Protocol Cover Sheet

Protocol Title:	The Efficacy, Safety, and Tolerability of Switching to a Bictegravir (BIC)/ Emtricitabine (FTC)/ Tenofovir Alafenamide (TAF) Regimen in Virally Suppressed HIV-Positive Patients Post-Renal Transplant
Principal Investigator:	Catherine Small, MD
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Funding Source(s): Gilead Sciences, Inc.

Principal Investigator:

Name	*Catherine B. Small, MD*
Address	*1300 York Avenue*
	Mailbox 125
	New York, NY 10065
Telephone	*914-552-5960*
Fax	*212-746-6320*
E-mail	*cbs9003@med.cornell.edu*

Participating Sites: *None*

Statement of Compliance

(1) The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the <specify NIH Institute or Center (IC) > Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. Protocol Summary

Full Title:	The Efficacy, Safety, and Tolerability of Switching to a Bictegravir (BIC)/ Emtricitabine (FTC)/Tenofovir Alafenamide (TAF) Regimen in Virally Suppressed HIV-Positive Patients Post-Renal Transplant
Short Title:	Switch to BIC/FTC/TAF after Renal Transplant
Clinical Phase:	IV
Principal Investigator:	Catherine B. Small, MD
Study Description:	Hypothesis: We hypothesize that BIC/F/TAF will be efficacious and safe in the management of HIV+ post renal transplant patients, and will have few adverse reactions and drug-drug interactions with tacrolimus in this population
Sample Size:	N = 20
Study Population:	Virally-suppressed HIV+ adults post-renal transplant
Enrollment Period:	November 2020 to May 2023
Study Design:	Single arm, open-label, switch study, following subjects for 48 weeks with a 6 month follow-up
Study Duration:	November 2020 – December 2024
Participant Duration:	In this single arm, open-label, switch study, we propose to switch virally suppressed HIV+ adults post-renal transplant to BIC/F/TAF and follow the subjects for 48 weeks with a 6 month follow-up (Section 6.1).
Study Agent:	BIC/F/TAF® (BIC/F/TAF)
Primary Objectives:	1. To determine the efficacy of BIC/F/TAF in HIV+ patients post renal transplant at 24 weeks and 48 weeks post-switch to BIC/F/TAF. 2. To assess the safety and tolerability of BIC/F/TAF in HIV+ patients post renal transplant at 24 weeks and 48 weeks post-switch to BIC/F/TAF. 3. To assess the pharmacokinetics of BIC/F/TAF in HIV+ patients post renal transplant and its interactions with immunosuppressive agents (Tacrolimus) at 12 weeks post-switch to BIC/F/TAF. 4. To assess renal biomarkers including urine protein/creatinine ratio; urine albumin/creatinine ratio; eGFR; serum BUN, creatinine and phosphorus; tacrolimus levels; retinol 2 binding protein and B2 microglobulin post renal transplant at 24 weeks and 48 weeks post-switch to BIC/F/TAF.
Secondary Objectives:	1. To assess the incidence of kidney graft rejection after switching to BIC/F/TAF post renal transplant at 24 weeks and 48 weeks post-switch to BIC/F/TAF. 2. To assess the immunologic activity (CD4 count/percentage) of BIC/F/TAF post renal transplant in conjunction with immunosuppressive agents (tacrolimus) at 24 weeks and 48 weeks post-switch to BIC/F/TAF. 3. To determine patient satisfaction with BIC/F/TAF post renal transplant by utilizing a questionnaire to assess health-related quality of life outcomes at 24 weeks and 48 weeks post-switch to BIC/F/TAF.

Primary Endpoints:	1. Proportion of subjects with plasma HIV-1 RNA <50 copies/ml at week 48. 2. Safety and tolerability (monitoring and recording adverse events) in subjects who switched from a prior ARV regimen to BIC/F/TAF. 3. Pharmacokinetics of BIC/F/TAF and tacrolimus, including intracellular TAF levels (dried blood spot, PBMC).
Secondary Endpoints:	1. Changes from baseline in CD4+ T lymphocyte cell count/percentages post renal transplant. 2. Incidence of rejection rates of the kidney transplant post renal transplant and correlation with tacrolimus levels. 3. Patient satisfaction with reduced pill burden and adverse events with BIC/F/TAF.

