**CCTG 584**

# Viral Dynamics and Pharmacokinetics of TDF and ABC Monotherapy versus the Combination Therapy of TDF – ABC in HIV-Infected Treatment Naïve Patients

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LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Phosphatase |
| AST | Aspartate Phosphatase |
| AUC | Area Under the Curve |
| BID | Twice Daily |
| BUN | Blood Urea Nitrogen |
| CBV | Carbovir |
| CCTG | California Collaborative Treatment Group |
| CD4 | CD4 lymphocytes |
| CI | Confidence Interval |
| Cmax | Maximum Plasma Concentration |
| Cmin | Minimum Plasma Concentration |
| $C_{24}$ | 24 hour Plasma Concentration |
| CRF | Case Report Form |
| CYP | Cytochrome |
| D.V. | Dynamics Visit |
| DAVG | Time average difference |
| HAART | Highly Active Antiretroviral Therapy |
| HBV | Hepatitis B Virus |
| Hct | Hematocrit |
| HIV-1 | Human Immunodeficiency Virus - 1 |
| Hgb | Hemoglobin |
| HSR | Hypersensitivity Reaction |
| IAS | International AIDS Society |
| IQR | Interquartile Range |
| ITT | Intention To Treat |
| iv | Intravenous |
| NRTI | Nucleoside analogue Reverse Transcriptase Inhibitor |
| | ABC Abacavir |
| | 3TC Lamivudine |
| | D4T Stavudine |
| | TDF Tenofovir |
| | ZDV Zidovudine |
| NNRTI | Non-Nucleoside analogue Reverse Transcriptase Inhibitor |
| | EFV Efaverenz |
| PI | Protease Inhibitor |
| | IDV Indinavir |
| PK | Pharmacokinetics |
| PBMC | Peripheral Blood Mononuclear Cells |
| QD | Once Daily |
| RT-PCR | Real Time – Polymerase Chain Reaction |
| STI | Structured Treatment Interruption |
| SAE | Severe Adverse Reaction |

| | |
|---|---|
| UA | Urinalysis |
| WBC | White Blood Count |

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SCHEMA

**Viral Dynamics and Pharmacokinetics of TDF and ABC Monotherapy versus the Combination Therapy of TDF – ABC in HIV-Infected Treatment Naïve Patients**

Design:

This is a comparative, open-labeled study of a dual NRTI regimen, TDF + ABC, compared to ABC and TDF monotherapy administered for 7 days. Each patient will be randomized to a 7-day sequence of either ABC or TDF once-daily followed by a 35-day washout period. After completion of the monotherapy sequence all patients will then receive dual NRTI therapy of TDF + ABC for an additional 7 days. After completion of the dual NRTI sequence patients will enter the HAART treatment stage with the addition of EFV and continue on a once-daily regimen of EFV + ABC + TDF for an additional 14 days. At day 63, TDF will be stopped and 3TC will be substituted. Patients will then continue on a once-daily regimen of EFV + ABC + 3TC for an additional 46 weeks.

Duration:

Total study duration is 59 weeks (including a 30 day screening period): Two 7-day viral dynamic sequences separated by a 35 day washout period; followed by 2 weeks of HAART treatment with EFV + ABC + TDF; followed by 46 weeks of HAART treatment with EFV + ABC + 3TC.

Sample Size:

20 subjects: 10 in TDF monotherapy arm, 10 in ABC monotherapy arm

Study Population:

HIV infected, treatment naïve (defined as no exposure to NRTI, NNRTI or PI therapy) patients. Patients must be $\geq$ 18 years old with CD4 cell counts above 200 cells/mm$^3$ and HIV RNA $\geq$ 5000 copies/mL.

Randomization and Stratification:

Patients will be randomized to receive 7 days of either ABC monotherapy or TDF monotherapy prior to the dual NRTI regimen. The randomization will be stratified by baseline plasma HIV RNA < 100,000 or $\geq$ 100,000 copies/ml.

Regimen:

The following short course regimens (dosing given for 7 days) will be compared by the two sequence design:

A. TDF 300 mg QD
B. ABC 600 mg QD
C. TDF 300 mg QD + ABC 600 mg QD

A screening genotype will be done to confirm that there are no resistance-associated mutations. The monotherapy sequence (regimen A or B) will continue for 7 days during which time 4 measurements for HIV RNA will be done to calculate the slope of the phase I viral decay. On day 1, PBMCs for baseline RT-PCR of nucleoside transport enzymes will be collected. On days 7 and 8, serial blood specimens will be collected for PK data for plasma and intracellular levels of TDF and ABC. A specimen of blood will be stored for future genotypic analysis if needed. This will be followed by a 35-day washout period after which patients will enter the dual NRTI therapy sequence (regimen C) for 7 days. During dual NRTI therapy, 4 measurements for HIV RNA will be done to calculate the slope of the phase I viral decay and on day 48 and 49, PK data on both plasma and intracellular levels of TDF + ABC will be collected, and a second genotype will be performed in real time. On day 49, after the second 7-day sequence, all patients will receive EFV in addition to the dual NRTI combination (regimen D) for 14 days. Afterwards, on day 63, a second sample of PBMC's for RT-PCR of nucleoside transport enzymes will be collected. On the same day, TDF will be discontinued and 3TC will be substituted. Patients will then continue for an additional 46 weeks of HAART (regimen E).

D: EFV 600 mg QD + ABC 600 mg QD + TDF 300 mg QD
E: EFV 600 mg QD + ABC 600 mg QD + 3TC 300 mg QD

## 1.0 STUDY OBJECTIVES

### 1.1 Primary Objectives

1.1.1 To evaluate the relative potencies of two monotherapy regimens (TDF alone or ABC alone) compared to a dual NRTI regimen of TDF + ABC as assessed by the short-term virologic response (slope of the phase I viral decay and change in HIV RNA at day 7).

1.1.2 To compare the plasma and intracellular PK data of the two monotherapy regimens to the dual NRTI regimen.

### 1.2 Secondary Objectives

1.2.1 To evaluate the change in cellular regulatory enzymes involved with nucleoside analogue transport across cell membranes as assessed by RT-PCR of specific mRNA transcripts after 21 days of TDF+ABC exposure.

1.2.2 To determine if NRTI-associated mutations emerge after 7 days of ABC or TDF monotherapy or after 7 days of dual NRTI therapy with ABC + TDF.

1.2.3 To compare the relative viral potency of TDF monotherapy versus ABC monotherapy.

1.2.4 To evaluate the long-term viral response to EFV + ABC + 3TC after two 7-day sequences of mono/dual-therapy.

1.2.5 To evaluate the relative toxicities of the two monotherapy treatment regimens.

## 2.0 INTRODUCTION

### 2.1 Background

Dual nucleoside analogues form the backbone of most potent antiretroviral regimens. Although many possible combinations are used there are relatively few clinical trials that have evaluated the relative potency of these dual NRTI regimens. Recently, several studies have suggested increased rates of early virologic failure when the combination of abacavir, tenofovir and lamivudine were used [1-3]. This is in contrast to other settings in which a four NRTI combination was used without evidence of increased rates of early virologic failure (eg. Trizivir® + tenofovir) [4].

The primary goals of this study are to evaluate: (1) the antiviral potency, as assessed by sort-term viral dynamics, of the dual NRTI combination of TDF – ABC relative to monotherapy of each NRTI and (2) the intracellular pharmacokinetics of ABC and TDF in monotherapy compared with dual-therapy in antiretroviral naïve subjects.

