Safety and Efficacy of Emtricitabine/Tenofovir Alafenamide as Part of Salvage Antiretroviral Regimens in Patients with Uncontrolled Viremia and Drug-Resistant HIV Infection

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Principal Investigator:	Alice K. Pau, PharmD
Medical Advisory Investigator:	H. Clifford Lane, MD
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IND Sponsor:	Office of Clinical Research Policy and Regulatory Operations (OCRPRO), Division of Clinical Research (DCR), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)
Pharmaceutical Support Provided by:	Gilead Sciences Inc.
Sponsor Medical Monitor (SMM):	H. Preston Holley, MD, FACP

Study Staff Roster

Principal Investigator:

Alice K. Pau, PharmD
Intramural Clinical Management and Operations Branch (ICMOB)/DCR/NIAID
10 Center Drive, Room 11C103
Bethesda, MD 20892
Phone: 301-451-3740
Email: apau@niaid.nih.gov

Medical Advisory/ Accountable Investigator:

H. Clifford Lane, MD
Laboratory of Immunoregulation (LIR)/NIAID
Phone: 301-496-7196
Email: clane@niaid.nih.gov

Associate Investigators:

Frank Maldarelli, MD, PhD
Host Virus Interaction Branch/National Cancer Institute (NCI)
Phone: 301-435-8019
Email: fmalli@mail.nih.gov

Maura Manion, MD
LIR/NIAID
Phone: 301-496-7196
Email: Maura.manion@niaid.nih.gov

JoAnn Mican, MD
ICMOB/DCR/NIAID
Phone: 301-402-1326
Email: jmican@niaid.nih.gov

James Mikula, Pharm.D.
Leidos Biomedical Research, Inc.
In support of NIAID
Phone: 301-451-1426
Email: james.mikula@nih.gov

Irini Sereti, MD, MHS
LIR/NIAID
Phone: 301-496-5533
Email: isereti@niaid.nih.gov

Study Coordinator:

Alexander Ober, RN, BSN
LIR/NIAID
Phone: 301-435-7912
Email: obera@mail.nih.gov

Study Assistant: **Lucila Suarez, BA**
ICMOB/DCR/NIAID
Phone: 301-827-0086
Email: lucila.suarez@nih.gov

Statistician: **Michael Proschan, PhD**
Biostatistics Research Branch/DCR/NIAID
Phone: 240-669-5245
Email: proscham@mail.nih.gov

Sponsor Medical Monitor: **H. Preston Holley, MD, FACP**
Medical Monitor
Leidos Biomedical Research, Inc.
Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704
Phone: 301-228-4005
Fax: 301-846-6224
Email: Preston.Holley@fnlcr.nih.gov
CSO email: rchspsafety@mail.nih.gov

Institutional Review Board (IRB): **NCI IRB**
9030 Old Georgetown Road
Bethesda, MD 20892-8200
Tel: 301-496-6375
Fax: 301-480-0106
Email: nciirbadmin@mail.nih.gov

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List of Abbreviations

ABC	Abacavir
ABC/3TC	Abacavir/lamivudine
AE	Adverse Event/Adverse Experience
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
Anti-HBc	Antibody to Hepatitis B Core Antigen
Anti-HBs	Antibody to Hepatitis B Surface Antigen
AR	Adverse Reaction
ART	Antiretroviral therapy
ARV	Antiretroviral
AUC	Area under the concentration-time curve
CBC	Complete Blood Count
CC	Clinical Center
CD4	Cluster of Differentiation 4
CrCl	Creatinine Clearance
CRIS	Clinical Research Information System
CRIMSON	Clinical Research Information Management System of NIAID
CSO	Clinical Safety Office
DCR	Division of Clinical Research
DEXA	Dual X-ray Absorptiometry
DOT	Directly Observed Therapy
DOTCOM	NCI Protocol #14-I-0009 concerning treatment-resistant HIV-1 infection
E/C/F	Elvitegravir/cobicistat/emtricitabine
eGFR	Estimated glomerular filtration rate
$eGFR_{CG}$	Estimated glomerular filtration rate by Cockcroft-Gault Equation
EIND	Emergency Investigational New Drug
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
F/TAF	Emtricitabine 200 mg/tenofovir alafenamide 25 mg
FTC/TDF	Emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg
HBeAg	Hepatitis B ‘e’ Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV-1	Human Immunodeficiency Virus Type 1
HLA	Human Leukocyte Antigen
HRPP	Human Research Protection Program
ICMOB	Intramural Clinical Management and Operations Branch
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
iRIS	Integrated Research Information System
LIR	Laboratory of Immunoregulation
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NRTI	Nucleos(t)ide Reverse Transcriptase Inhibitor

OBT	Optimized background therapy
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
RBP	Retinol-binding Protein
RNA	Ribonucleic Acid
RT	Reverse Transcriptase
SCr	Serum Creatinine
SAE	Serious Adverse Event/Serious Adverse Experience
SAR	Suspected Adverse Reaction
SERF	Safety Expedited Report Form
SMM	Sponsor Medical Monitor
SRCP	Safety Review and Communications Plan
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TAF	Tenofovir alafenamide
TAM	Thymidine analog resistance mutation
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-DP	Tenofovir diphosphate
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem That Is Not an Adverse Event

Protocol Summary

Full Title:	Safety and efficacy of emtricitabine/tenofovir alafenamide as part of salvage antiretroviral regimens in patients with uncontrolled viremia and drug-resistant HIV infection
Short Title:	TAF
Clinical Phase:	2
IND Sponsor:	OCRPRO/DCR/NIAID/NIH
Conducted by:	ICMOB/DCR and LIR/Division of Intramural Research
Principal Investigator:	Alice K. Pau, PharmD
Sample Size:	N = 20
Accrual Ceiling:	N = 25
Study Population:	Adults and adolescents (≥14 years) with human immunodeficiency virus-1 (HIV-1) infection who experienced virologic failure while on a second or greater antiretroviral therapy (ART) regimen and for whom tenofovir disoproxil fumerate (TDF) is not a good option (due to genotypic resistance mutations or risk of renal injury) and for whom abacavir/lamivudine (ABC/3TC) is not an optimal alternative (due to human leukocyte antigen [HLA]-B*5701 allele, resistance mutations or hepatitis B virus [HBV] co-infection).
Accrual Period:	2 years or until Food and Drug Administration (FDA) approval of the study agent
Study Duration:	Start Date: September 1, 2015 End Date: August 31, 2018 Length of individual participation: 52 weeks
Study Design:	Single-arm, single site, open-label study
Study Agent:	F/TAF fixed-dose combination (emtricitabine 200 mg/tenofovir alafenamide 25 mg)
Intervention description:	Patients will be hospitalized to receive directly observed therapy (DOT) with F/TAF (in place of F/TDF or ABC/3TC, if applicable) plus their pre-enrollment ART regimen for 9 days. On Day 10, patients will switch to F/TAF plus an optimized background therapy (OBT) while waiting for the report of the result of Day 10 HIV RNA.. Patients with a ≥0.5 $\log_{10}$ decline in HIV RNA from Day 1 to Day 10 will continue F/TAF + OBT for 48 weeks. Patients with an HIV RNA decline of <0.5 $\log_{10}$ will discontinue F/TAF and their study participation will end. They will continue OBT (with TDF/FTC

or ABC/3TC in place of F/TAF, as appropriate) under protocol 14-I-0009.

Primary Objective:

- To explore the safety and efficacy of F/TAF as part of a salvage antiretroviral regimen for patients who experienced virologic failure

Secondary Objective:

- To use stored blood samples for future research related to HIV and drug resistance

Study Endpoints:

- Percent of patients with HIV RNA ≥ 0.5 $\log_{10}$ copies/mL decline on Day 10 of DOT with F/TAF plus a failing regimen
- Change in log HIV RNA from Day 1 to Day 10 of DOT with F/TAF plus a failing regimen

The following Study Endpoints are for patients with ≥ 0.5 $\log_{10}$ copies/mL decline in HIV RNA from Day 1 to Day 10:

- HIV RNA at 1, 2, 4, 8, 12, 24, 36, and 48 weeks after starting F/TAF + OBT as compared to baseline
- For HBV co-infected patients, HBV DNA 1, 2, 4, 8, 12, 24, 36, and 48 weeks after starting F/TAF + OBT as compared to baseline
- Renal function assessment at 1, 2, 4, 8, 12, 24, 36, and 48 weeks after starting F/TAF + OBT as compared to baseline:
    - Serum measurements: creatinine, cystatin C, phosphorus, and estimated glomerular filtration rate (eGFR)
    - Urine measurements: creatinine, phosphorus, glucose, and solute-to-creatinine ratios for the following solutes: protein, albumin, beta-2-microglobulin, retinol-binding protein
- Bone mineral density at 24 and 48 weeks after starting F/TAF + OBT as compared to baseline
- Genotypic resistance testing at study time points after week 12, if presence of plasma viremia with HIV RNA >500 copies/mL

Précis

Despite the success of antiretroviral therapy (ART), a subset of HIV-1-infected patients have uncontrolled viremia, multiple drug class resistance, and limited treatment options. Tenofovir disoproxil fumarate (TDF) forms part of most ART regimens, however its long-term use is associated with renal tubulopathy and reduced bone mineral density. Viral mutations (eg, K65R, multiple thymidine analog mutations (TAMs) can confer resistance or reduced susceptibility to TDF.

