Impact of Weekly Administration of Rifapentine and Isoniazid on Steady State Pharmacokinetics of Tenofovir Alafenamide in Healthy Volunteers (YODA)

NIAID Protocol Number: 18-CC-0087

Version Number: 6.0

Date: August 3, 2021

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List of Abbreviations

ABCB1	ATP-binding cassette sub-family B member 1
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
ART	Antiretroviral therapy
ARV	AntiretroviralAST Aspartate transaminase
AUC	Area under the curve
$AUC_{0\text{-}24hr}$	Area under the curve from the dosing interval of 0 to 24 hours
$AUC_{0\text{-}12hr}$	Area under the curve from time 0 to 12 hours postdose
BTRIS	Biomedical Translational Research Information System
CBC/diff	Complete blood count with differential
CC	Clinical Center
CFR	Code of Federal Regulations
CK	Creatine kinase
CL/F	Apparent oral clearance
C_{max}	Maximum total plasma concentration
C_{min}	Minimum total plasma concentration
CPP	Clinical Pharmacology Program
CPRU	Clinical Pharmacokinetics Research Unit
CRIMSON	Clinical Research Information Management System of the NIAID
CRP	C-reactive protein
CYP	Cytochrome P450 isozymeDAIDS
DCR	Division of Clinical Research
DOT	Directly observed therapy
dp	Diphosphate
DPA	Durable power of attorney
DTG	Dolutegravir
EFV	Efavirenz
eGFR	Estimate glomerular filtration rate
EVG/c	Elvitegravir/cobicistat
FDA	Food and Drug Administration
FTC	Emtricitabine
GCP	Good Clinical Practice
GI	Gastrointestinal
GMR	Geometric mean ratio
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HRPP	Human Research Protections Program
ICH	International Council on Harmonisation
INH	Isoniazid
IRB	Institutional review board
ISM	Independent safety monitor
IV	Intravenous
LIR	Laboratory of Immunoregulation

LTBI	Latent tuberculosis infection
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OCRPRO	Office of Clinical Research Policy and Regulatory Operations
OHRP	Office for Human Research Protections
OHSRP	Office for Human Subjects Research Protections
OTC	Over-the-counter
sPBMC	Peripheral blood mononuclear cell
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PLT	Platelet
RAL	Raltegravir
RFB	Rifabutin
RIF	Rifampin
RPT	Rifapentine
SAE	Serious adverse event
SCr	Serum creatinine
SMC	Safety monitoring committee
$t_{½}$	Terminal half-life
TAF	Tenofovir alafenamide
TB	Tuberculosis
Tbili	Total bilirubin
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-dp	Tenofovir diphosphate
t_{max}	Time to maximum plasma concentration
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
ULN	Upper limit of normal
UP	Unanticipated problem
UPnonAE	Unanticipated problem that is not an adverse event

Protocol Summary

Full Title:	Impact of weekly administration of rifapentine and isoniazid on steady state pharmacokinetics of tenofovir alafenamide in healthy volunteers
Short Title:	YODA
Sample Size:	N = 18
Accrual Ceiling:	N = 75
Study Population:	Healthy volunteers ages 18-65 years
Accrual Period:	2 years
Study Duration:	Start Date: 01 May 2018 End Date: 30 August 2023 Total length of individual participation: 2-5 months
Study Design:	This is an open-label, fixed sequence, intrasubject drug-drug interaction study designed to evaluate the steady state pharmacokinetics (PK) of tenofovir alafenamide (TAF) and tenofovir (TFV) when administered with and without once-weekly rifapentine (RPT) and isoniazid (INH). The study will be composed of two phases: (1) TAF 25 mg once daily alone (days 1-14) and (2) TAF 25 mg once daily + weight-based RPT + INH once weekly (days 15-31).
Study Agent/ Intervention Description:	Participants will receive the following: - TAF 25 mg by mouth once daily x 31 days AND: - RPT 750 or 900 mg by mouth once weekly (3 doses) - INH 15 mg/kg (rounded to the nearest 50- or 100-mg dose, maximum dose of 900 mg) by mouth once weekly (3 doses) - Pyridoxine 50 mg by mouth once weekly (3 doses)
Primary Objective:	To evaluate the effect of once-weekly administration of weight-based RPT + INH (+ pyridoxine) on the steady-state plasma PK of TAF and TFV (administered as TAF 25 mg).
Secondary Objectives:	(1) To evaluate the effect of once-weekly administration of weight-based RPT + INH (+ pyridoxine) on the steady-state intracellular PK of TFV diphosphate (dp).

(2) To evaluate the safety of coadministration of TAF with once-weekly RPT +INH (+ pyridoxine) through documentation of adverse events (AEs) according to the Division of AIDS (DAIDS) AE Table for Grading the Severity of Adult and Pediatric Adverse Events Table and the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials AE table (total bilirubin [Tbili] only).

Primary Endpoint: Plasma area under the curve during the dosing interval of 0 to 24hours ($AUC_{0\text{-}24hr}$), maximum total plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), terminal half-life ($t_{½}$), apparent oral clearance (CL/F), and minimum total plasma concentration (C_{min}) for TAF and TFV.

Secondary Endpoints: (1) Intracellular $AUC_{0\text{-}24hr}$ and $t_{½}$ for TFV-dp.

(2) AEs and abnormal laboratory values, as graded according to the DAIDS AE table and the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials AE table (Tbili only). Key laboratory measures of interest include hepatic function (alanine transaminase [ALT], aspartate transaminase [AST], Tbili), renal function (serum creatinine [SCr], estimated glomerular filtration rate [eGFR]), complete blood count with differential (CBC/diff), creatine kinase (CK), and C-reactive protein (CRP).

Précis

Rifapentine (RPT) is a long-acting rifamycin that can be used weekly with isoniazid (INH) as a first-line regimen in the treatment of latent tuberculosis infection (LTBI). Although this regimen offers several potential benefits, the use of weekly RPT plus INH is limited in adults infected with human immunodeficiency virus (HIV) on antiretroviral therapy (ART) due to lack of drug interaction data with antiretrovirals (ARVs). Tenofovir alafenamide (TAF) is a preferred backbone agent by the current Department of Health and Human Services ARV guidelines and is a part of multiple recommended first-line regimens for the treatment of HIV. However, the use of TAF with rifamycins, including RPT, is not recommended due to potential drug interactions. Thus, the purpose of this study is to determine the effects of concomitant RPT and INH administration on the steady state pharmacokinetics (PK) of plasma TAF, plasma tenofovir (TFV), and intracellular TFV diphosphate (dp).

This is an open-label, fixed sequence, intrasubject drug-drug interaction study designed to evaluate the steady state PK of TAF, TFV, and TFV-dp with coadministration of once-weekly RPT + INH administered at doses used to treat LTBI. The study will consist of two phases: (1) TAF once daily alone (days 1-14) and (2) TAF once daily + weight-based RPT + INH once weekly (days 15-31). Participants will undergo periodic serial ARV PK blood draws over 24 hours on days 14-15, 22-23, and 31-32.

TAF, TFV, and TFV-dp PK will be determined using non-compartmental methods. The following PK parameters will be compared between phases: area under the curve over the dosing interval, maximum plasma concentration, time to maximum plasma concentration, terminal half-life, apparent oral clearance, and minimum plasma concentration. Adverse events will be graded and recorded.

1 Background Information and Scientific Rationale

1.1 Background Information

Tuberculosis (TB) is an infection caused by *Mycobacterium tuberculosis*, and up to one-third of the world's population is estimated to be infected with this pathogen.[1] The majority of infected individuals remain in an inactive state, referred to as latent TB infection (LTBI), which is characterized by a lack of symptoms or an ability to infect others. However, LTBI can be reactivated and develop into active disease. TB is particularly problematic in individuals infected with human immunodeficiency virus (HIV), as individuals are 26 times more likely to develop active TB infection than HIV-negative individuals,[1] with increasing risk as CD4 T lymphocyte counts decline[2] and viral loads increase.[3] TB is one of the most common opportunistic infections in the HIV population worldwide, and in 2014, HIV-positive individuals accounted for 12% of newly developed TB cases.[1] Furthermore, around 25% of all TB deaths were accounted for by those infected with HIV, and 33% of HIV/acquired immunodeficiency syndrome (AIDS) deaths were attributed to TB. The majority of TB cases and deaths are reported in developing countries in Africa and Asia. Higher-income countries, such as the United States, are associated with much lower incidence rates. Nevertheless, TB still poses a significant public health problem.

In order to reduce the morbidity and mortality observed in individuals with HIV, appropriate diagnosis and treatment of active and LTBI is essential. Currently, the first-line treatment recommendations for LTBI in HIV-positive individuals include (1) isoniazid (INH) 300 mg daily + pyridoxine 25 mg daily for 9 months or (2) INH 900 mg twice weekly (as part of directly observed therapy [DOT]) + pyridoxine 25 mg daily for 9 months.[4,5] Alternative treatment options include (1) rifampin (RIF) 600 mg given orally once daily for 4 months, or (2) rifabutin (RFB) (dose-adjusted for concomitant antiretroviral [ARV] drugs) for 4 months. INH-based therapies are highly effective for LTBI treatment. However, adherence and treatment completion is low in both HIV-infected and uninfected individuals due to long treatment courses and high pill burden.[6-8]

Once weekly rifapentine (RPT) and INH is another more recently added option to available LTBI treatments in HIV. This regimen was found to be similar in efficacy to INH 300 mg daily for 6 months[8] and 9 months[9] in HIV-infected individuals with LTBI not on antiretroviral therapy (ART), and noninferior to daily INH given for 9 months in a largely HIV-negative population.[7] RPT + INH is an attractive therapeutic option for LTBI as it is dosed once weekly over 12 weeks, can be given as part of DOT treatment support, and is well tolerated by patients receiving this therapy. Collectively, these advantages translate into higher rates of adherence comparatively to INH therapy, which requires daily dosing and 6 to 9 months of therapy (82%-95% vs. 48%-85%, respectively).[6-9]

Despite these potential benefits, the use of once weekly RPT with INH is limited in HIV-infected adults on ART in the US due to the lack of data on drug interactions between these agents.[5] Once-weekly RPT + INH is only recommended in patients receiving efavirenz (EFV)- or raltegravir

(RAL)-based regimens (in combination with either abacavir/lamivudine or tenofovir disoproxil fumarate/emtricitabine). As rifamycins can cause significant cytochrome P450 isozyme (CYP) 3A and P-glycoprotein (P-gp) transporter induction with daily administration,[10,11] prospective drug interaction studies between RIF or RFB and ARV agents have informed clinicians of whether to avoid certain combinations or make appropriate dose adjustments. However, the extent of interaction that may be observed with once weekly RPT is unknown and should be further investigated. Furthermore, although INH is not suspected to interact significantly with ARVs, its role in modulating transporter-mediated drug interactions is unknown and should also be further investigated.

1.2 Rifapentine

RPT is a long-acting rifamycin used in combination with INH in the treatment of LTBI. Compared to RIF, RPT has a longer terminal half-life ($t_{½}$, 13-14 hours vs. 2-3 hours) and 4-to-5-fold higher intracellular concentrations, resulting in a long post-antibiotic effect.[10] RPT is dosed by weight in 150-mg tablet increments, with a maximum oral dose of 900 mg.[12] Following oral administration of RPT at 600 mg, approximately 70% of the dose is absorbed, and the maximum concentration (C_{max}) is reached within 5-6 hours under fed conditions. Administration with food increases C_{max} and area under the curve (AUC) by 40%-51% comparatively to fasted conditions. RPT is primarily metabolized by esterases, which in turn leads to the formation of the active metabolite 25-desacetyl RPT.[12,13] RPT and its 25-desacetyl metabolite contribute to 62% and 38% of the antibiotic activity against *M tuberculosis*, respectively.

