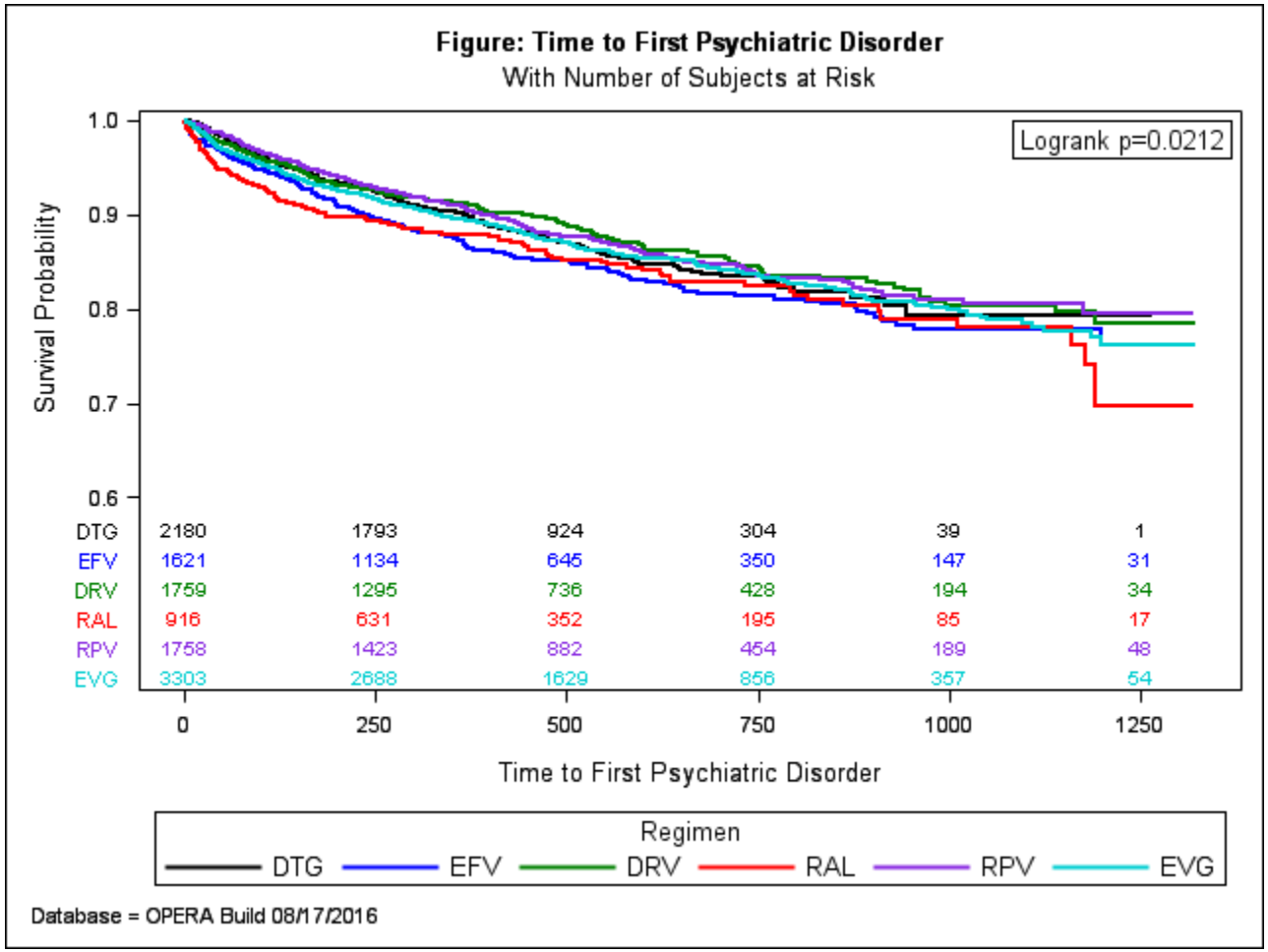