Tenofovir alafenamide (TAF) is an investigational oral prodrug of tenofovir. When compared to TDF, TAF demonstrated lower plasma tenofovir concentrations and more potent antiviral activity at approximately one-tenth of the dose. TAF has the advantage of reduced tenofovir exposure to the renal tubules and bone, potentially resulting in fewer kidney and bone effects. As with TDF, TAF has potent activities against hepatitis B virus (HBV), and may be a treatment option for patients with HIV/HBV co-infections. Phase 2 trials have demonstrated the non-inferiority of TAF to TDF in treating HIV-1 infection in ART-naïve patients. Smaller reductions in bone mineral density were measured with TAF than TDF. The most common adverse events were nausea and diarrhea.

This single-arm, single-site, open-label trial will explore the safety and efficacy of TAF in a fixed combination with emtricitabine (FTC) (F/TAF, Gilead Sciences Inc.) as part of a salvage antiretroviral regimen for HIV-1-infected adults and adolescents (≥14 years) who experienced virologic failure. The study will recruit patients who have failed TDF-containing regimens or cannot take TDF (due to resistance mutations or risk of renal injury) and for whom abacavir/lamivudine (ABC/3TC) is not an optimal alternative. Eligible patients will begin 9 days of inpatient directly observed therapy (DOT) with F/TAF plus their pre-enrollment background regimen. On Day 10, patients will switch to F/TAF plus OBT while waiting for the results of Day 10 HIV RNA results. Patients with an HIV RNA decline of <0.5 $\log_{10}$ from Day 1 to Day 10 will discontinue F/TAF, end their study participation, and continue OBT (with TDF/FTC or ABC/3TC in place of F/TAF, as appropriate) under the 14-I-0009 protocol. Patients with a ≥ 0.5 $\log_{10}$ decline in HIV RNA will continue on F/TAF + OBT for 48 weeks, with periodic outpatient assessments of adherence, safety, renal function, bone mineral density, HIV RNA, and CD4 T cell counts. Switching of one or more drugs in an ART regimen due to inadequate viral response will require inpatient DOT under 14-I-0009.

1 Background Information and Scientific Rationale

1.1 Background information

With the advances in ART, most HIV-infected patients who remain in care can achieve viral suppression with their prescribed regimens.[1] Despite this success, there remains a small subset of patients who have uncontrolled viremia, in some cases, with multiple-drug-class resistance and limited treatment options.[2] ART failure has been an independent risk factor of mortality in North America.[3]

TDF in a fixed-dose formulation with emtricitabine (FTC) is a potent 2-nucleoside reverse transcriptase inhibitor (NRTI) combination that forms part of most ART regimens for treatment-naïve as well as treatment-experienced patients. Approved by the U.S. FDA in 2003, TDF has demonstrated long-term antiretroviral efficacy. TDF is an oral prodrug of tenofovir (TFV), a nucleotide analog with activities against both HIV-1 and HBV. TFV itself has very low oral bioavailability. As a prodrug, oral TDF is rapidly absorbed and converts to TFV in the plasma, which in turn converts to TFV-diphosphate (TFV-DP) intracellularly. Long-term use of TDF, however, has been associated with renal tubulopathy,[4,5] potential for osteomalacia,[6] as well as increased incidence of reduced bone mineral density[7] and increased fracture risk.[7,8] Genotypic resistance to TDF has been reported, especially in the presence of the K65R mutation.[9-11] Additionally, the presence of multiple thymidine analog mutations (TAMs) can confer reduced susceptibility to TDF.[11]

TAF is an investigational oral prodrug of TFV. After absorption, it remains stable in the plasma and achieves low plasma concentration of TFV, but it is converted from TAF to TFV and then to TFV-DP intracellularly, where it exerts its activity as a reverse transcriptase (RT) inhibitor. The GS-US-120-0104 study evaluated the pharmacokinetics and viral kinetics of 300 mg of TDF and various doses of TAF monotherapy for 10 days in HIV-infected subjects. Compared to TFV, TAF demonstrated lower plasma TFV exposures, higher peripheral blood mononuclear cell (PBMC) intracellular TFV-DP levels, and more potent antiviral activity at approximately one-tenth of the dose (Table 1).[12]

Table 1. Pharmacokinetics and virologic responses of HIV-infected adults (n = 38) after 10 days of monotherapy with tenofovir (TFV) or tenofovir alafenamide (TAF)[12]

	TDF 300 mg	TAF 8 mg	TAF 25 mg	TAF 40 mg
Plasma TFV AUC (ng*h/mL)	1918	66	268	406
PBMC TFV-DP AUC (M*h)	3.0	3.5	21.4	74.5
Day 10 HIV RNA Δ (log_{10} copies/mL)	-0.81 ± 0.58	-0.98 ± 0.46	-1.50 ± 0.41	-1.74 ±0.19

AUC, area under the curve; PBMC, peripheral blood mononuclear cells; TFV-DP, tenofovir diphosphate

With the lower plasma TFV concentration, TAF has the advantage of reduced TFV exposure to the renal tubules as compared with TDF, potentially resulting a lesser degree of kidney and

bone effects. TAF is not a substrate for renal organic anion transporters, which may account for its reduced potential to cause proximal renal tubulopathy.[13] The higher PBMC concentrations with TFV may explain the greater 10-day virologic suppression.

TAF is a poor substrate of cytochrome P450 (CYP) enzymes, and is not an inducer or inhibitor of these enzymes. Thus, drugs metabolized by these enzymes are not expected to influence the pharmacokinetics of TAF, and TAF will not affect the pharmacokinetics of CYP substrates. TAF is a substrate for the intestinal efflux transporters P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP), and the hepatic update transporters organic anion transporting polypeptides (OATP) 1B1 and 1B3, thus, TAF exposures may be affected by inhibitors or inducers of the intestinal transporters, and inhibitors or genetic polymorphisms of OATPs. Systemic exposure of TAF can be increased by cobicistat (165% increase) and ritonavir-boosted atazanavir (91% increase).[11]

In a phase 2 trial of ART-naïve HIV-1 infected patients randomized 2:1 to TAF or TDF, both in combination with elvitegravir/cobicistat/emtricitabine (E/C/F), 87.5% of 112 subjects in the TAF arm and 89.7% of 58 subjects in the TDF arm achieved HIV RNA < 50 copies/mL at week 24 ($p = 0.48$).[14] In a pooled analysis of 2 treatment trials comparing E/C/F/TAF and E/C/F/TDF, 92.4% and 90.4% reported virologic success at week 48, demonstrating non-inferiority of TAF to TDF treatment.[15] In the intensive pharmacokinetic analysis in a subset of 26 patients, TFV plasma exposure (area under the plasma concentration curve [AUC_{tau}]) was 91% lower in the TAF arm than the TDF arm, whereas the intracellular TDF-DP levels in PBMCs were 5.3-fold higher in the TAF arm. The most common adverse events (AEs) were nausea and diarrhea, with nausea reported in 15% and 17% of patients treatment with TAF and TDF, respectively.[16] Significantly smaller reductions in bone mineral density in both the hip and spine were seen in the TAF group compared to the TDF group at week 48, as measured by dual energy X-ray absorptiometry (DEXA) scan.[14]

Median change in serum creatinine did not differ between the two arms (0.07 mg/dL vs. 0.10 mg/dL increase in the TAF and TDF arms, respectively) and stabilized at week 4 of therapy. As all study participants received cobicistat, a pharmacokinetic enhancer that has been associated with inhibition of tubular secretion of creatinine,[17] it is difficult to attribute the serum creatinine changes to TAF or TDF in this study. In pooled analysis of renal safety from various ART-naïve treatment studies, overall, there is less change in serum creatinine, eGFR, and less proteinuria in the TAF-treated compared to TDF-treated patients.[15] The pharmacokinetics of TAF 25 mg was compared between subjects with severe renal impairment (eGFR 15-29 mL/min) and matched healthy controls (eGFR > 90 mL/min). No difference in TAF exposure was observed, TFV concentrations were comparable to or below that seen in healthy volunteers with normal renal function prescribed TDF 300 mg dose.[15]

