CCTG 589

Nucleoside-Sparing Combination Therapy with Lopinavir/ritonavir (LPV/r) + Raltegravir (RAL) vs. Efavirenz (EFV) + Tenofovir Disoproxil Fumarate + Emtricitabine (TDF/FTC) in Antiretroviral-Naïve Patients

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Phosphatase
ARV	Antiretroviral Therapy
AST	Aspartate Phosphatase
AUC	Area Under the Curve
BID	Twice Daily
BUN	Blood Urea Nitrogen
CCR5	Chemokine Receptor 5
CCTG	California Collaborative Treatment Group
CD4	CD4 lymphocytes
CRF	Case Report Form
CYP	Cytochrome
EFV	Efaverenz
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
Hct	Hematocrit
HIV-1	Human Immuno-deficiency Virus - 1
Hgb	Hemoglobin
IAS	International AIDS Society
IQR	Interquartile Range
ITT	Intention To Treat
LPV	Lopinavir
LPV/r	Lopinavir/ ritonavir
NNRTI	Non-Nucleoside analogue Reverse Transcriptase Inhibitor
NRTI	Nucleoside analogue Reverse Transcriptase Inhibitor
PBMC	Peripheral Blood Mononuclear Cells
PI	Protease Inhibitor
PK	Pharmacokinetics
QD	Once Daily
RAL	Raltegravir
RTV	Ritonavir
TDF	Tenofovir disoproxil fumarate
SAE	Severe Adverse Reaction
VD	Viral Dynamics
WBC	White Blood Count

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SCHEMA

Nucleoside-Sparing Combination Therapy with Lopinavir/ritonavir (LPV/r) + Raltegravir (RAL) vs. Efavirenz (EFV) + Tenofovir Disoproxil Fumarate + Emtricitabine (TDF/FTC) in Antiretroviral-Naïve Patients

Design:	CCTG 589 is a randomized, open-label, pilot study comparing the efficacy, safety and tolerability of RAL plus LPV/r to EFV plus TDF/FTC in HIV-infected, treatment-naïve subjects. Subjects will be ineligible if they have any evidence of drug resistant virus in the past or at the time of screening (if never previously tested). Those who are found to be eligible will be randomized 1:1 to initiate either LPV/r (400/100 mg) plus RAL (400mg), both given twice-daily, or fixed dose combination of EFV (600 mg), TDF (300 mg) and FTC (200 mg) given as once-daily Atripla® for 48 weeks.
Duration:	48 weeks
Sample Size:	50 subjects (25 per treatment arm)
Study Population:	HIV-1-infected treatment-naïve men and women (defined as having never received any HIV antiretroviral agents in the past) at least 18 years of age with plasma HIV-1 RNA $\geq$ 5,000 copies/mL and CD4+ T-cell count $\geq$ 50 cells/mm^3 with no evidence of drug resistant virus detected by genotype.
Stratification:	Subjects will be stratified based upon screening plasma HIV-1 RNA greater than or equal to, or below 100,000 copies/mL.
Regimen:	Subjects will be randomized 1:1 to initiate combination therapy either with LPV/r (400/100 mg) plus RAL (400mg twice-daily) or fixed dose combination of EFV (600 mg), TDF (300 mg) and FTC (200 mg) taken as Atripla® once-daily for 48 weeks. The study will provide LPV/r and RAL, however, Atripla® must be provided by prescription.

1.0 STUDY OBJECTIVES

1.1 Primary Objectives

1.1.1 To compare the phase 1 viral decay rates between LPV/r + RAL vs. EFV/TDF/FTC treatment combinations.

1.2 Secondary Objectives

1.2.1 To determine the antiviral efficacy of LPV/r + RAL compared to EFV/TDF/FTC after 48 weeks of treatment.

1.2.2 To compare early (baseline to week 12) and late (week 12 to week 48) CD4+ T-cell recovery rates between treatment regimens.

1.2.3 To evaluate the association of phase 1 viral decay dynamics (baseline to day 14) on phase 1 (baseline to week 12) CD4+ T-cell recovery.

1.2.4 To evaluate the association of early changes in immune subsets (baseline to week 4) on phase 2 (week 12 to week 48) CD4+ T-cell recovery.

1.2.5 To compare the effect of LPV/r + RAL vs. EFV/TDF/FTC on change in fasting lipid profiles.

1.2.6 To evaluate the safety and tolerability of this novel nucleoside-sparing combination of LPV/r + RAL compared to EFV/TDF/FTC therapy.

2.0 INTRODUCTION

2.1 Background

Although current Department of Health and Human Services (DHHS) guidelines recommend either efavirenz (EFV) or a ritonavir-boosted protease-inhibitor (PI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) as initial therapy of treatment-naïve patients [1], combinations of EFV + two NRTIs have been preferred by most practitioners. Specifically, the fixed dose combination of EFV/TDF/FTC is currently one the most prescribed regimen used in therapy-naïve patients. However, certain treatment-limiting toxicities have been associated with EFV and TDF-based therapy, including: renal [2], CD4+ T-cell decline [3], central nervous system [4] and lipatrophy [5]. Recently, new drug classes have been developed and potential new NRTI and NNRTI-sparing treatment options may be considered for treatment-naïve patients.

The combination of LPV/r + RAL offers potential therapeutic advantages over current standard-of-care therapy that will be evaluated with the proposed study:

1. Antiviral Potency: Individually, LPV/r and RAL are potent antiretrovirals (ARVs) that act on distinct steps in viral replication. The combination of a late (i.e. LPV/r) and mid-cycle (i.e. RAL) viral target inhibitor could more efficiently stop viral replication from cell reservoirs leading to a more rapid early plasma viral decay rate than the combination of EFV/TDF/FTC which inhibits a common viral replication step.

2. Immune Recovery: Faster viral decay dynamics could result in greater phase 1 (baseline to week 12) $CD4^+$ T-cell recovery. In addition, the inclusion of LPV/r may further decrease activation-induced apoptosis and enhance subsequent phase 2 (week 12 to 48) T-cell regeneration.

2.1.1 Lopinavir/ritonavir (Kaletra®, LPV/r)

LPV is a potent inhibitor of HIV-1 protease. When coformulated with LPV, ritonavir inhibits the CYP3A-mediated metabolism of LPV, thereby providing increased plasma levels of LPV/r. LPV/r has been evaluated and approved by the FDA for use in combination with other ARV agents for the treatment of HIV-1 infection. LPV/r twice daily is one of the preferred PI in treatment-naïve HIV-infected patients in the DHHS HIV treatment guideline for adults and adolescents (DHHS 1-08).

2.1.1.1 Efficacy

The efficacy of LPV/r has been studied in ARV-naïve and ARV-experienced HIV-1 infected patients. The M97-720 study, a phase II study of LPV/r in combination with NRTIs in ARV- naïve HIV-1-infected subjects, was a randomized, dose-blinded, multicenter trial with two groups of subjects enrolled [6]. Group I subjects (n=32) were randomly assigned to 200 mg LPV/100 mg RTV Q12H or 400 mg LPV/100 mg RTV Q12H monotherapy. On day 22, all subjects added stavudine (d4T) and lamivudine (3TC). Group II subjects (n=70) were randomly assigned to 400 mg LPV/100 mg RTV Q12H or 400 mg LPV/200 mg RTV Q12H and received d4T and 3TC beginning on day 1. After 48 weeks, all subjects converted to open-labeled LPV/r 400mg/100mg BID dosing. At year 6, d4T / 3TC was substituted with TDF in combination with LPV/r in 37 subjects. Similar efficacy was observed across all dosing groups. However, a trend towards higher lipid levels and increased rates of gastrointestinal adverse events was seen in the highest dose group, 400 mg LPV/200 mg RTV. Based on a review of this and other phase I/II data, a dose of 400 mg LPV with 100 mg RTV BID was selected for development. After week 48, all subjects were converted to this dose.

At week 360 (7 year data), by intent-to-treat missing=failure (ITT M=F) analysis, 61% of all participants had HIV-1 RNA <400 copies/mL, while the corresponding on-treatment (OT) analysis showed 98% suppressed to this level. By ITT M=F analysis, 59% of study subjects had HIV-1 RNA <50 copies/mL (OT: 95%). During 7 years of treatment with LPV/r, there were 18 subjects that met the criteria for loss of virologic response, and 11 participants had at least one "blip" after week 24. Resistance tests were performed on 29 subjects. In 19 individuals with available results, no LPV or d4T resistance was observed. Four individuals demonstrated 3TC resistance with six demonstrating a new secondary mutation/ polymorphism in protease at rebound, but phenotypic LPV susceptibility was not affected.

In a phase III M98-863 study, the safety and efficacy of LPV/r versus nelfinavir (NFV) both in combination with d4T and 3TC was evaluated in ARV-naïve subjects. The M98-863 study was a randomized, double-blind, multicenter, international trial [6]. Overall, 326 subjects were assigned to the LPV/r group and 327 to the NFV group. The superior antiviral activity of LPV/r was demonstrated by the analysis of the proportion of subjects achieving a plasma HIV-1 RNA below 400 copies/mL at week 48 (75% vs. 63% respectively, ITT, $p<0.001$) and the analysis of the proportion of subjects achieving a plasma HIV-1 RNA below 50 copies/mL at week 48 (67% vs. 52% respectively, ITT, $p<0.001$). In the analysis of the time to loss of virologic response through week 48, superior antiviral activity of LPV/r was also demonstrated ($p<0.001$, Cox proportional hazards model) with 84% of LPV/r and 66% of NFV-treated subjects maintaining virologic suppression. Samples from 51 (69%) LPV/r-treated and 96 (78%) NFV-treated subjects could be amplified for resistance testing. No primary protease mutations were detected in the rebound sample from any of the LPV/r-treated subjects through week 108. In contrast, new protease mutations developed in 43 of 96 samples from NFV-treated subjects, and PI resistance was confirmed by phenotypic analysis. Resistance to 3TC and d4T was also significantly higher in NFV- than LPV/r-treated subjects.

2.1.1.2 Impact on CD4+ T-cell Recovery

In both of these trials in ARV- naïve patients, LPV/r led to a significant recovery of CD4 cells. In the M97-720 study, the mean increase in CD4+ T-cell counts between baseline and week 360 was 501 cells/mm^3. In the M98-863 study, LPV/r led to a similar CD4+ T-cell cell recovery in the LPV/r group than in the NFV group. The mean change in CD4+ T-cell count at week 48 was 207 cells/mm^3 for the LPV/r-treated group and 195 cells/mm^3 for the NFV-treated group.

2.1.1.3 Safety and Tolerability

LPV/r is generally well tolerated. In the M97-720 study, 38 subjects discontinued at or prior to week 360. Reasons for discontinuation probably or possibly due to study drugs include: AST/ALT increases (n=2), diarrhea (n=1), liver pain/enlargement, fatty deposits (n=1), arthralgia (n=1), elevated lipids (n=2), fat redistribution (n=5), and death of unknown cause (n=1) (10 days after thoracic spinal surgery with perioperative myocardial infarction). The most frequent adverse events of moderate or severe intensity and probable, possible, or unknown relationship to LPV/r in both M97-720 treatment groups were diarrhea (28%), nausea (16%), lipodystrophy (12%), abdominal pain (11%). The most frequent Grade ≥3 laboratory abnormalities were cholesterol >300 mg/dL (27%), triglycerides >750 mg/dL (29%), and AST/ALT >5 x ULN (11%).

