Bictegravir in the Elderly Living with HIV: Impact of Polypharmacy and Multimorbidity

Investigators: Qing Ma, PharmD, PhD, Allyssa Shon MD

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TEAM ROSTER

Qing Ma, PharmD, PhD
NYS Center of Excellence in Bioinformatics and Life Sciences
Department of Pharmacy Practice
University at Buffalo

Allyssa Shon, MD
Medical Director
Evergreen Health
Department of Medical
School of Medicine and Biomedical Sciences
University at Buffalo

Fatai Gbadamosi, MD
Senior Medical Director
Evergreen Health

Sibu Nair, MS
Clinical Trials Administrator
Evergreen Health

Shih-Ping Lin, MD
NYS Center of Excellence in Bioinformatics and Life Sciences
Department of Pharmacy Practice
University at Buffalo

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SCHEMA

Bictegravir in the Elderly Living with HIV: Impact of Polypharmacy and Multimorbidity

DESIGN: Prospective, open-label, single center switch study

SAMPLE SIZE: 160 evaluable HIV-infected subjects on Genvoya™ or Stribild™

REGIMEN: The project will have two phases: screening and treatment.

Screening:
HIV-infected subjects will be screened and enrolled into polypharmacy (PP, n=80) and non-PP groups (n=80). Baseline assessment will be performed.

Treatment:
Days 1-168: Administer bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF), containing 50 mg BIC, 200 mg FTC and 10 mg TAF single-tablet regimen, PO q day
Day 28: Week-4 assessment
Day 56: Week-8 assessment
Day 84: Week-12 assessment
Day 168: Week-24 assessment

STUDY DURATION: 24 Weeks

OBJECTIVES:

Primary:
1. Describe a decrease in PDDI when switched from Genvoya™ or Stribild™ to BIC/FTC/TAF in polypharmacy and non-polypharmacy subjects;
2. Determine the impact of PDDI reduction on health-related quality of life.

Secondary:
1. Determine adherence to BIC/FTC/TAF;
2. Determine changes in blood pressure, glucose, and lipid profiles after the switch.

ENDPOINTS:

Primary:
1. Incidence of PDDI prior to and after the switch
2. Health related quality of life assessments at baseline, week 12, and week 24.

Secondary:
1. Adherence at baseline, week 4, week 8, week 12, and week 24;
2. Lipid panel, blood pressure and blood glucose levels at baseline, week 12, and week 24

1.0 INTRODUCTION

1.1 Background

Antiretroviral treatment consisting of integrase strand inhibitors (INSTI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) has become the standard of therapy for HIV-1 infected patients (2017 DHHS Guidelines)[1]. The development and advancement of such therapy have resulted in improved prognosis, allowing a larger proportion of patients in United States (> 50%) with HIV-1 infection to be 50 years of age or older, which is defined by the CDC as "older adults"[2]. A novel INSTI, bictegravir, has been recently approved by FDA, available in a fixed dose combination with emtricitabine (FTC) and tenofovir alafenamide (TAF) as a novel single-tablet regimen (STR), BIKTARVY®. Similar to other INSTI, bictegravir prevents HIV replication by inhibiting HIV integration into the host cell. *In vitro* studies have shown its selectivity against HIV-1 infected cells with a low cytotoxic profile[3].

Elvitegravir, boosted with cobicistat, is currently available as part of a single-tablet formulation with FTC and TAF (Genvoya™) or with FTC and TDF (Stribild™). Unlike ritonavir, cobicistat has no antiretroviral activity, but has potent inhibitory effects on CYP3A4[4]. Elvitegravir is primarily metabolized by CYP3A4 and its co-administration with cobicistat boosts elvitegravir plasma concentration and prolongs its half-life[4]. Concurrent use of a potent CYP3A4 inhibitor, *e.g.*, cobicistat, with medications that are metabolized by CYP3A4 can significantly increase the risk of drug-drug interactions. With an increase in the average survivability age of HIV-infected patients, chances of polypharmacy due to multimorbidity, a term used to define the presence of two or more concurrent chronic medical conditions, increases[5]. Two studies have demonstrated that older HIV+ individuals engaged in polypharmacy are more likely to experience potential drug-drug interactions (PDDI). Many chronic medications such as antidepressants, HMG-CoA reductase inhibitors (statins), and cardiovascular medications are metabolized by CYP3A4. Concurrent administration of these medications with Genvoya™ and Stribild™can lead to increases in PDDI. Such interactions can result in more adverse drug reactions, drug-related toxicity of narrow therapeutic index drugs, and variations in the efficacy of concurrent medications. However, unlike elvitegravir, bictegravir does not require a booster such as cobicistat for pharmacokinetic enhancement. Its use can result in reductions in PDDI caused by cobicistat in adults with polypharmacy. This can improve quality of life in general, adherence and can directly avoid DDI-related adverse effects[6,7].

