TITLE PAGE

Information Type: Study Protocol

Title:	An Evaluation of Weight Gain in Patients Treated with Dolutegravir vs. Other Core Agents

Compound Number: GSK1349572

Development Phase IV

Effective Date: 12-Dec-2018

Subject: Weight gain with DTG

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1. LIST OF ABBREVIATIONS

1.1. HIV Medications (generic name) and corresponding abbreviations

Abbreviation	Medication Name
3TC	lamivudine
ABC	abacavir
ATV	atazanavir
ATV/c	atazanavir/cobicistat
ATV/r	atazanavir/ritonvavir
BIC	bictegravir
COBI or /c	cobicistat
DRV	darunavir
DRV/c	darunavir/cobicistat
DRV/r	darunavir/ritonavir
DTG	dolutegravir
DTG/ABC/3TC	dolutegravir/abacavir/lamivudine
EFV	efavirenz
EFV/TDF/FTC	efavirenz/tenofovir disoproxil fumarate/emtricitabine
EVG	elvitegravir
EVG/c	elvitegravir/cobicistat
EVG/c/TDF/FTC	elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine
EVG/c/TAF/FTC	elvitegravir/cobicistat/tenofovir alafenamide fumarate/emtricitabine
EVG/r	elvitegravir/ritonavir
FTC	emtricitabine
LPV	lopinavir
LPV/r	lopinavir/r
PI/c	cobicistat-boosted protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
RAL	raltegravir
RPV	rilpivirine
RTV or /r	ritonavir
TAF	tenofovir alafenamide fumarate
TDF	tenofovir disoproxil fumarate
Abbreviation	**Class Name**
INSTI	integrase strand transfer inhibitor
NNRTI	nonnucleoside reverse transcriptase inhibitor
PI	protease inhibitor

1.2. Other abbreviations

Abbreviation	Description

ADAP	AIDS drug assistance program
ADE	AIDS defining event
AIDS	Acquired Immunodeficiency Syndrome
ART	Anti-retroviral Therapy
BAA	business associates agreement
BID	twice daily
BMI	body mass index
CDC	Centers for Disease Control & Prevention
DHHS	Department of Health and Human Services
ELISA	enzyme-linked immunosorbent assay
EMR	electronic medical record
FDA	Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HITECH	Health Information Technology for Economic and Clinical Health Act
HIV	human immunodeficiency virus
HDL	high density lipoprotein cholesterol
ICD-9 (-10)	International Classification of Diseases v9 (v10)
IQR	Inter-Quartile Range
kg	kilogram
LDL	low density lipoprotein cholesterol
µL	microliter
mL	milliliter
m	meter
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
OPERA	Observational Pharmaco-Epidemiology Research & Analysis
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
QA	quality assurance
RNA	ribonucleic acid
US	United States
VACS	Veterans Aging Cohort Study
WIHS	Women's Interagency HIV Study

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2. **RESPONSIBLE PARTIES:** SPONSOR INFORMATION PAGE

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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3. ABSTRACT

Introduction:

Body composition among patients with HIV has evolved over time, from initial manifestations of severe muscle wasting in the pre-antiretroviral therapy (ART) era to observed gains in weight since the introduction of ART. Evidence demonstrates that the body mass index (BMI) of people with HIV is increasing over time. Studies have also observed pronounced increases in weight following ART initiation. Lipodystrophy has been seen primarily with older ART regimens but is still observed with regimens containing newer agents such as protease inhibitors, integrase strand transfer inhibitors, and non-nucleoside reverse transcriptase inhibitors. Apart from irregular body fat deposition, weight gain was previously attributed to an improvement in health, especially among those severely immunocompromised. However, in the current ART era, weight gain has been attributed to the effect of treatment rather than simply an improvement in health with weight gains observed in multiple settings.

Using data from a large population of HIV patients in the US, this analysis will describe weight outcomes among ART-experienced HIV patients using measures of BMI, lipid levels, and diagnoses of lipodystrophy. This analysis will also assess the association between specific core agent initiation and changes in BMI.

Objectives:

Primary:

1) Among new users of DTG, RPV, RAL, BIC*, EVG/c, and DRV(/r/c): To describe BMI categories, weight, lipid levels (e.g. total cholesterol, HDL, LDL, triglycerides), and lipodystrophy at core agent initiation and at 6, 12, and 24 months after core agent initiation, stratified by ART- naïve and ART-experienced.
2) Among ART-experienced new users of DTG vs. RPV, RAL, EVG/c, BIC*, or DRV(/r/c): To estimate the association between specific core agent initiation and changes in BMI at 6, 12, and 24 months after core agent initiation.

Secondary:

1) Among ART-experienced patients who were suppressed at switch (stable switch) to DTG, RPV, RAL, BIC*, EVG/c, or DRV(/r/c): To describe BMI categories, weight, and lipid panels levels (e.g. total cholesterol, HDL, LDL) at core agent initiation, and at 6, 12, and 24 months after core agent initiation.

*Patients taking BIC will be included for 6-month outcomes only

Study Design:

An observational clinical cohort analysis utilizing prospectively collected electronic medical record (EMR) data obtained from the OPERA® Observational Database will be used to address the study objectives. Subjects will be included from 01AUG2013 through 31DEC2017 and observed through 31DEC2018. HIV-1, ART-experienced patients who are at least 18 years of age and have been prescribed a core agent of interest for the first time will be included.