Similar to other rifamycins, RPT induces CYPs (most notably CYP3A4, 2C8, and 2C9), UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1), and P-gp/ATP-binding cassette sub-family B member 1 (ABCB1) transporter.[10-14] RIF's effect on the CYP system and P-gp/ABCB1 are well documented and characterized. RIF is the strongest CYP3A inducer of the rifamycin family, with RPT and RFB at 85% and 40% of RIF's induction potency, respectively.[10] CYP3A4 turnover estimates range between 10-140 hours based on available in vivo studies,[15,16] and maximal induction is typically observed after at least seven days of rifamycin therapy, with higher doses and shorter intervals demonstrating greater inductive effects.[11] P-gp/ABCB1 is a transmembrane efflux protein responsible for the removal/transport of toxins and xenobiotics out of cells. Both RIF and RPT have shown to significantly upregulate or induce P-gp/ABCB1 in a concentration-dependent manner.[14] In comparison to daily RIF, the inductive potential of once-weekly RPT is not well understood. However, current data suggest this induction occurs in a concentration- and frequency-dependent manner. Due to RPT being administered once weekly rather than daily, it is difficult to predict the type and extent of interactions that may take place with ARVs.

1.3 Isoniazid

INH is an antimycobacterial agent that can be used alone or in combination with RPT for the treatment of LTBI.[17] A number of dosing regimens can be utilized for LTBI in adults, including 5 mg/kg daily (maximum dose of 300 mg) for 6-9 months, 15 mg/kg 2-3 times per week (maximum dose of 900 mg per day) for 6-9 months if given alone, or 15 mg/kg once weekly (maximum dose of 900 mg) for 12 weeks if combined with RPT. C_{max} is reached 1-2 hours following oral administration on an empty stomach. Administration of INH with food can decrease C_{max} by 20%-50% and AUC by 12%-43%; thus, it is recommended to administer INH 1 hour before or 2 hours after a meal.[18-21] However, INH can be given with food for improved tolerability, and is usually administered concomitantly with other medications when given as part of DOT. INH is metabolized via acetylation and dehydrazination, and the rate at which acetylation takes place is dependent on the genetics of the individual receiving the medication.[17] The $t_{½}$ of INH is 1-1.8 hours in rapid acetylators, and 3-4 hours in slow acetylators.[22] Rapid or slow acetylators do not show significant differences in the efficacy of INH therapy.[17] However, slow acetylators may be at an increased risk of drug toxicity due to the decreased rate of elimination. INH is not described in the literature to be a victim or perpetrator in any transporter related drug-drug interactions. Due to this lack of data, the effects, if any, after combination of INH plus RPT will be difficult to predict.

1.4 Pyridoxine

Pyridoxine (vitamin B6) is an exogenous micronutrient obtained through various food sources in the human diet.[23,24] During INH therapy, pyridoxine supplementation is recommended in certain patient populations considered to be at high risk of developing pyridoxine deficiency and subsequent peripheral neuropathy.[17] These populations include alcoholics, diabetics, pregnant and lactating women, malnourished, the elderly, and HIV-infected individuals.[17,23,24] INH-induced pyridoxine deficiency is believed to result from binding of INH and pyridoxine, which then results in the inability of nerve tissue to use pyridoxine, in addition to an increase in urinary excretion of the INH-pyridoxine complex.[24]

The onset of INH-induced peripheral neuropathy appears to be related to drug exposure, with higher doses (16-24 mg/kg/day) and decreased elimination (eg, slow acetylators) conferring a higher risk of developing this AE.[23] Recommended doses of pyridoxine supplementation are 25 mg daily in HIV-infected individuals,[17] and range from 10-25 mg daily in HIV-negative populations.[25]

1.5 ARV Agent of Interest: Tenofovir Alafenamide

Tenofovir alafenamide (TAF) is a preferred nucleotide analog backbone agent currently recommended as part of the initial treatment of HIV.[4] TAF is dosed once daily in treatment-naïve individuals without evidence of pre-existing drug resistance mutations, has a high threshold for the development of resistance, and is overall well tolerated. For the treatment of HIV, TAF is

available in multiple coformulations including with the nucleoside analog emtricitabine, the integrase inhibitor elvitegravir/cobicistat (EVG/c), and the non-nucleoside analog rilpivirine. However, potential drug interactions between TAF and RPT are of concern. TAF is a prodrug that is preferentially taken up or loaded into peripheral blood mononuclear cells (PBMCs), where it is further phosphorylated to its major intracellular metabolite of interest, tenofovir-diphosphate (TFV-dp).[16] This selective intracellular uptake and cleavage of TAF allows for prolonged systemic exposure of TAF as intact prodrug and less conversion of TAF to tenofovir (TFV) in plasma. Higher and prolonged exposure of plasma TFV is reported to result in its uptake into various off target sites such as kidney and bone.[26] In fact, renal impairment including Fanconi syndrome and proximal renal tubulopathy as well as perturbations in bone metabolism has been described with an alternate prodrug, tenofovir disoproxil fumarate (TDF, marketed as Viread).

TAF is a substrate for the efflux drug transporter, P-gp.[15] P-gp is expressed variably throughout the body including intestinal enterocytes, blood-brain barrier, as well as in PBMCs.[27] RPT is capable of inducing drug transport in a dose- and frequency-dependent manner,[14] thereby affecting the transport of TAF from the gut to the plasma during the absorption phase as well as its uptake into PBMCs. This induction of transport may potentially result in lower plasma and intracellular concentrations of TAF and TFV-dp, respectively. RPT has not been evaluated with regard to how many days it would take to reach maximal induction effect of P-gp transport of TAF. However, a maximum of 3 weekly doses of RPT at 900 mg was studied with TDF in people with HIV infection and showed an overall decrease in the plasma minimum concentration (C_{min}) of TFV with minimal change in AUC.[28] This decrease was deemed to be clinically insignificant.

1.6 Drug Interaction Studies Between LTBI Agents and ARVs

To date, the full pharmacokinetic (PK) profile of RPT and ARVs has only been described with EFV,[29] a substrate of CYP2B6 and 3A4, and RAL,[30] a UGT1A1 substrate. Once-daily RPT at 10 mg/kg and INH at 300 mg administered with EFV at 600 mg over 4 weeks revealed that 88% of HIV-infected patients were able to maintain EFV trough concentrations > 1 µg/mL, and 97% remained virally suppressed.[29] In this study, inhibition of CYP2B6 by INH was hypothesized as a possible reason that significant induction with daily RPT was not observed. In a separate healthy volunteer study, RAL with once-weekly RPT at 900 mg (without INH) resulted in a 71% and 89% increase in AUC from time 0 to 12 hours postdose ($AUC_{0\text{-}12hr}$) and C_{max}, respectively, and a decrease in C_{min} by 12%. RAL with once-daily RPT at 600 mg revealed no change in $AUC_{0\text{-}12hr}$ or C_{max}, but did demonstrate a decrease in C_{min} by 41%.[30] A drug interaction study conducted in healthy volunteers with dolutegravir (DTG) and weekly RPT + INH was initiated recently by our group but was terminated early due to a serious unexpected AE.[31] Although PK data were derived from only 4 patients, significant induction of DTG was observed with weekly RPT + INH. Given the variability of published PK data, it is difficult to predict the significance of drug interactions that may result between RPT and other ARV agents, particularly when RPT is given as a once-weekly regimen for treating LTBI.

Table 1 Summary of Drug Interaction Studies with Rifamycins

ARV	ARV Dose	ARV Metabolism/Transport	LTBI Agent & Dose	ARV PK Results
Rifamycins				
EFV[29]	600 mg daily[a]	3A4, 2B6 (minor)	RPT 10 mg/kg QD + INH 300 mg QD	C_{min} > 1 mg/L maintained in 88%
RAL[30]	400 mg Q12hrs[b]	UGT1A1	RPT 900 mg QW	AUC_{0-12hr} ↑ 71% C_{max} ↑ 89% C_{min} ↓ 12%
			RPT 600 mg QD	AUC_{0-12hr} ↔ C_{max} ↔ C_{min} ↓ 41%
TDF[32]	300 mg QD[c]	P-glycoprotein	RIF 600 mg QD	AUC_{0-24hr} ↓12% C_{min} ↓ 15% C_{max} ↓ 16%
TDF[29]	300mg QD[d]	P-glycoprotein	RPT 900 mg QW	AUC_{0-24hr} ↓ 9% C_{min} ↓ 13% C_{max} ↔
DTG[31,33]	50 mg QD	UGT1A1 (major), 3A4 (minor)	RPT 900 mg QW + INH 900 mg QW	Day 14: AUC_{0-24hr} ↓ 46% C_{min} ↓ 74% C_{max} ↓ 34% Day 19: AUC_{0-24hr} ↓ 15% C_{min} ↓ 38% C_{max} ↓ 12%
	50 mg QD		RFB 300 mg QD	AUC_{0-24hr} ↓ 5% C_{max} ↑ 16% C_{min} ↓ 30%
	50 mg BID[e]		RIF 600mg QW	AUC_{0-24hr} ↓ 54% C_{max} ↓ 43% C_{min} ↓ 72%
	50 mg BID[f]			AUC_{0-24hr} ↑ 33% C_{max} ↑ 18% C_{min} ↑ 22%

ARV = antiretroviral; AUC_{0-12hr} = area under the curve from time 0 to 12 hours postdose; AUC_{0-24hr} = area under the curve from time 0 to 24 hours postdose; BID = twice per day; C_{max} = maximum concentration; C_{min} = minimum concentration; DTG = dolutegravir; EFV = efavirenz; INH = isoniazid; LTBI = latent tuberculosis infection; PK = pharmacokinetic(s); Q12hrs = once every 12 hours; QD = once per day; QW = once per week; RAL = raltegravir; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; TDF = tenofovir disoproxil fumarate; UGT1A1 = uridine diphosphate glucuronosyl transferase 1A1.

a RPT 10 mg/kg QD + INH 300 mg QD concomitantly administered with EFV.

ARV	ARV Dose	ARV Metabolism/Transport	LTBI Agent & Dose	ARV PK Results
b RAL 400 mg Q12hrs + RPT 900 mg QW x 3 and RAL 400 mg Q12hrs + RPT 600 mg QD vs. RAL 400 mg Q12hrs alone. c TDF 300 mg + RIF 600 mg QD vs. TDF 300 mg alone. d TDF 300 mg + RPT 900 mg QW x 3 vs. TDF 300 mg daily. e PK results for DTG 50 mg BID + RIF 600 mg QD vs. DTG 50 mg BID. f PK results for DTG 50 mg BID + RIF 600 mg QD vs. DTG 50 mg QD.				

1.7 Scientific Rationale

TAF is a substrate for P-gp that RPT may induce.[34] Although INH (+ pyridoxine) is not thought to play a role in this P-gp–mediated drug-drug interaction, it is included as part of this study to provide data with the full LTBI regimen. Additionally, although INH is not suspected to interact significantly with ARVs, its role in modulating transporter-mediated drug interactions is unknown and should also be further investigated. Thus, the effects of once-weekly RPT + INH regimen on the PK of TAF may result in lower overall plasma exposures of TAF and TFV, and intracellular (TFV-dp) exposure. Decreased exposure may result in subtherapeutic ARV levels and potentially loss of virologic control. Thus, studies are needed to determine the effects of once-weekly RPT + INH (+ pyridoxine) on the steady state PK of TAF, TFV, and TFV-dp. In order to avoid the risk of subtherapeutic ARV levels and virologic failure in HIV-infected individuals, this study will be conducted in healthy HIV-negative volunteers to assess whether a significant decrease in ARV drug levels may take place. Ultimately, the results of these studies will guide clinicians as to whether the once-weekly RPT + INH (+ pyridoxine) can be used in HIV-infected patients receiving TAF as part of their ARV regimen.