1.2 Study Objectives

The specific aims of this study are as follows:

1. To determine the efficacy, safety, and tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide (BIC/F/TAF) in HIV+ patients post renal transplant.
2. To assess the pharmacokinetics and drug/drug interactions with immunosuppressive agents (tacrolimus) of BIC/F/TAF in HIV+ patients post renal transplant and preservation of renal function.

1.2.1 Primary Objectives

The primary objectives of this study are as follows:

1. To determine the efficacy of BIC/F/TAF in HIV+ patients post renal transplant.
2. To assess the safety and tolerability of BIC/F/TAF in HIV+ patients post renal transplant.
3. To assess the pharmacokinetics of BIC/F/TAF in HIV+ patients post renal transplant and its interactions with immunosuppressive agents (Tacrolimus).
4. To assess renal biomarkers including urine protein/creatinine ratio; urine albumin/creatinine ratio; eGFR; serum BUN, creatinine and phosphorus; tacrolimus levels; retinol 2 binding protein and B2 microglobulin post renal transplant.

1.2.2 Secondary Objectives

1. To assess the incidence of kidney graft rejection after switching to BIC/F/TAF post renal transplant.
2. To assess the immunologic activity (CD4 count/percentage) of BIC/F/TAF post renal transplant in conjunction with immunosuppressive agents (tacrolimus).
3. To determine patient satisfaction with BIC/F/TAF post renal transplant by utilizing a questionnaire to assess health-related quality of life outcomes.

2. Background

At NewYork-Presbyterian Hospital-Weill Cornell Medicine, we have a robust Renal Transplant Program, including renal transplantation in HIV+ patients. The Renal Transplant Program works in close collaboration with the Transplant/Oncology Infectious Diseases Program, including clinical research trials. There have been 42 renal transplants performed in HIV+ patients at our institution in the past 10 years, including two HIV to HIV renal transplants. Thirty-seven patients (excluding HIV to HIV renal transplants) remain alive and are eligible for study consideration. Only four are receiving TAF-containing regimens; the remaining 33 are on various antiretroviral (ARV) regimens including protease inhibitors, cobicistat and ritonavir (started by and maintained by their community HIV primary care physicians), which increase drug-drug interactions with tacrolimus and jeopardize the kidney transplant, as well as increasing pill burden. Therefore, a new single tablet ARV with less

drug-drug interactions is important to this unique population. Data from 4 clinical trials (1-5) show that the single tablet regimen containing BIC/F/TAF (Bictegravir/Emtricitabine/Tenofovir Alafenamide) is safe and efficacious and non-inferior to other standard ARV regimens. No patients had to discontinue the drug due to renal events and no patients developed treatment-emergent resistance. BIC had no impact on severe renal impairment (eGFRCG 15-29 mL/min), no effect on actual GFR (iohexol clearance) and minimal effect on estimated GFR. There were no discontinuations due to adverse renal events and no proximal renal tubulopathy. TAF is a novel tenofovir prodrug (6,7) with improved renal and bone safety compared to Tenofovir. As reported in JAIDS 2016 (5), switching HIV-positive patients with mild to moderate renal impairment from a prior TDF-based regimen to Elvitegravir/Cobicistat/Emtricitabine/TAF (E/C/F/TAF) resulted in significant decreases in proteinuria, albuminuria and tubular proteinuria without dose adjustment.

Kidney transplantation is successful in HIV+ patients although rejection rates are higher than in non-HIV+ transplant patients (8). The greatest clinical challenge is to achieve therapeutic and nontoxic levels of the immunosuppressive drugs, especially Tacrolimus, in this population, due to the complicated pharmacokinetic interactions of these agents with antiretroviral agents (ARV), especially protease inhibitors, cobicistat, and ritonavir (8). Non-therapeutic exposure to tacrolimus contributes to higher rate of rejection, so it is important to study ARV agents with less drug-drug interactions that are safe in this special population. We are currently completing a manuscript addressing this issue at our institution and the kidney transplant team has presented preliminary data in a poster at the American Transplant Congress in 2018 (Al Jurdi, Clinical Outcomes of HIV-Infected Kidney Transplant Recipients With An Early Corticosteroid Withdrawal Protocol). It is important to closely follow the CD4 lymphocyte counts and percentages in this unique population and the effect on HIV infection and immunosuppression. Preferred ARV regimens in HIV+ patients post renal transplant include integrase inhibitors and TAF, with the goal to avoid protease inhibitors, ritonavir and cobicistat and decrease drug-drug interactions with tacrolimus (8,9).