Endpoints & Outcomes:

- Primary outcomes:
    - BMI (continuous and categories) and change in BMI (continuous)
    - Weight (continuous) and change in weight (continuous)
    - Total cholesterol, HDL, LDL and triglycerides (continuous and NCEP ATPIII categories)
    - Lipodystrophy diagnoses

4. AMENDMENTS AND UPDATES

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
<1>	<Date>	<Text>	<Text>	<Text>
<2>	<Date>	<Text>	<Text>	<Text>
<n>	<Date>	<Text>	<Text>	<Text>

5. MILESTONES

Milestone	Planned date
Start of data analysis	JAN 2019
End of data analysis	FEB 2019
Preliminary tables	MAR 2019
Final report of study results	APR 2019
Draft abstract	MAY 2019

6. BACKGROUND AND RATIONALE

6.1. Background

Highly active antiretroviral therapy (ART) has changed human immunodeficiency virus (HIV) infection from a fatal illness to a chronic disease [1, 2]. Since the mid-1990's, regimens containing multiple antiretroviral drugs from at least two classes have been the standard of care in HIV treatment [3]. Combination therapy presents multiple barriers to viral replication and limits the development of drug-resistant mutations [3]. Integrase strand transfer inhibitors (INSTI) are the newest tool for prolonging survival and improving quality of life for people with HIV [4]. This class of medications includes raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG) and bictegravir (BIC). INSTIs appear to result in a more rapid decline in viral load and higher increases in CD4 counts when compared to protease inhibitors (PI) or efavirenz (EFV) based regimens [5-12].

Body composition has been a concern for patients with HIV since the initial manifestations of severe muscle wasting in the pre-ART era [13-16]. However, these concerns have evolved over time as studies have observed increases in weight among people living with HIV since the introduction of ART [17-19]. Lipodystrophy was associated with primarily older ART regimens but is still observed with some regimens containing newer agents including PIs such as darunavir (DRV) or atazanavir (ATV), INSTIs such as RAL, and non-nucleoside reverse transcriptase inhibitors (NNRTI) such as rilpivirine (RPV) [20-23].

Apart from irregular body fat deposition, weight gain was attributed to an improvement in health initially, especially among those severely immunocompromised. More recently, it has been appreciated that obesity and body mass index (BMI) have been increasing in HIV populations over time both before the initiation of ART and after [19]. In a sample of 14,084 patients living with HIV in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), the percentage of patients who were obese at ART initiation increased from 9% to 18% between 1998 and 2010 [17]. In the Swiss HIV Cohort Study, overweight/obesity prevalence increased from 13% in 1990 to 38% in 2012 [24].

In the current ART era, weight gain has been attributed to the effect of the treatment rather than simply an improvement in health with increases in weight following initiation of ART reported in multiple studies [17, 18, 25, 26]. In the NA-ACCORD, 22% of patients with normal BMI at baseline became overweight and 18% of patients who were overweight at baseline became obese after just three years of ART [17]. Out of 1,255 HIV patients enrolled in the U.S. Military Natural History Study between 1985–2004 and followed up to 2007, 62% gained weight after HIV diagnosis, among whom BMI increased by 2.3 kg/m^2 on average from baseline to last visit (average rate of 0.55 kg/m^2 per year). The average weight gain was 7.3 kg with an average rate of 1.71 kg per year [18]. Among 1,600 HIV patients initiating ART in the Swiss HIV Cohort Study, BMI increased on average by 0.92 kg/m^2 per year (95% CI: 0.83, 1.0) in the first year of ART and 0.31 kg/m^2 per year (0.29, 0.34) during years 1–4 [24]. Among 1,160 women in the Women's Interagency HIV Study (WIHS), median BMI increases over 5 years were 0.21 kg/m^2 (90% CI: −1.33, 0.42) for normal baseline BMI, 0.39 kg/m^2 (90% CI: 0.15, 0.66) for overweight, 0.31 kg/m^2 (90% CI: −1.18, 0.67) for obese, and −0.36 kg/m^2 (90% CI: −2.04, 1.08) for morbidly obese women [25]. In the Veterans Aging Cohort Study (VACS), 4,311 ART-naïve patients initiating ART between 2000-2008 gained a median of 2.7 kg (IQR: −1.3 to 7.7) [26].

In addition, duration of ART exposure may also impact weight gain. Between 1999 and 2004 in the Multicenter AIDS Cohort Study (1,059 men living with HIV) and the WIHS cohorts (1,455 women living with HIV), a shorter duration of ART was associated with lower BMI [19]. These studies suggest that both ART initiation in general and time since initiation are associated with increases in BMI and weight [17-19, 25, 26].

To our knowledge, four recent studies have reported on weight or BMI increases associated with specific core agents [27-30]. One cohort study included 462 European patients on DTG for more than six months and observed a significant increase in weight (mean increase: 3 kg) and BMI (mean increase: 1 kg/m^2) over follow-up; 20% of the patients experienced >10% increase in weight [28]. However, the follow-up timepoints varied between patients and the study did not include a comparison group. Another cohort study following 495 patients virologically suppressed on EFV/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) from the Vanderbilt Comprehensive Care Clinic found that weight change over an 18-month period was highest among patients

switching to an INSTI-containing regimen (2.9 kg) when compared to switching to a PI-containing regimen (0.7 kg) or continuation with EFV/TDF/FTC (0.9 kg) [27]. The greatest change was observed for patients switching to DTG/abacavir (ABC)/lamivudine (3TC) specifically (5.3 kg) [27]. In the SCOLTA cohort, mean BMI increases were estimated among ART-experienced patients at 6 and 12 months following initiation of a new core agent [29]. Mean BMI increase with DTG (n=225) was 0.18 ± 0.08 at 6 months and 0.30 ± 0.10 at 12 months. With RAL (n=382), mean BMI increase was 0.17 ± 0.07 at 6 months and 0.24 ± 0.08 at 12 months. With EVG (n=148), mean BMI increase was 0.21 ± 0.07 at 6 months and 0.23 ± 0.10 at 12 months. With DRV (n=145), mean BMI increase was 0.32 ± 0.09 at 6 months and 0.41 ± 0.10 at 12 months. With RPV (n=218), mean BMI increase was 0.06 ± 0.07 at 6 months and 0.06 ± 0.08 at 12 months [29]. Although small, BMI increases from baseline were statistically significant ($p<0.05$) for all core agents assessed at both 6 and 12 months with the exception of RPV (6 months: $p=0.39$, 12 months: $p=0.51$) [29].