2 Study Objectives

2.1 Primary Objective

To evaluate the effect of once-weekly administration of weight-based RPT + INH (+ pyridoxine) on the steady-state plasma PK of TAF and TFV (administered as TAF 25 mg).

2.2 Secondary Objectives

1. To evaluate the effect of once-weekly administration of weight-based RPT + INH (+ pyridoxine) on the steady-state intracellular PK of TFV-dp.
2. To evaluate the safety of coadministration of TAF with once-weekly RPT + INH (+ pyridoxine) through documentation of AEs according to the DAIDS AE Table for Grading the Severity of Adult and Pediatric Adverse Events Table and the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials AE table (total bilirubin [Tbili] only).

3 Study Design

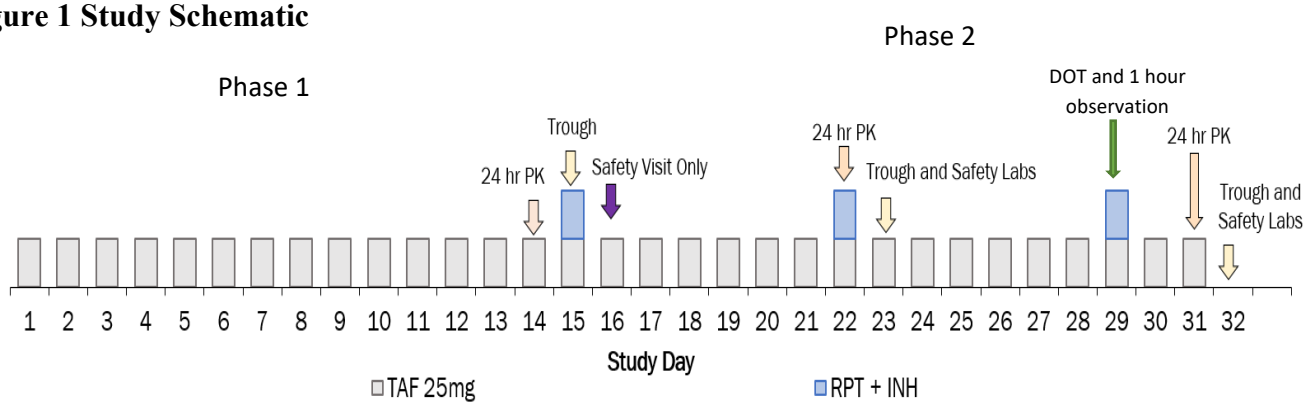
3.1 Description of the Study Design

This is an open-label, fixed sequence, intrasubject drug-drug interaction study designed to evaluate the steady state PK of TAF, TFV, and TFV-dp with and without coadministration of once-weekly RPT + INH (+ pyridoxine) given at doses used to treat LTBI. Fifteen healthy volunteers will enroll in and complete this study. A schematic of the study design is presented in Figure 1.

This study will be comprised of two phases: (1) TAF 25 mg once daily alone (days 1-14) and (2) TAF 25 mg once daily + weight-based RPT and INH (+ pyridoxine) once weekly (days 15-31) (Figure 1). Participants will undergo serial 24-hour PK blood draws after reaching steady state within each phase on days 14-15, 22-23, and 31-32. The phase 1 period lasts a total of fifteen days in order to assess PK parameters under plasma steady-state conditions. Steady state is typically reached after 3-5 half-lives (ie, > 90% of steady state), and the half-lives of plasma TAF, TFV, and intracellular TFV-dp are approximately 30 minutes, approximately 40 hours, and approximately 100 hours, respectively. Thus, steady state in plasma would be reached after approximately 150 minutes for TAF, approximately 200 hours (8 days) for TFV, and steady state intracellularly would be reached after approximately 500 hours (20 days).[34-36]

With the initiation of RPT dosing, subsequent PK visit days are scheduled to assess the degree of induction that is occurring across the RPT dosing interval. The first 24-hour PK assessment is scheduled to take place after 14 days of TAF administration. This visit will assess the steady-state plasma PK of TAF and TFV prior to the start of weekly administration of RPT. The second PK assessment is scheduled to take place 7 days after the first weekly dose of RPT. Rifamycins have been shown to reach maximal induction after 7 days of drug therapy. However, these observations have been made with daily administration of rifamycins, and thus it is unclear whether this same degree and pattern of induction will be observed with RPT when given once weekly. As the half-life of RPT is only approximately 14 hours, the majority of the drug will be eliminated from systemic circulation after 3-5 half-lives (ie, 2-3 days), and thus it is unclear to what extent induction will be observed with regard to potency or duration of effects. The second PK visit will assess the effects of weekly RPT on the steady-state plasma and intracellular PK of TAF, TFV and TFV-dp when given simultaneously (day 22). The third and last 24-hour PK assessment is scheduled 2 days following the final weekly dose of RPT and will assess the presumed maximal inductive effects of RPT on the steady state PK of TAF, TFV, and TFV-dp. Maximal induction is expected at this time point as the inductive potential of RPT is described to be dose- and frequency-dependent. Furthermore, PK data derived from a similar study performed by our group evaluating the impact of once-weekly RPT on the steady state PK of DTG revealed maximal induction occurred 48-72 hours after the second weekly dose compared to same day dosing of RPT and DTG.[31]

Figure 1 Study Schematic



Screening: Day -89 to 0.

Baseline visit: Day -6 to 0.

PK Visits: Days 14/15, 22/23, 31/32

- 9 blood samples for plasma PK (TAF, TFV) at 0 (predose), 0.25, 0.5, 1, 2, 4, 6, 8, and 24 hours postdose.
- 6 blood samples for PBMCs at 0 (predose), 1, 2, 6, 8, and 24 hours postdose.
- Study drugs administered with standardized breakfast and after time 0 sample collection.
- Safety labs drawn with predose sample.

Total Study Duration (excluding screening): 43-63 days

Safety visit and end of study phone call: Safety visit: 14 ± 3 days after administration of final study dose**. End of study phone call**: 28 ± 3 days after administration of final study dose.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoints of this study are plasma AUC during the dosing interval of 0 to 24 hours ($AUC_{0\text{-}24hr}$), total plasma C_{max}, time to maximum plasma concentration (t_{max}), $t_{½}$, apparent oral clearance (CL/F), and total plasma C_{min} for TAF and TFV.

3.2.2 Secondary Endpoints

1. Intracellular $AUC_{0\text{-}24hr}$ and $t_{½}$ for TFV-dp.
2. AEs and abnormal laboratory values, as graded according to the DAIDS AE table and the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials AE table (Version 2.1, July 2017).
3. Tbili only. Key laboratory measures of interest include hepatic function (alanine transaminase [ALT], aspartate transaminase [AST], Tbili), renal function (serum creatinine [SCr], estimated glomerular filtration rate [eGFR]), complete blood count with differential (CBC/diff), creatine kinase (CK), and C-reactive protein (CRP).

4 Study Population

4.1 Rationale of Participant Selection

Healthy volunteers will be studied, as opposed to patients with HIV infection, in order to reduce the risk of subjecting participants to subtherapeutic ARV exposure and virologic failure in the event that RPT causes induction of TAF transport. In addition, HIV patients are often on concomitant medications, which may interact with the study drugs being examined, and thus the final interpretation of study results could be affected. The presence or magnitude of this interaction may differ between healthy volunteers and HIV-infected individuals on the basis of previous PK and interaction studies.[37-39] However, the benefit of assessing this interaction in an HIV-infected population does not outweigh the risk of subtherapeutic drug exposure and possible virologic rebound at this time. Given the dose and duration of study drugs, the risks to healthy volunteers do not outweigh the benefit of data.

4.2 Recruitment Plan

This study is being conducted at a single site, the NIH CC. Up to 75 participants will be screened for a total of up to 18 healthy HIV-negative volunteers to enroll and complete this open-label study. Participation of all ethnic groups and genders will be actively encouraged. This will be done through the Office of Patient Recruitment, which recruits participants for volunteer studies conducted at the NIH CC. There is an active effort to recruit minorities and women through outreach programs in the Washington, DC metropolitan area. This study is not designed to assess the influence of gender, age, and/or ethnicity on the drug-drug interaction (if observed) between TAF + RPT + INH.

Recruitment of NIH employees: NIH employees and members of their immediate families may participate in this protocol. We will follow the Guidelines for the Inclusion of Employees in NIH Research Studies and will give each employee a copy of the "NIH Information Sheet on Employee Research Participation."

For NIH employees:

- NIH staff may be a vulnerable class of participants.
- Neither participation nor refusal to participate will have an effect, either beneficial or adverse, on the participant's employment or work situation.
- The NIH information sheet regarding NIH employee research participation will be distributed to all potential participants who are NIH employees.
- The employee participant's privacy and confidentiality will be preserved in accordance with NIH CC and NIAID policies, which define the scope and limitations of the protections.

- For NIH employee participants, consent will be obtained by an individual independent of the employee's team. Those in a supervisory position to any employee and co-workers of the employee will not obtain consent.
- The importance of maintaining confidentiality when obtaining potentially sensitive and private information from co-workers or subordinates will be reviewed with the study staff at least annually and more often if warranted.

4.3 Participant Inclusion Criteria

Individuals must meet all of the following criteria to be eligible for study participation:

1. Ages 18-65 years.
2. Weight ≥ 45 kg and ≤ 120 kg OR body mass index ≥ 18.0 and < 30.
3. Judged to be healthy based on medical history, physical examination, vital signs, and clinical laboratory tests: liver function tests (AST, ALT, Tbili) ≤ upper limit of normal [ULN], SCr ≤ ULN, platelets (PLT) > 150,000/μL, hemoglobin (Hgb) ≥ 13 g/dL (males); ≥ 12g/dL (females), C-reactive protein (CRP) ≤ ULN, CK ≤ 2x ULN, fasting total cholesterol < 240 mg/dL, or fasting triglycerides < 240 mg/dL, urine glucose < grade 2 (per DAIDS AE table), urine protein < grade 2 (per DAIDS AE table).
4. Negative QuantiFERON-TB Gold test at screening.
5. HIV-negative, as determined by standard serologic assays for HIV infection.
6. No laboratory evidence of active or chronic hepatitis A, B, or C infection.
7. Willing to abstain from alcohol consumption throughout the study period.
8. Agrees to genetic testing and storage of specimens for future research.
9. Able to provide informed consent.
10. Negative serum or urine pregnancy test for females of child-bearing potential.
11. Participants must agree not to become pregnant or impregnate a partner for the duration of the study. The use of hormonal contraceptives will not be permitted. Study participants must use one of the following methods of birth control when engaging in sexual activities that can result in pregnancy, beginning at screening until the final study visit. Male vasectomy and females who have undergone hysterectomy are acceptable forms of birth control.
    a) Male or female condom.
    b) Diaphragm or cervical cap with a spermicide.
    c) Intrauterine device without hormones.

4.4 Participant Exclusion Criteria

Individuals meeting any of the following criteria will be excluded from study participation:

1. Known hypersensitivity to TAF, TDF, INH, RPT, and other rifamycin analogues.
2. History or presence of any of the following:

a. Latent or active TB infection.
b. Gastrointestinal (GI) disease that is uncontrolled, requires daily treatment with medication, or would interfere with a participant's ability to absorb drugs (eg, diarrhea, pancreatitis, or peptic ulcer disease).
c. Renal impairment (chronic renal insufficiency of any chronic kidney disease stage, or acute renal failure not induced by drug therapy defined as eGFR < 90 mL/min or SCr > ULN).
d. Respiratory disease that is uncontrolled or requires daily treatment with medication (eg, asthma or chronic obstructive pulmonary disease).
e. Cardiovascular disease (eg, hypertension [systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg], heart failure, or arrhythmia).
f. Metabolic disorders (eg, diabetes mellitus).
g. Hematologic or bleeding disorders (eg, anemia, hemophilia, serious/major bleeding events, menorrhagia [female participants]).
h. Immunologic disorders.
i. Hormonal or endocrine disorders.
j. Psychiatric illness that would interfere with their ability to comply with study procedures or that requires daily treatment with medication.
k. Seizure disorder, with the exception of childhood febrile seizures.
l. Any current or history of malignancy, with the exception of cutaneous basal cell carcinoma, non-invasive squamous cell carcinoma, or any other malignancies not requiring systemic therapy.
m. Current or history of osteopenia and osteoporosis.