As with TDF, TAF has potent activities against HBV, and is therefore a treatment option for patients with HIV/HBV co-infections. When subjects with chronic hepatitis B were randomized (1:1:1:1:1) to daily doses of TDF 300 mg or TAF 8, 25, 40 or 120 mg, all 5 groups showed similar declines in HBV RNA at 4 weeks. No grade 3 or 4 adverse events were reported.[18]

Currently, a combination product of TAF/emtricitabine (F/TAF) (Gilead Sciences, Inc., Foster City, CA) is undergoing phase 3 clinical trials as a 2-NRTI backbone for antiretroviral regimens, as a treatment for HBV mono-infection (NCT01940471, NCT01940341) and as a treatment for HIV/HBV co-infection (NCT02071082 – in combination with elvitegravir and cobicistat). A new drug application (NDA) for F/TAF has recently been submitted to the FDA for approval, but it is anticipated that the product will not be commercially available until late spring 2016. NDAs for fixed-dose formulations of E/c/F/TAF 10mg, rilpivirine/F/TAF 25mg and darunavir/c/F/TAF 10mg are currently under evaluation at the FDA..

1.2 Rationale

The DOTCOM protocol (14-I-0009) aims to characterize and manage patients who experience virologic failure despite being on a second or greater regimen. Most if not all of such patients have been receiving FTC/TDF as part of their regimens for many years. Of the 5 subjects enrolled in DOTCOM thus far, 3 have extensive multiple-drug-class resistance, including the presence of several viral mutations that confer resistance to TDF by genotypic testing. In all 3 cases, phenotypic testing demonstrated partial sensitivity to TDF. Despite the reduced susceptibility, we chose to maintain FTC/TDF in the salvage regimen in the hope of attaining a partial antiviral effect. One of the 3 patients received F/TAF through an Emergency Investigational New Drug (EIND) protocol (14-I-9950) due to repeated episodes of acute kidney injury (peaked serum creatinine 4.4 mg/dL) after receiving TDF. After 24 weeks of treatment with an F/TAF containing regimen, this patient's renal function remains stable (last serum creatinine [SCr] = 1.36 mg/dL), with viral suppression (HIV RNA < 40 copies/mL). In a 4th subject, who has HBV co-infection, despite susceptibility to TFV, TDF was discontinued due to chronic kidney disease (last SCr = 2.22 mg/dL, eGFR = 36 mL/min). This patient is currently receiving a regimen including ABC/3TC as the NRTI backbone, despite the presence of the M184V mutation, which reduces susceptibility to ABC.

To date, there are few data on the efficacy of TAF in HIV-infected patients who harbor multiple-drug-class-resistant HIV, and who have reduced susceptibility to TFV in genotype or phenotype resistance testing. In these cases, FTC/TDF is often maintained as part of the salvage regimen despite the potential for resistance. Given the higher intracellular concentration of TFV-DP after administration of TAF as compared to TDF, we propose to replace FTC/TDF with F/TAF in salvage ART regimens of selected patients. In our study, a fixed dose combination of F 200mg/TAF 25mg will be used, regardless of antiretroviral drugs to be used in the OBT. The 25mg dose is used as it has been found to have potent antiviral activities in the ARV naïve populations, and as even at higher doses, TAF achieves significantly lower plasma TFV concentration and thus less systemic toxicities expected as compared to TDF 300mg dose.

2 Study Objectives

2.1 Primary Objective

To explore the safety and efficacy of F/TAF as part of a salvage antiretroviral regimen for patients who experienced virologic failure.

2.2 Secondary Objective

To use stored blood samples for future research related to HIV and drug resistance

3 Study Design

3.1 Description of study design

This is a single-arm, single site, open-label trial of F/TAF to be prescribed in place of FTC/TDF or ABC/3TC in combination with a selected OBT. OBT will be comprised of antiretroviral agents and designed based on prior ART history and drug tolerance, responses to therapy, and current and, if available, cumulative genotypic and/or phenotypic testing results.

To be eligible for enrollment, patients must be enrolled in the DOTCOM protocol where they will be admitted to the NIH Clinical Center (CC) to receive 7 days of their pre-enrollment ART regimen as self-guided DOT to confirm the lack of or suboptimal virologic efficacy of that regimen. Then, if eligible for and after signing the consent to this protocol, patients will begin 9 days of DOT with F/TAF in addition to their failing regimen. On Day 10 they will switch to F/TAF plus OBT while awaiting the results of the Day 10 HIV RNA. Most patients will be discharged on Day 10 with instructions to take F/TAF+OBT at home. Those patients who are able to remain hospitalized will be administered F/TAF+OBT as inpatient DOT until Day 12-15.

On Day 12-15, the Day 10 HIV RNA results will be reviewed by the study team. Patients with a ≥0.5 $\log_{10}$ decline in HIV RNA (from Day 1 to Day 10) will continue F/TAF plus OBT for 48 weeks. The Day 10 HIV RNA results may be shared with these patients by phone. Patients with an HIV RNA decline of <0.5 $\log_{10}$ will be asked to return to the NIH on Day 12-15 for a regimen change. They will discontinue F/TAF and their study participation will end. They will continue OBT (with TDF/FTC or ABC/3TC, as appropriate) under the DOTCOM protocol.

Patients who continue F/TAF during the 48 weeks of study will return for periodic outpatient assessments of adherence, safety, HIV RNA, and CD4 cell counts as outlined in Section 6. ART regimen changes due to inadequate viral response will require an additional 7 days inpatient DOT. After Week 48, if F/TAF is approved by the FDA, the patient will receive it through commercial source. If F/TAF has not yet received FDA approval, the patient will remain on this protocol to be followed every 3 months until F/TAF receives approval (or drug development is discontinued).

3.2 Study endpoints

- Percent of patients with ≥ 0.5 $\log_{10}$ decline in HIV RNA on Day 10 of DOT with F/TAF plus a failing regimen
- Change in $\log_{10}$ HIV RNA from Day 1 to Day 10 of DOT with F/TAF plus a failing regimen

For patients with ≥0.5 $\log_{10}$ copies/mL decline in HIV RNA from Day 1 to Day 10:

- HIV RNA at 1, 2, 4, 8, 12, 24, 36, and 48 weeks after starting F/TAF + OBT as compared to baseline
- For HBV co-infected patients, HBV DNA at 1, 2, 4, 8, 12, 24, 36, and 48 weeks after starting F/TAF + OBT as compared to baseline
- Renal function assessment 1, 2, 4, 8, 12, 24, 36, and 48 weeks after starting F/TAF + OBT as compared to baseline:
    - Serum measurements: creatinine, cystatin C, phosphorus
    - Urine measurements: creatinine, phosphorus, glucose, and solute-to-creatinine ratios for the following solutes: protein, albumin, beta-2-microglobulin, retinol-binding protein (RBP)
- Bone mineral density at 24 and 48 weeks after starting F/TAF + OBT as compared to baseline
- Genotypic resistance testing at study time points after week 12, if presence of plasma viremia with HIV RNA >500 copies/mL

4 Study Population

4.1 Rationale for Subject Selection

Patients who will be enrolled in this study represent a population of HIV-1-infected individuals who fail to achieve sustained viral suppression despite the use of current antiretroviral drugs. For patients with NRTI including TDF resistance mutations or where TDF (eg, renal tubulopathy, reduced bone mineral density) and/or to abacavir/lamivudine (eg, HLA-B*5701) are not optimal options, F/TAF may represent a new treatment option.

4.2 Recruitment Plan

Patients will be recruited from those enrolled in the DOTCOM protocol as well as locally and nationally through existing contacts with HIV primary care providers and clinics.