#### Tenofovir Disoproxil Fumarate (Viread®, TDF)

Tenofovir, PMPA, (9-[(R)-2-(phosphonomethoxy) propyl] adenine monohydrate) is an acyclic nucleotide analogue with activity in vitro against retroviruses, including HIV-1 and HIV-2. Tenofovir is metabolized intracellularly to tenofovir diphosphate (PMPApp), which is a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the growing DNA chain.

Tenofovir has limited oral bioavailability. TDF is a prodrug of tenofovir with good oral bioavailability in animals and humans and is rapidly converted to tenofovir following absorption.

An HIV-1 variant with a K65R mutation and a three-fold decrease in susceptibility to tenofovir was selected in vitro by serial passage. Tenofovir shows potent anti-HIV activity against a variety of drug-resistant viruses. Viruses containing the M184V mutation showed a slightly increased sensitivity to tenofovir in vitro [5]. ZDV-resistant, 3TC-resistant, and multi-nucleoside drug-resistant viruses (expressing the hallmark Q151M mutation and others) remain susceptible to tenofovir in vitro.

GS-907: This phase III, 48-week study enrolled 552 treatment-experienced subjects who had HIV-1 RNA levels of 400-10,000 copies/mL and were receiving stable antiretroviral therapy for at least 8 weeks prior to entering the study[6]. Subjects were randomized (2:1) to receive 300 mg of TDF (one pill once daily) or placebo in addition to their existing antiretroviral therapy. After 24 weeks of blinded, placebo-controlled dosing, subjects assigned to TDF or placebo were allowed to receive TDF for the remainder of the 48-week study period. At baseline, subjects had a mean HIV-1 RNA level of 3.36 log10 copies/mL, a mean CD4+ cell count of 427 cells/mm3, and a mean previous treatment duration of 5.4 years. About half of all study participants (n = 253) were randomly assigned to a virology substudy of this clinical trial. Baseline genotypic analysis of HIV isolates from these subjects revealed that 94% had evidence of NRTI resistance mutations, 58% had PI resistance mutations, and 48% had NNRTI resistance mutations.

Twenty-four-week data showed that TDF was associated with a statistically significant HIV-1 RNA decrease in mean average post-baseline change over 24 weeks (DAVG24) of -0.61 log10 copies/mL compared with -0.03 log10 copies/mL in the placebo group ($p < 0.0001$). Additionally, 45% (155/346) of subjects treated with TDF achieved HIV-1 RNA reductions to < 400 copies/mL at 24 weeks compared with 13% (23/172) in the placebo group ($p < 0.0001$). The DAVG24 for CD4+ cells was an increase of 12.6 cells/mm3 in the TDF group compared with a decrease of 10.6 cells/mm3 in the placebo group ($p = 0.0008$).

Through the 24-week, placebo-controlled portion of the trial, the incidence of Grade > 3 laboratory abnormalities and clinical adverse events was similar between the placebo and TDF arms. Drug discontinuation at 24 weeks was 6% in both arms of the study.

Study 903 was a randomized, double-blind, active-controlled clinical trial conducted at 81 sites in the United States, Europe, and South America. The trial was designed to compare the efficacy and safety of a treatment regimen of TDF, 3TC, and EFV with a regimen of d4T, 3TC, and EFV in 600 antiretroviral-naïve subjects with HIV infection. In the interim analysis of the ITT population, for which missing data are counted as

failures, an identical 87% of subjects in the TDF arm (n = 299) and the d4T arm (n = 301) achieved suppression of HIV-1 RNA to < 400 copies/mL at 48 weeks of treatment (95% confidence intervals [CI]: -6%, +5%) [7]. Additionally, subjects in both treatment groups experienced significant increases in CD4+ cell count. At 48 weeks, combination treatment including TDF was associated with a mean increase from baseline of 169 cells/mm3, and treatment including d4T was associated with a mean increase from baseline of 167 cells/mm3. In each treatment group, therapy was generally well tolerated and the study discontinuation rate was 9%. The incidence of Grades 3 and 4 AEs in the TDF-containing study arm was 19% compared with 17% in the d4T-containing study arm. The incidence of Grades 3 and 4 laboratory abnormalities in the TDF arm was 28% compared with 31% in the d4T arm. There were no differences by arm in changes in creatinine or hypophosphatemia.

For further information, please consult the most recent Viread® package insert.

Abacavir (Ziagen®, ABC)

ABC is a potent and generally well-tolerated nucleoside analogue which offers the convenience of once or twice daily dosing. ABC is a 2N-deoxyguanosine analogue, with activity against HIV-1. ABC is activated intracellularly to the triphosphate derivative of the carbocyclic guanine analogue 1144U88 (1R,4S)-9-(4-[hydroxymethyl])-2-cyclopentene-1-yl guanine, which is a potent in vitro inhibitor of HIV-1 reverse transcriptase with a $K_i$=20 nM.

High-level resistance to ABC is not rapidly selected in vitro, and multiple mutations are required to confer a 10-fold reduction in sensitivity. Mutations in the HIV-1 reverse transcriptase that correlate with ABC resistance include M184V, L65R, L74V, and Y115F.

Efficacy

The CNAB3014 study was a comparison of open-label ABC/3TC/ZDV with IDV/3TC/ZDV in 342 antiretroviral naïve adults for 48 weeks [8]. At randomization, subjects were stratified based on screening HIV-1 RNA: 5000-100,000 (63%) or >100,000 (37%) copies/mL. Median HIV-1 RNA was 4.78 $\log_{10}$ and 4.82 $\log_{10}$ and median CD4 count was 331 and 299 cells/μL for the ABC/3TC/ZDV and IDV/3TC/ZDV groups, respectively. HIV-1 RNA was measured at the sites using the <400 copies/mL assay and by a central laboratory using the <50 copies/mL assay. Study medication adherence was assessed via patient self-report. Based on an ITT (missing=failure) analysis at 48 weeks, 66% of subjects on ABC/3TC/ZDV had HIV RNA levels <400 copies/mL, as compared to

50% on IDV/3TC/ZDV ($p$=0.002). In the subset of subjects with baseline HIV RNA ≤100,000 copies/mL, the results were 70% and 49%, respectively, while in the subset with baseline >100,000, the results were 60% and 51%, respectively. Using the <50 copies/mL assay, 60% of subjects on ABC/3TC/ZDV compared with 50% on IDV/3TC/ZDV were below the threshold (ITT, missing=failure). In the ≤100,000 copies/mL stratum, the values were 67% and 53%, respectively, while in the >100,000 copies/mL stratum, the values were 48% and 46%, respectively. Over the 48 weeks, the time to treatment failure was significantly longer in the ABC group ($p$=0.001). Median CD4+ cell count increases were 148 and 152 cells/$mm^3$ in the ABC and IDV groups, respectively. Seven percent of subjects on ABC/3TC/ZDV experienced Grade 3/4 AEs, compared with 14% on IDV/3TC/ZDV; 6% of those on ABC experienced an HSR. At week 48, 46% of subjects on ABC/3TC/ZDV and 23% on IDV/3TC/ZDV reported taking all antiretroviral doses over the last 4 weeks.

Abacavir Once Daily Dosing

Study CNA 10905 provided the pharmacokinetic data of abacavir and intracellular carbovir triphosphate in a group (n= 20) of HIV-infected patients that had been on a stable abacavir 300mg BID regimen for at least 6 weeks or more [9]. Subjects were admitted to an inpatient setting where PK measurements were performed following a single a.m. dose. The evening dose was held and re-started the following day. Although the geometric mean intracellular carbovir triphosphate levels demonstrated little variation over time, there was a fair amount of individual variability; with $C_{max}$ levels of 29.7 fmol/mil cells versus $C_{tau}$ levels of 16.6 versus $C_{24}$ levels of 14.9 fmol/mil cells. The $t_{1/2}$ of intracellular carbovir triphosphate was approximately 21 hours.