In 1,809 ART-naïve patients randomized to ATV/ritonavir (r)/TDF/FTC, DRV/r/TDF/FTC, or RAL/TDF/FTC, weight increased on average by 3.8 kg and BMI by 1.3 kg/m^2 over 96 weeks [30]. Adjusted logistic regression with multiple imputation was performed to predict severe weight gain (i.e. ≥ 10% increase in weight if ≥ normal BMI at baseline; ≥ overweight at 96 weeks if underweight at baseline) and severe BMI increase (i.e. increase of one or more BMI categories at 96 weeks if ≥ normal baseline BMI; ≥ overweight at 96 weeks if underweight at baseline). Compared to RAL, patients prescribed ATV/r were less likely to experience a severe weight increase (aOR: 0.72, 95% CI: 0.53, 0.99) and those prescribed DRV/r were less likely to experience a severe BMI increase (aOR: 0.73; 95% CI:0.53, 0.99) [30]. The relative impact on weight gain of most common core ART agents has yet to be determined.

6.2. Rationale

Disentangling weight gain due to improved health status from weight gain due to an undesired effect of therapy requires an assessment of a large number of patients who may be progressing toward a stable health status or in whom a stable health status has been achieved and maintained.

Following raised disproportionality analysis (DPA) scores for both DTG and DTG/ABC/3TC detected through the routine pharmacovigilance, clinical trial data, spontaneous case reports, and published studies were reviewed. The cumulative evidence could not rule out an association between DTG exposure and weight gain, leading to a recommendation for a label change indicating weight gain as an uncommon ADR. This analysis, utilizing data from a large real-world population of treated HIV patients, will provide additional information to support the signal evaluation.

7. RESEARCH QUESTION AND OBJECTIVE(S)

Primary:

1) Among new users of DTG, RPV, RAL, BIC*, EVG/c and DRV(/r/c): To describe BMI categories, weight, lipid levels (e.g. total cholesterol, HDL, LDL, triglycerides), and lipodystrophy at core agent initiation and at 6,12, and 24 months after core agent initiation, stratified by ART- naïve and ART-experienced.
2) Among ART-experienced new users of DTG vs. RPV, RAL, BIC*, EVG/c or DRV (/r/c): To estimate the association between specific core agent initiation and changes in BMI at 6, 12, and 24 months after core agent initiation.

Secondary:

1) Among ART-experienced patients who were suppressed at switch (stable switch) to DTG, RPV, RAL, BIC*, EVG/c, or DRV(/r/c): To describe BMI categories, weight, and lipid panels levels (e.g. total cholesterol, HDL, LDL) at core agent initiation, and at 6,12, and 24 months after core agent initiation

*Due to recent approval and more limited potential follow-up, patients taking BIC will be included for 6-month outcomes only.

8. RESEARCH METHODS

8.1. Study Design

Study objectives will be evaluated through an observational analysis of a clinical cohort utilizing prospectively-collected EMR data obtained from the OPERA Observational Database. Study participants will be identified from the most recent database build available.

Period of subject inclusion:

- 01AUG2013 (DTG-approval)
- 31DEC2017

Period of observation:

- 01AUG2013 (DTG-approval)
- 31DEC2018

Population:

- A diagnosis of HIV-1, a positive HIV-1 Western Blot, or a positive HIV-1 enzyme-linked immunosorbent assay (ELISA); and a detectable HIV-1 viral load test
- At least 18 years of age at the index date
- Male or female

- Prescribed one of the following core agents as part of a 3-drug regimen for the first time between 01AUG2013 and 31DEC2017:
    - DTG (Tivicay®, Triumeq®)
    - RPV (Edurant®, Complera®, Odefsey®)
    - RAL (Isentress®, Isentress HD®)
    - EVG/c (Vitekta®, Stribild®, Genvoya®)
    - DRV (/r/c) (Prezista®, Prezcobix®, Symtuza®)
    - BIC (Biktarvy®)

- Not exposed to >1 core agent of interest concurrently

Index date: The index date for an eligible patient is defined as the first date of the first regimen of interest ever prescribed to a patient after 01AUG2013.

Baseline period: The 12-month baseline period preceding the index date will be used to assess patient demographic and clinical characteristics. Data from the visit closest to the index date will be used for analysis.

Observation period: Patients will be observed from their index date until 6,12, and 24 months post-initiation of the regimen of interest, with the final study end date on 31DEC2018.

Censoring events: (i) End of follow-up (6,12, or 24 months after core agent initiation), (ii) cessation of continuous clinical activity*, (iii) core agent discontinuation, (iv) pregnancy, (v) death, or (vi) study end (31DEC2018).

> * Continuous clinical activity is defined as at least one clinic visit within a 12-month period. Patients failing to meet the continuous clinical activity requirement will be censored 12 months after their last contact.

8.2. Study Population and Setting

The analysis population will be identified from the OPERA Observational Database according to the inclusion criteria defined below.

Primary population

1) A diagnosis of HIV-1, a positive HIV-1 Western Blot, or a positive HIV-1-specific ELISA; and a detectable HIV-1 viral load test

2) At least 18 years of age at the index date
3) Male or female patients
4) Prescribed DTG, RPV, RAL, BIC, EVG/c and DRV(/r/c) as part of a 3-drug regimen for the first time between 01AUG2013 and 31DEC2017
5) Not exposed to >1 core agent of interest concurrently

Subjects with the following criteria will be excluded from the study sample:

1) HIV-negative
2) A diagnosis of HIV-2, a positive HIV-1/HIV-2 Multispot, a positive HIV-2-specific ELISA, a positive HIV-2 Western Blot or a detectable HIV-2 viral load test
3) Women who are considered pregnant at the index date
4) Transgender patients (potential for weight changes due to hormone use)

Secondary population

The study population for the secondary objectives will be a subset of the primary study population meeting the following additional inclusion criteria:

1) Patients switching to DTG, RPV, RAL, BIC, EVG/c or DRV(/r/c) as part of a 3-drug regimen for the first time between 01AUG2013 and 31DEC2017 (excluding ART-naïve patients)
2) Patients with a viral load <200 copies/mL at last viral load test prior to switch to core agent of interest

The descriptive primary objective (1) will be stratified by prior ART exposure (ART-naïve and ART-experienced. The primary objective assessing association between core agent and BMI change (2), and the secondary objective will be restricted to ART-experienced patients. ART-experienced will be defined as history of ART prior to initiation of the core agent of interest, or a baseline viral load of <1000 copies/mL.