3. Current participation in an ongoing investigational drug protocol or use of any investigational drug within 30 days (based on last dose received) prior to receipt of any study drugs.
4. Therapy with any prescription, over-the-counter (OTC), herbal, or holistic medications, including hormonal contraceptives by any route, within 5 half-lives of the agent prior to receipt of any study medications will not be permitted with the following exception: Intermittent or short-course therapy (< 14 days) with prescription or OTC medications, herbals, or holistic medications within the screening period prior to starting study drugs may be permitted, and will be reviewed by investigators on a case-by-case basis for potential drug interactions. Receipt of influenza vaccination will be allowed prior to, during, and/or after the study.
5. Inability to obtain venous access for sample collection.
6. Inability to swallow whole capsules and/or tablets.
7. Pregnant or breastfeeding.
8. Drug use that may impair safety or adherence.
9. Use of nicotine-containing products, including cigarettes and chewing tobacco, nicotine patches, gum, electronic cigarettes, etc.

10. Organ or stem cell transplant recipient.
11. Uncorrected and persistent electrolyte abnormalities (eg, potassium, magnesium, and calcium).
12. Current alcohol use disorders (DSM-5 criteria).
13. Fasting total cholesterol > 240 mg/dL or fasting triglycerides > 240 mg/dL at screening.
14. Any condition that, in the opinion of the investigator, contraindicates participation in this study.

Co-enrollment guidelines: Co-enrollment in other trials is restricted, other than enrollment on observational studies. Study staff should be notified of co-enrollment as it may require the approval of the investigator.

4.5 Justification for Exclusion of Special Populations

Exclusion of pregnant women: Pregnant participants are excluded from this study to reduce the confounding effects of physiological changes during pregnancy on PK parameters of interest. Furthermore, the effects of RPT and INH on the developing human fetus are unknown with the potential for teratogenic or abortifacient effects. There are no human data of the use of TAF during pregnancy, but animal data studies show no developmental effects after TAF administration.

Exclusion of breastfeeding women: Because there is an unknown but potential risk for AEs in nursing infants secondary to exposure of the mother with TAF, RPT, or INH, breastfeeding participants are excluded from study participation.

Exclusion of children and persons > 65 years old: This study is intended to investigate the PK and safety profiles of agents in an adult population, as opposed to children, as age-related metabolic and transport processes in children differ from those of adults. TAF is not approved for use in pediatric populations.[34] However once-weekly RPT + INH regimen for LTBI has been found to be safe and effective in children 2-17 years of age.[40] However, as this is a preliminary study, there is no potential benefit to children, as a population, to justify their participation at this time.

As in children, changes in metabolic processes as a result of aging may confound findings from participants older than 65 years. Again, as this is a preliminary study, there is no potential benefit as a population to justify their participation. However, future investigators may include this population as well.

5 Study Agent/Interventions

5.1 Disposition, Dispensation, and Accountability

Study agents will be distributed and accounted for by the NIH pharmacy according to standard pharmacy procedures.

5.2 Formulation, Packaging, and Labeling

Each bottle will be individually labeled with the patient ID number, dosing instructions, recommended storage conditions, the name and address of the manufacturer, and that the agent should be kept out of reach of children.

5.3 Assessment of Participant Compliance with Study Agents

Participants will receive a memory aid card to log their doses of TAF and record AEs between study visits. This memory aid card will not be used as a source document. Each participant will receive telephone contact to remind them of appropriate adherence and/or of upcoming appointments. Additionally, participants will be instructed to bring all study agent bottles to each study visit for pill count.

5.4 Study Agent Storage and Stability

All study agents should be stored and dispensed from the NIH CC Pharmacy according to standard pharmacy procedures.

5.5 Preparation, Administration, and Dosage of Study Agents

Participants will receive once-daily dose of TAF (25 mg) for 31 days, and once-weekly doses of RPT (750 or 900 mg, depending on weight), INH (15 mg/kg, up to 900 mg), and pyridoxine (50 mg) from study days 15 to 29 (total of 3 doses of RPT, INH, and pyridoxine).

Each tablet of Vemlidy (Gilead Sciences, Inc [Foster City, CA]) contains 25 mg of TAF. Participants will be instructed to take one tablet daily at the same time (0800 $\pm$ 2 hours) every day with food on non-study days. At the 24-hour PK visit days, participants will be instructed to bring their study agent supply to the NIH Day Hospital or OP-8 Infectious Diseases Clinic for DOT administration.

Each tablet of Priftin (Sanofi-Aventis [Bridgewater, NJ]) contains 150 mg of RPT. Participants who weigh 45 to < 50 kg will take 750 mg (5 tablets), and participants who weigh $\geq$ 50 kg will take 900 mg (6 tablets). These tablets will be administered with food via DOT (NIH Day Hospital or OP-8 Infectious Diseases Clinic) once weekly on days 15, 22, and 29.

Each tablet of generic INH is formulated as 100 or 300 mg of the drug. Participants will be administered INH with food via DOT (NIH Day Hospital or OP-8 Infectious Diseases Clinic) based on weight, at approximately 15 mg/kg (up to 900 mg) with RPT on days 15, 22, and 29.

A dosing nomogram for RPT and INH is provided in Appendix A.

Each tablet of pyridoxine contains 50 mg of Vitamin B6. Participants will be administered B6 with food via DOT (NIH Day Hospital or OP-8 Infectious Diseases Clinic) with RPT + INH on days 15, 22, and 29.

5.6 Concomitant Medications and Procedures

All concomitant prescription and nonprescription (including OTC) medications taken during study participation will be recorded in the Clinical Research Information Management System of the NIAID (CRIMSON). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

5.7 Prohibited Medications and Procedures

To minimize potential drug interactions or AEs in healthy volunteers, therapy with any prescription, OTC, herbal, or holistic medications, excluding occasional use of acetaminophen (no more than 2 g/24 hrs), ibuprofen, naproxen, loperamide, or antihistamines (on non-PK days), will not be permitted throughout the study period unless discussed with and approved by the investigator.

6 Study Schedule

A flowchart of the study schedule is provided in Figure 2. A table of the study schedule is provided in Appendix B, and blood volumes are listed in Appendix C.

6.1 Screening (Day −89 to 0)

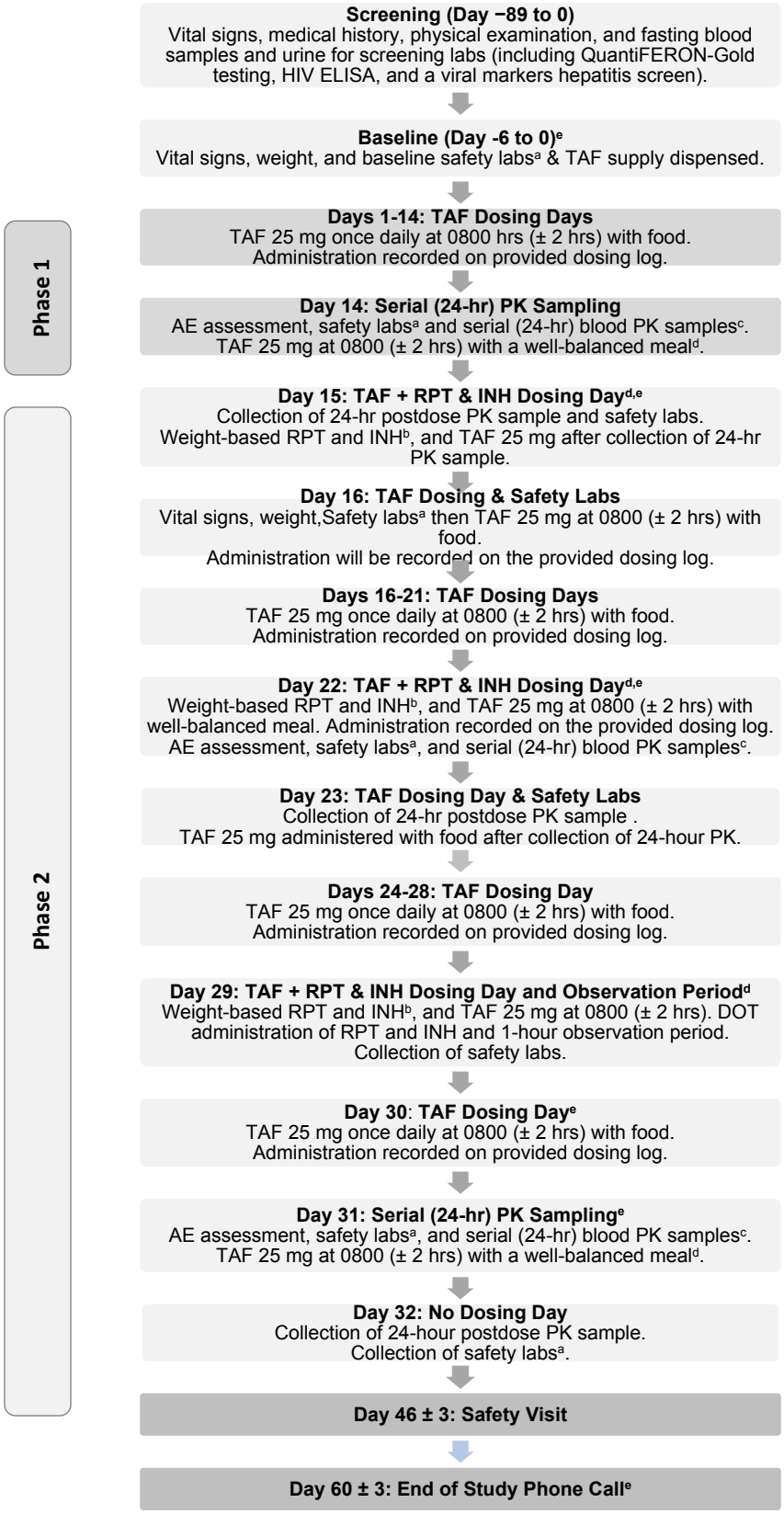
The participant will be required to fast for at least 8 hours before the screening visit. Screening evaluations to determine eligibility for this study are listed below. The participant will sign the informed consent form before undergoing any screening procedure. Blood draws and urine for labs may be repeated as clinically indicated at the discretion of the medically responsible investigator within 14 days of initial screening.