The CNA 30021 study was a double-blinded comparison in which 784 treatment-naïve patients were randomized to receive once daily ABC dosing with ABC QD/3TC/EFV (n=384) or standard ABC BID dosing with ABC BID/3TC/EFV (n=386) for 48 weeks [10]. Baseline subjects were similar between groups with median HIV RNA levels of 4.9 $\log_{10}$ and CD4+ counts of 264 cells/$mm^3$ in the once-daily dosing arm and median HIV RNA levels of 4.9 $\log_{10}$ and CD4+ counts of 262 cells/$mm^3$ in the BID ABC dosing arm. The primary endpoint of virologic suppression < 50 copies/mL at 48 weeks was reached by 66% in the ABC once daily dosing group and 68% in the ABC BID dosing group. When stratified for baseline HIV RNA levels (> 100K c/mL or ≤ 100K c/mL) the two groups continued to be similar. Median CD4+ count increases were 188 and 200 cells/$mm^3$ in the ABC BID and ABC once daily group, respectively. This study establishes the non-inferiority of ABC once daily compared to ABC BID in combination with 3TC QD and EFV.

Safety

More than 200,000 HIV-infected patients have been treated with abacavir, either in clinical trials or clinical practice. ABC is generally well tolerated. Most clinical AEs are mild to moderate in severity and generally self-limiting. The most frequently reported clinical AEs across phase III studies were nausea/vomiting, headache, malaise or fatigue, and diarrhea. Elevated triglycerides and anorexia have also been reported. Clinical AEs and clinical laboratory abnormalities common to some nucleoside antiretroviral agents (i.e., pancreatitis, peripheral neuropathy, anemia, and neutropenia) have not been commonly seen with ABC therapy. No differences in the safety profile of ABC based on gender, race, or age are apparent; however, safety in selected populations (i.e., moderate to severe hepatic impairment) has not been evaluated.

Abacavir and Lamivudine Fixed Dose Combination

Epzicom is the The Fixed Dose Combinations (FDC) of abacavir and lamivudine that was FDA approved in August 2004. Each tablet contains 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine.

Effect of Food on Absorption of EPZICOM:
EPZICOM may be administered with or without food. Administration with a high-fat meal in a single-dose bioavailability study resulted in no change in AUC last, AUC∞ and Cmax for lamivudine. Food did not alter the extent of systemic exposure to abacavir (AUC∞), but the rate of absorption (Cmax) was decreased approximately 24% compared to fasted conditions (n = 25). These results are similar to those from previous studies of the effect of food on abacavir and lamivudine tablets administered separately.

Impaired Hepatic Function: EPZICOM:
Abacavir is contraindicated in patients with moderate to severe hepatic impairment and dose reduction is required in patients with mild hepatic impairment. Because EPZICOM is a fixed-dose combination and cannot be dose adjusted, EPZICOM is contraindicated for patients with hepatic impairment.

Dose Adjustment: Because it is a fixed-dose tablet, EPZICOM should not be prescribed for patients requiring dosage adjustment such as those with creatinine clearance <50 mL/min, those with hepatic impairment, or those experiencing dose-limiting adverse events.

Hypersensitivity Reaction

In clinical studies, approximately 3%-5% of patients receiving ABC develop an HSR that in rare cases has proved fatal [11]. The abacavir hypersensitivity reaction is characterized by the appearance of symptoms indicating multi-organ involvement. The majority of patients have fever and/or rash as part of the syndrome, however reactions have occurred without rash or fever. Symptoms can occur at any time during treatment with abacavir, but usually appear within the first six weeks of initiation of treatment (median time to onset 11 days). The symptoms worsen with continued therapy and can be life threatening. These symptoms usually resolve shortly after discontinuation of abacavir. Frequently observed signs and symptoms include fever, rash, malaise or fatigue, gastrointestinal symptoms such as nausea, vomiting, diarrhoea, or abdominal pain and respiratory symptoms such as dyspnea, sore throat, or cough. Other signs and symptoms include myalgia, arthralgia, oedema, pharyngitis, headache, paresthesia or myolysis. Physical findings may include rash (usually maculopapular or urticarial), lymphadenopathy or mucous membrane lesions (conjunctivitis, mouth ulceration). Abnormal chest x-ray findings may also be present (predominantly infiltrates, which can be localised). Laboratory abnormalities may include elevated liver function tests (such as hepatic transaminases), increased creatine phosphokinase or creatinine levels, and lymphopenia. Anaphylaxis, hypotension, liver failure, renal failure, adult respiratory distress syndrome or respiratory failure may occur.

Some patients with hypersensitivity were initially thought to have respiratory disease (pneumonia, bronchitis, pharyngitis), a flu-like illness, gastroenteritis or reactions to other medications. This delay in diagnosis of hypersensitivity has resulted in abacavir being continued or re-introduced, leading to a more severe hypersensitivity reaction or death. Therefore, the diagnosis of hypersensitivity reaction should be carefully considered for patients presenting with symptoms of these diseases. If hypersensitivity reaction can not be ruled out, no medicinal product containing abacavir (Ziagen, Trizivir or the abacavir/lamivudine fixed dose combination) should be restarted.

**Patients who develop a hypersensitivity reaction must discontinue abacavir and must never be rechallenged with any medicinal product that contains abacavir (Ziagen, Trizivir or the abacavir/lamivudine fixed dose combination).** Restarting any abacavir-containing product following a hypersensitivity reaction results in a prompt return of symptoms within hours. **This recurrence of the hypersensitivity reaction may be more severe than on initial presentation, and may include life-threatening hypotension and death.**

Symptoms usually start to resolve soon (within 24 hours) after stopping therapy. Symptomatic support, such as intravenous fluids for those who develop hypotension, is advised. There are no clinical data demonstrating the benefit of antihistamines or corticosteroids in the management of hypersensitivity. Nevertheless, symptomatic and/or supportive treatment may be reasonable.

Treatment Interruptions with Abacavir and Risk of HSR

There have been infrequent reports of hypersensitivity reactions following reintroduction of abacavir, where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal or a respiratory symptom).On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction [12, 13]. Retrospective analyses have attempted to assess the safety of abacavir re-introduction after transient treatment interruptions in patients with no previous evidence of hypersensitivity reaction. In a cohort of 20 patients with a total of 25 treatment interruptions for a median of 13 days (IQR 6-41), none developed symptoms suggestive of re-challenge HSR [14]. GlaxoSmithKline conducted an analysis of 1442 cases of HSR, of which only seven reports were suggestive of re-challenge HSR in the setting of no previous HSR symptoms. None of these cases were fatal and only two had rapidly, progressive symptoms [12]. Thompson et al. [15], evaluated re-challenge HSR reactions during structured treatment interruption (STI). A study of 195 ARV-naïve patients were followed for 24 weeks, of which 70% had an STI of 2 days or more; none of these patients had evidence of HSR. Although 4 subjects did have symptoms suggestive of HSR in this study, review of MEMS caps data, did not suggest that patients had an unplanned STI. Although HSR to abacavir may occur after STI, it is unlikely that treatment interruption increases the risk of HSR to abacavir.

Drug Interactions

In vitro studies utilizing human liver microsomes demonstrated that ABC did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between ABC and drugs metabolized through these pathways.