8.3. Variables

8.3.1. Exposure definitions

Exposures

- First exposure to any core agent of interest (DTG vs. RPV, RAL, BIC, EVG/c or DRV(/r/c)), after inclusion in the OPERA database. Prior exposure to other core agents of interest is not allowed after inclusion in the OPERA database.

8.3.2. Outcomes of Interest

1. BMI/weight:
    - Weight (in kg) will be assessed at baseline, and at 6 months, 12 months, and 24 months after core agent initiation
    - BMI will be assessed at baseline, and at 6 months, 12 months, and 24 months after core agent initiation. BMI will be defined as:
        - $BMI = weight/height^2$
            - Weight measured in kg
            - Height measured in m
        - Baseline BMI identified using weight measured within 3 months prior to or on index date
    - BMI categories will be assessed at baseline, and at 6 months, 12 months, and 24 months after core agent initiation (shown in Table 11)
    - Changes in BMI after 6 months, 12 months, and 24 months on the core agent of interest will be calculated as:
        - $\Delta BMI = BMI_n - BMI_0$
            - Where BMI_n is BMI at 6, 12, or 24 months and BMI_0 is BMI at baseline
    - Changes in weight after 6 months, 12 months, and 24 months on the core agent of interest will be calculated as:
        - $\Delta Weight = Weight_n - Weight_0$

            Where $Weight_n$ is weight at 6, 12, or 24 months and $Weight_0$ is Weight at baseline
    - Time windows for BMI and weight
        - BMI/weight at 6 months: BMI measured the closest to 6 months after core agent initiation, between >3 and ≤9 months
        - BMI/weight at 12 months: BMI measured the closest to 12 months after core agent initiation, between >9 and ≤15 months
        - BMI/weight at 24 months: BMI measured the closest to 24 months after core agent initiation, between >21 and ≤27 months

2. Total cholesterol/HDL/LDL/triglycerides:

- Lipids (total cholesterol, HDL, LDL, triglycerides) will be assessed at baseline and at 6 months, 12 months, and 24 months after core agent initiation
- Time windows for lipid panels
  - Lipids at 6 months: lipids measured the closest to 6 months after core agent initiation, between >3 and ≤9 months
  - Lipids at 12 months: lipids measured the closest to 12 months after core agent initiation, between >9 and ≤15 months
  - Lipids at 24 months: lipid measured the closest to 24 months after core agent initiation, between >21 and ≤27 months
- Total cholesterol levels[1]
  - Normal: < 5.2 mmol/L or <200 mg/dl
  - Borderline Abnormal: ≥ 5.2 to < 6.2 mmol/L or ≥ 200 to < 240 mg/dl
  - Dyslipidemia: ≥ 6.2 to < 7.2 mmol/L or ≥ 240 to < 280 mg/dl
  - Severe dyslipidemia: ≥ 7.2 mmol/L or ≥ 280 mg/dl
- LDL levels[1]
  - Normal: < 2.5 mmol/L or <100 mg/dl
  - Borderline Abnormal: ≥ 2.5 to < 3.3 mmol/L or ≥ 100 to < 130 mg/dl
  - Dyslipidemia: ≥ 3.3 to < 4.1 mmol/L or ≥ 130 to < 160 mg/dl
  - Severe dyslipidemia: ≥ 4.1 to < 4.9 mmol/L or ≥ 160 to < 190 mg/dl
  - Very severe dyslipidemia: ≥ 4.9 mmol/L or ≥ 190 mg/dl
- HDL levels[1]
  - Normal: ≥ 1.54 mmol/L or ≥ 60 mg/dl
  - Borderline Abnormal: ≥ 1.03 to < 1.54 mmol/L or ≥ 40 to < 60 mg/dl
  - Dyslipidemia: < 1.03 mmol/L or < 40 mg/dl

[1] Cut-offs obtained https://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf

- Triglycerides levels[1]
  - Normal: < 1.7 mmol/L or <150 mg/dl
  - Borderline Abnormal: ≥ 1.7 to < 2.25 mmol/L or ≥ 150 to < 200 mg/dl
  - Dyslipidemia: ≥ 2.25 to < 5.64 mmol/L or ≥ 200 to < 500 mg/dl
  - Severe dyslipidemia: ≥ 5.64 mmol/L or ≥ 500 mg/dl

3. Lipodystrophy:
   - Existing lipodystrophy: diagnosis of lipodystrophy within 12 months prior to or on index date
   - New lipodystrophy: new diagnosis of lipodystrophy at 6, 12, or 24 months after core agent initiation

   A diagnosis of lipodystrophy will be identified in the EMR by searching for diagnosis codes and text consistent with lipodystrophy, lipohypertrophy, lipoaccumulation, hyperadiposity, or lipoatrophy.

Table 1. Changes in BMI categories

Baseline	**Follow-up**
Underweight (BMI: <18.5)	Underweight (BMI: <18.5)
	Normal weight (BMI: 18.5 – 24.9)
	Overweight (BMI: 25.0 – 29.9)
	Obese (BMI: ≥30)
Normal weight (BMI: 18.5 – 24.9)	Underweight (BMI: <18.5)
	Normal weight (BMI: 18.5 – 24.9)
	Overweight (BMI: 25.0 – 29.9)
	Obese (BMI: ≥30)
Overweight (BMI: 25.0 – 29.9)	Underweight (BMI: <18.5)
	Normal weight (BMI: 18.5 – 24.9)
	Overweight (BMI: 25.0 – 29.9)
	Obese (BMI: ≥30)
Obese (BMI: ≥30)	Underweight (BMI: <18.5)
	Normal weight (BMI: 18.5 – 24.9)
	Overweight (BMI: 25.0 – 29.9)
	Obese (BMI: ≥30)

8.3.3. Study covariates

The following patient demographic and clinical characteristics will be assessed when first entering the healthcare setting at one of the designated clinics or within the 12-month baseline period preceding the index date. Data from the visit closest to the index date will be used for analysis.