The safety and tolerability of LPV/r and NFV were also assessed in the M98-863 study. In this study, only 3% of subjects in the LPV/r treatment group and 4% of the subjects in the NFV group discontinued therapy at or before week 48 due to study drug-related adverse events. Diarrhea and nausea were the most frequently reported adverse events in both treatment groups. However, study drug interruptions and discontinuations related to diarrhea or nausea were infrequent, occurring in less than 2% of subjects in either treatment group. Adverse events consistent with body fat composition changes were reported in 5% of LPV/r and 6% of NFV-treated subjects through week 48. Five individuals receiving LPV/r and three NFV died. One death due to pancreatitis was considered possibly related to LPV/r; with the person also having lactic acidosis. Clinically significant laboratory abnormalities were infrequent in both treatment groups. Grade 3 or 4 elevations of cholesterol were noted in 9% of LPV/r-treated and 5% of NFV-treated subjects. Grade 3 or 4 triglyceride elevations were noted more frequently in LPV- than NLF-treated subjects (9% vs. 1%, respectively, p <0.001). However, Grade 3 or 4 elevations of lipids were generally intermittent with the majority of subjects who experienced such elevations not having persistent elevations above Grade 2. No subjects discontinued the study due to lipid elevations.

2.1.1.4 Drug Interactions and Special Populations

LPV is metabolized by CYP3A. Drugs that induce CYP3A activity are expected to increase the clearance of LPV resulting in lower plasma levels while those that inhibit CYP3A are expected to increase plasma levels of LPV (see Section 5.4 Concomitant Medications).

LPV/r has a pregnancy category C rating.

2.1.2 Raltegravir (Isentress®, RAL)

RAL is the first FDA approved agent in the class of integrase inhibitors. RAL targets the HIV-1 integrase enzyme which is required for viral replication. HIV-1 encoded integrase catalyzes the insertion of the HIV-1 DNA into the genome of the host cell. Raltegravir acts at the step of strand transfer and prevents transfer of HIV DNA into the host DNA.

2.1.2.1 Efficacy

RAL has been evaluated in several clinical trials in ARV- naïve and – experienced HIV-1 infected patients. The protocol 004 is a multicenter, double-blinded, randomized 2-part, dose ranging study. In part I, RAL was given as one of four different doses (100mg, 200mg, 400mg, 600mg BID) as monotherapy to 35 patients for 10 days. In part II, RAL was given as one of four different doses and compared to EFV both in combination with TDF + 3TC for 48 weeks. After 48 weeks, participants who received RAL at different doses, were continued at a RAL dose of 400mg BID combined with TDF/3TC and compared with the group receiving EFV/TDF/3TC. RAL was found efficacious when given as monotherapy in all evaluated doses with a mean decrease of HIV RNA from baseline to day 10 of 1.7 – 2.2 $\log_{10}$ copies/mL (Part I) [7]. The 48 week analysis of part II included 198 patients, 160 participants receiving RAL and 38 EFV [8]. At weeks 2, 4, and 8, the proportion of patients achieving an HIV-1 RNA level <50 copies/mL was greater in each of the RAL treated groups than in the EFV group. By week 24, all treatment groups appeared similar, with plasma HIV-1 RNA levels <400 copies/mL in 85% - 98% of subjects in the RAL group and 95% in the EFV group and <50 copies/mL in 85 - 95% of patients of subjects in the RAL groups and 92% in the EFV group. These viral load reductions were maintained through week 48 in 85% to 98% of patients and in 83% to 88% of patients, respectively. In a time-to-event analysis, patients receiving RAL at any dose achieved an HIV-1 RNA level < 50 copies/mL earlier than patients receiving EFV (log-rank test $p<0.05$). Five (3%) patients on RAL and 1 (3%) on EFV experienced virologic failure before week 48. In two patients with virologic failure on RAL, the N155H mutation was detected in the HIV-1 integrase region. NNRTI and NRTI mutations (including the K65R mutation) were found in the one patient failing in the EFV group.

Two phase III randomized controlled trials of treatment-experienced subjects have also been reported. These studies, BENCHMRK 1 and 2 were conducted in Europe, Asia/Pacific, Peru, and North and South America [9, 10]. In these studies, triple class resistant subjects were randomized 2:1 to RAL 400 mg BID or placebo plus optimized background therapy (OBT).

Results showed that 64% and 34% of subjects in the RAL and placebo arms, respectively, had plasma HIV-1 RNA < 50 copies/mL at 48 weeks.
A cross-sectional analysis of integrase resistance data from the BENCHMRK-1 and 2 studies have been presented. Mutations in the integrase region of HIV pol at Q148 or N155 in combination with at least one other mutation were associated with virological failure.

2.1.2.2 CD4+ T-cell Recovery

The mean increase in CD4+ T-cell count in Study 004 ranged from 70-104 cells/mm^3 across all treatment groups and continued to increase through week 32. The mean CD4+ T-cell increase was comparable between the different RAL groups and EFV.

2.1.2.3 Safety and Tolerability

RAL was overall well tolerated. In the study 004, there were overall fewer drug related clinical adverse events in the RAL group than in the EFV group (p=0.04 for 100mg , 400mg and p=0.07 for 200mg RAL). The most frequent drug related adverse events were nausea, headache, dizziness. Serious adverse event occurred in 6% in the RAL group experienced and 5% in the EFV group. None of the serious adverse events were considered drug related or led to treatment discontinuation.

In the BENCHMRK trials, there was overall no difference in the clinical or laboratory toxicity between those receiving OBT with RAL than with placebo. Drug-related clinical AEs were reported in $\geq$5% of subjects receiving RAL in BENCHMRK 1 for diarrhea (6.9%), with this occurring in 14.4% of controls. In BENCHMRK 2 clinical AEs occurring in $\geq$5% of RAL-treated subjects included diarrhea (13.9% versus 10.1% of controls), nausea (9.6% versus 9.2%), fatigue (5.2% versus 2.5%) and headache (8.7% versus 5.0%). Laboratory abnormalities reported in $\geq$ 5% of the RAL-treated subjects in BENCHMRK 1 included LDL$\geq$190 mg/dL (7.8% versus 6.4%), triglycerides >750 mg/dL (7.7% versus 2.5%), and alanine aminotransferase (ALT) $\geq$5.1 times ULN (6.5% versus 4.2%). In contrast, for BENCHMRK 2 such laboratory abnormalities were only seen at $\geq$5% of individuals for triglycerides >750 mg/dL (10.6% versus 7.6%) and creatine kinase > 10 times ULN (6% versus 4.2%).

2.1.2.4 Special Populations

RAL has a pregnancy category C rating.

2.1.3 Pharmacokinetic Compatibility of Lopinavir/ritonavir and Raltegravir

Data about potential pharmacokinetic interactions between LPV/r and RAL are available from healthy volunteer studies. In a PK study of 15 healthy volunteers RAL (400 mg twice-daily) and LPV/r (400/100 mg twice-daily) were given each as monotherapy followed by a combination of both drugs. The plasma concentrations of each drug were measured during monotherapy and while given in combination.

The LPV concentration was not influenced by the addition of RAL. However, RAL trough concentrations were 30% lower when LPV/r was given in combination (12 hour concentration of 49.4 ng/mL when given as monotherapy and 34.3.ng/mL when given in combination with LPV/r), but still above the estimated IC_{95} for wild-type virus of 15ng/mL. Additionally, elimination half-life of RAL was shortened from 5.9 hours when given as monotherapy to 3.6 hours when given in combination with LPV/r. In 12 out of 13 participants who completed the study, the trough level remained above the estimated 95% inhibitory concentration of RAL of 14.6 ng/mL. In one participant, the trough level was measured below the 95% inhibitory concentration of RAL. Of note, in part 1 of study 004 [7], RAL was given as one of four different doses (100mg, 200mg, 400mg, 600mg BID) as monotherapy to 35 patients for 10 days. All four arms had similar magnitudes of HIV viral decay, suggesting that RAL is sufficiently potent even at lower concentrations. The authors do not recommend any dose adjustment when using RAL in combination with LPV/r [11].

2.1.4 Atripla® (EFV/TDF/FTC)

Atripla® is fixed dose combination of EFV, TDF and FTC. Atripla® has been approved by the FDA in July 2006 for the treatment of HIV-1 infection in adults. Atripla® is one of the preferred NNRTI containing regimens for treatment-naïve HIV-infected patients in the DHHS HIV treatment guideline for adults and adolescents [1].

2.1.4.1 Efficacy

Several prospective clinical trials have demonstrated that EFV-based therapy is as effective or more effective than the drugs it has been compared with, including indinavir (IDV), nelfinavir (NFV), nevirapine (NVP), atazanavir (ATV), Trizivir® (fixed dose ZDV/3TC/ABC) [12-14]. For example, in a randomized, 48 week, open label study, in ARV–naïve HIV-1 Infected patients, more subjects randomized to efavirenz + AZT + 3TC had a HIV-1 RNA < 400copies/ml than subjects assigned to Indinavir + zidovudine + lamivudine (70% versus 48% ITT, $p<0.05$) or efavirenz + indinavir (70% versus 53% ITT, $p<0.05$) [14].

A randomized, double blinded study comparing EFV versus ATV, both combined with AZT and 3TC showed no differences in HIV-1 RNA levels

after 48 weeks (70% for ATV versus 64% for EFV) [12]. The ACTG 5095 study compared a triple NRTI regimen (ZDV +3TC+ ABC) versus two EFV based regimens (one in comniation ZDV+ 3TC and a second combination with ZDV+3TC+ABC) [13]. The EFV containing treatment groups had a much higher rate of HIV-1 viral suppression (61% for the triple NRTI arm and 89% for the combined EFV arms (p< <0.001). Twenty one percent of subjects in the triple NRTI arm failed this regimen which led to the discontinuation of this arm.

Study 934 is a phase III, randomized, open-label, multicenter study designed to compare EFV with either TDF 300 mg + FTC 200 mg QD or ZDV 300 mg + 3TC 150 mg BID as fixed-dose combination Combivir® [15]. After 144 weeks of treatment, 71% of subjects in the EFV + TDF + 3TC had HIV-1 viral load < 400 copies/mL in comparison to 58% of subjects in the EFV + ZDV + 3TC group (n=0.004 using the time to loss of virologic response algorithm). In general, resistance to an EFV-based regimen can developed within weeks when plasma HIV-1 RNA levels are not suppressed to below the assay limits of quantification. Mutation at codon 103 develops most often with the use of EFV which is associated with cross-resistance to many available NNRTIs.

2.1.4.2 CD4+ T-cell recovery

In the study 934, the mean increase of CD4 cell from baseline to week 144 was 312 cells/mL in the EFV/TDF/FTC group and 271 cell/mL in the efavirenz / combivir group. The mean CD4 cell increase was 176 cell/mm^3 versus 160 cell/mm^3 for ATZr versus EFV [12]and 201, 185, 180 cell/mm^3 for EFV + ZDV+3TC, EFV+ IDV and IDV + AZT+3TC [14].

2.1.4.3 Safety and Tolerability

The most common side effects of EFV are central nervous system (CNS) symptoms and rash. Fifty-three percent of subjects receiving EFV reported CNS symptoms, including but not limited to dizziness, impaired concentration, somnolence, abnormal dreams, and insomnia. Symptoms usually begin during the first or second day of therapy and generally resolve after 2 to 4 weeks of therapy. In clinical trials, 2.1% of EFV-treated subjects discontinued therapy because of CNS side effects. There have been reports (approximately 1 or 2 per thousand EFV-treated patients) of delusions and aberrant behavior, predominantly in those with a history of mental illness or substance abuse. Severe acute depression (including suicidal ideation/attempts) has also been infrequently reported in both EFV-treated (0.9%) and control-treated (0.5%) subjects. Subjects who experience these symptoms should contact their doctor immediately to assess the possibility that the symptoms may be related to EFV.