4.3 Subject Inclusion Criteria

1. Age ≥14 years
2. Documented HIV-1 infection (written documentation of positive standard ELISA or rapid HIV-1/HIV-2 antibody test with confirmatory Western Blot, or documentation of repeated HIV RNA of > 1,000 copies/mL)
3. Concurrent enrollment in the DOTCOM (14-I-0009) protocol
4. For females of childbearing potential, willingness to use effective contraception for the duration of the study
5. Willingness to be hospitalized for 10-15 days (with potential for day passes)
6. Willingness to have blood samples stored for future research that may include genetic testing
7. Multiple ART failure as defined by at least one of the following criteria:
    5a. HIV RNA > 1000 copies/mL and documented virologic failure on at least 1 prior ART regimen and at least 2 consecutive HIV RNA plasma measurements of > 1,000

copies/mL, including the last documented value, while on the currently prescribed ART regimen for at least 6 months; ***or***

5b. Documented extensive resistance to at least 3 antiretroviral (ARV) drug classes, and persistent plasma viremia (HIV RNA > 1,000 copies/mL for > 6 months) despite multiple regimen changes. The patient may be enrolled even if they have been prescribed their current regimens for less than 6 months.*

8. Where neither TDF nor ABC are optimal NRTI options as defined by at least one of the following criteria:

7a. Presence of the M184V mutation plus TDF-associated resistance mutations based on genotypic/phenotypic testing, specifically K65R alone, or with TAMs (such as 41L, 67N, 70R, 210W, 215Y/F, or 219Q/E) with or without other NRTI-associated mutations; ***or***

7b. FTC/TDF is not considered an option due to impaired renal function (eGFR by Cockroft-Gault equation [$eGFR_{CG}$]=30-60 mL/min), or risk of renal impairment because of conditions such as uncontrolled hypertension, diabetes mellitus, or history of renal toxicity while receiving a TDF-based regimen; ***and***

where ABC/3TC is contraindicated (ie, presence of HLA B*5701 allele or history of hypersensitivity reaction to ABC), or is a suboptimal option (eg, presence of ABC-associated resistance mutation(s) or in patients with HBV co-infection).

4.4 Subject Exclusion Criteria

1. Severe renal impairment ($eGFR_{CG}$ <30 mL/min)
2. Acute medical illness stemming from a significant co-morbidity (eg, malignancy requiring chemotherapy, treatment of an acute opportunistic infection or acute renal failture). Enrollment may be deferred up to 3 months to allow a condition to resolve or stabilize.
3. Pregnancy; however if a patient becomes pregnant while enrolled in the protocol, she may continue participation throughout her pregnancy.
4. Breastfeeding
5. Concomitant use of one of the following medications: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, bisphosphonate, St. John's wort, echinacea, milk thistle, sho-saiko-to, and probenecid.
6. Any illness or condition that, in the investigator's opinion, may substantially increase the risk of participation in the study, or compromise the scientific objectives.

4.5 Justification for Exclusion of Children and Pregnant Women (Special Populations)

Exclusion of children: There are limited data regarding dosing and efficacy of F/TAF in subjects younger than 12 years. Since the DOTCOM protocol enrolls subjects >14 years and we aim to have patients co-enroll in this protocol, age 14 will be used as the cutoff.

Exclusion of pregnant women: No adequate and well-controlled studies of F/TAF or its components have been conducted in pregnant women. Patients who enroll in the protocol may

experience a delay between study screening and an ART regimen change, during which uncontrolled viremia could increase the risk of HIV transmission to the fetus. Therefore, we do not think it is in the best interest of pregnant women and their unborn children to join this protocol.

Patients who become pregnant while enrolled may continue participation and continue F/TAF throughout pregnancy. Protocol-specified DEXA scan will be postponed until after delivery. Animal studies do not indicate direct or indirect harmful effects of TAF or FTC with respect to pregnancy, embryonal and fetal development, partition, or post-natal development. F/TDF is currently recommended in the United States as one of the preferred 2-NRTI for pregnant women for their treatment and for preventing mother-to-child transmission.[10] All women who become pregnant during this study will be followed until after delivery.

Exclusions of breastfeeding women: Women with uncontrolled viremia are discouraged from breastfeeding due to the potential for HIV transmission. In addition, emtricitabine and tenofovir (when used in TDF) are both excreted in breast milk and the risks in newborns are unknown.

5 Study Agent/Interventions

5.1 Disposition and Dispensation

F/TAF along with all co-administered ARV drugs will be distributed via the NIH CC Pharmacy according to standard pharmacy procedures. During the DOT period, all agents will be dispensed from the NIH CC Pharmacy to the inpatient nursing unit.

5.1.1 Formulation, Packaging and Labeling

FTC 200 mg/TAF 25 mg tablets are rectangular-shaped, film-coated blue tablets labeled with “225”. The formulation is packaged as 30 tablets in white bottles with child-resistant screw caps. Each bottle will be individually labeled with, dosing instructions, recommended storage conditions, the name and address of the manufacturer, Investigational Use Statement (“Caution: New Drug – Limited by Federal [USA] law to Investigational Use”) and that the agent should be kept out of reach of children.

5.2 Storage and Stability

F/TAF tablets must be stored at a room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). To ensure stability, the tablets should be dispensed only in the bottles in which they are supplied.

5.3 Preparation, Administration and Dosage

5.3.1 Dosing and administration

F/TAF will be orally self-administered as one tablet daily without regard to food. This dose is for adults and pediatric patients ≥12 years and weighing ≥35 kg. No dose adjustment is required for elderly patients. No dose adjustment is required for adults with mild to moderate renal impairment ($eGFR_{CG}$ ≥30 mL/min). See Section 7.1 for management of patients whose $eGFR_{CG}$ falls below 30 mL/min while on therapy.

5.3.2 Subject access to F/TAF at study closure

F/TAF is expected to become a licensed drug in 2016. In the event that F/TAF has not been licensed before the end of a subject's study participation, Gilead will continue to provide F/TAF until FDA approval or until development of F/TAF is discontinued by Gilead.

5.4 Assessment of Subject Compliance with Study Agent

Treatment adherence will be assessed at baseline and during follow-up visits using patient recall of doses missed in the past week, or since last clinic visit, and patient interviews.

5.5 Concomitant Medications and Procedures

All concomitant prescription medications taken during study participation will be recorded in the Clinical Research Information Management System of NIAID (CRIMSON). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in CRIMSON are concomitant prescription medications, over-the-counter medications and non-prescription medications taken at the time of AEs (all grades).

5.6 Prohibited Medications and Procedures

Concomitant use of any of the following medications is not allowed: carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, bisphosphonate, St. John's wort, echinacea, milk thistle, sho-saiko-to, and probenecid.

Treatment with investigational agents other than F/TAF will be permitted only if discussed with and approved by the principal investigator (PI) and by Gilead Sciences.

6 Study Schedule

6.1 Screening visit (Day -28 to Day -1)

Patients will come to the NIH CC to undergo the following procedures after signing informed consent. Evaluations or procedures will not be repeated if they were performed under another protocol within the visit window and results are available in CRIMSON or Clinical Research Information System (CRIS). The screening visit may occur during a DOTCOM protocol study visit.

- Review of eligibility criteria
- Physical exam and medical/social history
- Medication history/adherence assessment
- Urine collection for:
    - Pregnancy test (for women of childbearing potential)
    - Renal function assessments: creatinine, phosphorus, glucose, and solute-to-creatinine ratios for the following solutes: protein, albumin, beta-2-microglobulin, RBP
- Blood draw for
    - HIV-1 serology (if no prior written documentation of HIV status is available, repeated documents of positive HIV RNA > 1,000 copies/mL can be used as documentation of HIV status)

- Plasma HIV RNA levels
- CD4+ T cell count
- Complete blood count (CBC) with differential
- Acute care, mineral, and hepatic panels
- Genotypic/phenotypic resistance testing (described in section 7.2) for reverse transcriptase, protease, and integrase genes unless already performed and available from CRIMSON
- HLA B*5701 screening, unless available in CRIMSON or CRIS
- Hepatitis serology (anti-HAV [antibody to hepatitis A virus], Hepatits B surface antigen (HBsAg), antibody to HBsAg [anti-HBs], and antibody to hepatitis B core antigen [anti-HBc] anti-HCV [antibody to Hepatitis C virus]), unless available in CRIMSON
- If the subject has documented Hepatitis B surface antigen (HbsAg), HBV DNA and hepatitis B 'e' antigen (HBeAg) testing will be performed

Patients who meet the criteria for this study will complete one week of inpatient DOT on their pre-enrollment regimen under the DOTCOM protocol. Based on screening test results and outcomes from participation in DOTCOM, the study team will choose an OBT for each patient. The ARV treatment plans will be communicated to the patients' primary care providers.

6.2 Inpatient DOT with F/TAF+failing regimen: Day 1 to Day 9(+/-1 day)

Patients will receive F/TAF plus their pre-enrollment regimen for 9 days. If the same laboratory evaluations are conducted under DOTCOM within the visit window, they will not be repeated.