Demographic variables

- Age
  - Continuous (years)
  - Categorical:
    i. 18-25 years old
    ii. 26-49 years old
    iii. 50+ years old
- Gender
- Race/ethnicity (Black non-Hispanic, Black Hispanic, non-Black Hispanic, American Indian, Native Hawaiian, Pacific Islander, Asian, White non-Hispanic)
- History of injection drug use (yes/no)
- Marital status (e.g., single, married/domestic partnership, widowed, divorced/separated, unknown)
- Geographic region (i.e., Northeast, Midwest, South, West)
- Payer type (i.e. Medicaid, Medicare, commercial insurance, AIDS drug assistance programs (ADAP)/Ryan White, cash, no payer information available)

Virologic variables

- HIV viral load at baseline
  - Continuous (copies/mL and $\log_{10}$ copies/mL)
  - Categorical (naïve):
    - Low (<10,000 copies/mL)
    - Moderate (≥10,000 to <100,000 copies/mL)
    - High (≥100,000 copies/mL)
    - Missing
  - Categorical (experienced):
    - Undetectable (<50 copies/mL)
    - Suppressed (≥50 to <200 copies/mL)
    - Viremic (≥200 copies/mL)
    - Missing

Immunologic variables

- CD4 cell count at baseline
  - Continuous (cells/µL)
  - Categorical:
    - High (CD4 > 500 cells/µL)
    - Moderately High (CD4 count >350 to ≤500 cells/µL)
    - Moderate (CD4 count >200 to ≤350 cells/µL)
    - Moderately Low (CD4 count >50 to ≤200 cells/µL)
    - Low (CD4 count ≤50 cells/µL)
    - Missing

Clinical variables

- Year of ART initiation
- Length of previous regimen (ART-experienced patients only)
- Time between index and end of follow-up (months)
- AIDS defining illnesses at baseline
- Mortality Risk (VACS Mortality Index)
- Comorbid conditions occurring on or before the index date (including T2DM and thyroid disease)
- HCV and HBV co-infection
- Blood pressure
- Concomitant medications associated with weight gain [31, 32] (these medications will be characterized and considered for inclusion in the statistical adjustment set)
  - Definite:
    i. Antipsychotics and mood stabilizers
       1. chlorpromazine, clozapine, haloperidol, lithium, olanzapine, valproic acid, risperidone, quetiapine

    ii. Antidepressants
       1. phenelzine, tranylcypromine, citalopram, amitriptyline, nortriptyline, mirtazapine, paroxetine

    iii. Antihyperglycemics
       1. insulin, chlorpropamide, gliclazide, glyburide, pioglitazone, rosiglitazone, repaglinide, tolbutamide, rosiglitazone

    iv. Antihypertensives
       1. atenolol, metroprolol

    v. Corticosteroids

1. cortisone, prednisolone, prednisone, methylprednisolone, hydrocortisone

vi. Hormones
1. human growth hormone/somatropin
2. medroxyprogesterone

vii. Anticonvulsants
1. Gabapentin, valproic acid/sodium valproate, carbamazepine

viii. Antihistamines
1. cyproheptadine

- Concomitant medications associated with weight loss (these medications will be characterized and considered for inclusion in the statistical adjustment set)
  - Definite:

i. Anti-infectives
1. metronidazole, amphotericin, atovaquone, pyrimethamine, ethionamide

ii. Antineoplastics
1. aldesleukin and interleukin-2, capecitabine, carboplatin, cytarabine, dacarbazine, fluorouracil, hydroxyurea, imatinib, irinotecan, methotrexate, vinblastine sulphate, vinorelbine tartrate

iii. Bronchodilators
1. salbutamol sulphate, theophylline

iv. Cardiovascular drugs
1. amiodarone, acetazolamide, hydralazine HCl, quinidine

v. Stimulants
1. methylphenidate HCl, phentermine

vi. Antidepressants
1. fluoxetine, bupropion

vii. Anticonvulsants
1. topiramate

viii. Antihyperglycemics
1. exenatide, liraglutide, semaglutide

ix. Anti-inflammatories
1. sulphasalazine

x. Weight loss drugs
1. bupropion-naltrexone, liraglutide, lorcaserin, orlistat, phentermine-topiramate

xi. Dementia treatment
1. galantamine, rivastigmine

- Number of classes of ART experience prior to baseline (ART-experienced patients only)

8.4. Data sources

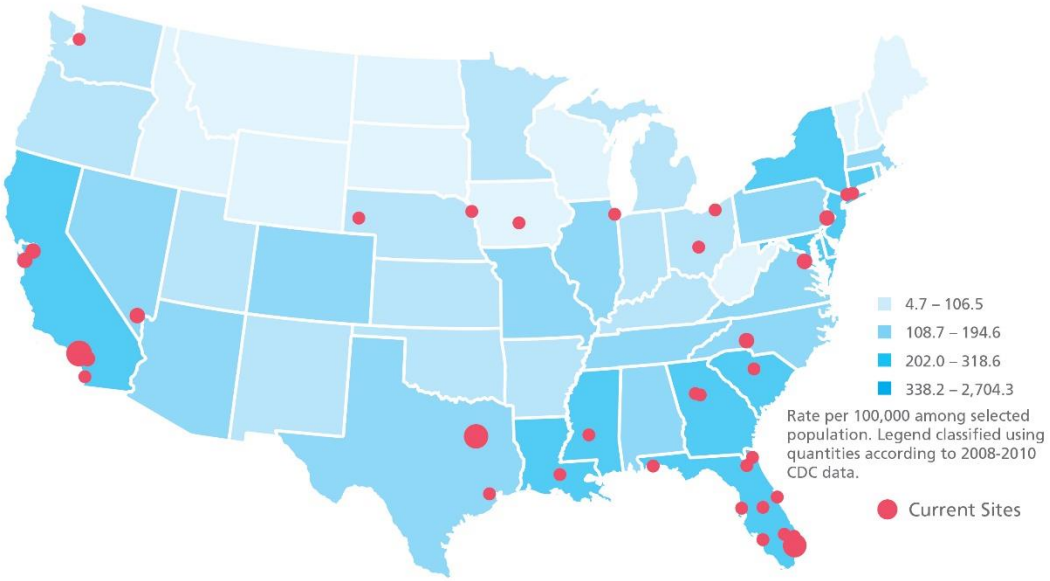
The OPERA® (Observational Pharmaco-Epidemiology Research & Analysis) database and research network is a multi-site observational database built from the complete patient health records managed in Electronic Health Record (EHR) systems from more than 400 participating caregivers 81 separate locations throughout the U.S. (see coverage map below).