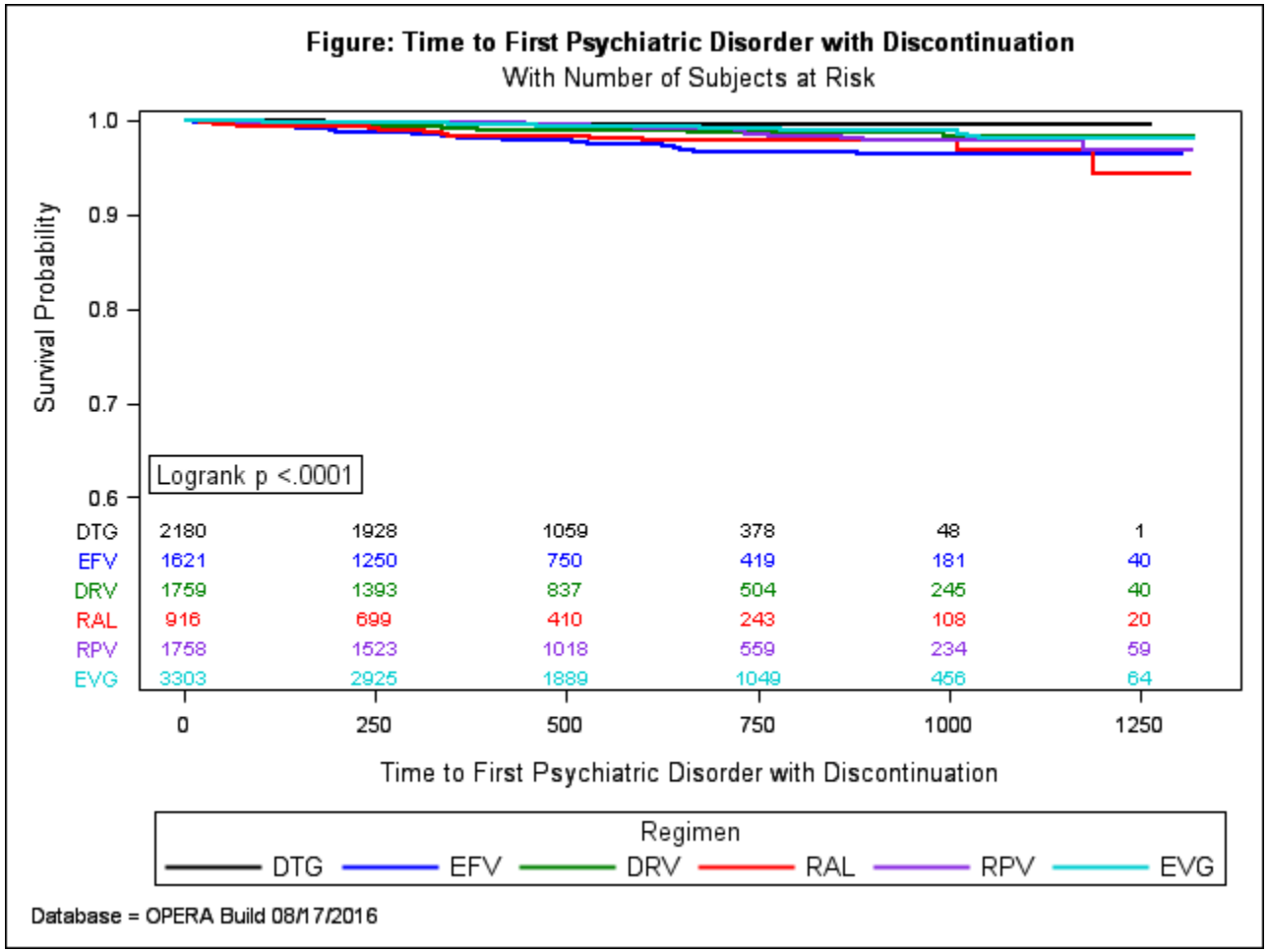