In treatment naïve adults with HIV-1 infection, switching from DTG, abacavir, and lamivudine to BIC/F/TAF proved to be a safe and efficacious option for the treatment of HIV-1 infection (1). The pharmacokinetics of BIC/F/TAF were assessed in this study, and the mean trough concentrations of BIC were 14 times higher than the protein-adjusted 95% effective concentration against wild type HIV-1 virus.

There is no current data about the pharmacokinetics of BIC/F/TAF in renal transplant recipients or the interactions of BIC/F/TAF with tacrolimus. Previous work has demonstrated sustained, zero-order, linear, release pharmacokinetic characteristics of TAF (10,11). TAF is metabolized via CES1 in hepatocytes, cathepsin A in PBMCs, and minimally with CYP3A. Tenofovir plasma levels significantly increase when administered to subjects with moderate to severe renal impairment, such that the dosing interval is adjusted in patients with baseline creatinine clearance below 50 mL/min based on modeling of single-dose pharmacokinetic data in non-HIV and non-HBV infected subjects with varying degrees of renal impairment (12).

TAF is hydrolyzed within cells to form tenofovir (major metabolite), which is phosphorylated to the active metabolite, tenofovir diphosphate. *In vitro* studies have shown that TAF is metabolized to tenofovir by CES1 in hepatocytes, and by cathepsin A in PBMCs and macrophages. Whether tenofovir can accumulate and lead to nephrotoxicity in conjunction with tacrolimus after tenofovir

alafenamide administration is not known. Moreover, the long-term renal safety of tenofovir alafenamide in HIV+ renal transplant recipients receiving tacrolimus is not known.

Dried blood spots have been used to determine markers of recent dosing and measures of anti-retroviral adherence (13,14). Comparison of tenofovir and FTC in dried blood spot versus plasma indicated that dried blood spot can be used as a plasma alternative for pharmacokinetic analyses in vivo (15). Measurement of intracellular TAF levels has not been done in the HIV+ renal transplant population. We will therefore incorporate the dried blood spot method and PBMC method to determine intracellular TAF levels and monitor adherence in the renal transplant population.

We therefore will determine concentrations of BIC, FTC, and TAF in serial samples of plasma and peripheral blood mononuclear cells over the course of 48 weeks in HIV+ renal transplant recipients (Section 6.1).

Preservation of renal function and graft survival is of primary importance in this HIV-infected renal transplant population, challenged by drug-drug interactions between ARV regimens and anti-rejection medications. In the 112 study (5), switching to E/C/F/TAF had no change in estimated or actual GFR and proteinuria, proximal renal tubular function, and BMD significantly improved over 48 weeks. In patients with eGFR <50 mL/min, adverse events were similar in grade and frequency to patients with GFR>50 mL/min. BIC/F/TAF has demonstrated high rates of virologic suppression and no treatment-emergent resistance through 48 weeks in phase 3 clinical trials among treatment naïve adults and among virologically suppressed adult patients who switched ARV regimens. Therefore, BIC/F/TAF promises to be an important ARV regimen to be studied in HIV+ post renal transplant patients, including drug-drug interactions with anti-rejection agents, especially tacrolimus. Pharmacokinetic studies, and drug-drug interactions are important to study in this unique population, as well as the efficacy, safety and tolerability of BIC/F/TAF.

In this single arm, open-label, switch study, we propose to switch virally suppressed HIV+ adults post-renal transplant to BIC/F/TAF and follow the subjects for 48 weeks to evaluate the efficacy, safety and tolerability of BIC/F/TAF, plus a 6 month follow-up. Health related quality of life outcomes are important in the evaluation of ARV treatment strategies, especially in the HIV+ renal transplant population. BIC/F/TAF and DTG-based regimens have been compared in treatment-naïve and HIV-1 suppressed adults, showing non-inferior efficacy and less drug-related adverse events in BIC/F/TAF arms compared to DTG-based regimens. To better understand the patients' experience with BIC/F/TAF post renal transplant, we will be using a specific quality of life questionnaire (Attachment 1). We hypothesize that BIC/F/TAF will be an important addition to the management of HIV+ post renal transplant patients, especially since it is a one pill daily dosing regimen, thereby decreasing the pill burden in this unique population.