Through their membership in OPERA, medical practices meet the Centers for Medicare & Medicaid Services (CMS) Electronic Health Record (EHR) Incentive Program for Integration with a Specialized Registry. OPERA-participating physicians and ancillary healthcare providers have documented the care of over 800,000 patients in their EHRs, including 80,000 HIV+ patients of which 14.8% are women, representing 7 percent of all the HIV+ patients linked to care in the U.S. The OPERA database is refreshed from these EHR databases at each clinic on a daily basis, making the OPERA database the largest continuously operating cohort of HIV+ patients in the U.S.

In total, there are more than 2.5 million documented prospective visits in the EHR systems for these HIV+ patients and 2.6 million prescriptions written for ART medications. The average years of follow-up (years of documenting patient visits prospectively in the EHR) for patients in OPERA is 4.2 years and there are 5,479 HIV+ patients who have nine years or more of follow-up.

In addition to HIV treatment, OPERA captures the diagnosis and treatment of co-morbid conditions and diagnoses of HIV negative patients. Epividian analyses other serious co-morbid conditions such as Hepatitis C with about 8% of HIV+ patients in OPERA co-infected.

Figure 1.. U.S. Map of OPERA HIV+ Population & CDC (2010) State-by-State Estimates



8.5. Data analysis

For each time point assessed (6,12, or 24 months), the study population will be restricted to patients with a follow-up greater or equal to that time point.

8.5.1. Analysis of primary objectives

Baseline descriptive analyses of demographic and clinical characteristics

Descriptive statistics will be conducted for patients prescribed a core agent of interest between 01AUG2013 and 31DEC2017. All baseline covariates listed in sections 8.3.2. and 8.3.3. will be described, as well as baseline BMI, weight, lipodystrophy and lipid panels; medians and interquartile ranges for continuous variables and counts and percentages for categorical variables will be provided. Pairwise comparisons between DTG and each of the other core agent groups will be evaluated by p-values calculated from the Pearson Chi-Square test for categorical variables. The Fisher's exact test will be used to compare frequencies with few events. The Wilcoxon Rank Sum test will be used to calculate p-values for continuous variables.

Description of follow-up levels of total cholesterol, HDL, LDL, triglycerides, weight and BMI

Lipids (total cholesterol, HDL, LDL, triglycerides), weight and change in weight, and BMI and change in BMI will be assessed continuously and compared between patients for each core agent at 6,12, and 24 months after initiation. BMI and lipids will also be assessed categorically, as the proportion of patients in each BMI and lipid category and the proportion of patients changing categories of BMI (see section 8.3.2 for a definition of changes in categories). Given that the data reflect routine clinical care, not all patients will have the lab values of interest at each time point. The denominator for proportions will be patients tested, excluding those with missing values. Pairwise comparisons will be performed using Pearson Chi-Square test or Fisher's exact test for categorical variables and Wilcoxon Rank Sum test for continuous variables.

Description of existing lipodystrophy at core agent initiation and new diagnoses of lipodystrophy

Existing lipodystrophy will be assessed as the proportion of patients diagnosed with lipodystrophy 12 months prior to or on the index date among patients initiating each core agent of interest. New cases of lipodystrophy will be assessed as the proportion of patients who develop lipodystrophy at 6,12, or 24 months after initiation among patients without lipodystrophy at baseline. Pairwise comparisons will be performed using Pearson Chi-Square test or Fisher's exact test.

Association between type of core agent initiation and changes in BMI:

Adjusted linear regression models will be used to assess the association between core agent and mean changes in BMI at 6, 12, and 24 months. Baseline variables included in the adjusted model will be selected a priori, based on the literature, including baseline age, sex, race/ethnicity, comorbid conditions and concomitant medications associated with weight gain and weight loss [33, 34], as well as change in viral load and CD4 cell count. Factors associated with the exposure and the outcome identified in the descriptive analyses will be considered for inclusion in the adjusted model if the requirements for confounding are met. Inverse probability-of-censoring weights will be used to account for patients who discontinue treatment or are lost to follow-up and constructed using a logistic regression model.

*This analysis will be stratified by baseline BMI categories (underweight, normal weight, overweight, obese).

8.5.2. Analysis of secondary objectives

These analyses will be conducted only among ART-experienced new users of RPV, RAL, EVG/c, BIC, DRV(/r/c), or DTG who were virologically suppressed at the time of switch to a core agent of interest (stable switch). Using data from the most recent visit in the 12-month baseline period preceding the index date of core initiation, patients with a HIV-1 RNA viral load measurement < 200 copies/mL will be considered suppressed.

Baseline demographic and clinical characteristics

All baseline outcomes and covariates listed in sections 8.3.2. and 8.3.3. will be summarized for patients who have achieved virologic suppression (<200 copies/mL) prior to switch to RPV, RAL, EVG/c, DRV(/r/c), BIC, or DTG between 01AUG2013 and 31DEC2017; medians and interquartile ranges for continuous variables and counts and percentages for categorical variables will be provided.

Description of follow-up levels of total cholesterol, HDL, LDL, triglycerides, weight and BMI

Total cholesterol, HDL, LDL, triglycerides, weight, and BMI will be assessed continuously at 6,12, and 24 months after initiation. BMI and lipids will also be assessed categorically, as the proportion of patients in each BMI and lipid category and the proportion of patients changing categories of BMI among patients initiating each core agent of interest (see section 8.3.2 for a definition of changes in categories).