Although antiretroviral therapy (ART), when used concurrently with certain medications, has an increased risk of PDDI, studies have suggested a low DDI profile of bictegravir[3,8]. In this study, such benefits of bictegravir will be assessed through the evaluation of polypharmacy, PDDI, health-related quality of life, and adherence[9,10] of HIV-infected subjects.

1.2 Rationale

The goals of the study are to 1) evaluate the probability of PDDI when switched from Genvoya™ (E/C/F/TAF) or Stribild™ (E/C/F/TDF) to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in polypharmacy adults, and 2) to determine the impact of BIC/FTC/TAF therapy on health-related quality of life and adherence. No published studies have addressed the following questions: 1) Is there a reduction in PDDI in polypharmacy HIV-infected adults when switched from a cobicistat containing regimen such as Genvoya™ to BIC/FTC/TAF? 2) What is the impact of polypharmacy on the health-related quality of life and on adherence in HIV-patients on BIC/FTC/TAF therapy? Current medical literatures have identified polypharmacy as one of the

predictors for the occurrence of potential drug interactions. The risk of potential drug interaction increases from 39% to 100% when patients are on more than six medications compared to when they are on 2-3 medications. Through an established collaborative network, we will address these questions in a prospective, open-label treatment trial of stable HIV-infected subjects currently on Genvoya™ or Stribild™ switching to BIC/FTC/TAF.

BIC/FTC/TAF related adverse drug events are possible in the study. Due to bictegravir's recent FDA approval, a comprehensive list on the possible adverse drug events has become available. Common side effects reported in clinical phase II and phase III studies include diarrhea, nausea, and headache[12]. Serious adverse events, including lactic acidosis, severe hepatomegaly have been reported with nucleoside reverse transcriptase inhibitors, but are uncommon. The standard regimen of BIC/FTC/TAF will be used; if a regimen change occurs, participation in the study will be discontinued. Participants will be carefully screened and those with pre-conditions, such as morbid obesity, hepatitis B virus, hepatitis C virus co-infection will be documented in the study.

1.3 Study Design

HIV-1 infected subjects on Genvoya™ or Stribild™ will be the study population. We will screen and enroll subjects. All subjects will switch from Genvoya™ or Stribild™ to BIC/FTC/TAF. Initial recruitment will occur after the IRB approval of this protocol.

1.3.1 Among 1,377 HIV+ patients at Evergreen Health, 96% (n=1,323) are currently receiving ART. The common regimens include protease inhibitors (n=303, 23%), integrase inhibitors (n=779, 59%), efavirenz or daily nevirapine (n=340, 26%). The demographics of patients on Genvoya™ and Stribild™ are summarized as follows:

Table 1. Demographics of patients on Genvoya™ or Stribild™ in Evergreen Health

	< 50 Years of Age	**≥ 50 Years of Age**	**Total**
Gender			
Male	132	94	226
Female	40	27	67
	172	121	293
Current Single Tablet Formulation Containing Integrase Inhibitor			
Genvoya™	118	87	205
Stribild™	54	34	88
Total	172	121	293

1.3.2 The patients with or without polypharmacy were summarized as Table 2.

Table 2. Polypharmacy (PP) in patients on Genvoya™ or Stribild™ in Evergreen Health

	PP (w/HM)	**nPP (w/HM)**	**PP (w/o HM)**	**nPP (w/o HM)**
Total n=191 # (%)	165 (86)	26 (14)	112 (59)	79 (41)
Age <50, n=107, # (%)	84 (79)	23 (21)	50 (47)	57 (53)
Age >=50, n=84, # (%)	81(96)	3 (4)	62 (74)	22 (26)