In controlled clinical trials, 26% (266/1008) of subjects treated with EFV 600 mg QD experienced new onset skin rash compared with 17% (111/635) of subjects treated in control groups (see the Sustiva® package insert). Rash associated with blistering, moist desquamation, or ulceration occurred in 0.9% (9/1008) of subjects treated with EFV. Among approximately 2200 treated subjects in all studies and expanded access, the incidence of Grade 4 rash (e.g., erythema multiforme and Stevens-Johnson syndrome) was 0.14%. The median time to onset of rash in adults was 11 days, and the median duration was 16 days. The discontinuation rate for rash in clinical trials was 1.7% (17/1008). EFV should be discontinued in subjects developing severe rash associated with blistering, desquamation, mucosal involvement, or fever; milder rashes often resolve with continued dosing, with antihistamines or transient corticosteroids given for symptomatic relief.

The most common adverse events in patients receiving TDF with other ARV therapy in clinical trials were mild to moderate gastrointestinal events, such as nausea, diarrhea, vomiting, and flatulence. Less than 1% of patients discontinued participation in the clinical studies because of gastrointestinal adverse events. Laboratory abnormalities observed in these studies occurred with similar frequency in the TDF and placebo-treated groups.

In rare cases, hypophosphatemia, proteinuria, glycosuria, and reduced creatinine clearance have been seen, and several cases of renal tubular injury have been reported. In a retrospective review, the rate of TDF discontinuation due to increased creatinine was evaluated in a review of a clinical database which included drug treatment, demographic, and laboratory data of 563 HIV-1-infected subjects who had been treated with TDF. Of these subjects, 11 (2%) had discontinued TDF due to elevated creatinine after a median of 4 months (range 2-9); of the 9 for whom renal biopsy was available, all showed evidence of acute tubular injury. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogues alone or in combination, including TDF, and other ARVs.

2.1.4.4 Drug Interactions and Special Populations

The U.S. FDA use-in-pregnancy category for EFV has been changed from Category C (Risk of Fetal Harm Cannot Be Ruled Out) to Category D (Positive Evidence of Fetal Risk). This change is a result of four retrospective reports of neural tube defects in infants born to women with first trimester exposure to EFV, including three cases of meningomyelocele and one of Dandy Walker syndrome. As EFV may cause fetal harm when administered during the first trimester to a pregnant woman, pregnancy should be avoided in women receiving EFV. Women of reproductive potential should be counseled on the possible risks associated with pregnancy. Women should be instructed not to breast-feed while taking

EFV. If a woman becomes pregnant while taking EFV during the first trimester of pregnancy, she should be apprised of the potential harm to the fetus.

For additional information concerning atripla, please refer to the Atripla™ U.S. package insert.

2.2 Rationale

2.2.1 Antiviral and Metabolic Outcomes

Raltegravir is an HIV-1 integrase inhibitor that has been shown to be efficacious, safe and well-tolerated [9, 10, 16, 17]. Studies of early viral decay kinetics, a surrogate measure of overall regimen potency and predictor of long-term viral suppression [18], demonstrate that RAL has viral decay rates that exceed those observed with PIs, NNRTIs or NRTIs [7]. In a dose-finding, comparative study of RAL (four dose arms: 100 mg to 600 mg daily) vs. EFV in combination with 2 NRTIs, a similar proportion of patients achieved plasma HIV-1 RNA less than 50 copies/mL at week 24 (RAL arms: 85 – 95% vs. EFV: 92%). These reductions in viral load persisted through 48 weeks of therapy with no significant difference in the long-term rates of viral suppression between the two arms. One explanation for these faster early viral decay rates is that already reverse transcribed pre-integration complexes can proceed through the replication cycle and generate RNA containing virions for the lifetime of the infected cell while RAL will block such complexes from integrating and generating RNA containing virions. Importantly, total cholesterol, low-density lipoprotein and triglyceride levels were relatively unchanged in the RAL groups. By contrast, all three of these lipid markers increased from baseline in the efavirenz subjects. Although large phase 3 trials comparing RAL- vs. EFV-based regimens in treatment-naïve patients are not yet available, preliminary data with 48 weeks of follow-up demonstrate a comparable degree of antiviral efficacy of RAL-based therapy compared with standard of care therapy with EFV-based regimens.

Comparisons between LPV/r- and EFV-based regimens have been less clear-cut. In one study, virologic response was similar between EFV and LPV/r [19], however a recent ACTG study, A5142 [20], demonstrated significantly better viral control rates with EFV-based regimens. A5142 is a prospective study that randomized 753 treatment-naïve patients to either an NRTI-containing regimen of LPV/r (400/100 mg twice-daily) or EFV (600 mg once-daily) combined with 3TC and a second NRTI, or a NRTI-sparing regimen of LPV/r (533/133 mg twice-daily) and EFV (600 mg once-daily) for 96 weeks. The EFV arm had a greater proportion of subjects with HIV RNA levels < 50 copies/ml than the LPV/r group (89% vs. 77%; P=0.003,

respectively). While median increases from baseline in total cholesterol were similar between nucleoside-containing regimens (33 mg/dL vs. 33 mg/dL), LPV/r-treated subjects had greater increases in triglycerides than those in the efavirenz arm (47 mg/dL vs. 14 mg/dL, $P \leq 0.01$). In contrast, EFV-treated subjects had a higher proportion of protocol-defined lipoatrophy than the LPV/r group (32% vs. 18%, $P \leq 0.01$) [21].

2.2.2 Immunologic Benefits

Suboptimal CD4+ T-cell recovery during antiretroviral therapy is a common clinical dilemma. Several studies have demonstrated greater CD4+ T-cell recovery during viral suppression in patients receiving LPV/r-based regimens compared to other combination therapies [12, 22-24]. Although A 5142 demonstrated that the EFV arm had a greater proportion of patients with plasma HIV RNA levels below 50 copies/mL, both LPV/r-containing treatment arms showed significantly higher absolute CD4+ T-cell gains after 96 weeks than patients receiving EFV (284 cells/mm^3 and 268 cells/mm^3 vs. 241 cells/mm^3; P=0.01) [24]. The mechanisms by which PI-based therapies may improve CD4+ T cell recovery are poorly understood. Interestingly, some PIs have been shown to inhibit lymphocyte apoptosis [25, 26]. Since CD4+ T-cell activation and apoptosis continues despite control of HIV-1 replication, PI-based regimens may improve T cell survival, and long term T-cell reconstitution. In addition, faster viral decay rates have been associated with more robust early CD4+ T-cell recovery [27]. Potentially, the addition of RAL may result in a more rapid viral clearance and consequently improved early CD4+ T-cell recovery than currently recommended EFV-based regimens.

2.2.3 Justification for an NRTI-sparing regimen

NRTIs in combination with PIs / NNRTIs have been the backbone of potent antiretroviral drug combinations since the introduction of HAART. However, NRTIs are associated with significant toxicity such as mitochondrial toxicity, lipoatrophy and others. Therefore, novel, NRTI-sparing and potent antiretroviral combinations are appealing. The feasibility using NRTI-sparing antiretroviral therapies has been demonstrated in the ACTG 5142 trial which compared LPV/r + EFV with EFV + NRTIs and LPV/r + NRTIs [28]. In this study, the NRTI-sparing arm was as effective as the EFV + NRTI arm and superior to the LPV/r + NRTI arm. However, a higher rate of laboratory abnormalities, especially elevated lipid levels, was reported in the LPV + EFV combination and limits its use.
RAL is a new and potent antiretroviral agent. Its ability to reduce HIV viral load is comparable to EFV with the additional benefit to decrease HIV RNA level faster to < 50 copies/mL than EFV [7]. In contrast to EFV, RAL showed no adverse effects on cholesterol and triglyceride lipids. Therefore, the combination of RAL + LPV/r is very appealing by providing a potent

NRTI sparing ARV regimen and with a lower risk of worsening blood lipid levels. Additionally, the high genetic barrier of LPV/r provides protection against mutations affecting RAL which has a low genetic barrier.

2.2.4 Hypotheses

1. The novel nucleoside-sparing combination of LPV/r + RAL will have a faster phase 1 viral decay rate compared to standard-of-care therapy with EFV/TDF/FTC in antiretroviral-naïve patients.

    a. Faster phase 1 viral decay dynamics will be associated with improved longer-term (week 48) viral suppression.
    b. Faster phase 1 viral decay dynamics will be associated with accelerated early (Day 0-14) clearance of cell-associated HIV DNA.
    c. Faster phase 1 viral decay dynamics will be associated with greater early (baseline to week 12) CD4+ T-cell recovery.

2. The LPV/r + RAL arm will have greater decreases in early (baseline to week 4) CD4/CD8 T-cell immune activation and apoptosis which will be associated with greater late (week 12 to week 48) CD4+ T-cell recovery.

3. Subjects treated with LPV/r + RAL arm will have smaller changes in total cholesterol and triglycerides from baseline than those receiving EFV/TDF/FTC.

3.0 STUDY DESIGN

CCTG 589 is a randomized, open-label, 48-week pilot study comparing the efficacy, safety and tolerability of RAL plus LPV/r to EFV/TDF/FTC in HIV-infected, treatment naïve subjects (defined as having never received any HIV antiretroviral agents in the past) with plasma HIV-1 RNA $\geq$5000 copies/mL and CD4+ T-cells $\geq$50 cells/mm^3 at or within 90 days of screening. Additional screening safety laboratories must be obtained within 30 days of study entry. Drug resistance testing is required prior to entry and can include any available test done prior to entry. Subjects will be ineligible if they have any evidence of drug resistant virus in the past or at the time of screening (if never previously tested). All resistance test results should be scanned and uploaded to the online data collection system for review and approval by the protocol team ant the site's investigator prior to enrollment. Those who are found to be eligible will be randomized 1:1 to initiate either LPV/r (400/100 mg) plus RAL (400mg), both given twice-daily, or fixed dose combination of EFV (600 mg), TDF (300 mg) and FTC (200 mg) given as once-daily Atripla® for 48 weeks. The study will provide LPV/r and RAL, however, Atripla® must be provided by prescription.

Eligible subjects will be HIV-1-infected, at least 18 years of age, treatment-naïve and have no evidence of drug resistant virus (per Inclusion Criteria, Section 4.1.) detected by any previous resistance test or at screening if not previously performed. Subjects must have CD4+ T-cell counts greater than or equal to 50 cells/mm^3 and screening plasma HIV-1 RNA greater than or equal to 5,000 copies/mL at or within 90 days of study screening.

Fifty subjects will be enrolled over approximately 48 weeks. Subjects will be stratified based upon screening plasma HIV-1 RNA (greater than or equal to or below 100,000 copies/mL) and will be followed for a total of 48 weeks. Subjects will have plasma HIV-1 RNA and CD4+ T-cell count measured at pre-entry and entry. The geometric and arithmetic means, respectively, of these measurements will be used to establish their baseline values. During the initial 2-week period, subjects will undergo intensive monitoring of viral decay dynamics with plasma HIV-1 RNA measured at baseline and days 2, 7, 10 and 14. Changes in CD4+ T-cells will be measured from baseline to week 12 (Phase 1) and week 12 to week 48 (Phase 2). In addition, extended immune phenotyping for activation, maturation and apoptosis markers will be measured on CD4+/CD8+ T-cells obtained from baseline, week 4 and week 24. From weeks 2 to 48, subjects will be monitored for treatment efficacy, including changes in CD4+ T-cells and plasma HIV-1 RNA levels, as well as for safety and tolerability with laboratories for hematology, chemistry, fasting lipids and a symptom questionnaire. Serial plasma and PBMCs will be stored for future studies. Genotypic drug resistance testing will be performed at screening (test not provided by study) if never performed in the past as well as at the time of virologic failure. Virologic failure will be defined as:

- Week 4:
  Confirmed failure to achieve ≤50 copies/ml or, if >50 copies/ml, a 1 $\log_{10}$ copies/ml reduction from the baseline level;

- Week 12:
  Confirmed failure to achieve ≤50 copies/ml or, if >50 copies/ml, a 2 $\log_{10}$ copies/ml reduction from baseline level;
  OR, if the Week 4 value is >50 copies/ml, confirmed rebound from the Week 4 value by >0.5 $\log_{10}$ copies/ml;
  OR, if the Week 4 value is ≤50 copies/ml, confirmed rebound to >50 copies/ml

- Week 24: Confirmed value >50 copies/ml.