Figure 2: Time to First Incident Psychiatric Disorder with Discontinuation of Regimen of Interest



4.9. Listings of Diagnoses Included in Psychiatric Disorders During Follow Up

Table 12: Listing of Diagnoses Included in Each PD Category during Follow up

[See separate document]

5. DISCUSSION

Psychiatric disorders were not frequent in the clinical development of DTG. Initial reports in real-world data suggested an unexpectedly high rate of psychiatric disorders in a hospital-based population. This analysis sought to evaluate both the importance of pre-existing conditions and to compare observed rates to other commonly prescribed ARV. PD diagnoses were prevalent at baseline in this large population of people living with HIV in the U.S. A history of PD was significantly more common in DTG. Neither prevalence of all PD events nor incidence of new PD events with DTG is higher than other commonly used ARV. DTG users experienced significantly fewer PD events with discontinuation within 14 days and experienced those events later.

This analysis is limited to PSs severe enough to be diagnosed by a clinician. There may have been mild events that were noted only as symptoms and not identified in this analysis. The frequency of the events suggest that many patients were diagnosed and the infrequency of discontinuations of the regimen of interest suggest they could be treated through or were not severe enough to discontinue the ART.

The important additions of this research to the previously published work were the ability to compare DTG to many other ARVs currently available and characterizing the prevalence of psychiatric disorders at baseline. It is important for clinicians to understand the risks and benefits of a given ARV in light of the other therapeutic options available. Further, PD diagnoses varied across groups significantly and was important for determining true differences in incidence. The etiology of psychiatric disorders is likely multi-factorial in HIV patients. Eliminating the bias of patients with pre-existing conditions helps to reduce some of the noise.

In a large HIV+ population in the U.S., DTG was prescribed to patients with a history of PDs preferentially. DTG is not associated with an increased prevalence or incidence of PDs and has a lower incidence of new PD events resulting in discontinuation of therapy. Further, PD events that do occur while on DTG therapy present later.

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TITLE PAGE

Information Type: ViiV Healthcare Epidemiology Study Protocol

Title:	Descriptive Analysis of Neuropsychiatric Diagnoses in Patients taking Dolutegravir in the OPERA® Observational Database

Compound Number: GSK1349572, GSK2619619

Development Phase IV

Effective Date: 11-MAY-2016

Subject: Dolutegravir, neuropsychiatric events

Author(s):
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2. PPD Epividian

Approved through email by:

PPD
VP and Head of Global Medical Strategy, & Head, Research and Development

11-MAY-2016
Date

PPD
VP, Head of Safety and Pharmacovigilance

11-MAY-2016
Date

Introduction:

Dolutegravir (DTG), an integrase strand transfer inhibitor formulated as a once-daily, single agent tablet (Tivicay®) and as a single tablet regimen (Triumeq®) with abacavir and lamivudine (ABC/3TC) has been recently introduced to the antiretroviral therapy (ART) marketplace. Both Tivicay and Triumeq have demonstrated a favorable safety profile and high tolerability during their clinical development programs. Grade 4 neuropsychiatric safety events were rarely seen (<1%) with individual grade 1 or grade 2 events being seen in up to 3% of the patients. Similarly, post-marketing spontaneous adverse event surveillance has reported neuropsychiatric diagnoses as non-serious adverse events infrequently and as serious adverse events rarely.

In contrast, a recent study from CROI 2016 (Poster #948, van den Berk et. al.) presented an unexpectedly high rate of intolerance to DTG, including various neuropsychiatric symptoms, in a real-world setting. Given the safety profile seen in the development programs and the low spontaneous reporting rates, a finding of unexpectedly high rates seen by van den Berk et. al. should be evaluated in an independent real-world setting to see if these rates can be reproduced.

Objectives:

To summarize neuropsychiatric tolerability diagnoses in a population of HIV-positive males and females who have been prescribed DTG including both ART naïve and ART experienced patients.

Study Design:

A descriptive analysis of neuropsychiatric diagnoses made within a large, geographically-diverse, real-world clinical setting utilizing prospectively-collected electronic medical record (EMR) data obtained from the OPERA® Observational Database will be performed. The observation period will begin on January 1, 2007 (the STR era) with study participants identified through April 30, 2015 on data through April 30, 2016. The study population will be limited to HIV-positive patients who have been prescribed DTG-based, efavirenz (EFV)-based, ralutegravir (RAL)-based, or darunavir (DRV)-based regimens by an OPERA caregiver including both treatment naïve and treatment experienced patients. Each patient will be followed from the first occurrence of one of these regimens until regimen change, lost to follow up or death. Multiple endpoints will be allowed per patient to capture all events a patient experienceds while on regimen of interest.