PP: polypharmacy; nPP: non-polypharmacy; defined as ≥5, HM: HIV medications

1.3.3 Schematic outline of the protocol is below

	Screening	BL	Week 4	Week 8	Week 12	Week 24	Discontinuation Visit
Time window (Day)	-42 to -1	0	21-35	49-63	77-91	161-175	
Informed consent (including eligibility assessment)	x						
Full assessment		x			x	x	x
HIV 20-Item Symptom Index		x			x	x	x
SF-12		x			x	x	x
Study drug dispensing (^including adherence assessment)		x	x^	x^	x^	x^	
Safety assessment (ADR)			x	x	x	x	x
Laboratory Assessments							
Blood							
Resistance Testing*			x	x	x	x	
HCV	x						
HBV	x						
RPR	x						
CD4+	x	x	x		x	x	
Hematology	x		x			x	
Chemistry (incl. liver func. & lactate)	x		x			x	
Prothrombin Time	x		x			x	
Plasma HIV RNA	x	x	x	x	x	x	
Chemistry (inc. albumin)		x	x			x	
Complete blood cholesterol							
HDL Levels		x				x	
LDL Levels		x				x	
Triglycerides		x				x	
Total Cholesterol		x				x	
Blood Glucose		x	x		x	x	
Vitals	x	x	x	x		x	
Urine							
Urine drug screen		x	x			x	
Urinalysis	x	x	x			x	
hCG*	x	x	x	x	X	x	

BL= Baseline; SF-12: short form health survey; *if indicated

1.3.4 The diagnosis of multimorbidity will be based upon clinical assessments and documentation from the electronic medical record database. Polypharmacy data with a focus on the total number and category of prescriptions medications corresponding to each multimorbidity will be collected throughout the study. PDDI will be particularly evaluated between cobicistat and cardiovascular, dyslipidemia, diabetes, psychiatric and other comorbidity-based medications. The probability of polypharmacy related PDDI risk will be evaluated using a software program based on the Drug Interaction and Probability Scale (DIPS) and current evidence[12]. The Contraindications and Drug Interactions sections of Genvoya™, Stribild™ and BIC/FTC/TAF monograph will be reviewed for PDDIs. PDDIs will be classified using categories defined by the University of Liverpool HIV Pharmacology Group[6,8]. “Red flags” will be combinations that are contraindicated or not to be coadministered. “Orange flags” include

combinations that should not be coadministered, could be given with dose adjustment or increased monitoring, or have not been studied for safety, efficacy, or clinical significance. An expert pharmacist will approve the product monograph abstraction instructions and review any unclear PDDIs. Product monographs for non-ARV medications will not be reviewed, and interactions among non-ARVs will not be studied.

1.3.5 Adherence will be assessed by pharmacy refills and pill count.

1.3.6 Health-related quality of life will be evaluated primarily using the 20-question HIV Symptom Index (HSI) for symptom distress, originally designed by the AIDS Clinical Trials Group (ACTG)[13,14]. The HSI is strongly associated with the physical and mental health summary scales of the MOS-HIV measure, disease severity, and is independent of CD4 cell count and viral load. Short form health survey (SF-12) will also be used to measure the impact of HIV infection on subject's health related quality of life.

1.4 Minimizing Risks to Subjects

Risks and reported adverse events of BIC/FTC/TAF will be clearly explained to each subject during the informed consent process. At each study visit, the study nurse will ask participants to report any symptoms they experience while taking BIC/FTC/TAF. Participants will be instructed to contact the Clinical Trials Unit in the event of adverse events by telephone 24 hours a day/7 days a week. Following a telephone interview, the Clinical Trials Unit will schedule a visit for an additional assessment as necessary. For serious adverse events, participants will be instructed to immediately discontinue BIC/FTC/TAF and to go the closest emergency room. Any Grade 3 or higher symptoms or laboratory abnormalities will result in termination of BIC/FTC/TAF. Subjects who experience renal function abnormalities with estimated creatinine clearance below 30 ml/min will also have the study drug terminated and complete the evaluations listed in Section 4.2. Subjects will also have the study drug terminated in cases of suspected drug-related toxicity, taking prohibited concomitant medications (see section 6.4.2), if a female subject is pregnant or breast-feeding, if the subject is judged by the investigators to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results, at the discretion of the investigator, institutional review board (IRB), FDA, pharmaceutical sponsor; or if the subject requests to withdraw from the study. In case of injury or serious adverse events, the investigators will assist the subject in obtaining appropriate medical treatment.

2.0 STUDY OBJECTIVES

2.1 Primary

2.1.1 Describe a decrease in PDDI when switched from Genvoya™ or Stribild™ to BIC/FTC/TAF in polypharmacy and non-polypharmacy subjects.
2.1.2 Determine the impact of PDDI reduction on health-related quality of life.