Subjects who meet criteria for confirmed virologic failure will undergo real-time genotypic resistance testing (testing not provided by study) and an alternative regimen will be chosen by the site investigator with recommendations of the protocol team. Follow-up intervals will continue per study protocol, but the site investigator may schedule additional non-study, safety visits as necessary. The patient will be followed off study medication but on study for the remainder of the 48 weeks of study.

Adherence to all study drugs will be monitored by self-report as per the Schedule of Events. During the viral dynamics visits, all study medication dosing times and dates will be recorded by the study coordinator at each visit. All subjects should be provided adherence reinforcement throughout the study, according to local standard practice. Subjects who modify their study regimen or miss more than one-day dose of medication or miss more than one visit during the viral dynamics sequence (days 2, 7, 10 and 14) will need to be replaced. However, subjects who discontinue/ change study medication after day 14 will not need to be replaced. For all subjects discontinued from the study for any reason a premature discontinuation visit should done within 4 weeks (see section 6.2.3 and 6.2.4).

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, as documented by any licensed screening antibody test, such as ELISA, and confirmed by a second antibody test, such as Western blot, at any time prior to study entry. HIV-1 culture, HIV-1 antigen, two plasma HIV-1 RNA $\geq$ 2,000 copies/mL. HIV-1 infection can also be documented by two plasma HIV-1 RNA $\geq$ 2,000 copies/mL.

4.1.2 Treatment naïve (defined as having never received any HIV antiretroviral agents in past).

4.1.3 CD4+ T-cell count greater than or equal to 50 cells/mm^3 determined by site clinical laboratory at or within 90 days of screening.

NOTE: Obtained locally in a CLIA-certified laboratory.

4.1.4 Screening plasma HIV-1 RNA greater than or equal to 5,000 copies/mL determined by site clinical laboratory at or within 90 days of screening.

NOTE: Obtained locally in a CLIA-certified laboratory.

4.1.5 Laboratory values obtained by screening laboratories within 30 days of entry:

- Absolute neutrophil count (ANC) $\geq$ 750/mm^3.
- Hemoglobin $\geq$ 8.0 g/dL.
- Platelet count $\geq$ 50,000/mm^3.
- Calculated creatinine clearance (CrCl) $\geq$ 60 mL/min as estimated by the Cockcroft-Gault equation:
  * For men, (140 - age in years) x (body weight in kg) ÷ (serum creatinine in mg/dL x 72) = CrCl (mL/min)
  * For women, multiply the result by 0.85 = CrCl (mL/min)

- AST (SGOT), ALT (SGPT), and alkaline phosphatase ≤ 5 x ULN.
- Total bilirubin ≤ 2.5 x ULN.

4.1.7 Females of childbearing potential must have a negative serum pregnancy test at screening and agree to use a double-barrier method of contraception throughout the study period.

4.1.8 Karnofsky performance score ≥ 70.

4.1.9 Men and women age ≥ 18 years.

4.1.10 Ability to obtain prescription for HIV antiretroviral medications and to have required prescriptions filled prior to entry.

4.1.11 Ability and willingness of subject to give written informed consent.

4.2 Exclusion Criteria

4.2.1 Pregnancy or breast-feeding

4.2.2 Use of any of the prohibited medications (section 5.4.2) within 30 days of study entry.

4.2.3 Known hypersensitivity to any of the study drugs.

4.2.4 Serious illness requiring systemic treatment and/or hospitalization until subject either completes therapy or is clinically stable on therapy, in the opinion of the investigator, for at least 30 days prior to study entry (day 0).

4.2.5 Acute therapy for serious infection or other serious medical illnesses (in the judgment of the site investigator) requiring systemic treatment and/or hospitalization within 14 days prior to study entry (day 0).

4.2.6 Evidence of HIV seroconversion within 6 months prior to study entry.

4.2.7 Evidence of any major resistance-associated mutation on any genotype performed prior to study entry or at the time of screening. Resistance testing results must be available for review by the site investigator and study protocol team prior to enrollment to ensure that there are no exclusionary resistance mutations. All resistance testing results should be scanned and uploaded to the on-line data collecting system (https://cfar.ucsd.edu/intranet).

NOTE: Subjects will be excluded if genotype shows presence of any HIV-associated resistance mutations listed per the Internation AIDS

Society-USA mutation list (update lists can be found at: http://www.iasusa.org).

4.2.8 History of chronic hepatitis C (defined as HCV antibody positive and HCV RNA detectable).

4.2.9 History of chronic active hepatitis B (defined as surface antigen positive and/or HBV DNA detectable).

4.2.10 Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.

4.2.11 Use of any immunomodulator, HIV vaccine, or investigational therapy within 30 days of study entry.

4.2.12 Use of human growth hormone within 30 days prior to study entry.

4.2.13 Initiation of testosterone or anabolic steroids within 30 days prior to study entry. (Exception: Chronic replacement dosages in patient's with diagnosed hypogonadism is allowed).

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, sites must have the protocol and consent form approved by their local institutional review board (IRB). Sites must be registered with and approved by the CCTG Data and Biostatistical Unit. Site registration must occur before any subjects can be enrolled in this study.

Once a candidate for study entry has been identified, details will be carefully discussed with the subject. The subject will be asked to read and sign the consent form that was approved by both the local IRB and the CCTG Data Center.

4.3.2 A patient identification number (PID) will be assigned to each patient screened for the study. PIDs will include a site code and three-digit extension. PIDs should not be reassigned even if the patient fails to enter the study. The PID must be included on every CRF and patient blood sample. Each site must maintain a master list of PIDs in a central location. The patient registration and inclusion/exclusion CRF must be completed on the online system (https://cfar.ucsd.edu/intranet).

4.4 Co-enrollment Guidelines

Co-enrollment in this study and other studies will be discussed with the protocol team and will be decided on a case by case basis.

5.0 STUDY TREATMENT

Study medications include

- Raltegravir (Isentress®)
- Lopinavir/ritonavir (Kaletra®)
- Efavirenz / Tenofovir / Emtricitabine (Atripla®).

5.1 Dosing, Administration, and Duration

5.1.1 Dosing

5.1.1.1 Raltegravir (Isentress®):

Each tablet contains 400 mg of RAL and will be administered twice a day, with or without food.

5.1.1.2 Lopinavir/ritonavir (Kaletra®): co-formulated tablet.

Each tablet contain 200 mg of LPV and 50 mg RTV. LPV/RTV will be dosed 400mg of LPV and 100mg RTV twice daily (two Kaletra® tablets twice a day). Kaletra needs to be administered with food.

5.1.1.3 Efavirenz / tenofovir disoproxil fumarate/ emtricitabine (Atripla®): co-formulated tablet.

Each tablet contain 600mg of EFV, 300mg of TDF and 200mg of FTC. Atripla® will be dose one tablet once a day without food.

5.1.2 Administration

At study entry, subjects will be randomized 1:1 to one of two treatment arms:

- LPV 400mg/RTV 100mg + RAL 400mg twice-daily
- Atripla® (EFV 600mg + TDF 300mg + FTC 200mg) once-daily.

5.1.3 Duration

Subjects will receive study treatment for 48 weeks.

5.2 Product Formulation and Preparation

5.2.1 Isentress® tablets should be stored at room temperature (25^0C / 77^0F). Do not store above 30^0C / 86^0F and protect from moisture.

5.2.2 Kaletra® film coated tablets should be stored at 20-25°C (69-77°F), excursion permitted to 15-30°C (59-86°F.)

5.2.3 Atripla® should be stored at 25^0C (77^0F), excursion permitted to 15-30^0C (59-86^0F).

5.3 Product Supply, Distribution, and Pharmacy

5.3.1 Study Product Acquisition

Study medication Isentress® will be provided by Merck and Kaletra® will be provided by Abbott Laboratories.
Atripla™ will not be supplied by the study, but will be made available to patients via prescription at cost to the patient and/or patient's health insurance.

5.3.2 Investigational Agent Accountability

The clinical site pharmacist is required to maintain complete records of all study products received from this study. All unused LPV/r and RAL products must be returned to the sponsors after the study is completed or terminated.

5.4 Concomitant Medications

5.4.1 Required Medications

5.4.1.1 Study medications (RAL + LPV/r or EFV/TDF/FTC).

5.4.1.2 PCP prophylaxis for CD4+ T-cells <200 cells/mm^3 is strongly recommended.

5.4.2 Prohibited Medications

5.4.2.1 All investigational drugs.

5.4.2.2 All HIV vaccines

5.4.2.3 Any immunomodulators

5.4.2.4 Systemic cytotoxic chemotherapy

5.4.2.5 All herbal products should be avoided because of the unknown drug interactions between herbal products and the antiretroviral drugs used in this study.

5.4.2.6 All of the following systemic drugs:

Table 1: Prohibited with LPV/r:

Agent by Class	**Agents**
Alternative/Complementary	St. John's wort *(Hypericum perforatum*)
Antiarrhythmics	Amiodarone
	Bepridil (Bepadin, Vascor™)
	Flecainide (Tambocor™)
	Propafenone (Rythmol®)
	Quinidine
Antihistamines	Astemizole (Hismanal™)
	Terfenadine (Seldane™)
Anti-infectives	Rifampin (Rifadin®, Rimactane®, Rifamate®, Rifater®)
	Voriconazole (Vfend™)
GI Motility	Cisapride (Propulsid™)
HMG Co Reductase Inhibitors	Lovastatin (Mevacor®)
	Simvastatin (Zocor ®)
Sedative/hypnotics	Midazolam (Versed®)
	Triazolam (Halcion®)
Other	Alfuzosin
	Dihydroergotamine (Migranal® and others)
	Ergonovine

Table 2: Prohibited with RAL:

Agent by Class	**Agents**
Anticonvulsants	Dilantin
	Phenobarbitol
Anti-infectives	Rifampin

Table 3: Prohibited with Atripla® (EFV / TDF / FTC)

Agent by Class	**Agents**
Alternative / Complementary	St. John's wort *(Hypericum perforatum*)
Antihistamines	Astemizole (Hismanal™)
	Terfenadine (Seldane™)
Anti-infectives	Voriconazole (Vfend™)
GI Motility	Cisapride (Propulsid™)
Sedative/hypnotics	Midazolam (Versed®)
	Triazolam (Halcion®)
Other	Dihydroergotamine (Migranal®) and others)
	Ergonovine
	Ergotamine
	Methylergonovine

5.4.1 Precautionary Medications

NOTE: Refer to the individual package inserts for additional information regarding potential drug interactions that may require therapeutic drug monitoring and/or adjustment of concomitant medications. Competition for primary CYP3A metabolism or other mechanisms by study drugs could result in inhibition or stimulation of the metabolism of these drugs and create the potential for serious and/or life-threatening reactions such as cardiac arrhythmias, prolonged or increased sedation, and respiratory depression.