Please refer to the Ziagen® package insert for complete prescribing information.

Tenofovir – Abacavir Combination

In a pilot study by Farthing C, et al. [2] showed increased rates of early virologic failure with the combination of abacavir, tenofovir and lamivudine. Twenty patients naïve to antiretrovirals were enrolled, of which 17 were available for analysis. At baseline, mean plasma HIV-1 RNA was 82,381 copies/ml [range: 7650-213,486] and mean CD4 count of 273 cells/$mm^3$ [range: 59-598]. The study was prematurely interrupted when 9/17 (52%) patients experienced viral rebound in spite of adherence rates of > 95% by pill count. Limited genotypic analysis showed M184V mutation in two patients and both M184V + K65R mutations is one patient (6 samples are pending).

A larger phase III trial, ESS30,009 [1], demonstrated similar failure rates in the abacavir, tenofovir and lamivudine arm (n=102). Patients were considered to be non-responder/failing if there was less than 2.0 $\log_{10}$ drop in plasma HIV RNA and viral load >50 copies/ml at week 8 or a greater than 1.0 $\log_{10}$ increase in plasma HIV RNA from nadir by week 8. Similarly, this study was also prematurely interrupted when 50/102 (49%) subjects met at least one of these criteria. Genotypic analysis of 11/12 patients at week 12 showed all had an un-mixed population of mutation M184V with six of those patients also having either a mixed population of K65R/K or a homogeneous population of K65R in addition to the M184V mutation.

Lamivudine (Epivir®, 3TC)

3TC is an approved, potent nucleoside reverse transcriptase inhibitor that is widely used for treating subjects with HIV infection. Although 3TC is an effective NRTI, virus with a resistance mutation at codon 184 rapidly emerges within 2 weeks of monotherapy and is also seen with dual-nucleoside regimens.

3TC is phosphorylated to its active 5'-triphosphate metabolite (3TC-TP). 3TC-TP inhibits HIV-1 reverse transcriptase by terminating viral DNA chains and also directly inhibits the RNA- and DNA-dependent DNA polymerase activities of reverse transcriptase. In all acute virus-cell infections (including monocytes and fresh, human peripheral blood lymphocytes) tested with 3TC, anti-HIV-1 activity was demonstrated.

Once daily-dosing of 3TC

The originally recommended dose of 3TC was 150 mg BID. However, the PK profile of 3TC suggests that it may be successfully dosed on a once daily basis and it has now been approved by the FDA for this once daily dosing regimen. The observed mean elimination half-life in HIV-infected subjects ranged from 5 to 7 hours. However, 3TC 5'-triphosphate has an intracellular half-life of 10.5 to 15.5 hours in HIV-infected and uninfected

human peripheral blood lymphocytes. The intracellular anabolic pathway for 3TC has a saturable formation step from the diphosphate to the active triphosphate. This allows pooling of 3TC-DP, which is the immediate precursor of 3TC-TP. Thus, 3TC-TP can still be formed when plasma concentrations are low long after dosing. The active moiety, 3TC-TP, is slowly eliminated from cells with an intracellular half-life of 11 to 13 hours in HIV-1 infected cells in vitro.

These findings have been supported by clinical data. A PK study of 3TC phosphorylation in peripheral blood mononuclear cells (PBMCs) from HIV-infected subjects found the 3TC-TP intracellular half-life to be approximately 15-16 hours, irrespective of dose, either 150 mg BID or 300 mg BID [16]. Another study demonstrated the PK equivalence of 3TC 300 QD to 3TC 150 mg BID in healthy volunteers with respect to plasma $AUC_{24,ss}$, $C_{ave,ss,}$ and intracellular $AUC_{24,ss}$, $C_{max,ss,}$ and $C_{ave,ss}$ [17]. Thus, the relatively long plasma and intracellular half-lives, pooling of the immediate precursor (3TC-DP) of the active moiety (3TC-TP), and the PK equivalence of both dosing schedules support the ongoing investigation of 3TC 300 mg once daily as a component of a multiple drug dosing regimen.

In addition to PK data, several clinical studies support the further evaluation of once-daily 3TC administration. Preliminary 24 week data from one clinical study suggest the combination of QD 3TC + nevirapine + ddI administered to both naïve and experienced subjects provides potent immunological and antiviral effects and warrants further evaluation [18]. In ICC-604, an open-label, pilot study evaluating QD 3TC + adefovir + ddI + efavirenz in subjects naïve to all four drugs (N = 11), 100% and 90% of subjects achieved <400 and <50 copies/mL plasma HIV-1 RNA at 24 weeks by intent-to-treat (ITT) analyses.

Two clinical studies have compared 3TC BID with 3TC QD. In EPV40001, 159 ART-naïve adults were randomized to one of three 3TC + ZDV + abacavir regimens (all given BID, 3TC given QD, or ABC given QD). At 48 weeks, both 3TC and ABC given QD demonstrated virologic equivalence compared with the respective twice daily regimens. All regimens were safe and well tolerated [19]. COLA4005 compared switching to 3TC once daily versus continuing 3TC BID in virologically suppressed adult subjects on a stable regimen of either 3TC + d4T + indinavir or 3TC + d4T + nelfinavir. At week 24, the proportion of subjects with HIV-1 RNA <50 copies/mL was similar in the subjects who switched to 3TC QD and in those who remained on 3TC BID (95% vs., 90%; $p = 0.679$, ITT M = F) [20].

Based on in vitro and supportive clinical data, the once daily administration of 3TC should pose no safety or efficacy issues and will add to the compact nature of study regimens.

Safety

3TC is an extremely well tolerated nucleoside analogue. Side effects include anemia, neutropenia, increased in liver function enzymes, peripheral neuropathy, rash, nausea, vomiting, diarrhea, headache, insomnia, malaise, fatigue, dizziness, and allergic reactions. Rare side effects include psychosis, mania, and thrombocytopenia.

Exacerbations of HBV-related hepatitis have been detected in HIV-HBV coinfected subjects that discontinued 3TC-containing antiretroviral regimens. Most episodes were self-limited, however fatalities have been reported. Coinfected subjects should be monitored for exacerbation of their hepatitis if 3TC is permanently discontinued.

For more information concerning 3TC, refer to the most recent package insert.

Efavirenz (Sustiva®, EFV)

Efficacy

EFV is a potent NNRTI that is widely used in combination with other antiretrovirals for the treatment of HIV-1 infection. Studies support its use for initial therapy as well as for salvage therapy.

A phase III study (DMP 266-006) compared the safety and efficacy of ZDV (300 mg BID) + 3TC (150 mg BID) + EFV (600 mg QD), EFV + indinavir (IDV) (800 mg Q8h), and ZDV + 3TC + IDV. IDV was administered in a fasted state [21]. A total of 1266 subjects who were EFV, NNRTI-, PI-, and 3TC-naïve at study entry were enrolled. The mean baseline CD4+ cell count was 341/$mm^3$, and the mean baseline HIV-1 RNA level was 4.78 $\log_{10}$ copies/mL. At 48 weeks, the proportion of subjects with HIV-1 RNA levels < 400 (< 50) copies/mL was 68% (62%) for the EFV/NRTI group, 55% (49%) for the EFV/IDV group, and 49% (43%) for the IDV/NRTI group. No differences in CD4+ cell count changes were noted among the groups. During long-term follow-up, the proportion of subjects with HIV-1 RNA < 50 copies/mL at 72 weeks was 58% for the EFV/NRTI group, 42% for the EFV/IDV group, and 36% for the IDV/NRTI group.