2.2 Secondary

2.2.1 Determine adherence to BIC/FTC/TAF.

2.2.2 Determine changes in blood pressure, glucose and lipid profiles after the switch

3.0 SELECTION AND ENROLLMENT OF SUBJECTS

Recruitment of Subjects

HIV-1 infected subjects will be recruited via IRB-approved posters and flyers and advertisements in local publications. IRB-approved flyers will also be posted in approved areas of the Evergreen Health. All necessary precautions will be taken to ensure participants confidentiality. Participants will be informed in the informed consent document that their participation shall be confidential and their information shall be protected.

3.1 Inclusion Criteria

3.1.1 Adult individuals > 18 years of age.

3.1.2 Able and willing to provide informed/signed consent.

3.1.3 Presence of HIV-1 infection as documented by a licensed ELISA test kit and confirmed by Western blot or HIV RNA.

3.1.4 Current antiretroviral therapy, Genvoya™ or Stribild™ for HIV-1 infection.

3.1.5 At least 1 or more concurrent prescription medication.

3.1.6 HIV VL < 50 for over 6 months, no current OI, no cancers

3.2 Exclusion Criteria

3.2.1 Use of drugs of abuse or alcohol which would interfere with adherence or completion of this study.

3.2.2 Current antiretroviral therapy other than Genvoya™ or Stribild™ for HIV-1 infection.

3.2.3 Pregnancy or breast-feeding. Women of childbearing potential must have a negative serum or urine pregnancy test within 14 days prior to study entry and day of entry.

3.2.4 Chronic, severe, or other medical conditions that, in the opinion of the investigator, would interfere with the subject's ability to participate in the protocol.

3.2.5 Use of prohibited protocol-specified drugs, prescription or over-the-counter medication (see Section 6.4.2) within 14 days prior to study entry.

3.2.6 Moderate or severe cognitive impairment by history that, in the opinion of the investigator, would interfere with the subject's ability to participate in the protocol

3.2.7 Laboratory parameters documented within 21 days prior to study entry that would increase the risk for adverse events:

a. Hemoglobin < 12.5 g/dL for men; < 11.5 g/dL for women;
b. Platelet count < 100,000 platelets/mm 3;
c. AST (SGOT) or ALT (SGPT) > 1.5 x the upper limit of normal (ULN);
d. Estimated GFR < 30 ml/min

4.0 CLINICAL AND LABOATORY EVALUATIONS

Signs and symptoms, laboratory results, and toxicities ≥ Grade 3 will be recorded on the appropriate case report forms (CRFs).

4.1 Screening and Entry Evaluations

4.1.1 Screening evaluations will occur within 42 days of study entry

4.1.1.1 Details of the study will be carefully discussed with subjects during screening and the subject will be asked to read and sign an informed consent approved by the IRB at Evergreen Health.

4.1.1.2 Demographic information will be collected including age, sex, ethnicity, substance use, education, and employment.

4.1.1.3 Documentation of HIV infection, as specified in Section 3.1.2 prior to study entry.

4.1.1.4 Brief medical history will be obtained and will include:

4.1.1.4.1 Previous diagnosis including liver disease, renal disease, fracture, osteoporosis, allergies, drug reactions, and most recent menses.

4.1.1.4.2 Current prescription and non-prescription medications taken within 14 days prior to entry.

4.1.1.4.3 Antiretroviral drug exposure within 1 month prior to entry.

4.1.1.4.4 Recent use of drugs of abuse or unprotected sexual contacts. Past use of needles.

4.1.1.4.5 A signs-and-symptoms assessment, including: vital signs, height, and weight. Vital signs will include temperature, blood pressure, and pulse rate.

4.1.1.5 The following laboratory tests must be performed within 42 days prior to study entry, unless otherwise noted: (This is for the times when there is no recent blood work done.)

4.1.1.5.1 Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count, differential white blood cell count, and platelet count.

4.1.1.5.2 Blood chemistries: electrolyte, blood urea nitrogen (BUN), creatinine, creatine kinase, glucose, phosphorus, amylase, lactate, and calcium.