Table 4: Precautionary Medications with LPV/r:

Agent by Class	**Agents**
Analgesics	Methadone / Propoxyphene (Darvon and others™) / Tramadol (Ultram®)
Antiarrhythmics	Disopyramide (Norpace™) / Lidocaine (systemic) (Xylocaine™) / Mexilitine (Mexitil™)

Agent by Class	Agents
Anticonvulsants	Carbamazepine (Tegretol™) / Lamotrigine (Lamictal™) / Phenobarbitol/ Phenytoin (Dilantin™) / Valproic Acid
Antacids, H2 blockers, Proton Pump Inhibitor	Cimetidine (Tagamet) / Famotidine (Pepcid) / Nizatidine (Axid) / Ranitidine (Zantac)
Anti-infectives	Atovaquone (Meprone®) / Caspofungin (Cancidas™) / Clindamycin (Cleocin™) / Clarithromycin (Biaxin®) / Miconazole (Monistat ™) / Rifabutin (requires dose reduction)
Anti migraine Agents	Eleptriptan / Zolmitriptan
Beta Blockers	Alprenlol / Atenolol / Bisoprolol \ (Zebeta™) / Carvedilol (Coreg ™) / Esmolol (Brevibloc ™) / Labetolol (Normodyne ™) / Metoprolol (Lopressor™ / Toprol™) / Pindolol Visken ™) / Propanolol (Inderal ™) / Timolol (Bocadren ™)
Calcium Channel Blockers	Amlodipine (Norvasc ™) / Aranidipine Cilnidipine / Diltiazem / Felodipine (Plendil ™) / Isradipime (Lacipil ™) / Lacidipine (Lacipil ™) / Lercandipine / Manidipine / Nicardipine (Cardene ™) / Nifedipine / Nivadipine / Nimodipine (Nimotop ™) / Nisoldipine (Sular ™) / Nitrendipine (Nitrendipine ™) / Verapamil
Chemotherapeutic Agnets	Cyclophosphamide / Irinotecan Ifosfamide / Etoposide
Hormonal Agents	Estrogens / Progesterones / Glucocorticoids
Hypoglycemics	Pioglitazone (Actos ™)

Agent by Class	Agents
HMG Co Reductase Inhibitors	Atorvastatin (Lipitor®)
Psychiatric Medications	Clozapine (Clozaril TM) / Buproprion (Wellbutrin, Zyban TM) / Fluoxetine / Paroxetine (Paxil TM) / Risperidone (Risperdal TM) / Venlafexine (Effexor TM) / Nefazadone (Serzone TM)
Tricyclic antidepressants	Amitripyiline / Desipramine / Imipramine/ Nortriptyline
Sedative/hypnotics	Alprazolam (Xanax TM) / Diazepam (Valium TM) / Estolam (ProSom TM) / Clorazepate / Flurazepam (Dalmane TM) / Oxazepam (Seraz TM) / Temazepam (RestorilTM) / Buspirone (BusparTM), Trazodone, Zalpeplon (SonataTM), Zolpedim (AmbienTM)
Other	Cyclosporine A / Digoxin / Rapamycin / Tacrolimus

Table 5: Precautionary Medications with Atripla® (EFV / TDF / FTC)

Agent by Class	Agents
Alternative/Complementary	Milk Thistle (Silymarin, Silybum, marianum)
Anti-convulsants	Carbamazepine (TegretolTM) / Phenytoin (DilantinTM) / Phenobarbitol
Anti-infectives	Caspofungin (CancidasTM) / Clarithromycin (Biaxin TM) / Itraconazole (Sporonox TM) / Ketoconazole / Rifampin and Rifabutin / Quinupristin/Dalfopristin (Synercid TM)
Antimigraine	Eletriptan (Relpax)

Agent by Class	Agents
HMG Co Reductase Inhibitors	Lovastatin (Mevacor®) / Simvastatin (Zocor ®)
Hypoglycemics	Pioglitazone (Actos™)
Sedative/hypnotics	Alprazolam (Xanax ™) / Diazepam (Valium ™) / Estazolam (ProSom ™) / Flurazepam (Dalmane ™) / Oxazepam (Serax ™) / Temazepam (Restoril ™) / Lorazepam (Ativan ™) / Buspirone (BuSpar ™) / Zaleplon (Sonata ™) / Zolpidem (Ambien ™)
Other	Warfarin
	Nephrotoxic agents such as amphotericinB, aminoglycosides, cidofovir, acyclovir, ganciclovir, vancomycin
	Methadone
	Sildenafil / Vardenafil / Tadalafil
	Sertraline
	Anyacids / H2-blockers / Proton Pump Inhibitors

NOTES: Drugs without trade names either have many marketed forms,

- or are not available in the US. Web-based information is available at: http://www.hiv-druginteractions.org/drug/pdf/pi_col.pdf

5.5 Adherence Assessment

Throughout the study, the documentation of adherence to study drugs and concomitant HIV medications is essential. During the viral dynamics visits an adherence diary will be completed by study personal that will include the date and time all study medications were taken. Afterwards a separate adherence questionnaire will be completed during each study visit at weeks 2, 8, 12, 24, 36 and 48.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events – Clinical Evaluations

	Screen	Pre Entry	Viral Dynamics					Follow-up							
	Within 30 days of entry		Day 0 (Entry)	Day 2 ±1 day	Day 7 ±1 day	Day 10 ±1 day	Day 14 ±1 day	Week 4 ±1 wk	Week 8 ±1 wk	Week 12 ±1 wk	Week 16 ±1 wk	Week 24 ±2 wk	Week 36 ±2 wk	Week 48 ±2 wk	Virologic Failure, Tox or Premature D/C
Informed Consent	X														
§ Documentation of prior HIV drug resistance testing	X														
Medical/Medication History	X														
Documentation of HIV	X														
Clinical Assessment / AE			X				X	X	X	X	X	X	X	X	X
Complete Physical Exam			X												
Targeted Physical Exam								X	X	X	X	X	X	X	X
Start Drug/ Dispense Drug			X					X	X	X	X	X	X	X	
Complete Adherence Diary or Questionnaire				X	X	X	X	X		X		X		X	X

§ Resistance testing results obtained anytime in the past is acceptable. If not available, then resistance testing should be done at screening (test not provided by study). Subject must have no evidence of major HIV drug-associated mutations to be eligible for the study (see Exclusion Criteria section 4.2.7).

Schedule of Events – Laboratory Evaluations

	Screen	Pre Entry	Viral Dynamics					Follow-up							
	Within 30 days of entry		Day 0 (Entry)	Day 2 ±1 day	Day 7 ±1 day	Day 10 ±1 day	Day 14 ±1 day	Week 4 ±1 wk	Week 8 ±1 wk	Week 12 ±1 wk	Week 16 ±1 wk	Week 24 ±2 wk	Week 36 ±2 wk	Week 48 ±2 wk	Virologic Failure, Tox or Premature D/C
Hematology (local lab)	X		X					X		X		X	X	X	X
Chem / LFT (local lab)	X		X					X		X		X	X	X	X
Fasting Lipids (local lab)			X					X				X		X	
Pregnancy test (local lab)	X		X and whenever suspected												
Immunology: CD4+/CD8+		X	X					X	X	X		X	X	X	X
§ CD4 ≥50 cells/mm^3	X														
§ HIV RNA ≥5000 cells/mL	X														
ΨHIV-1 RNA (local lab)								X	X	X	X	X	X	X	X
ΨHIV-1 RNA load (UCSD lab)		X	X	X	X	X	X								
†Extended flow cytometry			X					X				X			
† Proviral HIV DNA		X	X	X	X		X	X				X		X	
† PBMCs collection			X					X				X		X	
Ψ Plasma for storage		X	X	X	X	X	X	X	X	X		X		X	X
† Ambient ship to UCSD		X	X	X	X		X	X				X		X	
Ψ Dry-ice ship to UCSD							X							X	X

§ If available within 90 days of screen then do not need to repeat laboratory test and can use value obtained within 90 days as screen value

Ψ Plasma for HIV RNA loads for the viral decay dynamics (pre-entry to day 14) needs to be stored and shipped in batch to UCSD on day 14. Thereafter, all subsequent HIV RNA loads need to be done at the site's local lab and stored plasma can be shipped in batch after the subject completes week 48 or at time of premature study discontinuation.

† Samples for extended flow cytometry, proviral HIV DNA and PBMCs do not require local lab processing. All samples should be shipped immediately after collection with an ambient overnight to UCSD.

6.2 Definitions for Schedule of Events – Timing of Evaluations

6.2.1 Pre-Entry Evaluations

Occur prior to the subject taking any study medications, treatments, or interventions.

Patient Registration

A patient identification number (PID) will be assigned to each patient screened for the study. PIDs will include a site code and three-digit extension. PIDs should not be reassigned even if the patient fails to enter the study. The PID must be included on every case report form (CRF) and patient blood sample. Each site must maintain a master list of PIDs in a central location. The patient registration and inclusion/exclusion CRF must be completed on the online system (https://cfar.ucsd.edu/intranet).

Screening Site Clinical Labs

If plasma HIV-1 RNA and CD4+ T-cell counts were obtained at a CLIA-approved lab no more than 90 days prior to screening and results are available then these labs do not need to be repeated. Otherwise, a plasma HIV-1 RNA level and a CD4 cell count measurement need to be done at screening. Please record actual dates laboratories were done in the CRF.

All other study screening laboratories must be determined within 30 days of study entry (Day 0). Screening and entry evaluations must be separated by at least 48 hours. Hematology, chemistry and pregnancy testing will be coordinated through the site's local laboratory and results will be tracked by the CCTG Data Center.

Once the screening laboratories have been done the patient will be evaluated for study eligibility if all other entry criteria are satisfied.

The total blood volume for screening labs is 10 mL.

If the HIV RNA or other laboratory values are outside the eligible range, the site may re-screen a patient on one occasion. However, the study will not pay for additional re-screening laboratories.

Pre-Entry

Specimens for proviral HIV DNA need to be shipped by each site in real-time to the central laboratory (UCSD).

Plasma HIV-1 RNA and CD4+ T-cell counts should be obtained at the Pre-Entry visit. The CD4 cell count should be done at the site's local laboratory in real-time. However, the plasma for the HIV-1 RNA should be collected, stored then shipped in batch at Day 14 of study along with other phase 1 viral dynamic specimens.

The total blood volume for pre-entry labs is 30 mL.

Randomization

The screen HIV RNA value will be used to stratify the patient (at or above versus below 100,000 copies/mL) prior to randomization.

If the subject is randomized to the Atripla® arm, then this subject should be contacted and supplied with a prescription for Atripla®. Please remind the subject to fill medication as soon as possible and he/she must present with medication in hand on day of study entry. **The entry visit for all subjects should occur within 7 days of randomization.**

Entry

The entry evaluation should be scheduled within 30 days of the screening visit. The randomization should be completed and a 30-day supply of treatment medication should be provided. If the subject is randomized to the LPV/r arm, then study medications will be supplied by the study and dispensed by the site's pharmacy on day of entry. However, if the subject is randomized to the EFV/TDF/FTC arm, then a prescription must be provided prior to entry and the subject must present with medications in hand on day of entry. The first dose of LPV/r + RAL study medication should be given and witnessed by the study coordinator **after** drawing the baseline laboratories. The first dose of EFV/TDF/FTC should be taken the evening of study entry as a non-witnessed dose. A 14-day adherence diary should be completed by study personal during the viral dynamics sequence.