Day 1:

- Physical exam and medical/social history
- Urine collection for:
  - Pregnancy test (for women of childbearing potential)
  - Renal function assessments: creatinine, phosphorus, glucose, and solute-to-creatinine ratios for the following solutes: protein, albumin, beta-2-microglobulin, RBP
- DEXA scan scheduled: scan may be conducted either before inpatient DOT or within 7 days of the start of F/TAF. The scan will NOT be repeated during any additional weeks of DOT.
- Blood draw for:
  - CD4+ T cell count
  - Plasma HIV RNA
  - HBV co-infected patients only: HBV DNA and serum alanine aminotransferase (ALT)
  - CBC with differential
  - Acute care, mineral, and hepatic panels
  - Renal function assessment: creatinine, cystatin C, phosphorus, and calculated eGFR
  - Storage of plasma, serum, and PBMCs

- Begin self-guided DOT of F/TAF plus pre-enrollment regimen and continue for 9 days, with daily AE monitoring

Day 3 (+/- 1 day):

- HIV RNA
- HBV-coinfected patients only: HBV DNA

Day 5 (+/- 1 day):

- HIV RNA
- HBV-coinfected patients only: HBV DNA and serum ALT
- CBC with differential
- Acute care, mineral and hepatic panels

Day 8 (+/- 1 day):

- HIV RNA
- HBV-coinfected patients only: HBV DNA
-

Day 10 (+/- 1 day):

- HIV RNA
- HBV-coinfected patients only: HBV DNA
- CBC with differential
- Acute care, mineral and hepatic panels
- Begin F/TAF plus OBT at home OR as inpatient DOT until Day 12-15 only.
- In the event of intolerance of F/TAF or OBT, the patients will be asked to return to the NIH CC. A new treatment plan will be made in conjunction with the patients' primary care team.

Day 12-15 (+/-1 day):

- Results of Day 10 HIV RNA will be available for evaluation.
- Patients with a ≥0.5 $\log_{10}$ decline in HIV RNA from day 1 to day 10 will continue F/TAF + OBT for 48 weeks. The investigator may phone the patients to inform them of their Day 10 HIV RNA results.
- Patients with an HIV RNA decline of <0.5 log10 will return to the NIH CC and their results will be discussed with them. These patients will discontinue F/TAF (TDF/FTC or ABC/3TC may be resumed on a case-by-case basis) and will be discontinued from this protocol. They will continue OBT under the DOTCOM protocol.

6.3 Follow-up assessments at 1, 2, 4, 8 and 12 weeks (see Appendix B for visit windows) after starting F/TAF+OBT (for patients continuing F/TAF)

- Urine pregnancy test (for women of childbearing potential)
- Urine renal function assessments: creatinine, phosphorus, glucose, and solute-to-creatinine ratios for the following solutes: protein, albumin, beta-2-microglobulin, RBP
- Physical exam and medical/social history
- Medication history

- Adherence assessment and counseling
- AE monitoring
- Blood draw for:
    - HIV RNA
    - HBV-coinfected patients only: HBV DNA
    - CBC with differential
    - Acute care, mineral and hepatic panels
    - Serum renal function assessments: creatinine, cystatin C, phosphorus, and calculated eGFR
    - *12 weeks only*: CD4+ T cell count
- Patients with reduced HIV RNA levels during DOT but with viral rebound during post-DOT follow-up will be managed as detailed in Section 7.1

6.4 Follow-up assessments at 24, 36, and 48 weeks after starting F/TAF+OBT (+/- 2 weeks)

- Urine pregnancy test (for women of childbearing potential)
- Urine renal function assessment (as detailed in 6.2)
- Physical exam and medical/social history
- Medication history
- Adherence assessment and counseling
- AE monitoring
- *24 and 48 weeks only*: DEXA scan
- Blood draw for:
    - HIV RNA
    - HBV-coinfected patients only: HBV DNA
    - CD4 T cell count
    - Acute care, mineral and hepatic panels
    - CBC with differential
    - Serum renal function assessments (as detailed in 6.3)
    - Genotypic/phenotypic resistance testing for patients with plasma HIV RNA > 500 copies/mL
    - Storage of plasma, serum and PBMCs

6.5 Unscheduled visits

Patients will be advised to return to the CC as needed in the event of viral rebound, drug intolerance, or hepatitis flare as per the PI and the study team. Additional adherence counseling and a repeat blood draw for clinical purposes may be done during these visits.

7 Study Procedures/Evaluations

7.1 Clinical Evaluations

Physical exam and medical/social history including vital signs, targeted physical exam, and questions/discussion regarding social issues that may impact medication adherence.

Urine collection for pregnancy and renal function tests.

Phlebotomy: Blood will be collected for routine serologic, hematologic, and clinical chemistry evaluations as listed Section 6.

Adherence assessment and counseling: Medication adherence will be assessed by a clinical pharmacist or other member of the study staff via patient interview or patient recall of doses missed in the past week, or since the last clinic visit.

Management of subjects with reduced HIV RNA levels during DOT and viral rebound during the post-DOT follow-up: For this study, since the enrolled patients are heavily treatment-experienced, virologic failure is defined as either (1) confirmed HIV RNA rebound to >200 copies/mL after viral suppression with F/TAF + OBT; or (2) failure to have a >1 $\log_{10}$HIV RNA decline at week 24. For patients with extensive treatment experience, multiple drug-class resistance, and less than 2-3 fully active antiretroviral drugs in the regimen, maximal suppression may not be feasible, thus, virologic success may have to be defined on a case-by-case basis. In general, it has been shown that even partial viral suppression (eg, > 1-2 log reduction in HIV RNA copies/mL) with a stable CD4 cell count can provide clinical benefit. In the event of viral rebound during the post-DOT period, we will begin with adherence assessment and counseling. Genotype +/- phenotype resistance testing may be performed to identify emergence of new resistance-associated mutations or changes in phenotypic susceptibility to the ART regimen. Unless factors can be identified that would indicate that a change in the treatment regimen might be successful (ie, treatment-related AEs), we will keep patients on their respective regimens and continue to follow them while emphasizing the importance of adherence.

Management of HBV co-infected subjects: Due to the risk of hepatitis flare upon initation and discontinuation of F/TAF, HBV-coinfected patients will be monitored for clinical signs of hepatitis and changes in laboratory measures of HBV DNA and serum ALT. Patients will be informed to contact the study team with any new symptoms compatible with hepatitis. Adherence counseling will discourage patients from abruptly stopping their F/TAF regimen. Subjects with HIV/HBV coinfections who discontinue F/TAF will be monitored (with clinical and laboratory assessments) at least monthly for up to 3 months after stopping treatment either by the study team or by their primary care physician.The study team will work with the subjects' primary care physician to identify commercially available HBV treatment for subjects who discontinue F/TAF.

For the purpose of this protocol, hepatitis flare is defined as confirmed serum ALT increase to 2 times Day 1 value and >5x the upper limit of normal, with or without associated symptoms. If serum ALT measures indicate hepatitis flare, other liver-associated parameters, including total bilirubin and international normalized ratio (INR) will be assessed. Efforts will be made to identify other causes of serum transaminase elevation, including a review of other concomitant medications and history of recent alcohol use. Viral hepatitis serology (HAV IgM, HCV RNA, and HBV DNA) will also be done. On a case-by-case basis, if the total bilirubin is greater than 2 times the Day 1 value and INR is >0.5 above the Day 1 value (provided if both are >ULN), the study team in consultation with Gilead will determine whether to continue F/TAF and monitor ALT weekly until it returns to Day 1 value, or if it is necessary to discontinue F/TAF portion of the regimen.

Management of Potential Nephrotoxicity: Any patient whose eGFR falls below 30 mL/min must have serum creatinine and cystatin C repeated within 3 business days. eGFR by CKD-EPI (cystatin C) should be calculated.[19] Any subject who have an $eGFR_{CG}$ <30 mL/min and also experience >20% reductionfrom baseline in eGFR by CKD-EPI (cystatin C) or who have clinical and/or laboratory evidence of acute renal failure will be discussed with the SMM and may discontinue from F/TAF if deemed appropriate. For subjects with $eGFR_{CG}$ in whom F/TAF has not been discontinued and considered to have stable renal function per Principal Investigator and/or SMM, it is not mandatory to repeat eGFR assessments within 3 days, and can be monitored per protocol.

7.2 Research Evaluations

Inpatient self-guided DOT: Patients will be admitted to the CC for 10-15 days to assess the change in HIV RNA while receiving an ART regimen by DOT. Patients will be instructed to request the antiretroviral drugs from the nursing staff at a pre-arranged time reflecting their home medication schedule. If patients do not request to have their antiretroviral drugs administered within 2 hours of the scheduled time, the nursing staff will automatically administer the drugs to them 2 hours after the scheduled time. The nursing staff will monitor patients as they take each dose and document the time of administration. A self-guided DOT plan will be established by the study team in conjunction with the patients and their parent(s)/guardian(s) for adolescents ages 14-18 (exception will be given to emancipated adolescents).