1. Physical exam with vital signs and weight.
2. Medical history review.
3. Serum or urine pregnancy test (for participants who are able to become pregnant).
4. Blood draw for screening labs:
    a. HIV-1/2 antigen/antibody testing.
    b. QuantiFERON-TB Gold tuberculosis testing.
    c. Viral markers hepatitis screen (hepatitis B surface antigen, anti-hepatitis C antibody, anti-hepatitis A IgM).
    d. Acute care, hepatic, and mineral panels.
    e. CRP.
    f. Creatine kinase.

g. Lipid panel.
h. CBC/diff.
i. Amylase
j. Lipase

5. Urine for screening labs:
   a. Protein.
   b. Glucose.

Figure 2 Study Schedule and Procedures



[a] Safety laboratory assessments will be collected at baseline, with the time 0 (predose) measure on each PK day, 24 hours after 1st and 2nd doses of RPT + INH + pyridoxine, and 48 hours after the final dose of RPT + INH + pyridoxine. Assessments will include serum or urine pregnancy test for females of child-bearing potential; a basic chemistry [acute care panel including Na, K, CO2, anion gap, BUN, serum creatinine, estimated glomerular filtration rate, glucose, albumin], hepatic [including AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin], and mineral panel [Ca, Mg, Phos]; C-reactive protein, creatine kinase, amylase/lipase (at baseline and Day 16 only), and complete blood count with differential [WBC, RBC, Hgb, HCT, platelets, differential]

[b] RPT dosed by weight of participant (ie, 750 mg [5 x 150-mg tablets] if 45 to < 50 kg, 900 mg [6 x 150-mg tablets] if ≥ 50 kg). INH dosed by weight (15 mg/kg rounded to nearest 50- or 100-mg dose, max 900-mg dose).

[c] 24-hr plasma PK sampling times will occur at time: 0 (predose), 0.25, 0.5, 1, 2, 4, 6, 8, and 24 (± 2) hours postdose. Blood will be collected for PBMCs at 0 (predose), 1, 2, 6, 8, and 24 hours postdose. The participant will be discharged after collection of the 8-hour postdose sample, to then return for the 24-hour postdose sample collection the following day.

[d] TAF + RPT and INH (with pyridoxine) administered in clinic setting.

[e] Telephone contact to remind participant on day 0 (Monday) to start taking TAF on day 1 (Tuesday) of study. Telephone contact on day 10 ± 1, day 18 ± 3, and day 30 to remind the participant of upcoming PK visits on days 14, 22, and 31, respectively. On day 25 ± 3, telephone contact to remind participant of 8-10-hour observation period on day 29. On day 60 ± 3, telephone contact to assess side effects.

6.2 Baseline (Day −6 to 0)

Participants will return to the NIH CC after eligibility has been confirmed for medical history/medication review, vital signs, weight, and to receive a 34-day course of TAF. The TAF regimen for this study only requires 31 tablets (a 31-day supply), but participants will be provided with three additional days of study agent to allow for possible minor scheduling variances. Participants will be counseled on the importance of study agent adherence throughout the study, and will be instructed to take their TAF doses at approximately the same time each day (0800 ± 2 hours) with a food at home. They will also receive a phone call on day 0 to remind them to start their course of TAF on day 1.

Participants will receive a memory aid to serve as a reminder of the appropriate drug administration schedule, and to also serve as a memory aid during visit interviews regarding any AEs they may have experienced. Participants will be instructed to bring their memory aid cards and all bottles of study agent to each study visit to assess for study agent adherence and self-reported AEs.

If the screening visit happened more than 6 days before the first dose of TAF, then participants will be instructed to fast for at least 8 hours before the baseline visit so blood can be collected for baseline evaluation (same as screening labs, and excluding urine, HIV, TB, and hepatitis tests, which will not be done again). Additional blood will not be collected (and fasting will not be required) if screening happens within 6 days of the first dose of TAF.

Participants of childbearing potential will always have their baseline visit scheduled for day 0 so a serum or urine pregnancy test can be done within 24 hours of the first dose. The pregnancy test must be negative for the participant to proceed with the study.

6.3 TAF Dosing Period (Days 1-14)

Day 1, which is the first dose of TAF, will always be scheduled for a Tuesday to ensure that other study visits also occur on weekdays (Appendix D). Participants will self-administer 25-mg TAF once per day with food for days 1-13. Participants will receive a phone call around day 10 to remind them of their upcoming visit on day 14. In preparation for this visit, they will be instructed to fast for 8 hours and refrain from eating or drinking any beverage besides water after midnight prior to the day 14 PK visit (NIH Day Hospital or OP-8 Infectious Diseases Clinic). They will also be instructed to not take any study agent prior to arrival to the NIH Day Hospital clinic, and to instead bring their study agent supply with them to the day 14 PK visit for administration following the predose (time 0) blood draw. At the day 14 visit, participants will have the following evaluations:

- AE assessment and memory aid review.
- Medical/medication history.
- Pill count/study agent adherence review.

- Measurement of vital signs and weight.
- Serum or urine pregnancy test (if of childbearing potential, which must be negative to proceed with the study).
- Insertion of intravenous (IV) catheter to collect blood for safety labs, pharmacogenomic testing, and the time 0 (predose) plasma and PBMC PK samples.
- Urine sample for safety labs: urine protein and glucose.

Participants will then be provided with a standardized breakfast that consists of a well-balanced, moderate fat meal containing > 500 calories, which will be provided by the NIH metabolic unit kitchen. During breakfast, participants will be administered a single dose of TAF with 240 mL of water by nursing staff. Serial blood PK samples will be collected at 0.25, 0.5, 1, 2, 4, 6, and 8 hours postdose. Blood for PBMCs will be collected at 1, 2, 6, and 8 hours postdose. Participants will be provided with lunch no sooner than 4 hours after the standardized breakfast. Participants will also be given the option of dinner, which they may accept or decline per individual preference. The participant will be dismissed from the clinic after collection of the 8-hour postdose sample and removal of the IV catheter.

6.4 TAF and RPT + INH Dosing Period (Days 15-32)

6.4.1 First 24-hour PK (Trough)

In anticipation of the PK visit on day 15 (24-hour trough), participants will be instructed to fast for 8 hours and refrain from eating or drinking any beverage besides water after midnight prior to the day 15 PK visit (NIH Day Hospital or OP-8 Infectious Diseases Clinic). Participants will also be instructed to not take any study drug prior to arrival to the NIH Day Hospital clinic, and to instead bring their study agent supply with them to the day 15 PK visit. At this visit, participants will do the following:

- AE assessment and memory aid review.
- Medical/medication review.
- Pill count/study agent adherence review.
- Measurement of vital signs and weight.
- Blood draw for safety labs and 24-hour (± 2 hours) postdose plasma and PBMC PK sample collections.
- Serum or urine pregnancy test (if of childbearing potential, which must be negative to proceed with the study).

After these procedures, participants will be provided with breakfast and administered their daily dose of TAF and first weekly weight-based dose of RPT and INH (and pyridoxine), as described in section 5.5. Participants will return again on day 16 for AE assessment, medical/medication history, vital signs and weight, pill count, pregnancy test, and blood draw for safety labs before

administration of TAF. Participants must fast for 8 hours and refrain from eating or drinking any beverage besides water after midnight prior to the day 16 visit.

6.4.2 Second 24-hour PK

Daily self-administered dosing of TAF will continue between days 17 and 21, and participants will be contacted by phone on day 18 (± 3 days) for remote AE assessment and reminder for the day 22 PK visit. The second 24-hour PK visit will be on day 22 when the second weekly dose of RPT + INH (+ pyridoxine) will be administered (+ TAF); participants will have been instructed to fast for 8 hours prior to this visit and refrain from eating or drinking any beverage besides water after midnight prior to day 22. The following evaluations will be done at this visit:

- AE assessment and memory aid review.
- Medical/medication history.
- Pill count/study agent adherence review.
- Measurement of vital signs and weight.
- Serum or urine pregnancy test (if of childbearing potential, which must be negative to proceed with the study).
- Insertion of IV catheter to collect blood for safety labs and predose plasma and PBMC PK.

Participants will then be provided with a standardized breakfast, during which they will be administered TAF and RPT + INH (+ pyridoxine). Participants will be provided with lunch no sooner than 4 hours after the standardized breakfast. Participants will also be given the option of dinner, which they may accept or decline per individual preference. Serial blood PK samples will be collected at 0.25, 0.5, 1, 2, 4, 6, and 8 hours postdose, with extra blood collected for PBMCs at 1, 2, 6, and 8 hours postdose.

The visit on day 23 will be similar to the day 15 visit. Participants will be instructed to fast for 8 hours and refrain from eating or drinking any beverage besides water after the preceding midnight. Participants will also be instructed to not take any study drug prior to arrival to the NIH Day Hospital clinic, and to instead bring their study agent supply with them. Day 23 procedures are the following:

- AE assessment and memory aid review.
- Medical/medication review.
- Pill count/study agent adherence review.
- Measurement of vital signs and weight.
- Blood draw for safety labs and 24-hour (± 2 hours) postdose PK and PBMC sample collections.
- Serum or urine pregnancy test (if of childbearing potential, which must be negative to proceed with the study).

After these procedures, participants will be provided with breakfast and administered their daily dose of TAF.

Daily self-administered dosing of TAF will continue again between days 24 and 28. Participants will receive a phone call around day 25 to remind them of their upcoming visit on day 29.

6.4.3 Third Dose of RPT + INH + Pyridoxine

Participants will return to the NIH OP8 Clinic on day 29. Participants will be instructed to fast for 8 hours and refrain from eating or drinking any beverage besides water after the preceding midnight. Day 29 procedures are the following:

- AE assessment and memory aid review.
- Medical/medication review.
- Pill count/study agent adherence review.
- Measurement of vital signs and weight.
- Blood draw for safety labs.
- Serum or urine pregnancy test (if of childbearing potential, which must be negative to proceed with the study).

After these procedures, participants will receive their third and final weekly dose administration of RPT + INH (+ pyridoxine), and will be observed for 1- hour postdose.

In an earlier study conducted by our group that evaluated INH + RPT and a different antiretroviral, dolutegravir, 2 out of 4 enrolled participants experienced SAEs including elevations in liver function tests and flu-like syndrome approximately 8 hours after study drug administration after the third weekly dose of INH + RPT. Although a different antiretroviral is under investigation in this study, participants will still receive RPT + INH. Therefore, to ensure the safety of the participants, a 8-10-hour observation period was included to check vitals and safety labs. This 8-10 hour observation period was conducted for the first three participants who reached this point in the study, after which time the need for this observation period was re-assessed and revised by the study team in consultation with the SMC for the remainder of potential study participants.

6.4.4 Third 24-hour PK

The third PK sampling visit is days 31 and 32, and participants will receive a phone call on day 30 to remind them of this visit. The schedule for these days is the same as days 22 and 23 (section 6.4.2) but without administration of RPT + INH (+ pyridoxine). In anticipation of this PK visit, participants will be instructed to fast for 8 hours and refrain from eating or drinking any beverage besides water after midnight prior to the visits on days 31 and 32 (NIH Day Hospital or OP-8 Infectious Diseases Clinic). Day 31 is also the final dose of TAF, so the participants will not

receive another dose on day 32 after assessments and collection of the 24-hour PK, blood for safety labs, and pregnancy test.

6.5 Safety Visit (Day 46 ± 3) and End-of-Study Phone Call (Day 60 ± 3)

Participants will return to the NIH CC for a final follow-up visit on day 46, approximately 2 weeks after the end of third PK visit. AEs will be assessed, vital signs and weight measured, and blood drawn and urine collected for safety labs. Participants who can become pregnant will have a blood or urine pregnancy test. A follow-up phone call for remote AE assessment will be scheduled approximately 2 weeks later (4 weeks after the end of the third PK visit). Participation ends after the phone call.

6.6 Early Termination Visit

If participants terminate the study early, they will be asked to return for drawing end-of-study labs (14 ± 3 days after the final dose of any study drug[s]) and will receive a physical exam and AE assessment.

6.7 Pregnancy and Follow-up Visit

Participants who become pregnant while on study will discontinue study agents and procedures, and will be instructed to follow-up with their physician for prenatal care; they will also be followed to delivery for purposes of safety monitoring for this study.