2.1 Risk/Benefit Assessment

2.1.1 Known Potential Risks

The most common adverse reactions with BIC/F/TAF (incidence greater than or equal to 5%, all grades) are diarrhea, nausea, and headache. Other potential warnings and precautions include the immune reconstitution syndrome, new onset or worsening renal impairment, and lactic acidosis/severe hepatomegaly with steatosis.

2.1.2 Known Potential Benefits

BIC/F/TAF has demonstrated high rates of virologic suppression and no treatment-emergent resistance through 48 weeks in phase 3 clinical trials among treatment naïve adults and among virologically suppressed adult patients who switched ARV regimens. BIC/F/TAF also has lower pill burden than other anti-retroviral regimens, due to a one-pill composition.

3. Study Design

3.1 Overall Design

We hypothesize that BIC/F/TAF will be efficacious and safe in the management of HIV+ post renal transplant patients, and will have few adverse reactions and drug-drug interactions with tacrolimus in this population.

Eighteen subjects will be enrolled in this Phase IV, single arm, open-label, single-site, switch study. In this study, virally suppressed HIV+ adults will be switched post-renal transplant from their current anti-retroviral regimen to BIC/F/TAF and will be followed for 48 weeks with a 6 month follow-up (Section 6.1). Informed consent will be obtained before starting the study (Section 6.1).

Patients will have bloodwork completed throughout the study, as shown in the Schedule of Assessments (Section 6.1).

A health-related quality of life questionnaire (Appendix) will be administered to each patient to assess satisfaction with a one pill regimen as well as adverse events (Section 6.1).

Pharmacokinetic (PK) studies will be assessed at Week 12 when the renal function is stable (decided by PI). Intracellular TAF levels by dried blood spot will be collected during the Week 12 visit as well as Week 24, Week 36, Week 48, Month 6 Follow-up. Intracellular TAF levels by PBMC will be collected once during the Week 12 visit. An intensive pharmacokinetic day will take place at the Week 12 visit. This bloodwork is outlined in Section 6.1. Bloodwork for the intracellular TAF level testing and pharmacokinetic testing will be stored and sent to Dr. Peter Anderson at the University of Colorado's Antiviral Laboratory. (14-16)

Note: Patients switched post-renal transplant from their current anti-retroviral regimen to BIC/F/TAF prior to identification for this study may also be enrolled. This group will be referred to as “Group 2”. Pharmacokinetic testing for Group 2 subjects will be completed once each Group 2 subject's tacrolimus levels are stable as per the Principal Investigator for 2-4 weeks. All standard of care lab values and concomitant medications will be collected from Group 2 subjects for 60 days prior to and after the Biktarvy switch date and for the duration of Biktarvy therapy. Any adverse events related to Biktarvy prior to enrollment will be recorded.

Sample Collection
Samples include plasma and peripheral blood mononuclear cells (PBMC). Blood is collected in EDTA tubes for plasma separation. CPT vacutainers are used to isolate PBMC, which are counted with an

automated countess cytometer (InvitrogenTM, Thermo Fisher Scientific Corporation, Carlsbad, CA) and lysed. BIK, F, and TAF in plasma are assayed using a validated LC/MS/MS methodology with a lower limit of quantification (LLOQ) of 10 ng/mL (16).

Determination of Pharmacokinetic Variables

The pharmacokinetic variables for BIC/F/TAF are calculated from the concentration-time data using noncompartmental methods. The peak drug concentration (Cmax) and time of peak drug concentration are obtained directly from the observed data. The terminal elimination rate constant (kel) is obtained from a log-linear regression of the plasma concentration compared to time data in the terminal post distribution phase. The elimination half-life (t1/2) is calculated from 0.693/kel. The area under the plasma drug concentration-versus-time curve (AUC0–24) and the area under the moment curve from 0 to 24 h (AUMC0–24) are calculated by the log-linear trapezoidal rule. The area under the plasma drug concentration-versus-time curve from time zero to time infinity (AUC0–□) is obtained from the following equation: AUC0–24 • Ct/kel, where Ct is the last measurable concentration and kel is the terminal elimination rate constant. The total body clearance (CL) is obtained from the equations dose/AUC0–□ and dose/AUC0–24 (presumed steady state, where 24 h is the dosing interval), respectively. The volume of distribution (Vd) is calculated as follows: Vd= CL/kel. The steady-state volume of distribution (Vss) is calculated from the product of CL and the mean residence time. The mean residence time is obtained from the following equation: (AUMC0–□/AUC0–□) T/2, where AUMC0–□ is extrapolated from [(Ct x t)/kel x Ct/kel2] and where T is the infusion time, all other terms having been previously defined.