Bone mineral density test: A DEXA scan of the lumbar vertebrae and hip will be performed to generate mean bone mineral density scores. Subjects who become pregnant during study participation will not have DEXA scans.

Urinary RBP: Urine samples will be stored and will later be shipped to Gilead Sciences Inc. or a designated contract laboratory for assessment of urinary RBP.

PBMCs, plasma, and serum storage: For investigations related to HIV treatment failure, viral resistance, immunologic responses, and subsequent responses to therapy.

HIV genotypic and phenotypic resistance testing: Genotypic testing will be done using genotype testing and Genotypic resistance testing will be performed using Trugene HIV-1 at baseline in the Viral Isolation Laboratory, Clinical Services Program, Frederick National Laboratory for Cancer Research. Phenotypic assay will be performed at Monogram Sciences using the PhenoSense assay. In the event that a patient is found to have rebound viremia after the initial virologic response, or has persistent viremia despite a new antiretroviral regimen, stored plasma samples may be used to perform the HIV genotypic resistance testing. If phenotypic resistance testing is deemed necessary, a stored sample will be sent to a commercial laboratory from the repository.

7.2.1 Specimen Preparation, Handling, and Shipping

All clinical care and research blood specimens will be handled according to NIAID and NIH CC standard procedures. Urine samples for RBP will be stored in Frederick and then batched and shipped to Gilead Sciences or a contract laboratory.

8 Potential Risks and Benefits

8.1 Potential Risks

F/TAF: TAF has been given experimentally to more than 1,000 subjects, including individuals with both HIV infection and renal insufficiency. Single and multiple doses of the F/TAF combination or FTC+TAF were generally well tolerated in healthy subjects. Most AEs were mild in severity and considered unrelated to the study drug. A serious adverse event (SAE) of spontaneous abortion was reported during one study and was considered related to the drug by the investigator. The most commonly reported AEs were headache, diarrhea, nausea and upper respiratory tract infection, with ≥10% of subjects experiencing one or more of these events. Vomiting, abdominal pain, dyspepsia, flatulence, rash, and fatigue were less common (≥1% and <10%).

Older NRTIs such as didanosine, stavudine and didanosine had been associated with mitochondrial toxicities manifested as lactic acidosis and severe hepatomegaly with steatosis. These events are seldom reported with newer NRTIs such as ABC or TDF, and has not been reported with F/TAF to date. Treatment with F/TAF should be suspended in patients who develop clinical or laboratory findings suggestive of lactic acidosis. Upon initiation of effective ART, patients with severe immunodeficiency have experienced immune reconstitution syndrome manifesting as inflammatory reactions such as cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, or *Pneumocystis jiroveci* pneumonia.

F/TAF in HIV/HBV co-infected subjects: Hepatitis flare, defined as an abrupt rise in serum ALT to >5 times upper limit of normal may occur after initiation or discontinuation of HBV treatment, or may occur spontaneously. The clinical presentation varies from asymptomatic to acute hepatitis to hepatic decompensation. Patients with positive HBeAg are at higher risk of flares.[20] In a study of a TDF-containing regimen as treatment for chronic hepatitis B-monoinfected patients, 6% of 426 subjects had hepatitis flare, nearly all in the first 2 months of treatment.[21] In HIV/HBV co-infected patients who are typically treated with nucleo(t)side therapy active against both HBV and HIV, immune reconstitution from HIV viral suppression may also lead to hepatitis flare. In one study, hepatitis flare was reported in 1 of 10 patients who received a combination of lamivudine and TDF and in 2 of 10 patients who received TDF alone.[22]

HBV-coinfected subjects who experience hepatitis flare or who discontinue F/TAF will be managed as described in Section 7.1.

Bone mineral density test (DEXA scan): The total amount of radiation exposure from 3 DEXA scans is 0.00024 rem for adults or 0.00012 rem for children (<18 years). The radiation exposure in this study is below the limits set for research subjects by the NIH Radiation Safety Committee. These limits are 5 rem per year for adults and 0.5 rem per year for children. There is no direct evidence that radiation exposure at this level is harmful, but, as with all radiation exposure, there may be a very slight increase in the risk of cancer. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. A copy of the pamphlet, “An Introduction to Radiation for NIH Research Subjects”, will be provided to patients upon request. If a subject

becomes pregnant during enrollment, protocol-specified DEXA scan will be postponed until after delivery.

Phlebotomy: The risks associated with phlebotomy include discomfort, bruising, local hematoma formation and, on rare occasions, lightheadedness, fainting, and infection at the puncture site. The amount of blood drawn for research purposes will be within the limits allowed for adult and pediatric subjects at the NIH CC (Medical Administrative Policy 95-9: Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center: http://cc-internal.cc.nih.gov/policies/PDF/M95-9.pdf).

HLA typing and other genetic testing: Some HLA types have been associated with an increased risk of certain diseases like arthritis and other rheumatologic disorders, or a faster progression to AIDS. The presence of the HLA B*5701 allele has been associated with hypersensitivity reactions to abacavir, an HIV NRTI.[23] Results from this test will guide the team regarding whether or not abacavir can be prescribed to a specific patient. Results from the HLA typing will become part of each patient's medical record at the NIH. Medical records containing this information are maintained in a secure place.

Other genetic testing may be performed on stored samples in the future to identify genetic components related to HIV-1 pathogenesis and virologic failure. Results from genetic testing may have psychological implications for patients, such as revelations about future health risks, incurable conditions, and/or information contradictory to stated biological relationships. Genetic counseling and advice is available from the NIH to help patients understand the implications of these findings, if necessary. All information relating to the participant's genetic testing will be stored and maintained in a secure database (CRIMSON).

Following the genetic testing, data will be shared in a controlled-access public database in accordance with NIH guidelines, for other investigators to benefit from the information (eg, the Database of Genotypes and Phenotypes or dbGaP). However, no personal, identifiable information will be shared in this process, as the results will only be shared with a code.

Inpatient admission for DOT: Patients may become bored and restless during their inpatient stay. Patients will have access to game rooms, television, wireless internet access, patient library, and a fitness center. They may receive visitors and request a pass to leave during the day.

8.2 Potential Benefits

There is no guarantee that patients will benefit from participating in this study. Along with F/TAF, patients will receive an individualized ART plan designed to achieve optimal HIV suppression. If sustained viral suppression can be achieved, it may prevent further disease progression or further emergence of new resistance associated mutations.

9 Research Use of Stored Human Samples, Specimens or Data

Intended use: PBMCs, serum, and plasma samples, and data collected under this protocol may be used to further study the pathogenesis of HIV infection, including virologic and immunologic studies in this population. HLA testing will be performed at baseline, unless such testing results are available from participation in other NIAID studies. Other genetic testing may be performed from stored samples for research purposes only. For any other research or experimental treatments done under this or other protocols, IRB permission will be obtained.

In the future, other investigators (both at the NIH and outside) may wish to study the samples and/or data. In that case, IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.

Storage: Access to stored samples will be limited using a locked room or a locked freezer. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

Tracking: Samples will be tracked utilizing the repository operated by Leidos Biomedical Research, Inc. Data will be stored and maintained in the CRIMSON database.

Disposition at the completion of the protocol: At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.

- In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, IRB approval must be sought prior to sharing any coded samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.
- At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.

Reporting the loss or destruction of samples/specimens/data to the IRB:

- Any loss or unanticipated destruction of the samples or data (for example, due to freezer malfunction) that meets the NIH Intramural protocol violation definition or results in a violation that compromises the scientific integrity of the data collected for the study will be reported to the NCI IRB.
- Additionally, subjects may decide at any point not to have their samples stored. In that case, the PI will destroy all known remaining samples and report what was done to the subject and the IRB. This decision will affect the subject's participation in this protocol, but it may not affect participation in other protocols at the NIH.

10 Assessment of Safety

10.1 Definitions

Adverse Event: An AE is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (eg, abnormal physical exam or laboratory finding), symptom, or

disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR): An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR): An AE for which there is a reasonable possibility that the investigational agent caused the AE. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than AR, which implies a high degree of certainty.

Serious Adverse Event: An SAE is an AE that results in one or more of the following outcomes:

- death
- a life threatening event (places the subject at immediate risk of death from the event as it occurred)
- an inpatient hospitalization (other than protocol specified DOT) or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- a medically important event*

* Medical and scientific judgment should be exercised in deciding events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event: An AE is unexpected if it is not listed in the Investigator's Brochure or Package Insert (for marketed products) or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR): A SUSAR is a SAR that is both Serious and Unexpected.

Unanticipated Problem (UP): A UP is any event, incident, experience, or outcome that is

1. unexpected in terms of nature, severity, or frequency in relation to
   a. the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents; and
   b. the characteristics of the subject population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. (Per the IND Sponsor, an AE with a serious outcome will be considered increased risk.)