In another study (DMP 266-049), subjects who had HIV-1 RNA levels < 50 copies/mL while receiving a regimen containing a PI and two NRTIs were randomized to continue their PI/NRTI regimen or switch to EFV (600 mg QD) + the same two NRTIs. Overall, 266 subjects were in the EFV group and 120 were in the PI group. Mean CD4+ cell count at baseline was 578 cells/$mm^3$ for the EFV group and 566 cells/$mm^3$ for the PI group. At 24 weeks, the proportion with HIV-1 RNA levels < 50 copies/mL was 89% for the EFV group and 81% for the PI group. Confirmed viral rebound (HIV-1 RNA > 50 copies/mL) rates were 3% for the EFV group and 10.2% for the PI group ($p = 0.011$). No differences in CD4+ cell counts were noted between the two groups. No differences in nonfasting lipid levels or AST/ALT were noted between the two groups. Subjects receiving EFV noted the following Grade ≥ 2 adverse experiences: abnormal dreams (7%), rash (5%), dizziness (4%), insomnia (3%), impaired concentration (3%), and increased triglycerides (3%).

Safety

The most significant adverse events observed in subjects receiving EFV were nervous system symptoms, psychiatric symptoms, and rash (see efavirenz package insert). Fifty-three percent of subjects noted central nervous system (CNS) complaints. Nervous system symptoms usually begin during the first 1 or 2 days of therapy and generally resolve after the first 2 to 4 weeks. Dosing at bedtime improves the tolerability of these symptoms and is recommended during the first weeks of therapy and in subjects who continue to experience these symptoms.

Serious psychiatric adverse experiences have been reported including severe depression, suicidal ideation or attempts, aggressive behavior, paranoid reactions, and manic reactions. Rash is usually mild to moderate and occurs within the first 2 weeks of initiating therapy. In most subjects, rash resolves with continuing EFV therapy within 1 month. EFV can be reinitiated in subjects interrupting therapy because of rash.

Malformations have been observed in fetuses from EFV-treated monkeys that received doses resulting in plasma drug concentrations similar to those in humans given 600 mg/day. Therefore, pregnancy should be avoided in women receiving EFV and barrier contraception should always be used in combination with other methods of contraception (e.g., oral or other hormonal contraceptives).

It is recommended that EFV be taken on an empty stomach, preferably at bedtime. For more information concerning Sustiva® refer to the most recent package insert.

## 2.2 Rationale

In light of the recent clinical data suggesting increased rates of early virologic failure in the setting of an abacavir + tenofovir combination, further studies are needed to evaluate potential mechanisms for this clinical observation. Individually the relative potency of tenofovir and abacavir are among the more potent in this class. There are several reasons to evaluate the dual NRTI combination of TDF and ABC alone and in combination:

1. TDF combined with ABC is a potentially potent regimen that has not been fully evaluated. Recent data suggest increased rates of virologic failure when given with lamivudine alone. However, this failure rate was not observed when given with zidovudine in addition to lamivudine.

2. The relative potency of the dual NRTI (TDF + ABC) combination can be evaluated by short term phase I viral decay kinetics relative to the decay rates of each NRTI given alone.

3. Plasma and intracellular concentrations of the dual NRTI combination (TDF + ABC) can be evaluated and compared to pharmacokinetic data when the NRTI is given as monotherapy.

4. Induction or suppression of certain transport enzymes that control influx and efflux of nucleoside analogues can be evaluated by measuring baseline and steady state mRNA expression in PBMCs via RT-PCR.

Possible explanations for the increased rates of virologic failures when the TDF + ABC + 3TC combination was used include: (1) a pharmacodynamic phenomena in which drug-drug antagonism results; decreasing relative NRTI potency, (2) a pharmacokinetic interaction resulting in reduced intracellular or plasma levels, or finally (3) a low viral genetic barrier to resistance results from the combination of this particular nucleoside combination.

First, the evaluation of the relative antiviral potency of individual nucleosides or dual combinations is complicated by the inability to administer these regimens for long durations due to the risk of development of resistance. Antiretroviral potencies of drugs and drug doses has been evaluated in studies of first phase decay rates and magnitude of HIV RNA reductions in studies of 2 weeks or less [22]. One supposition of these studies is that the phase one decay rate is a predictor of antiviral potency of a regimen and that differences between the decay rates of different regimens might translate into differences in longer term virologic suppression. Analysis of phase I HIV RNA decay kinetics in

studies of 2 weeks or less has been used as a predictor of antiviral potency of perspective NRTI regimens. It is unclear whether the gain in precision of the measurement (by doing multiple HIV RNA measures over the 1- 2 week interval) of virologic potency truly justifies the cost and inconvenience of calculating the slopes. Thus, if some simpler method could give the same information as the slope, then that measure could be used instead of the slope. Wu et al have shown a high correlation between the change in HIV RNA at week 1 and the slope of the phase I decay [23-25].

The short duration of NRTI mono or dual therapy also allows for the prompt addition of drugs to comprise a fully acceptable combination regimen before significant risk of drug resistance develops. Brief courses of monotherapy for several antiretroviral drugs, including TDF and ABC, have been given and found to be safe without the emergence of premature resistance: In a viral dynamics study of TDF monotherapy in 10 antiretroviral-naïve patients no evidence of nucleoside mutations were detected after 21 days of treatment [26]. An escalating-dose study of TDF monotherapy for 28 days in 38 antiretroviral patients also did not show emergence of new nucleoside mutations from baseline [27]. Abacavir monotherapy has been given in several studies for short durations with subsequent good clinical responses upon addition of a fully potent regimen [28]. Miller et al. evaluated antiviral potency and genotypic and phenotypic susceptibility of abacavir monotherapy followed by the addition of zidovudine and lamivudine [29]. Sixty antiretroviral-naïve patients were randomized to receive 100, 300 or 600mg abacavir twice daily. With the exception of one patient at week 8 who developed the K65R mutation, no subjects developed new RT mutations prior to week 12. However at week 12, 26/38 subjects were still on abacavir monotherapy and had genotypic data: 18 out of 26 subjects had new RT mutations. **These data indicate that short courses of TDF and/or ABC monotherapy should be safe and unlikely to result in new on-treatment RT mutations.**

The pharmacokinetic interaction of ABC + TDF will be evaluated by comparing steady-state intracellular and plasma concentrations of each nucleoside alone and then again when dosed in combination. Although preliminary data has not suggested a significant intracellular interaction: The Tonus Study [3], a pilot study of once daily ABC/TDF/3TC, plasma concentrations were evaluated at month 1: 32/37 patients had adequate Cmin concentrations for all three nucleosides. In a random subset of 14 patients intracellular nucleoside concentrations were also measured and failed to show a major interaction. In a study by Hawkins et al [30], CBV-TP and TDF-DP were evaluated in a cohort of 13 subjects with viral suppression and on a stable regimen of ABC/TDF/3TC. After substitution of either TDF or ABC with another nucleoside, intracellular

concentrations were measured of the companion nucleoside. No change in intracellular concentrations was noted for either TDF-DP or CBV-TP. This study is limited, however, because all patients had successfully suppressed their plasma HIV RNA on the triple nucleoside regimen. Thus, if altered pharmacokinetics only occurs in patients with failure on this triple nucleoside regimen, then this study would not be able to detect this difference as no patients were failing at enrollment. CCTG 584 will better evaluate a potential PK interaction by: (1) evaluating monotherapy and combination therapy separately, (2) comparing concentrations of intracellular triphosphate levels and (3) by evaluating the induction or suppression of certain cellular enzymes critical for cellular nucleoside transportation.