8.5.3. Study size considerations

The sample size required to detect a range of differences in mean BMI with 80% power for the adjusted linear regression looking at the association between specific core agent initiation and continuous BMI has been estimated under the following assumptions [35]:

- Number of predictors:
  The exposure of interest is a 5-level categorical variable, which is equivalent to 4 factor variables, thus requiring 4 degrees of freedom. Calculations were performed assuming a total of 10 covariates included in the model in addition to the exposure variables.

- Effect and variability:

Partial correlations ranging from 0.02 to 0.20 were assumed, corresponding to detectable differences in mean BMI ranging from 0.04 to 0.41. The equivalence between partial correlation and difference in mean BMI was calculated as:

$$\rho = \frac{d}{\sqrt{d^2 + 4}}$$

where ρ = partial correlation and d = difference in mean BMI

The sample sizes required to detect effect sizes ranging from ρ=0.02 to ρ=0.20 with 80% power are presented numerically with corresponding differences in mean BMI (Table 2). They are also presented graphically across a range of partial correlations in Figure 2, along with the estimated sample size available in each stratum of baseline BMI in OPERA, based on the following assumption:

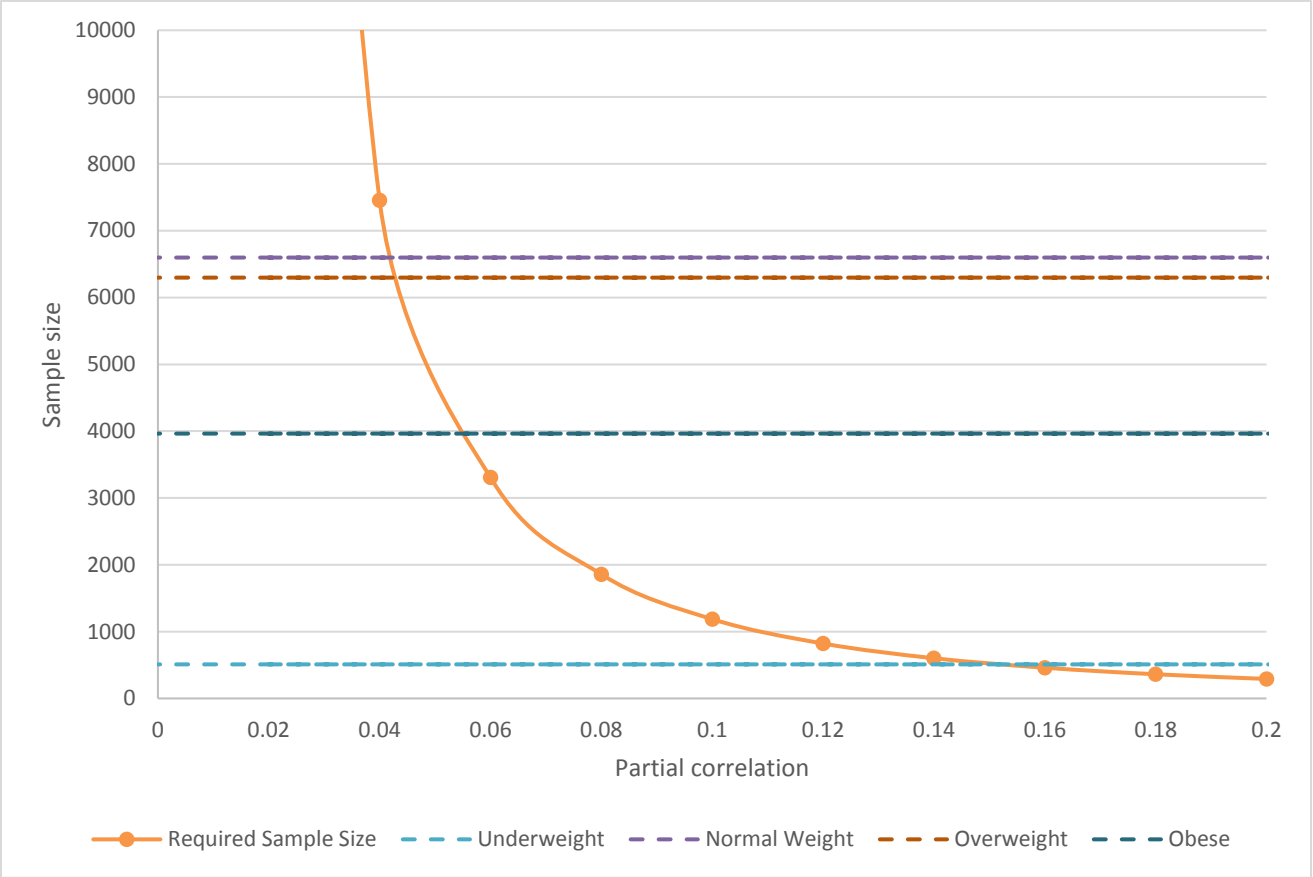
- Estimated sample size in OPERA, stratified by baseline BMI category:
  As of August 17, 2018, there were 91,415 HIV+ patients in OPERA, among whom 17,370 were ART-experienced, had a baseline BMI and initiated one of the core agents of interest for the first time between August 01, 2013 and December 31, 2017. Of these, 510 patients were underweight, 6,598 were normal weight, 6,298 were overweight, and 3,964 were obese at baseline.

Table 2. Required sample size for the multivariate linear regression of BMI on core agent, by correlation factor and difference in mean BMI, assuming 80% power

Power	Correlation Factor	Difference in Mean BMI	Sample Size Required*
0.80	0.02	0.04	29832
0.80	0.04	0.08	7453
0.80	0.06	0.12	3309
0.80	0.08	0.16	1858
0.80	0.10	0.20	1187
0.80	0.12	0.24	822
0.80	0.14	0.28	602
0.80	0.16	0.32	460
0.80	0.18	0.37	362
0.80	0.20	0.41	292

*The estimated sample sizes for each BMI stratum are 510 patients classified as underweight; 6,598 classified as normal weight; 6,298 classified as overweight; and 3,964 classified as obese

Figure 2. Sample size required and available for the multivariate linear regression of BMI on core agent, by correlation factor



These estimates of sample size required to detect a range of differences in mean BMI are likely a overestimation of the sample size required when inverse probability of censoring weights are included. However, given the use of a continuous outcome, the minimal detectable difference in mean BMI remains small even with sample sizes much smaller than the estimated sample size available in OPERA. For example, only 292 patients are required to detect a difference of 0.4 units in BMI; the smallest stratum available in OPERA is the underweight group, with 510 patients.