Statistical Analyses and Sample Size

This is a pilot study of the efficacy, safety, and pharmacokinetics of BIC/F/TAF in HIV+ renal transplant recipients. Sample size is based upon feasibility of enrolling the current cohort of patients on the WCM/NYPH renal transplant service who are currently receiving antiretroviral therapy. Among the 37 HIV+ renal transplant recipients who are followed at NYPH and who are currently eligible for the study, we project that 20 patients will enroll into this study and complete treatment.

We hypothesize that in the transition from a standard antiretroviral regimen to a BIC/F/TAF regimen, there would be high probability of a sustained suppression of HIV- RNA (1). In the randomized, double-blind, multicenter, active-controlled, phase 3, non-inferiority clinical trial of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1 by Molina et al, the primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 that fulfilled the prespecified non-inferiority margin of 4%, where three (1%) of 282 in the bictegravir group had HIV-1 RNA of 50 copies per mL or higher at week 48 versus one (<1%) of 281 participants in the dolutegravir group (difference 0·7%, 95·002% CI -1·0 to 2·8; p=0·62).

The number of 20 subjects who are projected for enrollment and study completion will provide sufficiently robust data for pharmacokinetic studies to yield a coefficient of variation of <15%, which will permit a robust analysis and model development.

Outcome variables and adverse events will be reported using descriptive statistics, including means, medians, ranges, and standard errors.

The relationship between renal function, tacrolimus levels, BIC/F/TAF plasma concentrations, and intracellular concentrations of TAF will be determined by linear regression analysis.

4. Subject Selection

4.1 Study Population

Virally suppressed HIV+ adults post-renal transplant who meet the inclusion and exclusion criteria will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Be ≥18 years of age on day of signing informed consent.
2. Have documented positive results for human immunodeficiency virus (HIV) antibody (HIV-Ab) test at time of enrollment.
3. Received a previous renal transplant.
4. Must have controlled HIV infection, defined as HIV-1 RNA < 50 copies/ml for ≥ 3 months prior to enrollment.

4.3 Exclusion Criteria

1. Has renal function of CrCl <30 mL/min at time of enrollment. CrCl will be calculated using the Cockcroft-Gault equation using the most recently obtained and available serum creatinine value collected.
2. BIC/F/TAF is the only antiretroviral therapy ever used for treatment of HIV infection.
3. Is allergic to any of the HIV meds in BIC/F/TAF (bictegravir, emtricitabine, or tenofovir alafenamide).
4. Pregnant or breastfeeding.
5. Is currently taking dofetilide or rifampin.
6. Has severe hepatic impairment (Child-Pugh Class C).
7. ALT or AST > 5 x ULN.

4.4 Lifestyle Considerations

No lifestyle restrictions are required based on study procedures.

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a renal function value exclusion may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.6 Strategies for Recruitment and Retention

The Renal Transplant Program works in close collaboration with the Transplant/Oncology Infectious Diseases Program, including clinical research trials. Recruitment will primarily rely on referrals from the Renal Transplant Program and/or existing patients of the infectious disease investigators. Recruitment will primarily be sources from outpatient clinics, such as the Infectious Disease Clinic and the Renal Transplant Clinic. The target enrollment is 20 subjects. Monthly enrollment logs will be collected.

Subjects will be compensated $40 per outpatient visit, as a stipend to cover travel costs. For visits that require pharmacokinetic blood sampling, subjects will be compensated $200 per outpatient visit, as a stipend to cover travel costs and time.