Unanticipated Problem that is not an Adverse Event (UPnonAE): A UP that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such

events would be considered a non-serious UP. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation: Any change, divergence, or departure from the IRB-approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur

Serious Protocol Deviation: A deviation that meets the definition of a SAE or compromises the safety, welfare or rights of subjects or others.

Non-compliance: The failure to comply with applicable NIH Human Research Protection Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human subjects. Non-compliance is further characterized as

1. Serious: Non-compliance that
    a. Increases risks, or causes harm, to participants
    b. Decreases potential benefits to participants
    c. Compromises the integrity of the NIH-HRPP
    d. Invalidates the study data
2. Continuing: Non-compliance that is recurring
3. Minor: Non-compliance that is neither serious nor continuing

10.2 Documenting, Recording, and Reporting Adverse Events

All AEs occurring from the time the informed consent is signed through the final study visit will be documented, recorded, and reported.

At each contact with the subject, information regarding AEs will be elicited by appropriate questioning and examinations and will be:

- immediately documented in the subject's medical record/source document,
- recorded in CRIMSON, and
- reported as outlined below (eg, IND Sponsor, IRB, and FDA).

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the AE.

A laboratory abnormality will not be reported as an AE if ALL of the following criteria are met:

- It is no more than "Grade 1" or "Mild" per the protocol specified toxicity table (or investigator assessment if not listed on the table); AND
- It does NOT require an intervention (eg, discontinuation of treatment, dose reduction/delay, additional assessments, or treatment); AND
- It is assessed by the PI as NOT related to the study agent(s); AND
- It is assessed by the PI as NOT clinically significant (eg, the abnormal value does

NOT suggest a disease or organ toxicity)

All abnormal laboratory findings will be reviewed on a routine basis by the PI to identify potential safety signals. An abnormal lab not included on the toxicity table should be assessed in a similar fashion to the criteria above.

10.3 Investigator Assessment of Adverse Events

The Investigator will assess all AEs with respect to **Seriousness** (criteria listed above), **Severity** (intensity or grade), and **Causality** (relationship to study agent and relationship to research) according to the following guidelines.

10.3.1 Severity

The Investigator will grade the severity of each AE according to the "Division of Aids Table for Grading the Severity of Adult and Pediatric Adverse Events" Version 2.0, November 2014 which can be found at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_Grading_Table_v2_NOV2014.pdf

Some Grade 1 lab parameters on the DAIDS Toxicity Table (Fibrinogen, Potassium (low), Uric Acid (males only, elevated)) fall within the NIH lab reference range for normal values. These normal values will not be reported as Grade 1 AEs. The Grade 1 values for these tests will be reported as follows:

- Fibrinogen: 100-176 mg/dL
- Potassium (low): 3.0-3.3 mmol/L
- Uric Acid (males): 8.7-10.0 mg/dL

10.3.2 Causality

Causality (likelihood that the event is caused by the study agent(s)) will be assessed considering the factors listed under the following categories:

Definitely Related
- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related
- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related
- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related
- does not have a reasonable temporal relationship

OR

- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship

OR

- definitely due to an alternative etiology

Note: Other factors (eg, dechallenge, rechallenge) should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

10.4 Investigator Reporting Responsibilities to the Sponsor

10.4.1 Adverse Events

AE data will be submitted to the IND Sponsor when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

10.4.2 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be reported on the Safety Expedited Report Form (SERF) and sent to the Clinical Safety Office (CSO) by fax or e-mail attachment. Deaths and immediately life threatening SAEs must be reported to the CSO within 1 business day after the site becomes aware of the event. All other SAEs must be reported within 3 business days of site awareness.

Clinical Safety Office contact information:

Clinical Safety Office
5705 Industry Lane
Frederick, MD 21704

Phone 301-846-5301
Fax 301-846-6224
E-mail: rchspsafety@mail.nih.gov

SAEs that have not resolved by the final study visit are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (eg, the subject is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator on the AE CRF and the SERF.

SAEs that occur after the final study visit that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

10.4.3 Unanticipated Problems

Unanticipated Problems that are also AEs must be reported to the CSO by fax or e-mail attachment no later than 7 calendar days of site awareness of the event. UPs that are not AEs

are not reported to the CSO. Report UPs that are also AEs to the CSO on a SERF or IRB UP form.

10.4.4 Pregnancy

All pregnancies will be reported on the Pregnancy Notification/Outcome Form to the CSO within 1 business day of site awareness.

Pregnancy outcome data (eg, delivery outcome, spontaneous or elective termination of the pregnancy) will be reported to the CSO within 3 business days of the site's awareness.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (eg, congenital anomaly/birth defect) are reportable on the SERF.

In the event of pregnancy, the subject may continue study participation. The research subject will be advised to notify her obstetrician of study participation and study agent exposure.

10.5 Investigator Reporting Procedures to the IRB

10.5.1 National Cancer Institute IRB Expedited Reporting of Unanticipated Problems and Deaths

The protocol PI will report to the NCI IRB:

- All deaths, except deaths due to progressive disease.
- All protocol deviations (except for visits outside of the protocol schedule window).
- All UPs.
- All serious non-compliance.

Reports must be received by the NCI IRB via the Integrated Research Information System (iRIS) within 7 working days of the PI's awareness of the events.

10.5.2 National Cancer Institute IRB Requirements for Principal Investigator Reporting at Continuing Review

The protocol PI will report the following to the NCI IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation, and any corrective action.
2. A summary of any instances of non-compliance.
3. A tabular summary of the following AEs:
   - All Grade 2 **unexpected** events that are possibly, probably, or definitely related to the research.
   - All Grade 3 and 4 events that are possibly, probably, or definitely related to the research.
   - All Grade 5 events regardless of attribution.
   - All SAEs regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

10.6 Sponsor's Reporting Responsibilities

Serious and unexpected suspected adverse reactions (SUSARs) as defined in 21 CFR 312.32 and determined by the IND Sponsor will be reported to FDA and all participating investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

10.7 Pausing Rules for an Individual Subject

Pausing is the suspension of administration of study agent to a single subject until a decision is made whether or not to resume administration of the study agent.

The pausing criteria for a single subject in this study include any of the following:

- A subject experiences an SAE that is unexpected and possibly, probably, or definitely related to a study agent;
- A subject experiences (2) Grade 3 or greater AEs (not including total bilirubin in subjects taking atazanavir) that are unexpected and possibly, probably, or definitely related to a study agent;
- Any safety issue that the site investigator determines should pause administration of a study agent to a single subject.

The CSO, in collaboration with the PI, may also pause for an entire group if a safety concern is identified.

10.7.1 Reporting a Pause

If a pausing criteria is met, a description of the AE(s) or safety issue must be reported by the PI, within 1 business day, to the CSO, the IRB, and Gilead Sciences, Inc. by fax or email.

10.7.2 Resumption of a Paused Study

The CSO in collaboration with the PI will determine whether or not it is safe to resume administration of the study agent to the subject. The PI will notify the IRB and Gilead Sciences Inc. of the decision on resumption of the study agent.

10.7.2.1 Discontinuation of Study Agent

A subject who does not resume study agent will continue to be followed for safety.

10.8 Halting Rules

Halting the study requires immediate discontinuation of study agent administered for all subjects and suspension of enrollment until a decision is made whether or not to continue enrollment and study agent administration.

The halting rules are:

- Two or more subjects experience the same or similar SAEs that are unexpected and are possibly, probably, or definitely related to the study agent

OR

- Three or more of the same or similar AE in different subjects that are grade 3 or above and are unexpected and possibly, probably, or definitely related to the study agent

OR

- Any safety issue that the PI, Gilead Sciences, Inc and/or the CSO determines should halt the study

The PI, Gilead Sciences Inc, and/or CSO will determine if the study should be halted. In addition, the FDA may halt the study at any time following review of any safety concerns. A local IRB may halt the study at their site.

10.8.1 Reporting a Study Halt

If a halting rule is met, a description of the AE(s) or safety issue must be reported by the PI, within one business day, to the CSO, the IRB, and Gilead Sciences, Inc. by fax or email. The fax or email should specify in the Subject Line that a halting rule has been met with the study name or number.

10.8.2 Resumption of a Halted Study

The IND Sponsor, in collaboration with the PI will determine if it is safe to resume the study. The PI will notify the IRB of the decision on resumption of the study.

10.8.3 Discontinuation of Study Agent

Subjects who do not resume study agent will continue to be followed for safety.