7 Study Procedures/Evaluations

Blood draw: The amount of blood drawn for research purposes will be within the limits allowed for adult research participants by 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). Blood samples will be used for the following:

- Screening labs (see section 6.1).
- 24-hour plasma PK of TAF and TFV.
- Collection of PBMCs for measurement of intracellular PK of TFV-dp.
- Pregnancy testing
- Safety labs: safety panels (acute care, hepatic, mineral), CRP, amylase (study day 16), lipase (study day 16), CBC/diff, CK.
    - Results of safety lab assessments will be reviewed as they become available, with appropriate clinical follow-up through resolution as necessary for any abnormal results.

Pharmacogenomics: A single blood sample (10 mL) on day 14 will be collected for pharmacogenomic testing (targeted sequencing).

Urine: Urine samples will be used for the following:

- Screening labs (urine protein and urine glucose).
- Safety labs: urine protein and glucose on study day 14 and end of study visit.
- Pregnancy testing.

8 Potential Risks and Benefits

8.1 Potential Risks

TAF: In clinical trials of TAF in people with hepatitis B infection, the AEs (all grades) observed in more than 5% of study participants were headache, abdominal pain, fatigue, cough, nausea, and back pain.[34]

Renal impairment, including cases of acute renal failure and Fanconi syndrome, has been reported with use of TFV prodrugs in animal toxicology and human trials.[34] In clinical trials of TAF alone (in patients with hepatitis B) or in combination with FTC and EVG/c (in patients with HIV infection), there have been no reports of patients experiencing proximal renal tubulopathy or Fanconi syndrome.[41,42] In a 24-week trial in HIV-infected adults (n = 248) with baseline renal impairment (eGFR = 30-60 mL/min), FTC/TAF + EVG/c was discontinued for 2 patients who experienced worsening renal function.[43]

Lactic acidosis (including life-threatening cases) as well as hepatic steatosis have been reported with the use of nucleoside analogs including FTC and TDF. This is a rare but recognized AE of nucleoside analogues and is described to occur as a result of mitochondrial toxicity. The incidence of lactic acidosis varies based on the case definition and has a reported incidence in HIV-infected patients of 1.9/1000 to 14.8/1000.[44] Described characteristic symptoms in patients reported to have experienced lactic acidosis include elevated lactate levels (> 5 mmol/L), elevated liver function tests, and abdominal pain.

In a 96 week trial, three percent of patients with chronic hepatitis B experienced elevations in amylase (> 2 x ULN). Eight out of 866 participants receiving TAF experienced elevated amylase with associated symptoms of nausea, low back pain, abdomninal tenderness; and biliary pancreatitis and pancreatitis.[34] Of these eight, two participants discontinued TAF. Amylase and lipase will both be assessed in healthy volunteers receiving TAF during the study.

TAF, TDF, and TFV have been associated with bone mineral density loss in clinical trials of HIV-infected participants.[41,42] This has also been observed in clinical trials of TAF in patients with hepatitis B.[34] The long-term clinical significance of these changes is not known.

RPT: In clinical trials and post-marketing surveillance, the most frequent AEs (> 1%) with prolonged RPT-based treatment of active TB included hematologic changes (anemia, lymphopenia, neutropenia, leukocytosis, thrombocytosis, thrombocytopenia, lymphadenopathy),

GI symptoms (dyspepsia, vomiting, nausea, diarrhea), back and abdominal pain, fever, anorexia, increases in ALT and AST, arthralgia, headache, dizziness, hemoptysis, coughing, rash, increased sweating, pruritus, and maculopapular rash.[12] AEs were less common with once-weekly administration of RPT compared to the twice-weekly regimen. Hypersensitivity reactions were the most common AE (≥ 1%) observed in treatment of LTBI. RPT may produce a red-orange discoloration of body tissues and/or fluids (eg, skin, teeth, tongue, urine, feces, saliva, sputum, tears, sweat, and cerebrospinal fluid).

Other serious warnings and precautions for RPT include hepatotoxicity, hypersensitivity reactions (hypotension, urticaria, angioedema, acute bronchospasm, conjunctivitis, thrombocytopenia, neutropenia, or flu-like syndrome), discoloration of bodily fluids, *Clostridium difficile*-associated diarrhea, and contraindication to use in patients with porphyria. Rifamycins can also cause transient increases in direct bilirubin as a result of inhibition of the major bile salt exporter pump and/or dose-dependent competition with bilirubin clearance.[45,46]

Studies in HIV-negative and HIV-infected patients have revealed higher rates of hepatotoxicity with daily INH therapy for 9 months vs. weekly RPT + INH.[7,9] However, greater discontinuation rates in the RPT + INH group because of hypersensitivity or flu-like reactions were observed in the study with a largely HIV-negative population.[7] The flu-like reaction was characterized by symptoms of headache, nausea, chills, fatigue, and myalgia.[47] In post hoc analyses of patients experiencing these reactions with RPT + INH, risk factors for the development of this AE included being 35 years of age older, female sex, lower body mass index, and white non-Hispanic race/ethnicity. In a more recent study in HIV-infected individuals, 2/207 (1%) study participants developed this AE with RPT + INH, compared to none in the INH-only arm.[9] However, these hypersensitivity reactions were not observed in a separate study comparing weekly RPT + INH therapy to daily INH in HIV-infected individuals,[8] or in studies looking at RPT + INH for active TB treatment.[48,49]

Because healthy volunteers will be limited to three doses of RPT given at weekly intervals, the risk to participants in this study is expected to be significantly less than in the long-term treatment studies.

INH: In clinical trials and post-marketing surveillance, the most frequent AEs with daily INH administration included peripheral neuropathy (dose- and risk factor–related) and mild elevation of serum transaminase levels (10%-20%).[17] Transaminase elevations are more common with concomitant use of RIF, usually occur within 1 to 3 months of initiating therapy, and typically normalize with continued treatment. Mild increases do not require treatment discontinuation. Other AEs include GI symptoms (nausea, vomiting, epigastric distress, and pancreatitis), hematologic changes (agranulocytosis; hemolytic, sideroblastic or aplastic anemia; thrombocytopenia; and eosinophilia), hypersensitivity reactions (fever, skin reactions, lymphadenopathy, toxic epidermal necrolysis, and drug reaction with eosinophilia syndrome), metabolic and endocrine reactions

(pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis, and gynecomastia), rheumatic syndrome, and systemic lupus erythematosus-like syndrome. Other serious AEs, which are uncommon with conventional doses, are convulsions, toxic encephalopathy, optic neuritis and atrophy, memory impairment, and toxic psychosis.

INH carries a black box warning for severe and sometimes fatal hepatitis that can develop after several months of therapy, and development of this AE is related to increased age and daily consumption of alcohol. In clinical trials comparing once-weekly RPT and INH to daily INH therapy, once-weekly therapy was associated with lower rates of grade 3 or 4 transaminase elevations (0.3% vs. 2.0% in Sterling et al,[7] and 1.5% vs. 5.5% in Martinson et al[8] for RPT + INH vs. daily INH). Drug discontinuation as a result of hepatotoxicity was significantly higher with daily INH therapy (1% for RPT + INH vs. 4% for daily INH, $p = 0.05$). However, as discussed previously, there were greater discontinuation rates in the RPT + INH group as a result of hypersensitivity reactions in a largely HIV-negative population.[7] These hypersensitivity reactions were not observed in a separate study comparing weekly RPT-based therapy to daily INH in HIV-infected individuals.[8] As healthy volunteers will be limited to three doses of INH given at weekly intervals, and patients will be counseled to abstain from alcohol consumption during the study period, the risk to participants in this study is expected to be less in frequency and severity than in the clinical trials with daily INH therapy.

Pyridoxine: In the studies examining once-weekly RPT + INH for LTBI, pyridoxine was coadministered once weekly with the LTBI regimen at a dose of 25 mg[8] or 50 mg.[7] The risk of pyridoxine toxicity is very low as this vitamin is water-soluble, and doses up 100 mg/day are considered a safe upper limit for supplementation.[24] However, toxic sensory peripheral neuropathy has been observed in individuals taking pyridoxine at doses > 200 mg/day for several months at a time. As participants in this study will be healthy volunteers, and INH therapy will be limited to three doses at once weekly intervals, the risk of peripheral neuropathy due to INH in this study population is considered low. The addition of pyridoxine at clinically utilized doses is an added safety measure to further reduce the risk of INH-induced deficiency and subsequent AEs.

Blood draw and IV catheter: The risks of drawing blood include pain, bruising, bleeding, and, rarely, fainting or infection. Insertion of an IV catheter for collection of blood can also result in inflammation of the skin and vein.

Pharmacogenomic testing: There are no foreseeable risks with pharmacogenomic testing. Results of pharmacogenomic testing will not become a part of the participant's medical record at the NIH. Records containing this information are maintained in a secure manner. Genetic information about the participant will not be revealed to others, including the participant's relatives, without the participant's permission. We will not release any information about the participant to any insurance company or employer unless they sign a document allowing release of information.

8.2 Potential Benefits

This is not a therapeutic trial; therefore, study participants will not experience direct benefits from their participation. However, the results of this study may help in the care of patients receiving these or similar medications in the future.

9 Research Use of Stored Human Samples, Specimens, and Data

Intended Use: Samples, specimens, and data collected under this protocol will be used to assess plasma and intracellular concentrations of TAF, TFV and TFV-dp. Genetic testing may be performed. Method development for drug assays (TAF, TFV, TFV-dp) and sample processing will be performed by Drs. William Figg and Cody Peer.

Storage: Samples collected for PK assessments will be stored at −80°C in a locked freezer in the NCI Clinical Pharmacology Program (CPP) under the management of the director (Dr. William Figg). Other samples collected under this study may be stored at the Frederick National Laboratory for Cancer Research. Samples and data will be stored using codes assigned by the investigators or their designees. All stored computer data will be password protected. Only investigators will have access to the samples and data.

Tracking: Samples acquired under this protocol will be tracked using a database located on a password-protected computer. Data will be stored and maintained in CRIMSON database.

Disposition at the Completion of the Protocol:

- In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. Before any sharing of samples, data, or clinical information, either institutional review board (IRB) approval must be obtained or the NIH Office of Human Subjects Research Protections (OHSRP) must determine that the research is exempt from IRB oversight. OHSRP can make this determination for some research where the samples or data have no personal identifying information about the study participant and the researcher is not able to ascertain it.
- At the time of protocol termination, samples will either be destroyed, or after IRB approval, transferred to another existing protocol. Data will be archived by the study team in compliance with requirements for retention of research records; alternatively, after IRB approval, the data may be either destroyed or transferred to another repository.

Loss or Destruction:

- Any loss or unanticipated destruction of samples (for example, due to freezer malfunction) or data (for example, misplacing a printout of data with identifiers) that meets the definition of a protocol deviation or unanticipated problem (UP), and/or compromises the scientific integrity of the data collected for the study, will be reported to the IRB.

- Additionally, participants may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the participant and to the IRB. This decision will not affect the individual's participation in this protocol or any other protocols at NIH.

10 Data Sharing Plan

Human data generated in this study will be shared for future research as follows:

- De-identified data in an NIH-funded or approved public repository.
- Identified data in the Biomedical Translational Research Information System (BTRIS, automatic for activities in the CC).
- De-identified or identified data with approved outside collaborators under appropriate agreements.
- Through publications and/or public presentations.

Data will be shared before, at the time of or shortly after publication.

11 Remuneration Plan for Participants

Participants will be compensated for their time and inconvenience per study visit as described in the following table:

Compensation schedule	
Screening	$50
Baseline	$50
Days 14-15	$400
Day 16	$50
Days 22-23	$400
Day 29	$200
Days 31-32	$400
Day 46	$50
Total	**$1600**

If the participant requires additional clinical follow-up outside of scheduled study visits based on medical advisory investigator discretion, then the participant may be compensated an amount consistent with NIH CC policies and guidelines for additional follow-up visits/procedures. Payment will be issued after the final study visit. Travel and/or lodging expenses may be provided as per PI discretion.