5. Registration Procedures

5.1 Subject Registration

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

Study procedures are outlined in the Schedule of Assessments (Section 6.1)

6.1 Schedule of Assessments*

Activity	D 1	D 3	D 8	D 15	D 22	W 4	W 8	W 12	W 16	W 24	W 32	W 36	W 48	FU – M3	FU – M6	UV[k]
Visit Window (Days)	±1	±3				±7										
Informed consent	X[a]															
Inclusion/Exclusion Criteria	X															
Research study visit, including weight	X	X[j]	X[j]	X[j]	X[j]	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X					X[b]		X[b]		X		X[b]	X	X[b]	X[b]	X[b]
Questionnaire booklet administration	X															
Questionnaire completion[c]						X		X		X		X	X	X	X	X
Dispense study medication	X										X					
T-lymphocytes, HIV viral load	X					X		X		X		X	X	X	X	X
HIV-resistance testing		As needed, as per investigator[d]														
Tacrolimus level	X	X[j]	X[j]	X[j]	X[j]	X	X	X	X	X	X	X	X	X	X	X
BUN, creatinine		X[j]	X[j]	X[j]	X[j]	As needed, as per investigator[e]										
Clinical Safety Labs[f]	X					X	X	X	X	X	X	X	X	X	X	X
TAF levels, intracellular (dried blood spot)[g]								X		X		X	X		X	X
TAF levels, intracellular (PBMC)[h]								X								
Pharmacokinetics[i]								X								

Abbreviations: D = Day; W = Week; M = Month; FU = Follow-up; UV = Unscheduled Visit

*If services outside of the study (standard of care, or "SOC") are completed for a patient during the study period, only the research-related tests and procedures will be billed to the study. SOC tests and procedures are expected throughout the study period for this population.

[a] Informed consent may be obtained up to 2 months before D1. Subjects enrolled into Group 2 will begin the study schedule at the Day 1 visit and will then be inserted into the Schedule of Assessments at the discretion of the Principal Investigator based on stability of the subject's HIV viral load and tacrolimus levels.

[b] If there are complications, as deemed by the investigator, a physical exam will be conducted at this time point. If institutional restrictions limit outpatient visits, the most recent physical exam completed by the primary care physician will be used to avoid direct contact or exposure of patients.

[c] Questionnaires may be completed by phone or returned by mail, if institutional restrictions limit outpatient visits.

[d] HIV resistance testing will be performed if there are two consecutive breakthrough HIV viral loads >50 copies/mL, spaced 4-6 weeks apart.

[e] Additional BUN and/or creatinine labwork may be drawn at these timepoints, if deemed necessary for safety purposes by the investigator.

[f] Clinical Safety Labs include: CBC, complete metabolic panel, urinalysis, eGFR, urine protein/creatinine ratio, urine albumin/creatinine ratio, phosphorus, retinol binding protein, and beta 2 microglobulin. For subjects enrolled in Group 2, all standard of care lab values and concomitant medications will be collected for 60] days prior to the Biktarvy switch date and the duration of Biktarvy therapy will also be recorded.

[g] Three samples will be collected on W12 at 0, 4, and 24 hours (the 24 hour time point is optional, if feasible), and 1 sample will be collected at visits W24, W36, and W48, and FU – M6. Stored samples will be sent to Dr. Peter Anderson at the University of Colorado's Antiviral Laboratory.

[h] Three samples will be collected on W12 at 0, 4, and 24 hours (the 24 hour time point is optional, if feasible). Stored samples will be sent to Dr. Peter Anderson at the University of Colorado's Antiviral Laboratory.

[i] Six samples will be collected on W12 at 0, 0.5, 1, 2, 4, and 24 hours (the 24 hour time point is optional, if feasible). Pharmacokinetic testing for Group 2 subjects will be completed once the subject's tacrolimus levels are stable as per the Principal Investigator for 2-4 weeks.

[j] The study visits and bloodwork at these timepoints will be optional, to be completed as needed, as per the investigator.

[k] If a subject needs to stop treatment as per the Data and Safety Monitoring Plan (Section 12), the subject will be seen as soon as possible for an Unscheduled Visit and will continue to be followed for the duration of the study as per the Schedule of Assessments for non-terminated patients.

Informed consent will be obtained on Day 1 or up to 2 months prior to Day 1, before starting the study (switch day) (Section 6.1).

Patients will have bloodwork completed throughout the study, as shown in the Schedule of Assessments (Section 6.1).