Finally, the third possibility of a low genetic barrier to resistance leading to increased rates of virologic resistance will be evaluated by serial genotypic evaluations. Specimens for genotypic analysis will be collected and run in real-time at baseline and after NRTI dual-therapy with ABC + TDF. If significant mutations are detected, then day 7, post-monotherapy, samples will be analyzed and mutations can be discerned as either preexisting or de novo. If more than one patient develops any new NRTI or NNRTI-associated resistance mutations as defined by the updated IAS-USA mutation list, the study will hold enrollment and study progression for those subjects in Sequence I and present the data to an independent review committee for evaluation. Based upon the independent committee's recommendations the study may either continue, continue with study design modification or be discontinued. Multiple specimens for stored plasma will be collected during the mono- and dual-therapy sequences for possible future genotypic analysis of low frequency mutant variants not detected on standard pooled genotypes.

## 3.0 STUDY DESIGN

This is a comparative, open-labeled study of a dual NRTI regimen, TDF + ABC, compared to ABC and TDF monotherapy administered for 7 days. Each patient will be randomized to a 7-day sequence of either ABC or TDF once-daily followed by a 35-day washout period. After completion of the monotherapy sequence and washout period all patients will then receive dual NRTI therapy with TDF + ABC for an additional 7 days. After completion of the dual NRTI sequence patients will enter the HAART treatment stage with the addition of EFV and continue on a once-daily regimen of EFV + ABC + TDF for an additional 14 days. At day 63, TDF will be stopped and 3TC will be substituted. Patients will then continue on a once-daily regimen of EFV + ABC + 3TC for an additional 46 weeks.

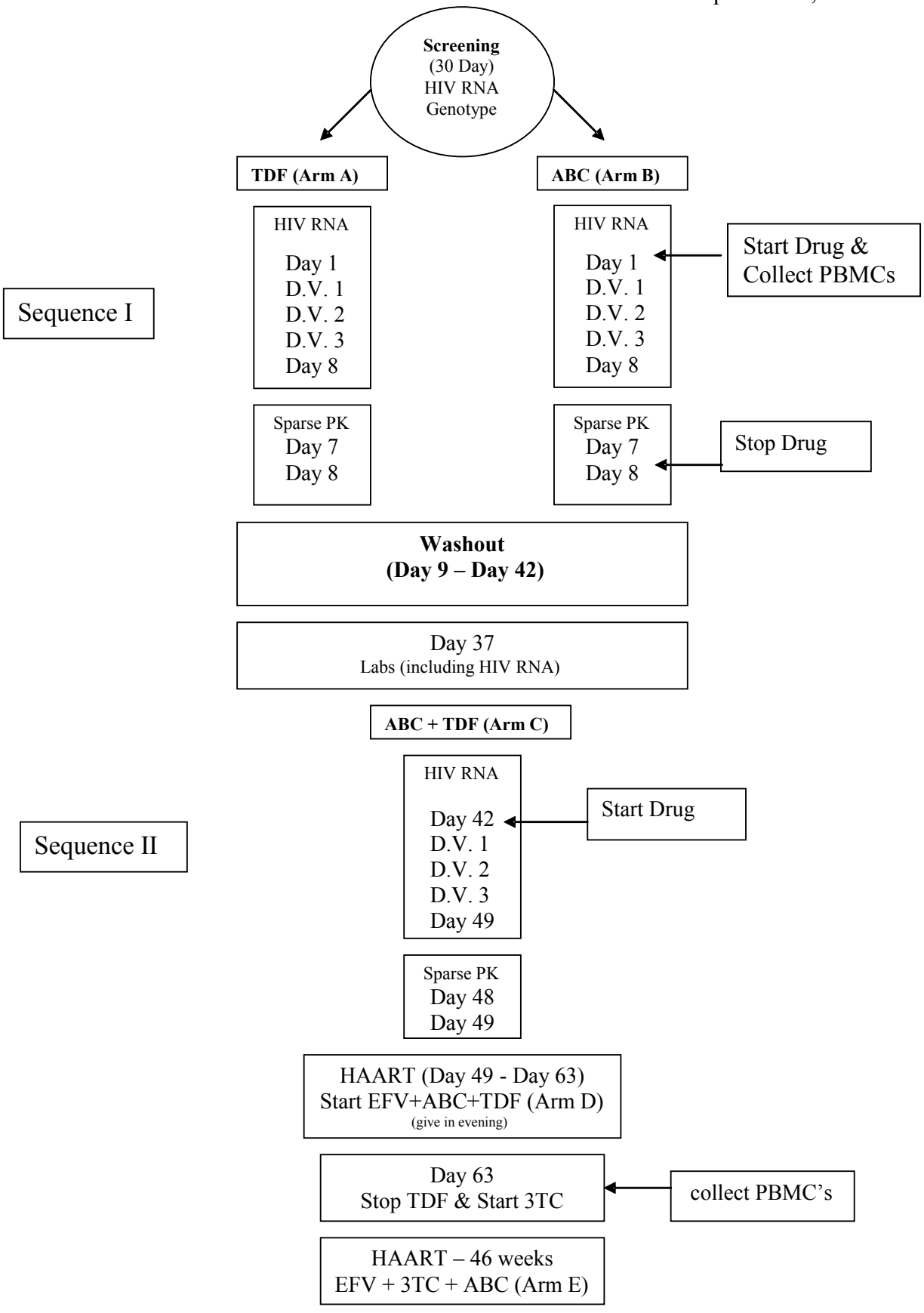
The following short course regimens (dosing given for 7 days) will be compared by the two sequence design:

A. TDF 300 mg PO QD
B. ABC 600 mg PO QD
C. TDF 300 mg PO QD + ABC 600 mg PO QD

A screening genotype will be done to confirm that there are no resistance-associated mutations. The monotherapy sequence (regimen A or B) will continue for 7 days during which time 4 measurements for HIV RNA will be done to calculate the slope of the phase I viral decay. On day 1, PBMCs for baseline RT-PCR of nucleoside transport enzymes will be collected. On days 7 and 8, serial blood specimens will be collected for PK data for plasma and intracellular levels of TDF and ABC. A specimen of blood will be stored for future genotypic analysis if needed. This will be followed by a 35-day washout period after which patients will enter the dual NRTI therapy sequence (regimen C) for 7 days. During dual NRTI therapy, 4 measurements for HIV RNA will be done to calculate the slope of the phase I viral decay and on day 48 and 49, PK data on both plasma and intracellular levels of TDF + ABC will be collected and a second genotype will be performed in real time. On day 49, after the second 7-day sequence, all patients will receive EFV in addition to the dual NRTI combination (regimen D) for 14 days. Afterwards, on day 63, a second sample of PBMC's for RT-PCR of nucleoside metabolic enzymes will be collected. On the same day, TDF will be discontinued and 3TC will be substituted. Patients will then continue for and additional 46 weeks of HAART (regimen E).