4.1.1.5.3 Liver function tests: total bilirubin, AST, ALT, alkaline phosphatase, and albumin.

4.1.1.5.4 Coagulation: prothrombin time, international normalized ratio, partial thromboplastin time.

4.1.1.5.5 Urinalysis, including urine glucose and protein.

4.1.1.5.6 Estimated glomerular filtration rate (eGFR)

4.1.1.5.7 For women of childbearing potential: Serum or urine pregnancy test.

4.1.1.5.8 HIV RNA in blood plasma.

4.1.1.5.9 Lymphocytes subset in blood (including CD4+ and CD8+ T-cell absolute counts and percent).

4.1.1.5.10 Hepatitis C and hepatitis B serological testing

4.1.1.5.11 Rapid plasmin reagent (PRP)

4.1.1.5.12 Drug resistance mutation genotyping in blood. If available, records documenting same can be obtained from Primary Care Physician in place of performing the drug resistance mutation genotyping.

4.1.2 Baseline (Entry) Evaluation: Within 42 days of the screening evaluation, eligible and consenting subjects will enter the study. Additional assessments will be performed and study drug will be dispensed.

4.1.2.1 A complete medical history and physical examination will be performed:

4.1.2.1.1 Prior diagnoses including liver disease, renal disease, fracture osteoporosis, allergies, drug reactions, and most recent menses.

4.1.2.1.2 Current symptoms including those of an active systemic illness (e.g., fever) and bleeding or easy bruising.

4.1.2.1.3 Prescription and non-prescription medication taken within 14 days prior to entry.

4.1.2.1.4 Antiretroviral drug exposure within 1 month prior to entry.

4.1.2.1.5 Weight, and vital signs, including temperature, blood pressure, and pulse rate.

4.1.2.1.6 20-question HIV Symptom Index and SF-12 Questionnaires

4.1.2.2 The following laboratory tests will be performed:

4.1.2.2.1 Complete blood cholesterol test: Total cholesterol, LDL, HDL, and triglycerides.

4.1.2.2.2 Metabolic Panel

4.1.2.2.3 Urinalysis

4.1.2.2.4 HIV RNA in blood plasma.

4.1.2.2.5 Lymphocytes subset in blood (CD4+ and CD8+ T-cell absolute counts and percent) including CD4+ T-cell peak and nadir levels.

4.1.2.2.6 For women of childbearing potential: Serum and urine pregnancy test.

4.1.2.2.7 A urine drug screen will be performed.

4.1.3 A four week supply of BIC/FTC/TAF will be dispensed.

4.2 On -Treatment Evaluations

4.2.1 Four-Week Assessment: Subject will return at day 28 (one-week window) for safety assessments that will include:

4.2.1.1 Brief safety-focused clinical assessment:

4.2.1.1.1 Weight, and vital signs including temperature, blood pressure, and pulse rate.

4.2.1.1.2 A medical history assessment including symptoms and signs of adverse reactions.

4.2.1.1.3 Study drug adherence assessment.

4.2.1.2 The following laboratory evaluations will be performed:

4.2.1.2.1 Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count, differential white blood cell count, and platelet count.

4.2.1.2.2 Blood chemistries: electrolytes, blood urea nitrogen (BUN), creatinine, creatinine kinase, glucose, phosphorus, amylase, lactate, and calcium.

4.2.1.2.3 Liver function tests: total bilirubin, AST, ALT, alkaline phosphatase, and albumin.

4.2.1.2.4 Coagulation: prothrombin time, international normalized ratio, partial thromboplastic time.

4.2.1.2.5 Estimated glomerular filtration rate (eGFR)

4.2.1.2.6 Complete blood cholesterol test: Total cholesterol, LDL, HSL, and triglycerides.

4.2.1.2.7 For women of childbearing potential: urine pregnancy tests.

4.2.1.2.8 HIV RNA in blood plasma.

4.2.1.2.9 Lymphocytes subset in blood (CD4+ and CD8+ T-cell absolute counts and percent) including CD4+ T-cell peak and nadir levels.

4.2.1.3 Drug dispensing: four additional weeks of study drug will be dispensed from the research pharmacy.

4.2.2 Events Between Week 4 and Week 24 Visits

4.2.2.1 The study coordinator will inquire about signs or symptoms of adverse effects as well as medication adherence at the drug dispensing visits on week 8 and week 16 if subject is willing. Results will be recorded on CRF. If any symptoms are reported, the subject will be evaluated by the study nurse and investigator (see Section 6.6).

4.2.2.2 Drug dispensing: Four weeks of study drug will be dispensed at Weeks 8 and 12.

4.2.3 Week 24 Assessments

4.2.3.1 A complete medical history and physical examination will be performed:

4.2.3.1.1 Prior diagnoses including liver disease, renal disease, fracture, osteoporosis, allergies, drug reactions, and most recent menses.