Pharmacokinetic (PK) studies will be assessed at Week 12 when the renal function is stable (decided by PI). Intracellular TAF levels by dried blood spot will be collected during the Week 12 visit at 0, 4, and 24 hours post-dose (the 24 hour time point is optional, if feasible). Additionally, 1 sample will be collected at Week 24, Week 36, Week 48, Month 6 Follow-up. Over the course of the study, 7 dried blood spot collections will be completed per patient. Intracellular TAF levels by PBMC will be collected once during the Week 12 visit at 0, 4, and 24 hours post-dose (the 24 hour time point is optional, if feasible). An intensive pharmacokinetic day will take place at the Week 12 visit, during which up to 7 samples will be collected at 0, 0.5, 1, 2, 4 and 24 hours post-dose (the 24 hour time point is optional, if feasible). This bloodwork is outlined in Section 6.1. Bloodwork for the intracellular TAF level testing and pharmacokinetic testing will be stored and sent to Dr. Peter Anderson at the University of Colorado's Antiviral Laboratory. (14-16)

A health-related quality of life questionnaire (Appendix) will be administered to each patient to assess satisfaction with a one pill regimen as well as adverse events (Section 6.1).

If a subject needs to stop treatment as per the Data and Safety Monitoring Plan (Section 12), the subject will be seen as soon as possible for an Unscheduled Visit and will continue to be followed for the duration of the study as per the Schedule of Assessments for non-terminated patients.

If services outside of the study (standard of care, or "SOC") are completed for a patient during the study period, only the research-related tests and procedures will be billed to the study, regardless of study visit date overlap. SOC tests and procedures are expected throughout the study period for this population.

Sample Collection

Samples include plasma and peripheral blood mononuclear cells (PBMC). Blood is collected in EDTA tubes for plasma separation. CPT vacutainers are used to isolate PBMC, which are counted with an automated countess cytometer (InvitrogenTM, Thermo Fisher Scientific Corporation, Carlsbad, CA) and lysed. BIK, F, and TAF in plasma are assayed using a validated LC/MS/MS methodology with a lower limit of quantification (LLOQ) of 10 ng/mL (16).

7. Study Intervention

7.1 Study Intervention/Device Description

BIC/F/TAF is a three-drug fixed dose combination product containing 50 mg of bictegravir (BIC), 200 mg of emtricitabine (FTC), and 25 mg of tenofovir alafenamide (TAF). The recommended dosage of BIC/F/TAF is one tablet taken orally once daily with or without food in adults. BIC/F/TAF should be stored below 86°F (30°C).

7.2 Availability

BIC/F/TAF is an FDA-approved agent, to be supplied to investigators by Gilead.

7.3 Acquisition and Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents/device received from Gilead on a Drug Accountability Record Form.

8. Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled subjects.

8.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

9. Regulatory Considerations

9.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, before study initiation.

Before initiation of the study, the protocol, the ICF, other written material given to the patients, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the IP is released to the Investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The Investigator will report promptly to the IRB any new information that may adversely affect the safety of the patients or the conduct of the study. The Investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will

be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial participants. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

Once protocol amendments or consent form modifications are implemented at the lead site, Weill Cornell Medicine, updated documents will be provided to participating sites, as applicable. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission.

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

9.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

9.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB requirements, applicable laws and regulations.

9.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

9.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the IP. In addition, all subjects medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

10. Statistical Considerations

10.1 Study Design/Endpoints

We hypothesize that in the transition from a standard antiretroviral regimen to a BIC/F/TAF regimen, there would be high probability of a sustained suppression of HIV- RNA (1). In the randomized, double-blind, multicenter, active-controlled, phase 3, non-inferiority clinical trial of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1 by Molina et al, the primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 fulfilled the prespecified non-inferiority margin of 4%, where three (1%) of 282 in the bictegravir group had HIV-1 RNA of 50 copies per mL or higher at week 48 versus one (<1%) of 281 participants in the dolutegravir group (difference 0·7%, 95·002% CI-1·0 to 2·8; p=0·62).

The number of 20 subjects who are projected for enrollment will provide sufficiently robust data for pharmacokinetic studies to yield a coefficient of variation of <15%, which will permit a robust analysis and model development. Outcome variables and adverse events will be reported using descriptive statistics, including means, medians, ranges, and standard errors. The relationship between renal function, tacrolimus levels, BIC/F/TAF plasma concentrations, and intracellular concentrations of TAF will be determined by linear regression analysis.

Expected Outcomes:
1. We expect sustained suppression of the HIV viral load throughout the study.
2. We expect that BIC/F/TAF will be well tolerated in the HIV+ renal transplant population with minimal adverse events and preservation of renal function with stable tacrolimus levels.
3. Plasma concentrations of BIC/F/TAF will follow those reported in HIV+ non-renal transplant recipients and drug/drug interactions with tacrolimus will be minimal, allowing easy adjustment with minimal detrimental effects on renal function.