12 Assessment of Safety

12.1 Toxicity Scale

The Investigator will grade the severity of each AE according to the "DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events" most recent Version 2.1, July 2017, which can be found at: https://rsc.tech-res.com/docs/default-source/safety/division-of-aids-(daids)-table-for-grading-the-severity-of-adult-and-pediatric-adverse-events-corrected-v-2-1.pdf?sfvrsn=2.

Some Grade 1 lab parameters on the DAIDS Toxicity Table fall within the NIH lab reference range for normal values. These normal values will not be reported as Grade 1 AEs.

Total bilirubin will be graded according to the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Trials", as indicated in the table below. The full table can be accessed through the following link: http://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977. Only the total bilirubin measure (not direct or indirect bilirubin individually) will be used to determine whether pausing rules have been met. Direct and indirect bilirubin measures will still be collected as AEs.

Serum Test	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Total bilirubin – when accompanied by any increase in LFTs (eg, AST, ALT) increase by factor.	1.1-1.25 x ULN	1.26-1.5 x ULN	1.51-1.75 x ULN	> 1.75 x ULN
Total bilirubin – when LFTs (eg, AST, ALT) are all normal; increase by factor.	1.1-1.5 x ULN	1.6-2.0 x ULN	2.0-3.0 x ULN	> 3.0 x ULN
ALT = alanine transaminase; AST = aspartate transaminase; LFT = liver function test; ULN = upper limit of normal.				

12.2 Recording/Documentation

At each contact with the participant, starting from the time the informed consent form is signed through the end of the final study visit, information regarding AEs will be elicited by appropriate questioning and examinations. All events, both expected/unexpected and related/unrelated, will be recorded on a source document. Source documents will include progress notes, laboratory reports, consult notes, phone call summaries, survey tools, and data collection tools. Source documents will be reviewed in a timely manner by the research team. All reportable AEs that are identified

will be recorded in CRIMSON. The start date, the stop date, the severity of each reportable event, and the principal investigator's judgment of the AE's relationship and expectedness to the study agent/intervention will also be recorded in CRIMSON.

12.3 Definitions

- Please refer to Policy 801 and Policy 802 for definitions

NOTE: The following hospitalizations are not considered SAEs in this clinical study:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event).
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

1.

12.4 Reporting Procedures

AE and SAE reporting to the NIH IRB will be done as per Policy 801 and Policy 802.

12.4.1 Waiver of Reporting Anticipated Protocol Deviations, Expected non-UP AEs, and Deaths

Anticipated deviations in the conduct of the protocol will not be reported to the IRB unless they occur at a rate greater than anticipated by the study team. Expected AEs will not be reported to the IRB unless they occur at a rate greater than that known to occur in a healthy population. If the rate of these events exceeds the rate expected by the study team, then the events will be classified and reported as though they are UPs.

12.5 Pregnancy

Although pregnancy itself is not an AE, events occurring during pregnancy, delivery, or in the neonate (eg, congenital anomaly/birth defect) may be AEs or SAEs.

In the event a participant or female partner of a participant becomes pregnant, prenatal care will not be provided by the study and the following steps will be taken:

- Discontinue the study agents and procedures but continue to follow-up until delivery for safety.
- Enroll in antiretroviral pregnancy registry.
- Report to safety oversight committee and/or the IRB.
- Advise research participant to notify the obstetrician of study participation and study agent exposure.

12.6 Type and Duration of the Follow-up of Participants after Serious Adverse Events

SAEs that have not resolved by the end of the follow-up period will be followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (eg, the participant is lost to follow-up), then the reason a final outcome could not be obtained will be recorded by the investigator in CRIMSON.

12.7 Pausing Rules for An Individual Participant

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

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

- A participant experiences a $\geq$ Grade 3 AE that is unexpected and possibly, probably, or definitely related to a study agent (except absolute lymphocyte count);
- A participant experiences a Grade 2 AE of transaminase elevations that are possibly, probably, or definitely related to the study agents.

Any safety issue that the site investigator determines should pause administration of a study agent to a single participant.

12.7.1 Reporting a Pause

If a pausing criterion is met, then a description of the AE(s) or safety issue must be reported by the principal investigator within 1 business day to the IRB and the safety monitoring committee (SMC) by fax or email.

12.7.2 Resumption of a Paused Participant

A participant who experiences an SAE will not be permitted to resume the study agents but will continue to be followed for safety.

12.7.3 Discontinuation of Study Agent

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

12.8 Halting Rules for the Protocol

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

The halting rules are:

- 2 or more participants experience the same or similar ≥ Grade 3 AEs that are possibly, probably, or definitely related to the study agents (except for absolute lymphocyte count);
  OR
- 2 or more participants experience Grade 2 events of transaminase elevations that are possibly, probably, or definitely related to the study agents;
  OR
- Any safety issue that the principal investigator and/or the safety oversight committee determines should halt the study.

The principal investigator and SMC will determine if the study should be halted.

12.8.1 Reporting a Study Halt

If a halting rule is met, then a description of the AE(s) or safety issue must be reported by the principal investigator within 1 business day to the IRB and SMC by fax or email.

12.8.2 Resumption of a Halted Study

The principal investigator and safety oversight committee will determine if it is safe to resume the study. The principal investigator will notify the IRB and safety oversight committee of the decision on resumption of the study.

12.8.3 Discontinuation of Study Agent

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

12.9 Study Discontinuation

The IRB, the NIAID, the SMC, and other oversight bodies as applicable, as part of their duties to ensure that research participants are protected, may discontinue the study at any time. Subsequent review of serious, unexpected, and related AEs by the IRB may also result in suspension of enrollment and further trial interventions/administration of study agent.

12.10 Premature Withdrawal of a Participant

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

- An individual participant's decision. (The investigator should attempt to determine the reason for the participant's decision.)
- Participant loses ability to provide ongoing informed consent.
- Non-compliance with study procedures to the extent that it is potentially harmful to the participant 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 participant.

12.11 Replacement of Withdrawn Participants or Participants Who Discontinue Study Treatment

Participants who withdraw or are withdrawn from the study prior to day 31 will be replaced. If a participant is replaced, all the data collected from that participant will still be included for the safety assessment.

12.12 Safety Monitoring Committee

An independent SMC consisting of 3 individuals will review the study prior to initiation and at specific time points as agreed upon by the SMC. The SMC will focus on participant safety and will include subject matter experts. The independent experts do not have direct involvement in the conduct of the study and have no significant conflicts of interest as defined by NIAID policy.

Prior to each SMC review, the principal investigator will submit data as requested by the SMC. After each SMC review, a recommendation as to whether the study is to continue, be modified, or be terminated will be provided in a summary report. All SAEs and all UPs will be reported by the principal investigator to the SMC at the same time they are submitted to the IRB. The SMC will be notified within 1 business day if pausing or halting rules are met, and the SMC will provide a recommendation for continuation, modification, or termination of the study. The principal investigator will submit the written SMC summary reports with recommendations to the IRB.

13 Study Monitoring

Accrual and safety data will be monitored by the PI, who will provide oversight to the conduct of this study. The PI will continuously evaluate implementation of the protocol for any unusual or unpredicted complications that occur and will review the data for accuracy and completeness.

The NIH CC's Quality Assurance Program will conduct study monitoring at least annually or more frequently as required. Participant consent documents, primary outcome and safety laboratory results, and diagnostic test results will be monitored for accuracy, correct dating, and agreement

between case report forms and source documents. All regulatory reports, reviews and amendments, AEs and problem reports related to study, along with investigator credentials, training records, and the delegation of responsibility log will also be reviewed during monitoring visits. The PI will be responsible for reporting any problems to the IRB as defined in Section 12.4, Reporting Procedures. .

14 Statistical Considerations

14.1 Primary Study Hypothesis

In healthy volunteers receiving TAF concomitantly with RPT + INH (+ pyridoxine), significant RPT induction of P-gp will not be observed, and thus levels of TAF, TFV and TFV-dp will not be significantly decreased. A significant decrease in TAF and TFV levels is defined as a 25% or greater decrease in the AUC geometric mean ratio (GMR) of phase 2 comparatively to phase 1.

14.2 Sample Size Justification

As described above, power calculations were performed to estimate the probability of declaring that there is less than a 25% interaction for different sample sizes assuming there is no interaction. Intrasubject variability (CV%) was assumed as 27% for TFV based on available PK data.[36,50] If θ denotes the phase 2:phase 1 GMR, the procedure we use may be viewed in either of the following equivalent ways:

1. Test the null hypothesis that $\theta \leq 0.75$ versus the alternative hypothesis that $\theta > 0.75$ using a log transformation and a one-tailed test at $\alpha = 0.05$. If the test rejects the null hypothesis, then declare the interaction effect to be less than 25%.
2. Compute the lower confidence limit of a 2-sided, 90% confidence interval for θ (again by log transforming and then transforming back at the end). If the lower limit is > 0.75, then declare the interaction effect to be less than 25%.

From the tables below, a sample size of 15 participants provides an 88% chance of correctly declaring that the interaction effect is less than 25% (ie, $\theta > 0.75$). Equivalently, the probability that the lower limit of the confidence interval exceeds 0.75 is 88%. If the test is not significant (equivalently, the lower confidence limit is less than 0.75), AND if the upper limit of the confidence interval is less than 1, then we will have demonstrated that there is a statistically significant, nonzero interaction. If the truth is that there is a 25% interaction (phase 2:phase 1 GMR $\theta = 0.75$), then the probability that the upper interval is less than 1 is given in the table below. Thus, for example, with a sample size of 15, if the truth is that there is a 25% interaction, then the probability that the upper limit of the confidence interval is less than 1 is 88%.

Power and Sample Size (n) Tables for TFV

n	6	7	8	9	10	11	12	13	14	15	16	17	**18**
Power	0.49	0.560	0.621	0.676	0.723	0.765	0.800	0.831	0.858	0.880	0.990	0.916	**0.930**

Power is the same whether we define it as P (declare $\theta > 0.75$) when θ is actually 1, or P (declare $\theta < 1$) when θ is actually 0.75.

Power and Sample Size (n) Tables for TAF

n	6	7	8	9	10	11	12	13	14	15	16	17	**18**
Power	0.366	0.420	0.470	0.517	0.560	0.600	0.638	0.672	0.703	0.732	0.759	0.783	**0.805**

Power is the same whether we define it as P (declare $\theta > 0.75$) when θ is actually 1, or P (declare $\theta < 1$) when θ is actually 0.75.

14.3 Description of the Analyses

TAF, TFV, and TFV-dp PK parameters will be determined using noncompartmental methods with Phoenix WinNonlin (version 6.03; Pharsight Corporation, Mountain View, CA). C_{max}, t_{max}, and C_{min} for TAF, TFV, and TFV-dp will be obtained directly by visual inspection of the plasma concentration vs. time profiles. The apparent elimination rate constant (λ_Z) will be determined by calculating the absolute value of the slope of the log-linear regression of at least 3 points of the plasma concentration-time plot. The $t_{½}$ will be calculated as $0.693/\lambda_Z$. The $AUC_{0–24hr}$ will be calculated using the linear trapezoidal rule. CL/F will be calculated as CL/F = 25 mg/$AUC_{0\text{-}24hr}$ for TAF.

Steady-state PK parameters ($AUC_{0\text{-}24hr}$, C_{max}, t_{max}, $t_{½}$, CL/F, and C_{min}) for TAF 25 mg daily will be compared alone and in combination with once weekly RPT and INH (dose-adjusted by participant weight). GMRs (in combination vs alone) with 90% confidence intervals will be calculated using paired t-tests. A p-value less than 0.05 will be accepted as statistically significant.