4.2.3.1.2 Current symptoms including those of an active systemic illness (e.g., fever) and bleeding or easy bruising.

4.2.3.1.3 Height, weight and vital signs, including temperature, blood pressure, and pulse rate.

4.2.3.2 20-question HIV Symptom Index and SF-12 Questionnaire.

4.2.3.3 The following laboratory tests will be performed:

4.2.3.3.1 Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), white blood cell count, differential white blood cell count, and platelet count.

4.2.3.3.2 Blood chemistries: electrolytes, blood urea nitrogen (BUN), creatinine, creatinine kinase, glucose, phosphorus, amylase, lactate and calcium.

4.2.3.3.3 Liver function tests: total bilirubin, AST, ALT, alkaline phosphatase, and albumin.

4.2.3.3.4 Coagulation: prothrombin time, international normalized ratio, partial thromboplastin time.

4.2.3.3.5 Complete blood cholesterol test: Total cholesterol, LDL, HSL, and triglycerides.

4.2.3.3.6 Urinalysis, including urine glucose and protein. A Urine drug screen will also be performed.

4.2.3.3.7 Estimated glomerular filtration rate (eGFR).

4.2.3.3.8 For women of childbearing potential: Serum or urine pregnancy test.

4.2.3.3.9 HIV RNA in blood plasma.

4.2.3.3.10 Lymphocytes subset in blood (CD4+ and CD8+ T-cell absolute counts and percent) including CD4+ T-cell peak and nadir levels.

4.2.3.4 Subjects will be strongly encouraged to have an appointment with a primary care provider scheduled within a week prior to the final study visit to obtain a prescription and allow for clinical dispensing of continuing antiretroviral therapy.

4.3 Premature Discontinuation

Subjects who prematurely discontinue study treatment will undergo an assessment similar to the one detailed for Week 24 with the following exceptions.

4.3.1 Following up with a primary care provider will be discussed with the study subject.

4.4 Off-Drug Requirements

Additional safety monitoring and reporting of Serious Adverse Events (SAEs) continues to be required upon completion or discontinuation of study treatment regardless of whether a protocol follow-up period is scheduled to occur. Adverse experiences occurring during the immediate 8-week period after the last dose of study treatment which meet SAE Reporting Requirements must be reported to the sponsor and the

Institutional Review Board (IRB). If the study subject discontinues study treatment, after 8 weeks OFF study treatment, there are 4 types of events which must be reported to the sponsor and the IRB if the relationship to the study treatment is assessed by the site physician as definitely, possibly, or unable to judge: DEATHS, NEW ONSET CANCERS, CONGENITAL ANOMALIES, PERMANENT DISABILITIES. The study nurse will call the study subject eight weeks after the last study visit to determine if an SAE has occurred.

5.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENTS-REPORTING

5.1 Records to Be Kept

Case report forms (CRF) will be provided for each subject. Subjects must not be identified by name on any study documents. Subjects will be identified by the Patient Identification Number (PID) and Study Identification Number (SID).

All data on the CRF must be legibly recorded in black ink or typed. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to it. The correction must be initialed and dated by the investigator or a designated qualified individual. Any requested information that is not obtained as specified in the protocol should have an explanation noted on the CRF as to why the required information was not obtained.

5.2 Monitoring

5.2.1 The investigators will review the research records for accuracy, completeness, and legibility. The investigators will also regularly inspect regulatory files to ensure that regulatory requirements are being followed.

5.2.2 The investigator will make study documents (e.g., consent forms, drug distribution forms, and case report forms) and pertinent hospital or clinic records readily available for inspection by the FDA for confirmation of the study data.

5.3 Serious Adverse Events (SAE) Reporting

SAE will be documented on the SAE Reporting Form and submitted to the sponsor and the IRB within 24 hours of the investigator becoming aware of the event.

Stopping Guidelines
BIC/FTC/TAF has recently received US Food and Drug Administration approval. The safety in this small, investigator-initiated study is expected to reflect those in larger phase II and phase III clinical trials. In the event that an unexpected and serious safety signal emerges, such as more than 33% of subject having SAEs requiring treatment discontinuation, the investigators will strongly consider temporarily suspending or prematurely ending the trial. If the participant is discontinued because of SAE, the end study laboratory tests will be included as a measure of safety.