Study Endpoints:

The study endpoints will include the following neuropsychiatric diagnoses of interest (grading/severity not available) and time to discontinuation:

1) abnormal behavior
2) abnormal dreams
3) aboulia/diminished motivation
4) affective disorder
5) aggression
6) agitation

7) alcoholism
8) anger
9) anxiety
10) bipolar disorder
11) bulimia nervosa
12) suicide (ideation, attempted, completed)
13) confused state
14) delusion
15) depressed mood
16) depression
17) depressive symptoms
18) disinhibition
19) disorientation
20) dissociation
21) dissociative disorder
22) drug dependence
23) elevated mood
24) emotional disorder
25) emotional distress
26) encopresis
27) euphoric mood
28) hallucination, auditory
29) hallucination, visual
30) impatience
31) impulsive behavior
32) insomnia
33) intentional self-injury
34) irritability
35) libido increased
36) loss of libido
37) mania
38) mental disorder
39) mental status changes
40) middle insomnia
41) mood alteration
42) mood swings
43) nervousness
44) nightmares
45) obsessive rumination
46) obsessive thoughts
47) orgasm abnormal
48) panic attack
49) panic reaction
50) paranoia
51) persecutory delusion
52) personality change
53) psychiatric symptom
54) psychotic disorder
55) restlessness
56) self injurious behavior
57) sleep disorders
58) somnambulism
59) stress
60) suicidal ideation
61) suicide attempt
62) thinking abnormal
63) time perception altered

Study Covariates:

The following patient demographic and clinical characteristics will be assessed at baseline, the initiation of the first DTG, EFV, RAL or DRV-containing regimen in the study period.

Demographic variables

- Age
- Gender
- Race (African American or not)
- Ethnicity (Hispanic or not)
- Possible Route of Infection (MSM or not)

Clinical variables

- HIV Status at baseline
  - HIV RNA viral load
  - CD4 count

  - AIDS status
  - ART experience (naïve or not)
  - Backbone ARTs given
- Neuropsychiatric comorbidities at baseline
  - Major Depressive Disorder
  - Bipolar Disorder
  - Alcoholism
  - Alcohol Use
  - Illicit drug/chem sex drug use
  - Other mental/emotional/behavioral disorder
  - Presence of neuropsychiatric concomitant medications

Statistical Analysis:

Patient demographics, baseline clinical characteristics and neuropsychiatric diagnoses will be described using frequency distributions. Medians with interquartile ranges will be used to describe time to neuropsychiatric event.

1. Addendum 1 (original neuropsychiatric event analysis; due May 27, 2016)
    a. Frequency of events distributions for:
        i. DTG-based regimens (with dose stratification)
2. Addendum 1a (due May 27, 2016)
    a. Frequency of events distributions for:
        i. EFV-based regimens
        ii. RAL-based regimens
        iii. DRV-based regimens
3. Addendum 1b (due August 20, 2016)
    a. Frequency of events distributions for:
        i. Complera regimens
        ii. Stribild regimens
4. Addendum 1c (due October 14, 2016)
    a. Comparison of demographics for:
        i. Patients on DTG with neuropsychiatric events
        ii. Patients on DTG without neuropsychiatric events

Regulatory and Ethical Considerations:

Data Aggregation, Informed Consent, Data Privacy, and the handling of Personally Identifiable Information (PII) follow the guidance of the HIPAA and HITECH guidelines.

Clinical data aggregation occurs via a secure and encrypted connection with security and confidentiality maintained through Epividian's validated de-identification algorithms with regular and routine statistical audits of the de-identification process. No personally identifiable information is available in the OPERA® Database. The OPERA® Clinical Advisory Board provides clinical and methodological review & oversight.

Business Associate Agreements (BAA) in place between Epividian and all medical practices govern the encryption, transportation, aggregation, de-identification and use of all clinical data in the OPERA® Database. All medical practices are responsible for obtaining proper HIPAA consent for their patients. With BAA's in place, a separate informed consent for each individual, non-interventional study is not required.

The study design is to analyse the patient level information recorded in the OPERA database from electronic health records in an aggregate manner. Reporting of adverse events by Epividian to competent authorities is not applicable as the healthcare information used in this study will not contain physician attribution of adverse event causality to any medicinal product.

References:

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