The method employed here is considered appropriate when calculating sample sizes for a multiple regression analysis with continuous or categorical predictors, and a continuous outcome [35, 36]. Our approach is based on partial correlations, but an alternative is based on the proportion of variation explained by the model (R^2) [37]. However, the R^2 approach requires knowledge of the expected R^2 values for the full and reduced models (or the difference between them) based on previous research. The R^2 approach seemed less appropriate in this setting due to the lack of published data on the relationship between the core agents of interest in this study and BMI. Another method is to perform sample size calculations based on the one-way analysis of variance (ANOVA) [38]. One important limitation of this approach is that the influence of additional covariates in the model are not accounted for in these power calculations which assumes one degree of freedom. Another limitation of the one-way ANOVA approach is that it requires making some assumptions about the data that may not be

appropriate, such as the mean BMI for each of the five exposure groups and the overall standard deviation [38].

8.6 Quality control and quality assurance

Epividian has working practices & procedures governing the use of observational data, the development of analysis specifications and plans, the development of analytical programming and the analytical quality assurance (QA) process and the scientific review of reports as well as clinical advisory charters for the clinical review of output intended for public domain. Working practices for the development of analysis specifications include basic identifying information, background material, relevant definitions of key study variables, population definitions, baseline definitions, specific requirements for dataset creation, and statistical requirements such as eligibility criteria, exposures, outcomes and model fitting. Working practices for programming include naming conventions, proper code documentation and commentary, content, appearance, efficiencies (i.e. use of macros), and organization of output, maintainability and generalizability. Working practices for programming QA include self-reviews of observational counts, missing data values, many-to-many merges, variable formatting, numeric-character & character-numeric conversions, uninitialized variables, unresolved macro references, report completeness and report-to-specification correspondence, and system errors and logs. The QA team review may include small sample spot-checking, coding log reviews, complete coding review, selected observations from intermediary dataset reviews, and/or independent programming to reproduce the results. Documentation of non-public domain reports includes market, scientific, statistical, and clinical review. Documentation of scientific protocols, reports and manuscripts intended for public domain follows two sequential steps: an internal-to-Epividian epidemiological, statistical, and clinical review, followed by a clinical/epidemiological external advisory board review.

All analytical data, coding algorithms, QA documentation and report outputs will be retained per Epividian standard practices.

9. PROTECTION OF HUMAN SUBJECTS

Clinical information is originally compiled into separate CHORUS databases for each clinic. This PHI is used in the creation of the CHORUS analytics and reporting used by each practice and its providers as part of Quality Improvement activities in an effort to improve care of patients. The data collection occurs via a secure and encrypted connection as part of Epividian's privacy and security policies and systems, which are routinely reviewed by a third-party privacy and security advisory organisation.

Subsequently, the clinical data in each CHORUS database is de-identified and aggregated into the OPERA® Database following the guidelines of the Health Insurance Portability

and Accountability Act (HIPAA) and the Health Information Technology for Economic and Clinical Health Act (HITECH).

9.1. Ethical approval and subject consent

Business Associate Agreements (BAAs) in place between Epividian and all medical practices govern, following the guidelines established in HIPAA and HITECH, the encryption, transportation, aggregation, de-identification and use of all clinical data in either the CHORUS reporting platform or the OPERA® Database. All medical practices are responsible for obtaining proper HIPAA consent for their patients. With BAAs in place and subsequent de-identification, a separate informed consent for each individual, non-interventional study is not required.

9.2. Subject confidentiality

All clinical data in CHORUS is PHI and managed as such according to HIPAA, HITECH and relevant state regulations. The CHORUS portal, as a Quality Improvement activity, is accessed securely by clinic staff to view PHI for only those patients seen at the practice. All clinical data is subsequently de-identified as per HIPAA and HITECH in OPERA® with all reports submitted at the aggregated population level in OPERA®. No personally identifiable information is available in the OPERA® Database. The OPERA® Epidemiology & Clinical Advisory Board provides clinical and methodological review & oversight.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

There is no potential to collect serious and non-serious adverse events (AEs), pregnancy exposures, or incidents related to any ViiV Healthcare product during the conduct of this research, as the minimum criteria needed to report AEs, pregnancy exposures, and incidents are not present in the data source. Specifically, the data are insufficient to establish attribution between a potential safety event and an individual patient using a ViiV Healthcare product as the study design is to analyse the patient level information recorded in the OPERA database from electronic health records in an aggregate manner. Therefore, a study specific pharmacovigilance plan will not be developed.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Target Audience

Health care practitioners, health plan population based decision-makers.

11.2. Study reporting and publications

Final report to be submitted to sponsor. Study results will be submitted to a conference or a peer reviewed journal.

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13. APPENDICES

13.1. DHHS 2017 Guideline Recommendations for Initiation and Continuation of Therapy for HIV Infection

	INSTI	PI	NNRTI
Recommended	• DTG/ABC/3TC • DTG + TDF/FTC • DTG + TDF + 3TC • EVG/c/TDF/FTC • RAL + TDF/FTC • RAL + TDF + 3TC • DTG + TAF/FTC • DTG + TAF + 3TC • RAL + TAF/FTC • RAL + TAF + 3TC • EVG/c/TAF/FTC		
Recommended in Certain Clinical Situations	• RAL + ABC/3TC	• (DRV/r or /c) + TDF/FTC • (DRV/r or /c) + TAF/FTC • DRV/c/TAF/FTC • (ATV/r or /c) + TDF/FTC • (ATV/r or /c) + TAF/FTC • (DRV/r or /c) + ABC/3TC • (ATV/c or /r) + ABC/3TC	• EFV/TDF/FTC • EFV + TAF/FTC • RPV/TDF/FTC • RPV/TAF/FTC
Consider when ABC, TDF, TAF cannot be used		• DRV/r + RAL • LPV/r (bid) + 3TC (bid)	