6.2.2 On-Study Evaluations

Evaluations should be counted from entry (Day 0). **Start dates for the viral decay sequence can occur on Monday thru Wednesday. Viral dynamic visits should occur on days 2, 7, 10 and 14 or within a visit window of ± 1 day. Since blood for proviral HIV DNA needs to be shipped in real-time for all visits (except day 10) viral dynamic visits should be planned in ahead to occur only from Monday to Thursday – avoiding Fridays.** Thereafter, while on follow-up phase of the therapy, study evaluations will occur on weeks 4 (± 1 week), 8 (± 1 week), 12 (± 1 week), 16 (± 1 week), 24 (± 2week), 36 (± 2 week) and 48 (± 2 week). In instances of virologic failure

and/or premature treatment discontinuation evaluations would also need to occur within 4 weeks.

Total blood volume for laboratory evaluations for viral dynamics sequence (entry to day 14) will be approximately 167 mL.

Total blood volume for laboratory evaluations for follow-up phase (week 4 to week 48) will be approximately 266 mL.

6.2.3 Evaluations and plan for randomized or registered subjects that do not complete the viral dynamics portion of the study:

a. Those subjects that do not start treatment will be replaced and will have no follow-up evaluations performed.

b. Subjects on the viral dynamics (entry to Day 14) portion of the study that discontinue antiretroviral therapy before end of Day 14 will be replaced and will have no follow-up evaluations performed.

c. Subjects on the viral dynamics (entry to Day 14) portion of the study that miss more than one scheduled visit or 1-day equivalent of study medication will be replaced and followed on study but will not have proviral HIV DNA, extended flow cytometry or PBMC collected for storage.

6.2.4 Evaluations and plan for subjects that complete the viral dynamics but not the remainder of the study

a. Subjects who complete the viral dynamics portion of the study but then discontinue their antiretroviral regimen while on the follow-up portion of the study (weeks 2 to 48) will not be replaced and will be followed per protocol but will not have proviral HIV DNA, extended flow cytometry or PBMC collected for storage.

b. Subjects that prematurely stop antiretroviral medications after the viral dynamics portion of the study and do not want to continue on study will not be replaced and a Premature Treatment Discontinuation vist (see Section 6.1) should occur within 4 weeks.

6.2.5 Change in Antiretroviral Regimen

Subjects who change their treatment regimen for any reason, should continue to be followed until the completion of the study. However, they will not have proviral HIV DNA, extended flow cytometry, PBMC collection for storage.

If the regimen change is due to toxicity, then the subject would be followed per criteria of a Change of Therapy Due to Toxicity visit (section 6.1).

If the regimen change is due to virologic failure, then the subject would be evaluated per criteria for Virologic Failure visit (section 6.1).

6.2.6 Virologic Failure

Virologic failure will be defined as:

- Week 4:

Confirmed failure to achieve ≤50 copies/ml or, if >50 copies/ml, a 1 $\log_{10}$ copies/ml reduction from the baseline level;

- Week 12:

Confirmed failure to achieve ≤50 copies/ml or, if >50 copies/ml, a 2 $\log_{10}$ copies/ml reduction from baseline level;
OR, if the Week 4 value is >50 copies/ml, confirmed rebound from the Week 4 value by >0.5 $\log_{10}$ copies/ml;
OR, if the Week 4 value is ≤50 copies/ml, confirmed rebound to >50 copies/ml

- Week 24: Confirmed value >50 copies/ml.

Confirmatory plasma HIV-1 RNA test must be performed within 4 weeks of the initial HIV-1 RNA sample with suspected virologic failure. Subjects who meet criteria for confirmed virologic failure will undergo real-time genotypic resistance testing (testing not provided by study) and an alternative regimen will be chosen by the site investigator with recommendations of the protocol team. Follow-up intervals will continue per study protocol, but the site investigator may schedule additional non-study, safety visits as necessary. The patient will be followed off study medication but on study for the remainder of the 48 weeks of study.

6.2.7 Post-Treatment Evaluations

All randomized subjects who complete the study will complete the week 48 End of Study Visit.

6.2.8 Premature Treatment Discontinuation

These evaluations are required at the subject's final visit.

6.2.9 Pregnancy

Women who become pregnant during the study will be required to permanently discontinue their study regimens and will not continue to be followed on study. They should be advised to seek best available medical care for their pregnancy according to US PH Guidelines.

6.3 Special Instructions and Definitions of Evaluations

6.3.1 Documentation of HIV

HIV-1 infection, as documented by any licensed screening antibody test, such as ELISA, and confirmed by a second antibody test, such as Western blot, at any time prior to study entry. HIV-1 culture, HIV-1 antigen, two plasma HIV-1 RNA $\geq$ 2,000 copies/mL. HIV-1 infection can also be documented by two plasma HIV-1 RNA $\geq$ 2,000 copies/mL.

6.3.2 HIV Drug Resistance Testing

All subjects must have resistance testing (genotype) obtained from any laboratory and made available for review by the protocol team and site investigator **prior to** randomization. Obtaining resistance testing for patients with HIV infection is part of standard medical care according to current guidelines. If a historic resistance test is not available at the time of screening then resistance testing will need to be done at screening. However, the study will not provide the resistance assay. Resistance testing results should be scanned and uploaded to the on-line data collecting system (https://cfar.ucsd.edu/intranet).

6.3.3 Medical and Laboratory History

At screening, a medical history will be obtained and must be recorded in the source documents. The medical history should include any previous HIV-related diagnoses and AIDS-defining events.

In addition, prior to obtaining screening laboratories, documentation of plasma HIV-1 RNA load $\geq$ 5000 copies/mL and CD4+ T-cell counts $\geq$ 50 cells/mL must be recorded in the source documents.

6.3.4 Medication History

At screening, a medication history (**only if within last 30 days prior to entry**) with actual or estimated start and stop dates should be obtained and recorded in the source documents and the concomitant medication CRF, including:

All prescription medications. Including medications taken for the treatment or prophylaxis of opportunistic infections.

Non-prescription medications.

Alternative therapies and/or dietary supplements.

Allergies to any medications and their formulations must be documented.

6.3.5 Concomitant Medications

During study visits (See section 6.1 for specific dates) all concomitant medications taken since the last visit will be recorded in the source documentation and entered into the concomitant medication log CRF.

6.3.6 Study Treatment Modifications

All modifications to study drug(s) including initial doses, patient-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation of HIV antiretrovirals need be recorded on the CRFs at each visit.

6.3.7 Clinical Assessments

Complete Physical Exam

A complete physical examination will be performed at entry. Documentation must include a complete review of systems.

Targeted Physical Exam

A targeted physical examination will be based on any signs or symptoms previously identified that the subject has experienced within 30 days of entry or since the last visit. This examination will be performed at weeks 4, 8, 12, 16, 24, 36 and 48 of therapy and in instances of virologic failure/toxicity or premature treatment discontinuation if they should occur.

Height and Weight

Height and weight should be measured at study entry.

Signs and Symptoms

All signs, symptoms, deaths, and toxicities must be documented in the subject's record. At entry, record all signs/symptoms experienced within 30 days of entry on the CRFs. For all other visits and at the time of confirmation

of virologic failure, record all Grade ≥ 2 signs and symptoms, HIV-related and AIDS-defining events and deaths on the CRFs that have occurred since the last visit. Any signs or symptoms that lead to a change in treatment, regardless of Grade, must be recorded on the CRF. The source document must include date of onset and date of resolution, but the CRF will only record prevalence of a given adverse event since the previous study visit.

Refer to the Division of AIDS Table for Grading Adult Adverse Experiences, which can be found on the CCTG website: www.cctg.ucsd.edu

Diagnoses

The following should be recorded on the CRFs: HIV-related diagnoses, malignancies, AIDS-defining events and death. Any other diagnosis that is, in the opinion of the site investigator, associated with study medications, should be recorded on the adverse event CRF. The source document must include date of diagnosis and date of resolution.

Karnofsky Performance Status

A Karnofsky performance status must be completed within 30 days before study entry.

Vital Signs

Temperature, pulse, and blood pressure collected at all visits and kept as a part of the source document.

6.3.8 Laboratory Evaluations

For all visits record all Grade ≥ 2 laboratory values on the CRFs throughout the course of the study. All values, regardless of toxicity, of specific laboratories will also be recorded on the laboratory CRF; including: wbc, neutrophil count, hemoglobin, platelets, blood urea nitrogen, creatinine, glucose, AST/ALT, alkaline phosphatase, total bilirubin, total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides.

Any laboratory toxicities that lead to a change in treatment, regardless of Grade, must be recorded on the adverse event CRF.

Refer to the Division of AIDS Table for Grading Adult Adverse Experiences, which can be found on the CCTG website: www.cctg.ucsd.edu

Hematology:

Hemoglobin, hematocrit, white blood cell count (WBC), differential WBC, absolute neutrophil count (ANC), and platelet count will be performed in real time at the site's local laboratory.

Blood volume: 3 mL

Liver & Kidney Function Tests

Total bilirubin, AST (SGOT), ALT (SGPT), and alkaline phosphatase, BUN, creatinine and electrolytes (sodium, potassium, chloride, and bicarbonate) will be performed in real time at the site's local laboratory.

Estimated creatinine clearance should be calculated each time a creatinine level is determined. To estimate creatinine clearance, use the following method of Cockcroft and Gault:

For men: [(140 - age in years) x (body weight in kg)] ÷ (serum creatinine in mg/dL x 72).

For women: use the same calculation as for men, then multiply the result by 0.85.

A calculator is available at the Data Management Center Web site at https://www.fstrf.org/ACTG/.

Blood volume: 7 mL

Fasting Lipid Profile

Total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides will be performed in real time at the site's local laboratory.

Blood volume: 7 mL

Pregnancy Test

For women with reproductive potential: Urine β-HCG (urine test must have a sensitivity of $\leq$ 50 mIU/mL) should be done at the site's local laboratory during screening, at study entry and whenever clinically suspected.

5 ml urine

6.3.9 Immunologic Studies

Nadir CD4+ T-cell count

The subject's prior nadir CD4+ T-cell count (absolute value and date) should be documented during screening and, when possible, a copy of the nadir CD4+ T-cell count report should be included in the source document. If this documentation is not available, then subject recollection will suffice. For subjects who do not know the exact nadir value and for whom there is no source documentation, then recall of the categorical nadir (e.g., <50, <100, <200 cells/mm^3) will suffice.

CD4/CD8

All CD4/CD8 count and percentages must be performed at the site's local laboratory prior to study entry. Pre-entry and entry measurements must be obtained at two separate time points at least 48 hours apart. The mean of the pre-entry and entry measurements will be used as the baseline value. See section 6.1 for specific collection dates.

Because of the diurnal variation in CD4+ and CD8+ T-cell counts; all determinations should be obtained consistently in either the morning or the afternoon throughout the study, if possible.

Blood volume: 5 mL

Extended Flow Cytometry Markers

Extended flow markers for activation, maturation, apoptosis and regulatory function will be evaluated on CD4+/CD8+ T-cells. Samples will be collected at entry and on weeks 4 and 24. These analyses will be done on fresh samples in real-time. **Specimens will need to be shipped ambient, overnight and in real-time to the UCSD central laboratory**.