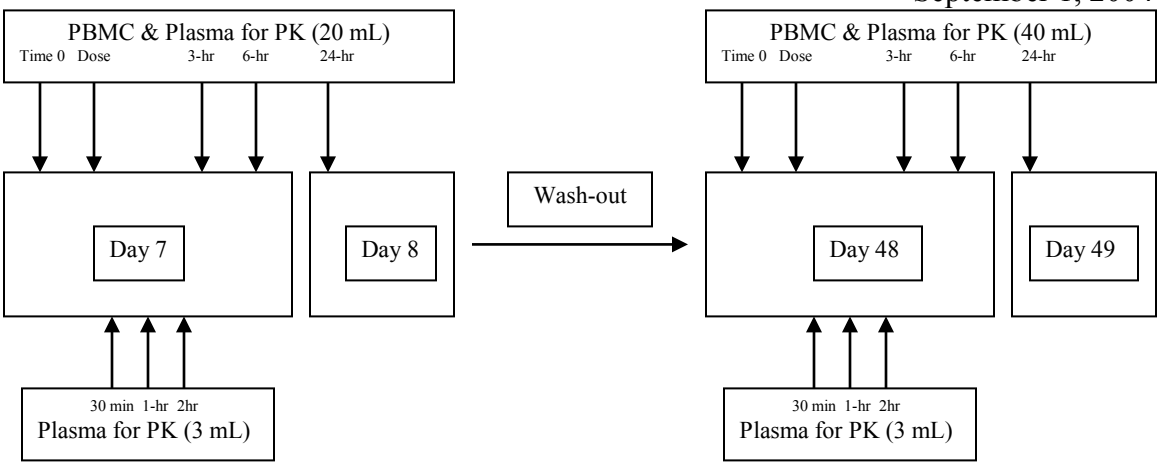
D: EFV 600 mg QD + ABC 600 mg QD + TDF 300 mg QD
E: EFV 600 mg QD + ABC 600 mg QD + 3TC 300 mg QD

A total of 20 patients will be randomized to receive the two sequences of therapy. The sequences will be given in the following fashion (note: D.V. means viral Dynamic Visit):


Screening
(30 Day)
HIV RNA
Genotype
TDF (Arm A)
ABC (Arm B)
Sequence I
HIV RNA
Day 1
D.V. 1
D.V. 2
D.V. 3
Day 8
HIV RNA
Day 1
D.V. 1
D.V. 2
D.V. 3
Day 8
Start Drug &
Collect PBMCs
Sparse PK
Day 7
Day 8
Sparse PK
Day 7
Day 8
Stop Drug
Washout
(Day 9 – Day 42)
Day 37
Labs (including HIV RNA)
ABC + TDF (Arm C)
Sequence II
HIV RNA
Day 42
D.V. 1
D.V. 2
D.V. 3
Day 49
Start Drug
Sparse PK
Day 48
Day 49
HAART (Day 49 - Day 63)
Start EFV+ABC+TDF (Arm D)
(give in evening)
Day 63
Stop TDF & Start 3TC
collect PBMC's
HAART – 46 weeks
EFV + 3TC + ABC (Arm E)

A total of 20 patients will be randomized in a 1:1 fashion in the first sequence to receive 7 days of monotherapy with TDF or ABC alone. After the washout period all patients will receive 7 days of TDF + ABC dual therapy in the second sequence. If both the study site and the patient are willing and able to attend a Saturday visit then it would be preferable to initiate Sequence 1 and/or Sequence 2 on a Wednesday or Thursday. This will allow for doses of study medication prior to PK assessment to be witnessed doses. Otherwise patients would need to initiate Sequence 1 and Sequence 2 on a Tuesday. This would allow for all visits to occur during the work week, obviating the need for weekend visits, with sparse PK collection occurring on Monday-Tuesday of the following week after initiation of study drug. Since 100% medication adherence is necessary for an accurate PK assessment, patients will be asked to allow phone calls from study personal to remind them to take study medication on days that do not require a study visit. **During Sequence 1 and Sequence 2 all medication should be taken with food as a single *morning* dose. During the HAART portion of the study medications should also be taken with food, but as a single *evening* dose.**

Samples for sparse TDF and ABC plasma and intracellular levels will be collected on days 7-8 and days 48-49. During Sequence 1: the first intracellular (PBMC) and plasma PK sample will be collected (time 0) and then a witnessed dose of medication will be given, and subsequent intracellular and plasma samples will be collected at 3-hr and 6-hr post dose. Additional, low-volume blood samples for plasma PK will be collected after the witnessed dose at 30 minutes, 1 hour and 2 hour post witnessed dose. No additional doses of TDF or ABC monotherapy will be given after day 7. The following day the patient will return for a fourth specimen that will represent the 24-hr post-dose. During Sequence 2: the first intracellular (PBMC) and plasma PK sample will be collected (time 0) and then a witnessed dose of medication will be given, and subsequent intracellular (PBMC) and plasma samples will be collected at 3-hr and 6-hr post dose. Additional, low-volume blood samples for plasma PK will be collected after the witnessed dose at 30 minutes, 1 hour and 2 hour post witnessed dose. On the following day, day 49, the a.m. dose will be held and the 24-hr post dose PK level will be collected. That same evening the patient will begin the HAART portion of the study with the addition of EFV to continue on a once-daily regimen for EFV + ABC + TDF for the next 14 days. For the remainder of the study, patients will be encouraged to continue p.m. dosing.




PBMCs will also be collected to evaluate potential interactions of nucleoside analogues and host cell transport enzymes responsible for cellular influx and efflux of nucleoside analogues. A baseline sample will be collected on day 1 followed by a second collection on day 63. On day 63, TDF will be stopped and 3TC will be substituted. The patients will then continue for an additional 46 weeks of HAART with once-daily EFV + ABC + 3TC.

If a patient develops a treatment-limiting toxicity during Sequence 1 or Sequence 2 of the study that results in a need to change or stop therapy then that patient will be removed from study and replaced with another study subject. Likewise if a patient misses more than one visit during the viral dynamic measurements he/she will be removed from the study and will be replaced. Additionally, given the risks of prolonged mono and dual-therapy, patients will not be allowed to take more than 7 days of study drug during Sequence 1 and 2. Therefore, a patient will not be able to continue on the study if he/she is not able to complete both PK visits as scheduled.

Patients will have HIV RNA levels drawn on day 37. An HIV genotype will be drawn and run in real time at day 49, but will not be available until shortly after the patient begins the HAART. If the genotype reveals any evidence of drug resistance, the regimen can be modified by the investigator (in consultation with the protocol chairs) to provide the best possible therapy. Any discovery of resistance mutations at day 49 will also prompt retrospective evaluation of stored plasma from day 7 to determine if the resistance was present prior to the start of the second sequence. The protocol team will monitor the day 48 genotypes in real time and data listings will be provided every 3 months. If more than one patient develops any new NRTI or NNRTI-associated resistance mutations as defined by the updated IAS-USA mutation list, the study will suspend enrollment and subjects in Sequence 1 will not progress to Sequence 2. Data will be presented to an independent review committee for evaluation.

Based upon the independent committee's recommendations the study may either continue, continue with study design modification or be discontinued.

Since the study's principle endpoints will be reached at day 63, patients will be offered the option of stopping HAART if their screening and baseline CD4 count as greater than 350 cells/$mm^3$ and plasma HIV RNA was less than 55,000 copies/mL. Otherwise HAART therapy will continue for an additional 46 weeks (48 weeks after completion of the second sequence). Monitoring will include HIV RNA, CD4 cell counts, routine chemistry and hematology and CCTG adherence questionnaires.

Patients who develop a treatment-limiting toxicity during the HAART portion of the study thought to be related to one of the NRTIs, can have one or both of their NRTIs modified at the discretion of the site investigator in consultation with the protocol team (alternate therapy will not be provided by study). Patients who develop a treatment-limiting adverse event related to EFV can receive the best available therapy as recommended by the site investigator (the protocol team should also be consulted). Patients that develop virologic failure will receive a genotype resistance assay (if the HIV RNA is > 1000 copies/mL) and can receive the best available therapy as recommended by the site clinician. Follow up will continue for 48 weeks from start of HAART for the patients with virologic or toxicity failures.