6.0 STUDY TREATMENT

6.1 Drug Regimens, Administration, and Duration

Days 1-28: Give BIC/FTC/TAF (50 mg BIC, po q day).
Day 28: Assess therapy adherence.
Day 29-168: Continue BIC/FTC/TAF (50 mg BIC, po q day).
Day 168: Assess health related quality of life and therapy adherence.

BIC/FTC/TAF (50 mg BIC, po q day) can be administered as a single dose with or without food.

6.2 Drug Formulations

BIKTARVY tablets are purplish brown, capsule-shaped, and film-coated with “GSI” debossed on one side and “9883” on the other side. Each bottle contains 30 tablets (NDC 61958-2501-1), a silica gel desiccant, polyester coil, and is closed with a childresistant closure. Each BIKTARVY tablet contains 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF).
Store below 30 °C (86 °F).

- Keep container tightly closed.
- Dispense only in original container.

6.3 Drug Supply, Distribution, and Pharmacy

6.3.1 Dispensing and monitoring drug-taking behavior

Subjects will be asked to bring medication bottles with any remaining medication to each visit. Adherence will be assessed through pill count and documented by project staff on appropriate CRFs.

6.3.2 Study supply acquisition

The study treatment will be supplied by Gilead Sciences to the study site and will then be dispensed by the research pharmacy.

6.3.3 Accountability

The study pharmacist will maintain complete records of all study medications received and subsequently dispensed in an accountability log.

All unused study medication will be returned to the study pharmacy and discarded following standard operating procedure.

6.4 Concomitant Medications

6.4.1 Precautions

Bictegravir has been recently approved by the FDA. A comprehensive list on precautionary medications has become available in the package insert[15]. Pharmacokinetic studies have shown bictegravir is metabolized primarily by CYP3A4 and UGT1A1. BIC/FTC/TAF should NOT be recommended with strong CYP3A4 and UGT1A1 inducers such as rifampin that can significantly decrease bictegravir plasma concentration. Co-administration of BIC/FTC/TAF should also be NOT recommended with potent inhibitors of both CYP3A4 and UGT1A1 that can result in elevated bictegravir plasma concentrations.

6.4.2 Contraindications

BIKTARVY is contraindicated to be co-administered with: ① dofetilide due to the potential for increased dofetilide plasma concentrations and associated serious and/or life-threatening events; ② rifampin due to decreased BIC plasma concentrations, which may result in the loss of therapeutic effect and development of resistance to BIKTARVY. Specific case-by-case exemptions may be considered by the study investigators.

6.5 Management of Selected Toxicities

6.5.1 New Onset or Worsening Renal Impairment

Renal impairment, including acute renal failure and Fanconi syndrome, has been reported with prodrugs of tenofovir. A tenofovir prodrug, tenofovir alafenamide is a component of BIC/FTC/TAF. If renal impairment occurs as indicated by a decrease of estimated creatinine clearance below 30 mL/min, study treatment will be discontinued and subjects will complete the evaluations listed in Section 4.2.

6.5.2 Lactic Acidosis/ Severe Hepatomegaly

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors (NRTI). Treatment with BIC/FTC/TAF should be suspended in any subject who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

6.5.3 Fat Redistribution and Immune Reconstitution Syndrome

Redistribution/accumulation of body fat and immune reconstitution syndrome have been reported in patients treated with antiretroviral therapy such as NRTI and possibly INSTI, which may necessitate further evaluation and treatments.

Any grade 3 or higher symptoms or laboratory abnormalities will result in termination of the subject from the study (see Section 4.2 for post-treatment evaluations).

6.6 Criteria for Treatment Discontinuation

6.6.1 The Subject or legal guardian refuses further treatment and/or follow-up evaluations.

6.6.2 The investigator determines that further participation would be detrimental to the subject’s health.

6.6.3 The subject fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results.

6.6.4 The subject requires treatment with medications that are disallowed while on this study (Section 6.4.2).

6.6.5 Drug toxicities as defined in Section 6.5.

6.6.6 Pregnancy.

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design Issues

The first objective of this study is to evaluate PDDI when switched from Genvoya™ or Stribild™ to bictegravir/F/TAF. This will be accomplished by selecting subjects who are currently on Genvoya™ or Stribild™. More than one provider prescribing medications can cause discrepancy in polypharmacy related data collection. In this study, all prescribed medication as well as non-prescription medication in each subject's regimen will be collected prior to (4-8 weeks) and after switch and analyzed. For the other first and secondary objectives, which is to evaluate health related quality of life and adherence, we will consider response biases in these measures. We will include all participants >50 years old for overall analysis followed by post hoc analyses of medication type and number related to the changes in the outcomes.