A paired t-test and confidence interval will be conducted on log-transformed values of PK parameters. The confidence interval for GMR will be obtained by exponentiating the limits of the log-transformed interval.

The primary analysis will be conducted in patients who report no missing doses. Sensitivity analysis will also be conducted in all participants.

15 Ethics/Protection of Human Participants

15.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research participant. It is an ongoing conversation between the human research participant and the researchers which begins before consent is given and continues until the end of the participant'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. Participants will be given the opportunity to ask questions and have them answered.

The participants will sign the informed consent document prior to undergoing any research procedures. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The researcher will document the signing of the consent form in the participant's medical record. The rights and welfare of the participants 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.

15.1.1 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 Medical Administrative Series Policy M77-2, NIH HRPP Standard Operating Procedure 12, and Title 45 of the United States Code of Federal Regulations (CFR) Part 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 interpreter will interpret all oral communications (English to target language and conversely) between the investigator and a limited English-proficient participant, facilitate discussions, and clarify information as necessary.

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.

15.2 Participant Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized individuals 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 participant, except as necessary for monitoring by the IRB, NIAID, and OHRP.

16 Data Handling and Record Keeping

16.1 Data Capture and Management

Study data will be maintained in CRIMSON and collected directly from participants during study visits and telephone calls, or will be abstracted from participants' 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 investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

16.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP guidelines. Study records will be maintained by the principal investigator according to the timelines specified in 45 CFR 312.62 or a minimum of 5 to 7 years, and 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.

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Appendix A: Dosing Nomogram for Rifapentine and Isoniazid

Weight (kg)	Rifapentine		Isoniazid		
	Dose	Quantity[a] 150-mg tablet	Dose	Quantity[a,b] 300-mg tablet	Quantity[a,b] 100-mg tablet
45 to < 48.4	750 mg	5	700 mg	2	1
48.4 to < 50	750 mg	5	750 mg	2.5	0
50 to < 51.7	900 mg	6	750 mg	2.5	0
51.7 to < 55	900 mg	6	800 mg	2	2
55 to < 58.4	900 mg	6	850 mg	2.5	1
≥ 58.4	900 mg	6	900 mg	3	0

a Quantity of tablets per dose. For the total quantity of tablets required for the entire study period, multiply the quantity per dose by 3.
b If the total quantity of tablets required for the entire study period contains a half-tablet dose, then round up to the nearest whole number.

Appendix B: Schedule of Procedures/Evaluations

Evaluation		Screening (Day −89 to −0)	Baseline (Day −6 to 0)	Day 10 (± 1)	Day 14	Day 15	Day 16	Day 18 (± 3)	Day 22	Day 23	Day 25 (± 3)	Day 29	Day 30	Day 31	Day 32	Day 46 (± 3)	Day 60 (± 3)	Early Termination Visit
Informed Consent		X																
Medical/Medication History		X	X		X	X	X		X	X		X		X	X			X
Vital Signs/Weight		X	X		X	X	X		X	X		X[a]		X	X	X		X
Case Manager Assessment[b]			X		X	X	X		X	X		X		X	X	X		
LIP Clinical Assessment[b]		X	X													X		X
Telephone Reminder/ Assessment[c]			X (day 0 reminder)	X				X			X		X				X	
Acute Care Panel	4 mL Li-Heparin	X	X[d]		X	X	X		X	X		X[e]		X	X	X		X
Hepatic Panel	4 mL Li-Heparin	X	X[d]		X	X	X		X	X		X[e]		X	X	X		X
Mineral Panel	4 mL Li-Heparin	X	X[d]		X	X	X		X	X		X[e]		X	X	X		X
CBC/diff	3 mL purple	X	X[d]		X	X	X		X	X		X[e]		X	X	X		X

Evaluation		Screening (Day −89 to −0)	Baseline (Day −6 to 0)	Day 10 (±1)	Day 14	Day 15	Day 16	Day 18 (±3)	Day 22	Day 23	Day 25 (±3)	Day 29	Day 30	Day 31	Day 32	Day 46 (±3)	Day 60 (±3)	Early Termination Visit
Lipid Panel	4 mL Li-Heparin	X	X[d]															
CRP	4 mL Li-Heparin	X	X[d]		X	X	X		X	X		X[e]		X	X	X		X
CK	4 mL Li-Heparin	X	X[d]		X	X	X		X	X		X[e]		X	X	X		X
Amylase	4 mL Li-Heparin	X	X[d]				X											
Lipase	4 mL Li-Heparin	X	X[d]				X											
Pregnancy Testing[f]	Blood or Urine	X	X		X	X	X		X	X		X		X	X	X		X
Anti-HIV-1/2		X																
QuantiFERON-Gold TB Testing		X																
Viral Markers Hepatitis Screen		X																

Evaluation		Screening (Day −89 to −0)	Baseline (Day −6 to 0)	Day 10 (±1)	Day 14	Day 15	Day 16	Day 18 (±3)	Day 22	Day 23	Day 25 (±3)	Day 29	Day 30	Day 31	Day 32	Day 46 (±3)	Day 60 (±3)	Early Termination Visit
Urine Safety Labs: Protein and Glucose		X			X											X		X
Study Labs: TAF Serial plasma PK collection	6 mL purple top				X[g]	X[h]			X[g]	X[h]				X[g]	X[h]			
Study Labs: Serial PBMC collection	8 mL CPT tube				X[g]	X[h]			X[g]	X[h]				X[g]	X[h]			
Study Labs: Pharmacogenomics	10 mL purple top				X[i]													
Study Drugs (TAF) Dispensed			X[j]															
Study Drugs (TAF): DOT Administration[k]					X	X	X		X	X		X		X				

Evaluation		Screening (Day −89 to −0)	Baseline (Day −6 to 0)	Day 10 (± 1)	Day 14	Day 15	Day 16	Day 18 (± 3)	Day 22	Day 23	Day 25 (± 3)	Day 29	Day 30	Day 31	Day 32	Day 46 (± 3)	Day 60 (± 3)	Early Termination Visit
Study Drugs (RPT, INH, Vit B6) Dispensed and DOT Administration [1]						X			X			X						

Evaluation		Screening (Day −89 to −0)	Baseline (Day −6 to 0)	Day 10 (± 1)	Day 14	Day 15	Day 16	Day 18 (± 3)	Day 22	Day 23	Day 25 (± 3)	Day 29	Day 30	Day 31	Day 32	Day 46 (± 3)	Day 60 (± 3)	Early Termination Visit
CBC/diff = complete blood cell count with differential; CK= creatine kinase; CRP= C-reactive protein; DOT = directly observed therapy; INH = isoniazid; LIP= licensed independent practitioner; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; RPT = rifapentine; TAF= tenofovir alafenamide; TB= tuberculosis; Vit B6 = vitamin B6; X = to be performed. [a] Vital signs will be collected at the time of study drug administration and at the discretion of the medically advisory investigator as clinically indicated throughout the Day 29 observation period. [b] LIP assessments will take place at the screening (Day −89 to 0), baseline (Day −6 to 0) and end-of-study (Day 46 ± 3) visits, and as clinically indicated during the study period. The remaining clinical assessments refer to case manager assessments during which AE assessments, medication reconciliations, and adherence assessments will be completed. [c] Phone call on Day 0 to remind participant to start taking TAF study medication starting Day 1. Reminder phone calls for long study visit days 14, 22, 29, and 31. Assessment of study medication tolerability will also be performed. Follow-up phone call assessment for side effects at day 60 ± 3. [d] Blood will only be collected at baseline if the baseline visit is more than 6 days after screening. [e] Safety labs will be repeated during the Day 29 observation period at the discretion of the medically advisory investigator as clinically indicated. [f] Pregnancy test must be negative to proceed in the study. Pregnancy test will be performed at every visit prior to study drug administration. Pregnancy test may be conducted with blood and/or urine. [g] Blood for serial PK time points (plasma) are 0 (predose), 0.25, 0.5, 1, 2, 4, 6, and 8 hours postdose. Blood for serial PK time points (PBMCs) are 0 (predose), 1, 2, 6, and 8 hours postdose. Samples will be processed and stored by the Figg Laboratory Clinical Pharmacology Program Page: 102-11964. Phone: 240-760-6180 or 240-760-6190. [h] 24 hour postdose trough collection (plasma and PBMC). Samples will be processed and stored by the Figg Laboratory Clinical Pharmacology Program:102-11964. Phone: 240-760-6180 or 240-760-6190. [i] Sample collection for pharmacogenomics will be drawn PK time point 0. Send to Frederick as whole blood to be frozen and stored. NIH Contact: Cathy Rehm. Frederick Contact: Ven Natarajan 301-846-1258. [j] A 31-day supply (+ 3 additional tablets) will be dispensed to the participant at the baseline visit. Participant will be reminded to bring the TAF study medication supply to each visit. [k] On study day visits 14, 15, 16, 22, 23, 29, and 31, participants will be reminded to bring in their TAF study medication supply to the NIH to be administered at the clinic or Day Hospital under DOT.																		

Evaluation		Screening (Day −89 to −0)	Baseline (Day −6 to 0)	Day 10 (± 1)	Day 14	Day 15	Day 16	Day 18 (± 3)	Day 22	Day 23	Day 25 (± 3)	Day 29	Day 30	Day 31	Day 32	Day 46 (± 3)	Day 60 (± 3)	Early Termination Visit
[1] On study day visits 15, 22, and 29, study drugs RPT, INH, and vitamin B6 will be dispensed from the pharmacy and administered to the participant at the clinic or Day Hospital under DOT.																		

Appendix C: Blood Volumes for Specimen Collection

Evaluation	Study day											Early termination visit
	Screening (days −89 to 0)	Baseline[a] (day −6 to 0)	14	15	16	22	23	29	31	32	46 (± 3)	
HIV-1/2 antigen/antibody testing	8											
QuantiFERON Gold	3											
Viral markers hepatitis screen	8											
Acute care panel[b]	4	4	4	4	4	4	4	4	4	4	4	4
Hepatic panel[b]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Mineral panel[b]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Creatine kinase[b]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Lipase[b]		(4)			(4)							
Amylase[b]		(4)			(4)							
Lipid panel[b]	(4)	(4)										
CRP[b]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Serum pregnancy test[b]	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
CBC/diff	3	3	3	3	3	3	3	3	3	3	3	3
PK blood			48	6		48	6		48	6		
PBMCs			40	8		40	8		40	8		
Pharmacogenomics[c]			10									
Daily volume (mL)	26	7	105	21	7	95	21	7	95	21	7	7
Cumulative volume (mL)	26	33	138	159	166	261	282	289	384	405	412	

CBC/diff = complete blood count with differential; CRP = C-reactive protein; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics.

a Blood will only be collected at baseline if this visit is more than 6 days after screening.

b A single volume of blood will be collected for acute care, hepatic, mineral, and lipid panels, amylase, lipase, CRP, creatine kinase, and pregnancy test.

c Sample collection for pharmacogenomics. Send to Frederick as whole blood to be frozen and stored. NIH Contact: Cathy Rehm. Frederick Contact: Ven Natarajan 301-846-1258.

Appendix D: Study Initiation Calendar

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12
Day 13	**Day 14**	**Day 15**	**Day 16**	Day 17	Day 18	Day 19
Day 20	Day 21	**Day 22**	**Day 23**	Day 24	Day 25	Day 26
Day 27	Day 28	**Day 29**	Day 30	**Day 31**	**Day 32**	Day 33
Day 34	Day 35	Day 36	Day 37	Day 38	Day 39	Day 40
Day 41	Day 42	Day 43	Day 44	Day 45	**Day 46**	Day 47
Day 48	Day 49	Day 50	Day 51	Day 52	Day 53	Day 54
Day 55	Day 56	Day 57	Day 58	Day 59	Day 60	
Days with study visits to the NIH are bolded.						