10.9 Withdrawal Criteria for an Individual Subject

An individual subject will be withdrawn for any of the following:

- An individual subject's decision. (The investigator should attempt to determine the reason for the subject's decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- The investigator determines that continued participation in the study would not be in the best interest of the subject.

10.9.1 Replacement of Withdrawn Subjects or Subjects Who Discontinue F/TAF

Subjects who withdraw will continue to be followed and included in safety assessments. No replacement of subjects will be necessary.

10.10 Safety Oversight

10.10.1 Safety Review and Communications Plan (SRCP)

A Safety Review and Communication Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the PI and the CSO, which delineates the safety oversight responsibilities of the PI, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

10.10.2 Sponsor Medical Monitor (SMM)

A Medical Monitor, representing the IND Sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The SMM will be responsible for performing safety assessments as outlined in a Safety Review and Communications Plan (SRCP).

11 Clinical Monitoring Structure

11.1 Site Monitoring Plan

As per International Conference on Harmonization (ICH) Good Clinical Practice (GCP) 5.18 FDA 21 CFR 312.50, if under IND, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines". Monitors under contract to the NIAID/OCRPRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the ICF process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information or CRIMSON data abstracts with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators' are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections-OHRP), the FDA, and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make the study documents (eg, consent forms, CRIMSON data abstracts, and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the principal investigator and study staff prior to enrollment. The plan will outline the frequency of the monitoring visits based on factors such as the study enrollment, data collection status, and regulatory obligations.

12 Statistical Considerations

12.1 Description of the Analyses

The primary outcome is the change in $\log_{10}$HIV RNAfrom baseline to day 10, analyzed using a one-sample t-statistic if the data are not skewed. The estimated change will then be expressed in terms of a confidence interval for the percentage change from baseline. If changes from baseline appear skewed, we will use a Wilcoxon signed rank test instead of a t-test. Similar analyses will be applied for changes from baseline in other continuous outcomes. The

proportion of patients with HIV RNA ≥0.5 $\log_{10}$ decline on day 10 will be computed, along with an exact 95% confidence interval using the binomial distribution.

A secondary analysis will fit a mixed model to $\log_{10}$HIV RNA data across multiple time points. The model will include subject-specific random effects for intercepts, slopes, and quadratic terms.

Power calculations are problematic because it is difficult to estimate the standard deviation of 1-week change in log viral load for these patients. The most similar trial was Akil et al, but their reported standard deviation of change was after adjusting for several factors.[24] The standard deviation of a raw change is likely to be substantially larger than their reported value of 0.18. If we assume a standard deviation of change of 0.50, a sample size of 20 participants provides 90% and 80% power to detect changes from baseline approximately equal to 0.38 and 0.33 logs, respectively. These are large effects, but much smaller than those observed in Akil et al (2014).

13 Ethics/Protection of Human Subjects

13.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to decide voluntarily whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers, which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks, and benefits. Subjects will be given the opportunity to ask questions and have their questions answered.

Subjects will sign the informed consent document prior to undergoing any study procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the process of signing the consent form in the subject’s medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.1.1 Assent or Informed Consent Process (in Case of a Minor)

Assent forms will be used for all study subjects ≥14 years to <18 years of age who are capable to give their assent to participate. Parental consent will be obtained for all study subjects under the age of 18. Study subjects <18 years will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

13.1.2 Non-English–Speaking Participants

If a non-English speaking participant is unexpectedly eligible for enrollment, the participant will be provided with the CC Short Written Consent Form for Non-English Speaking Research Participants in the participant’s native language and a verbal explanation of the purpose, procedures and risks of the study as described in MAS Policy M77-2, NIH HRPP SOP 12 and

45 CFR 46.117(b)(2). The IRB-approved English consent form will serve as basis for the verbal explanation of the study. The investigator will obtain an interpreter unless the investigator is fluent in the prospective participant's language. Preferably, the interpreter will be someone who is independent of the participant (ie, not a family member). Interpreters provided by the CC will be used whenever possible. The interpreters will translate the IRB-approved English consent form verbatim and facilitate discussion between the participant and investigator.

The IRB-approved English consent form will be signed by the investigator obtaining consent and a witness to the oral presentation. The CC Short Written Consent Form will be signed by the participant and a witness who observed the presentation of information. The interpreter may sign the consent document as the witness and, in this case, will note "Interpreter" under the signature line. A copy of both signed forms will be provided to the participant to take home.

The investigator obtaining consent will document the consent process in the participant's medical record (CRIMSON), including the name of the interpreter. Further, all instances of use of the CC Short Written Consent Form will be reported to the IRB at the time of annual review. If the CC Short Written Consent Form is used three times or more for the same language, this will be reported to the IRB immediately.

13.2 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records. Records will be kept locked and 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 NCI IRB, NIAID, or Office for Human Research Protections.

14 Data Handling and Record Keeping

14.1 Data Capture and Management

Study data will be maintained in CRIMSON and CRIS (Clinical Research Information System), and collected directly from subjects during study visits and telephone calls, or they will be abstracted from subjects' medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data entry into CRIMSON will be performed by authorized individuals. The PI is responsible for assuring that all the data collected are complete, accurate, and recorded in a timely manner. Any outside medical records pertinent to protocol participation will be uploaded into the CRIMSON repository (also known as CRIMSON Cloud).

14.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the International Conference on Harmonization Good Clinical Practice Guidelines. Study records will be maintained by the PI for a minimum of 3 years or in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the PI wish to assign the study records to another party and/or move them to another location, he/she must provide written notification of such intent to NIAID/OCRPRO with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from NIAID/OCRPRO.

Appendix A: Scientific References

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Appendix B. Schedule of Procedures

	Screeningvisit	Inpatient DOT: Day 1 to Day 10 *or* Day 1 to Day 12-14 (+/-1 day)[1]						Follow-up evaluations (No. of weeks after starting F/TAF plus OBT)							
Study day or week	Day -28 to Day -1	Day 1	Day 3	Day 5	Day 8	Day 10	Day 12-15[2]	1 week (+/- 2 working days)	2 weeks (+/- 2 working days)	4 weeks (+/- 2 working days)	8 weeks (+/- 4 working days)	12 weeks (+/- 1 wk)	24 weeks (+/- 2 wks)	36 weeks (+/- 2 wks)	48 weeks (+/- 2 wks)
Procedures															
Informed consent	X														
Urine pregnancy test[3]	X	X						X	X	X	X	X	X	X	X
Physical exam, medical/social history	X	X						X	X	X	X	X	X	X	X
Medication history	X							X	X	X	X	X	X	X	X
Adherence assessment/counseling	X	X						X	X	X	X	X	X	X	X
Urine renal function assessments[4]		X						X	X	X	X	X	X	X	X
Urinary retinol-binding protein (Gilead)	X	X						X	X	X	X	X	X	X	X
DEXA scan[5]		X											X		X
Adverse event monitoring			X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of Day 10 HIV RNA results							X								
Blood evaluations															
HIV-1 serology[6]	X														
Hepatitis serology[7]	X														
Genotypic +/- phenotypic resistance testing[8]	X												X	X	X

HLA B*5701 screening[6]	X														
Plasma HIV RNA	X	X	X	X	X	X		X	X	X	X	X	X	X	X
HBV DNA[9]	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Hepatitis B 'e' antigen[9]	X														
CD4 T cell count	X	X										X	X	X	X
CBC with differential	X	X		X		X		X	X	X	X	X	X	X	X
Acute care, mineral, hepatic panels	X	X		X		X		X	X	X	X	X	X	X	X
Cystatin C	X	X						X	X	X	X	X	X	X	X

[1]If the same laboratory evaluations are conducted under DOTCOM within the visit window, they will not be repeated.
[2]Patients who do not have a ≥0.5 log10 decline in HIV RNA after 9 days of F/TAF + failing regimen will be prescribed a regimen change on Day 12-15 (to include and TDF/FTC or ABC/3TC instead of F/TAF, as appropriate) and their study participation will end. They will continue to be followed under the DOTCOM protocol
[3]Women of childbearing potential
[4]Renal function assessment: creatinine, cystatin C, phosphorus, and calculated eGFR
[5]Will not be perfomed if patient is pregnant
[6]Will not be repeated if available in CRIMSON database or from outside medical records, documentation of HIV RNA >1000 copies/mL x 2 can be used in place of HIV-1 serology
[7]Antibody to hepatitis A (anti-HAV), hepatitis B surface antigen (HbsAg), antibody to HBsAg (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), anti-HCV (antibody to HCV). Will not be repeated if available in CRIMSON or CRIS.
[8]All patients at baseline. Patients with HIV RNA >500 copies/mL at time points after 12 weeks
[9]Patients with documented HBsAg (+)