7.1.1 Endpoints

7.1.1.1 Primary endpoints

7.1.1.1.1 Probability of PDDI particularly with cobicistat and concurrent medications will be assessed throughout the study.

7.1.1.1.2 Health related quality of life assessments at baseline, week 12 and week 24.

7.1.1.2 Secondary endpoints

7.1.1.2.1 Adherence assessment at baseline, week 4, week 8, week 12 and week 24.

7.1.1.2.2 Lipid panel, blood pressure and blood glucose levels at baseline, week 12 and week 24.

7.2 Sample Size and Accrual

Sample size of 160, consisting of 80 subjects who are engaged in polypharmacy (⩾5 meds) and 80 subjects who are not, will be sufficient for the primary objective to determine the impact of polypharmacy and the reduced probability of PDDI on the quality of life. Among 160 subjects, 80 (50%) will be the elderly (⩾50 years old) evenly distributed in the two groups. The impact of aging will be evaluated in two ways: (1) age as a continuous variable and (2) old (⩾50 years old) *vs.* young (<50 years old). The basic study design proposed is a parallel, open-label approach that will permit adequate power to determine the effect of polypharmacy and reduced PDDI, mainly related to cardiovascular and neurological medications, on the quality of life after the regimen switch. Our power analysis indicates that a sample size of 80 in each group

(polypharmacy vs. non-polypharmacy) will be sufficient for the comparisons we need to make. Previous studies on polypharmacy in HIV+ elderly (⩾50) indicate that the incidence of polypharmacy will be approximately 40-50% (16-18). We have also assumed that a 15-20% difference or greater in quality of life or levels of well-being would be of clinical importance (19, 20). The component of this study comprising the comparative evaluation of quality of life and PDDI in polypharmacy and non-polypharmacy patients is a parallel design. A sample size of 160 (80 in each group) will be needed to detect a 20% difference at a power of between 0.75 and 0.80. This will accommodate the relatively high incidence of polypharmacy and PDDI among the elderly living with HIV and permit an analysis for the effect of switch from Genvoya™ or Stribild™ to bictegravir on quality of life.

Any subject who prematurely discontinues study participation prior to completing at least one on-treatment assessment including health related quality of life questioners and data collection will be replaced by another subject. The alternative approach is to allow subjects currently receiving HIV care from the Erie County Medical Center to participate in the study.

7.3 Monitoring and Analysis

The safety and tolerability of the study medications will also be monitored closely by the protocol team comprising an HIV pharmacist with experience in clinical trials, an expert in HIV clinical trials, and an expert in clinical research. Reports and responses will be prepared by the protocol team.

8.0 HUMAN SUBJECTS

8.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the Institutional Review Board at each participating institution. Written informed consent will be obtained from the subject. Subjects who are unable to provide consent due to neurocognitive impairment or other causes will not be enrolled. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject (or legal guardian).

8.2 Data Storage and Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified by a coded number only to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA or the pharmaceutical sponsor.

8.3 Costs to the Subjects

All study costs will be covered by the study sponsor as specified in the existing contract. There will be no costs to the subject associated with participation in the study.

8.4 Compensation for Participation

Subjects will be reimbursed $10 for phlebotomy (no more than once per visit) and $10 for completion of forms. Subjects who completes all assessments will be compensated a total of $70. By visit, subjects who complete all assessments will receive $10 at screening, $20 at entry at weeks 2 and 24.

8.5 Study Discontinuation

The study may be discontinued at any time by the investigators, the pharmaceutical sponsors, or the FDA. Discontinuation by the pharmaceutical sponsor must follow guidelines set forth in the contract with the award recipient institution, the University at Buffalo.

9.0 PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical sponsors prior to submission. The investigators will retain the right of final revision of all presentations, abstracts, and manuscripts.

10.0 BIOHAZARD CONTAINMENT

As the transmission of blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control.

All infectious specimens will be sent using the ISS-1 SAF-T- PAK mandated by the International Air Transport Association Dangerous Goods Regulations-Packing Instruction 602. Please refer to individual carrier guidelines (e.g., FedEx, Airborne) for specific instructions.

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