Blood volume: 10 mL

6.3.10Virologic Studies

Proviral HIV-1 DNA

Whole blood for proviral HIV-1 DNA quantitation should be collected at Pre-Entry and during the Viral Dynamic Sequence [Day 0, 2, 7 and 14 (**except** Day 10)] and at weeks 4, 24 and 48. Specimens should be shipped immediately after collection to the **central lab (UCSD).**

Blood volume: 10 mL

Plasma HIV-1 RNA

Pre-entry HIV-1 RNA must be collected and stored prior to study entry then shipped in batch on Day 14 to the central lab (UCSD). Pre-entry and entry measurements must be obtained at two separate time points at least 48 hours apart. The mean of the pre-entry and entry measurements will be used as the baseline value. See section 6.1 for specific collection dates.

Plasma HIV-1 RNA during the Viral Dynamic Sequence should be collected at every study visit (Day 0, 2, 7, 10 and 14) and stored until shipped in batch to the **central lab (UCSD)** after completion of the viral decay dynamics (Day 14). Afterwards, during the follow-up phase of the study, the HIV RNA load should be determined at the **site's local laboratory** at weeks 4, 8, 12, 16, 24, 36 and 48.

Genotype Resistance Assay

If a historic genotype resistance test is not available at screen, a baseline genotype test should be done at screening (this test will not be provided by the study). In addition, samples for genotypic analysis obtained at the time of virologic failure should be done in real time a the local laboratory for subject management by the site's investigator (this test will not be provided by the study). All resistance testing results should be scanned and uploaded on the on-line data collection system for review by the protocol team (https://cfar.ucsd.edu/intranet).

Stored Plasma

Stored Plasma will be collected at screening, study entry, all visits of the viral dynamics sequence and during weeks 4, 8, 12, 24 and 48.

* Specimens obtained during pre-entry, entry and viral dynamics will be stored at the site's local laboratory and batched shipped to the central laboratory (UCSD) after completion of the viral dynamics sequence.

** Specimens obtained at weeks 4, 8, 12, 24 and 48 will be stored at the site's local laboratory and batched shipped to the central laboratory (UCSD) after completion of week 48 or upon premature discontinuation from study.

Blood volume for combined HIV RNA and stored plasma: 15 mL
Blood volume for HIV RNA: 5 mL

6.3.11 PBMCs for storage

Blood for PBMCs will be collected in and **shipped ambient, overnight and in real-time to the central laboratory (UCSD)** at entry and weeks 4, 24 and 48.

Blood volume: 10 mL

6.3.12 Adherence Questionnaires

Medication diaries will be conducted by study personal during the viral dynamics sequence. Dosing dates and exact times of study medications will need to be recorded. Afterwards, on the follow-up portion of the study, adherence questionnaires (standard ACTG style questionnaires) will be conducted on weeks 4, 8, 12, 16, 24, 36 and 48 of therapy and in instances of virologic failure and/or premature treatment discontinuation.

6.4 Off-Drug Requirements

Additional safety monitoring and reporting of serious adverse experiences (SAEs) continues to be required upon completion or discontinuation of study treatment regardless of whether a protocol follow-up period is scheduled to occur. Adverse experiences occurring during the immediate 8-week period after the last dose of study treatment which meet SAE reporting requirements must be reported to the **CCTG Data Center**. Additionally, after 8 weeks OFF study treatment, there are four types of events that must be reported to the **CCTG Data Center** if the relationship to the study drug is assessed by the site physician as definitely, possibly, or unable to judge: DEATHS, NEW ONSET CANCERS, CONGENITAL ANOMALIES, AND PERMANENT DISABILITIES.

7.0 TOXICITY MANAGEMENT

Only toxicities related to study medications (LPV/r, RAL, TDF, 3TC and EFV) will be considered in the toxicity management section. The management of these medication related toxicities should be undertaken by the local investigators, with guidance available from the protocol team, protocol pharmacist and pharmaceutical sponsor, to insure the optimal safety and efficacy for the individual subject.

Toxicity resulting from any non-study medications (other than study medications as listed above) should be managed per standard of care. The grading system is located in the Division of AIDS Table for Grading Adult Adverse Experiences, which can be found on the Division of AIDS Regulatory Compliance Center Web Site: http://rcc.tech-res-intl.com.

NOTE: The study Co-chairs and the study protocol team need to be notified by e-mail regarding any toxicities that result in a change in regimen. In case an EFV containing regimen needs to be discontinued, consideration should be given to

discontinue EFV prior to stopping the other components of the antiretroviral regimen. Simultaneous discontinuation of an EFV containing regimen leads to de facto EFV mono-therapy due to difference of half lives between EFV and other ARV drugs.

7.1 Grade 1 or 2

Subjects who develop a Grade 1 or 2 adverse event or toxicity may continue study drugs without alteration of the dosage, except for Grade ≥ 2 creatinine elevation in subjects receiving TDF (component of Atripla®). Those subjects experiencing Grades 1 or 2 adverse events which results in discontinuation of, or substitution, for any of the study drugs should be reported to the protocol team.

7.2 Grade 3

Management of Grade 3 toxicities should be discussed with the protocol team via email. Please refer to the subsequent sections for management of specific events.

Subjects who develop a Grade 3 adverse event or toxicity judged to be study drug-related should have all medications held or have the toxicity causative study drug switched to an alternative drug. In the event that the regimen is held, that subject should be re-evaluated weekly until the adverse event returns to Grade ≤ 2, at which time the study drugs may be reintroduced at the discretion of the investigator or according to standard practice. Subjects experiencing Grade 3 adverse events requiring permanent discontinuation of any study drug should be followed weekly until resolution of the adverse event. The treatment regimen should be modified at the discretion of the site investigator and subjects should be encouraged to remain in the study. Exemptions include asymptomatic elevations of CPK, cholesterol or triglycerides. For these laboratories, medication may be continued at the discretion of the site investigator and laboratories repeated within 2 weeks. If the toxicity or laboratory elevation is thought not to be due to study medication, the study medication may be continued with follow-up at the discretion of the primary provider.

7.3 Grade 4

Management of Grade 4 toxicities should be discussed with the protocol team via email.

Subjects who develop a Grade 4 adverse event or toxicity judged to be study drug related will have the presumed causative study drug(s) permanently discontinued and another drug will be substituted. Subjects experiencing Grade 4 adverse events should be followed weekly until resolution of the adverse event. At that time, they will resume study visits and evaluations according to the Schedule of Events. A new regimen may be chosen at the discretion of the local investigator. Exemptions

include: asymptomatic elevations of cholesterol or triglycerides that can be managed with diet and/or lipid lowering therapy or CPK, if the CPK elevation is not felt to be related to study medications. For these laboratories, medication may be continued with follow-up at the discretion of the site investigator. If the toxicity or laboratory elevation is thought **not** to be due to study medication, the study medication may be continued and laboratories repeated within 2 weeks. If it is not possible for the investigator to discern the causative agent, then all study medications must be discontinued.

7.4 Rash

Rash may be caused by therapies in any of the major antiretroviral classes or by other therapies commonly used as concurrent medications, such as cotrimoxazole. As it is not possible to provide an exhaustive list of products that may cause rash in this protocol, please consult the product information leaflets for other products for information relating to rash.

Rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events.

If the etiology of the rash can be definitively diagnosed as being due to a specific medical event or a concomitant medicinal product, routine management should be performed and documentation of the diagnosis provided.

For Grade 2 rash antihistamines, topical corticosteroids, or a brief course of systemic corticosteroids, at the discretion of the site investigator, may be prescribed and subjects may continue all study medications. The subject should be advised to contact the physician immediately if there is any worsening of the rash. EFV (as part of Atripla®) may be temporarily discontinued along with all other study medications, at the site investigator's discretion, until the cutaneous toxicity returns to Grade $\leq$1, at which time therapy should be reinstituted at full dose. The subject should be closely monitored for recurrence of the rash. The protocol team should be consulted.

If the rash is considered to be most likely due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject should be treated symptomatically until the rash resolves.

For Grade 3 rash thought to be related to the study medications, subjects should either discontinue all drugs or consider switching from the likely causative agent.

For Grade 4 rash subjects should discontinue all study medications. The Protocol team should be consulted.

NOTE: In the event that Grade 2, 3, or 4 rash fails to resolve, increases in severity,

is associated with systemic (fever, malaise, nausea) or allergic (e.g., urticaria) symptoms, or is associated with exfoliative dermatitis or mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson syndrome or necrosis requiring surgery, all study medications should be temporarily discontinued until symptom resolution. Some or all study medications may then be reintroduced.

7.5 Skin hyperpigmentation

Development of skin hyperpigmentation, if assessed as being related to FTC, can be followed without modification of therapy, at the discretion of the site investigator.

7.6 Nausea and Vomiting

Nausea and vomiting may be treated symptomatically with oral antiemetics or antiemetic suppositories. For Grade >3 nausea or vomiting thought to be secondary to study drugs that fails to improve on antiemetics to Grade <2, all study drugs may be held until Grade <2. If Grade >3 nausea or vomiting recurs with reinstitution of study drugs or persists beyond 14 days despite symptomatic management, then other antiviral agents may be substituted.

7.7 Diarrhea

For Grade $\leq$2 diarrhea the study treatment should continue without interruption. Subjects with diarrhea of any toxicity grade may be treated symptomatically with permitted antimotility agents. For Grade 3 or 4 diarrhea that is unresponsive to antimotility agents and for which an alternative etiology (e.g., infectious diarrhea) is not established, all study medications should be interrupted until resolution of diarrhea to Grade $\leq$ 2 or baseline and then study treatment can be resumed at the discretion or the site investigator. If Grade $\geq$ 3 diarrhea recurs upon the resumption of study medications, all study medications should be interrupted and the protocol team should be notified for alternative antiretroviral therapy.

7.8 Hyperglycemia

Fasting hyperglycemia of > 110 to 125 mg/dL is considered evidence of impaired glucose tolerance. A fasting blood glucose level above 126 mg/dL is highly suggestive of diabetes mellitus. Subjects with previously undiagnosed fasting hyperglycemia may continue study medications at the discretion of the investigator, but should be discussed with the protocol team via email. A confirmatory fasting glucose must be obtained within 4 weeks and prior to the institution of medical therapy. Hyperglycemia may be treated with oral hypoglycemic agents or insulin according to standard guidelines.

7.9 AST/ALT Elevations

All study medications may be continued for asymptomatic Grade ≤3 AST/ALT elevations at the discretion of the site investigator after discussion with the protocol team. Careful assessments should be done to rule out the use of alcohol, non-study medication-related drug toxicity, or viral hepatitis as the cause of the Grade 3 elevation. The possibility of lactic acidosis syndrome should also be explored.

For symptomatic Grade 3 and all Grade 4 elevations of AST or ALT, all study drugs should be stopped and the protocol team consulted, Repeat laboratories should be performed and all study medications held until the toxicity returns to Grade ≤ 2. If symptomatic Grade 3 or any Grade 4 elevation in AST or ALT recurs upon reinitiation of therapy, treatment should be stopped and alternative ARV therapy considered in consultation with the protocol team.

7.10 Lipase elevation

Pancreatitis will be reported as either clinical (i.e., symptomatic) or chemical (i.e., persistent elevation in enzymes without any symptoms).

For asymptomatic lipase elevation Grade ≥ 3, lipase should be repeated within 2 weeks and triglyceride levels should be checked. For Grade ≥ 3 asymptomatic lipase elevation on repeat testing, the implicated drug(s) should be stopped at the discretion of the site investigator and in consultation with the protocol team. When lipase returns to Grad ≤ 2, the implicated drug(s) may be restarted or may be replaced if a substitution can be identified, at the discretion of the site investigator. Routine evaluation of lipase are not required by the study.

Symptomatic pancreatitis is not commonly associated with study-provided drugs. If clinical pancreatitis is suspected, please refer to the ACTG Definition of Pancreatitis, located at
http://aactg.s-3.com/members/download/other/pancdefv2.doc.
The protocol team should be informed.