11. Adverse Events

11.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

11.2 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

Subjects enrolled in Group 2 will have pre-enrollment adverse events recorded, if they are related to Biktarvy following their switch from previous antiretroviral therapy.

11.3 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

11.4 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

11.5 Reporting of SAE to Gilead

Institution will send Gilead copies of any and all serious adverse event reports filed with the FDA or other applicable regulatory authorities, as well as copies of any correspondence with the FDA or other applicable regulatory authorities, regarding any and all serious adverse events, irrespective of association with the Study Drug(s) in the course of the Clinical Trial, within 3 business days of such report or correspondence being sent to the FDA or other applicable regulatory authorities.

11.6 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the subject discontinues participation from the study.

12. Data and Safety Monitoring Plan (DSMP)

The WCM DSMB will be used for this investigator-initiated study. The following information will be submitted to the WCM DSMB every 6 months from the time of the first enrollment:

Laboratory results

- T-lymphocytes, HIV viral load: From Day 1, Week 4, Week 12, Week 24, Week 36, Week 48, 3-month Follow-up, and 6-month Follow-up
- Select clinical safety labs[1]: From Day 1 and all visits from Week 4 through 6-month Follow-up

- BUN, creatinine: From Days 3 through Day 22, and if needed at additional time points, as per investigator
- Tacrolimus levels: All time points
- Any HIV-resistance testing needed, as per investigator

[1] Clinical Safety Labs include: CBC, complete metabolic panel, urinalysis, eGFR

Adverse Events and Stopping Rules

The following adverse events will be submitted to the WCM DSMB and may cause the subject to terminate protocol treatment:

1. Severe drug reaction, including rash or fever (as determined by the PI)
2. Inability to control tacrolimus levels, as defined by the primary renal transplant provider, which may lead to renal graft failure
3. ALT or AST > 5 x ULN
4. Virologic failure, as determined by the Principal Investigator, which would be defined as: On-treatment HIV-1 RNA ≥50 copies/mL twice sequentially, separated by 4-6 weeks
5. Development of documented resistance to BIC/FTC/TAF

Renal dysfunction requiring evaluation is defined as a decrease in creatinine clearance to CrCl < 30 mL/min. The evaluation of renal dysfunction will be completed by the primary renal transplant team, in conjunction with the PI.

If the CrCl is below 30 mL/min, the BIC/F/TAF will be held and an evaluation will be performed by the primary renal transplant physician in conjunction with the PI. The evaluation of the cause will be explored by the primary renal transplant physician in conjunction with the PI. The patient will be discontinued from the study at the discretion of the PI, after discussion with the primary renal transplant physician, if deemed necessary.

WCM IRB policies will be followed for this study, including the Immediate Report Policy. Any SAEs will be reported to the IRB following these policies, and will also be reported to the funding source (Gilead Sciences, Inc.) within 3 business days of the study team learning of the SAE. The WCM DSMB comments/review will be submitted to the IRB at the time of continuing review and submitted to the funding source (Gilead Sciences, Inc.) at the time of each WCM DSMB completion.

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Appendix. HIV Treatment Satisfaction Questionnaire

HIV TREATMENT SATISFACTION QUESTIONNAIRE

SUBJECT IDENTIFIER _____

DATE _____

The following questions are concerned with your medical treatment for HIV and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

2. How well controlled do you feel your HIV has been recently?

very well controlled 6 5 4 3 2 1 0 very poorly controlled

3. How satisfied are you with any side effects of your present treatment?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

4. How satisfied are you with the demands made by your current treatment?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

5. How convenient have you been finding your treatment to be recently?

very convenient 6 5 4 3 2 1 0 very inconvenient

6. How flexible have you been finding your treatment to be recently?

very flexible 6 5 4 3 2 1 0 very inflexible

7. How satisfied are you with the extent to which the treatment fits in with your lifestyle?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

8. Would you recommend your present treatment to someone else with HIV?

yes, I would recommend 6 5 4 3 2 1 0 no, I would definitely not recommend

9. How satisfied would you be to continue with your present form of treatment?

very satisfied 6 5 4 3 2 1 0 very dissatisfied

Please make sure that you have circled one number on each of the scales.

Thank you for taking the time to complete this questionnaire.