7.11 Creatinine Elevations

Discontinue TDF if confirmed creatinine clearance becomes < 50 mL/min. Subjects should be followed as medically indicated until the creatinine returns to Grade < 2. The protocol team should be notified within 48 hours of any permanent therapy discontinuations.

7.12 Hypertriglycredemia / Hypercholesterolemia

Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study drugs. Only triglyceride levels obtained in a fasting state should be evaluated for toxicity management. For Grade ≥3, confirmatory fasting triglyceride should be obtained within 4 weeks and must be obtained prior to the institution of medical therapy for hyperlipidemia.

Subjects with asymptomatic triglyceride or cholesterol elevation should be counseled on dietary modification. Oral antihyperlipidemic agents should be considered at the discretion of the site investigator (and documented on the concomitant drug CRF). Guidelines for the treatment of hyperlipidemia are available on the ACTG web site (http://aactg.s-3.com/members/download/other/metabolic/Chol.rtg).

Resin binding agents, such as cholestyramine and colestipol, should be avoided as they may interfere with absorption of LPV/r as well as the absorption of other drugs and fat-soluble vitamins.

7.13 CNS Symptoms with EFV

Subjects should be informed that these symptoms are likely to improve with continued ARV therapy. Dosing at bedtime improves the tolerability of these symptoms and is recommended. Subjects receiving EFV should be alerted to the potential for additive CNS effects when EFV is used concomitantly with alcohol or psychoactive drugs. In addition, taking EFV with food may increase blood levels and CNS symptoms. In the event of treatment-limiting (in the opinion of the site investigator) CNS AEs attributable to EFV, the protocol team should be informed and EFV should be discontinued and alternative regimens discussed.

7.14 Pregnancy

Women who become pregnant on study must continue all study medications immediately and must prematurely discontinue the study. The protocol team should be notified. In addition, pregnancy outcome data will be collected and recorded in her source document and on the CRF.

Sites are strongly discouraged to register any pregnancy that occurs on study with The Antiretroviral Pregnancy Registry as soon as the site become aware of it. More information is available at www.apregistry.com. Phone: 800-259-4263; Fax; 800-800-1052.

8.0 CRITERIA FOR TREATMENT DISCONTINUATION

8.1 Criteria for Treatment Discontinuation

- Drug-related toxicity (see section 7, Toxicity Management).
- Requirement for prohibited concomitant medications (see section 5.4.2)

8.2 Criteria for Discontinuation from the Study

- Pregnancy or breast-feeding.

- Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.
- Failure by the subject to attend three consecutive clinic visits during the follow-up portion may result in discontinuation.
- Request by the subject to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the subject.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity management of the protocol.
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the CCTG, FDA, investigator, or pharmaceutical sponsors.

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a 1:1 randomized, open-label, pilot study of RAL+ LPV/r vs. Atripla® in HIV-1-infected, treatment-naïve subjects for 48 weeks. During the initial 2-week period, subjects will undergo intensive monitoring of viral decay dynamics (baseline, days 2, 7, 10, 14) and immune T-cell subset changes (baseline and week 4). From weeks 4 to 48, subjects will be monitored for treatment efficacy (CD4+ cell counts, and plasma HIV-1 RNA levels) and safety/ tolerability (hematology, chemistry, fasting lipids and symptom questionnaire).

9.2 Endpoints

Primary:

The viral decay rate of the phase 1 decay in HIV RNA.

Secondary:

1. The proportion of participants with plasma HIV RNA $\leq$ 50 copies/mL at week 48.

2. The proportion of participants with treatment failure at week 48.

3. Time to treatment failure.

4. The change in CD4+ T-cell absolute count and percentage from baseline week 48.

5. The change in CD4+ T-cell absolute count and percentage during phase 1 (baseline to week 12) and phase 2 (weeks 12 to 48) immune recovery.

6. The proportion of CD4+/CD8+ T-cell immune activation, maturation, regulatory and apoptosis markers at baseline and weeks 4 and 24.

7. Fasting lipid profiles (total cholesterol, high-density cholesterol, calculated LDL cholesterol, triglycerides) at baseline weeks 12, 24 and 48.

8. Grades $\geq$ 2 laboratory abnormalities and signs and symptoms.

9. Time to treatment discontinuation due to toxicity.

9.3 Sample Size

Primary objective: To compare the antiviral potency as measured by phase 1 plasma viral decay rates between RLT + LPV and EFV + TDF + FTC.

In A5160, a viral dynamics sub-study of A5142, the first-phase viral decay rate (d_1) for EFV + 2 NRTI regimen (n=25 subjects) was 0.638 $days^{-1}$ (IQR: 0.577, 0.703) and 0.530 $days^{-1}$ (IQR: 0.414, 0.662) for LPV + 2 NRTI (n=22 subjects) combinations. EFV-containing combinations had a significantly faster decay rate that LPV/r-based regimens (difference of 0.108 $days^{-1}$; P=0.03). Although similar intensive phase 1 viral decay data are not yet available, plasma HIV RNA levels were 70% lower at day 14 of treatment in RLT + TDF/3TC vs. EFV + TDF/3TC treated patients (Murray J, et al., Abstract TUAB103). Therefore, we hypothesize that the RLT + LPV/r combination will have a greater phase 1 viral decay rate compared to EFV + TDF + FTC.

The study is powered to compare the phase 1 viral decay rate between the EFV+TCD+FTC and RLT+LPV/r groups using a two-sided, two-sample t-test with alpha=0.05. Assuming the phase 1 viral decay rate for EFV+TCD+FTC (d1) is 0.638, we calculated power for the following situations.

Table 1. Power to declare difference in phase 1 decay rate d1, for various differences and standard deviations with n=25 per group.

Difference between arms in d_1	**SD, decay rate**	**Power**
0.1	0.1	93%
0.1	0.12	82%
0.12	0.15	79%

Assuming the SD of the viral decay rate is 0.12, the study has 82% power to detect a 0.1 difference in the decay rates between the EFV+TCD+FTC and RLT+LPV/r

with n=25 subjects per group (alpha=0.05).

9.4 Methods of Analysis

9.4.1 Analysis of Primary Objectives

Repeated HIV RNA measured at different time points (baseline, days 2, 7, 10, 14) will be treated as the outcome variable in a linear mixed-effects model. The primary fixed effects will include time, treatment group, treatment group-by-time interaction; random effects will include both intercept and slope allowing each subject to have individual baseline viral load and viral decay rate. The treatment group-by- time interaction term in the model will indicate the difference in viral decay rates between the two treatment groups. Baseline covariate adjustment will be included if necessary.

9.4.2 Analysis of Secondary Objectives

Secondary analyses will include descriptive statistics and tests of significance between the two treatment arms. All significance tests will be two-sided and no adjustment for multiple comparisons will be made. If necessary due to assumption failures, appropriate non-parametric statistical tests will be applied.

1a. Differences in the proportion of participants on each arm with plasma HIV RNA < 50 copies/mL at week 48 will be compared via Fisher's exact test (intention to treat analysis with data imputation for missing data).

1b. Differences in the proportion of participants on each arm with plasma HIV RNA < 50 copies/mL at week 48 will be compared via Fisher's exact test (no data imputation for missing data).

2. Differences in the proportion of participants on each arm with treatment failure (defined as non-completer, protocol-defined virologic failure, treatment discontinuation, or change in treatment regimen) at week 48 will be compared via Fisher's exact test.

3. Differences in time to treatment failure (defined as non-completer, protocol-defined virologic failure, treatment discontinuation, or change in treatment regimen) will be compared via Kaplan-Meier curves and the log-rank test.

4. Differences in the change in CD4+ T-cell absolute count and percentage from baseline to week 48 will be compared via a two-sample Student t-test.

5a. Differences in the change in CD4+ T-cell absolute count and percentage from baseline to week 12 (Phase 1) and week 12 to week 48 (Phase 2) will be compared via separate two-sample Student t-tests.

5b. Association between viral decay kinetics and Phase 1 CD4 recovery will be determined via Pearson's correlation analysis.

6a. Differences in the proportion of CD4+/CD8+ T-cell immune activation, maturation, regulatory and apoptosis markers at baseline and weeks 4 and 24 will be separately compared cross-sectionally via Fisher's exact test.

6b. Association between change in early immune subsets and phase 2 CD4 recovery will be assessed via Pearson's correlation analysis

7. Differences in fasting lipid profiles (total cholesterol, high-density cholesterol, calculated LDL cholesterol, triglycerides) at baseline weeks 12, 24 and 48 will be compared cross-sectionally via two-sample Student t-tests.

8. Differences in proportions of grades > 2 laboratory abnormalities and signs and symptoms will be compared via Fisher's exact test.

9. Differences in time to treatment discontinuation because of toxicity/intolerance will be compared via Kaplan-Meier curves and the log-rank test.

9.5 Monitoring

It is the responsibility of the Principal Investigator and the CCTG protocol team to interpret the viral response and toxicity data and make any decisions needed to protect patients from undue risk. Safety and tolerability of the study medications will be monitored by means of adverse event reports (AER) and bimonthly toxicity reports presenting laboratory and clinical data. Safety data will be tabulated by study arm and reviewed by the statisticians but study arm assignment will be blinded to protocol team and site investigator's unless safety issues require an un-blinding. These reports will be discussed by the protocol team on monthly conference calls. Accrual and toxicity summaries will be provided to the Protocol Chairs and CCTG Investigators by the Data Manager and Biostatistician.

The study will undergo an internal review by the protocol chairs and study team when either twelve subjects in the RAL+LPV/r arm have enrolled or after one year has elapsed from when the first subject was enrolled, whichever comes first. The study would be reviewed by an independent Study Monitoring Committee if protocol chairs deemed necessary or if greater than 30% of subjects in the RAL+LPV/r arm (and at least 12 subjects enrolled in this arm) experience virologic failure. The independent review committee will be composed of at least 3 people (including one statistician) outside the protocol team. The committee will make specific recommendations about changes to the study protocol.

10.0 DATA COLLECTION AND MONITORING AND ADVERSE EXPERIENCE REPORTING

10.1 Records to Be Kept

Case report forms (CRF) will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by the patient identification number (PID) provided by the **C**CTG Data and Biostatistical Unit upon registration.

10.2 Role of Data Management

10.2.1 Instructions concerning the recording of study data on CRFs will be provided by the CCTG Data and Biostatistical Unit.

10.2.2 It is the responsibility of the CCTG Data and Biostatistical Unit to assure the quality of computerized data for this study.

10.3 Clinical Site Monitoring and Record Availability

10.3.1 Site monitors provided by the CCTG will visit participating clinical research sites to review the individual subject records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

10.3.2 The investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the Food and Drug Administration (FDA), the pharmaceutical sponsor(s), or the sponsor's designee for confirmation of the study data.

10.4 Serious Adverse Experience (SAE) Reporting

Serious adverse experiences must be documented on the Serious Adverse Experience (SAE) Reporting Form and submitted to the CCTG Data and Biostatistical Unit.

11.0 HUMAN SUBJECTS

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from

the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the OHRP, the pharmaceutical supporter(s), or the supporter's designee.

11.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the pharmaceutical supporter(s), the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by CCTG policies. Any presentation, abstract, or manuscript will be made available for review by the pharmaceutical supporters prior to submission.

13.0 BIOHAZARD CONTAINMENT

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

All infectious specimens will be transported using packaging mandated in the Federal Code of Regulations, CDC 42 CFR Part 72. Please also refer to individual carrier guidelines, e.g., FedEx, Airborne, for specific instructions.

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