## 4.0 SELECTION AND ENROLLMENT OF SUBJECTS

### 4.1 Inclusion Criteria

4.1.1 HIV-1 infection, as documented by any licensed ELISA test kit and confirmed by Western blot at any time prior to study entry. HIV-1 culture, HIV-1 antigen, plasma HIV-1 RNA, or a second antibody test by a method other than ELISA is acceptable as an alternative confirmatory test.

4.1.2 Antiretroviral naïve defined as no prior therapy.

4.1.3 CD4+ cell count $\geq$ than 200 cells/ $mm^3$ determined by site clinical laboratory within 90 days of screening.

4.1.4 HIV-1 RNA level $\geq$ 5000 copies/mL obtained by site clinical laboratory within 90 days of screening.

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

- Absolute neutrophil count (ANC) ≥ 750/mm$^3$.
- Hemoglobin ≥ 8.0 g/dL.
- Platelet count ≥ 50,000/mm$^3$.
- Calculated creatinine clearance (CrCl) ≥ 50 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.

4.1.6 Negative serum or urine pregnancy test within 30 days of study entry.

4.1.7 Karnofsky performance score ≥ 70.

4.1.8 Men and women age ≥ 18 years.

4.1.9 Ability and willingness of subject or legal guardian/representative to give written informed consent.

4.1.10 If the subject has evidence of recent HIV-1 infection (defined as acquisition in the past 24 months), a resistance assay (either genotype or phenotype from any laboratory) must be obtained and made available for review by the protocol team prior to the screening genotype assay. (The protocol will not provide the resistance assay.) The protocol team will make the decision on whether significant resistance is present that might make randomization into the study a potential risk for the subject.

## 4.2 Exclusion Criteria

4.2.1 Any NRTI or NNRTI-associated resistance mutations as defined by the updated IAS-USA mutation list.

4.2.2 Pregnancy and breast-feeding.

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

4.2.4 Urgent need to initiate antiretroviral therapy, as determined by the patient's primary provider.

4.2.5 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 14 days prior to study entry.

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

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

4.2.8 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 faxed to the UCSD [(619) 298-1379].

## 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

## 5.1 Regimens, Administration, and Duration

### 5.1.1 Regimens

At entry subjects will be randomized to one of two arms with each arm enrolling no more than 10 subjects each. This first 7-day course of mono NRTI comprises Sequence 1:

Sequence 1: Day 1 - Day 7

Arm A: TDF 300 mg q day **(given as an a.m. dose – with food)**

Arm B: ABC 600 mg q day **(given as an a.m. dose – with food)**

After completion of Sequence 1 and a 35-day washout period, subjects will receive a 7 day course of dual NRTI therapy that comprises Sequence 2:

Sequence 2: Day 42 – 48

Arm C: TDF 300 mg q day + ABC 600 mg q day **(given as an a.m. dose – with food)**

After completion of Sequence 2, subjects will enter the HAART portion of the study by the addition of EFV to the dual NRTI regimen of Sequence 2.

HAART: Day 49 through Day 63 (first two weeks of HAART)

Arm D: TDF 300 mg q day + ABC 600 mg q day + EFV 600 mg q day **(given as a p.m. dose – with food)**

On day 63, TDF will be stopped and 3TC will be substituted for the remainder of the 48 week HAART portion of the study.

HAART: Day 63 through week 48 (46 weeks)

Arm E: [3TC 300 mg q day + ABC 600 mg q day] fixed dose combination + EFV 600 mg q day **(given as a p.m. dose – with food)**

5.1.2 Administration

NOTE: All antiretrovirals should be administered at the same time. **During Sequence 1 and Sequence 2, study medications should be administered as a single a.m. dose. On days occurring during a study visit the dose should be witnessed and recorded in a CRF. On days not occurring on a study visit, the dose should be recorded via telephone adherence from study staff (if such calls permitted by patient).** Thereafter, during the HAART portion, it is preferable but not required, that study medications should be taken as a single p.m. dose with food.

5.1.2.1 EFV will be administered as a single 600 mg capsule PO q day with food

5.1.2.2 TDF will be administered as a single 300 mg tablet PO q day with food.

5.1.2.3 ABC will be administered as two 300 mg tablets PO q day with food.

5.1.2.4 3TC will be administered in combination with ABC as a fixed dose combination tablet with each tablet containing 300 mg of lamivudine and 600 mg of abacavir.

5.1.3 Duration

5.1.3.1 Sequence 1: Each subject will receive 7 days of therapy.

5.1.3.2 Sequence 2: Each subject will receive 7 days of therapy.

5.1.3.3 HAART: Each subject will receive 48 weeks of therapy.

5.2 Product Formulation and Preparation

5.2.1 Efavirenz (Sustiva®, EFV): 200 or 600 mg capsules. Store at room temperature; 15º - 30º C (59º – 86º F).

5.2.2 Tenofovir (Viread®, TDF): 300 mg tablets should be stored and dispensed in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity and should remain in the original container. Store at 25°C (77°F), excursions permitted to 15°-30°C (59°-86°F).

5.2.3 Abacavir (Ziagen®, ABC): 300 mg tablets. Store 20°-25° C (68°-77°F).

5.2.4 Abacavir and Lamivudine fixed dose combination (Epzicom®) is available as tablets. Each tablet contains 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

## 5.3 Product Supply, Distribution, and Pharmacy

### 5.3.1 Study Product Acquisition

Study medications will be provided by GSK. EFV 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 study 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

### 5.4.2 Prohibited Medications

#### 5.4.2.1 All investigational drugs.

#### 5.4.2.2 Any antiretroviral drug, except study medications

#### 5.4.2.3 All HIV vaccines

#### 5.4.2.4 Any immunomodulators

#### 5.4.2.5 Systemic cytotoxic chemotherapy

#### 5.4.2.6 All of the following systemic drugs:

| Agent by Class | Agents |
|---|---|
| Alternative/Complementary | St. John's wort *(Hypericum perforatum*) |
| | |

| Agent by Class | Agents |
|---|---|
| Antiarrhythmics | Flecainide (Tambocor™) |
| | Propafenone (Rythmol®) |
| | |
| Antihistamines | Astemizole (Hismanal™) |
| | Terfenadine (Seldane™) |
| | |
| Anti-infectives | Rifampin (Rifadin®, Rimactane ®, Rifamate®, Rifater®) |
| | |
| GI Motility | Cisapride (Propulsid™) |
| | |
| HMG Co Reductase Inhibitors | Lovastatin (Mevacor®) |
| | Simvastatin (Zocor ®) |
| | |
| Hormonal Agents | Dexamethasone |
| | Human growth hormone |
| | |
| Psychiatric Medications | Pimozide (Orap®) |
| | |
| Sedative/hypnotics | Midazolam (Versed®) is allowed as a single dose given under monitored conditions for procedures |
| | Triazolam (Halcion®) |
| | |
| Other | Dihydroergotamine (Migranal® and others) |
| | Ergonovine |
| | Ergotamine (Ergostat™, Ergomar™, and others) |
| | Methylergonovine (Methergine™) |

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

5.4.3 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.

5.4.3.1 Systemic medications that interact at CYP3A as substrates, inhibitors, or inducers of the enzyme must be used with caution. These include but are not limited to:

| Agent by Class | Precautionary Concomitant Medications |
|---|---|
| Alternative/complementary | Milk Thistle |
| | |
| Analgesics | Opioids, including: |
| | Codeine |
| | Methadone |
| | Meperidine |
| | Morphine |
| | Pentazocine (Talwin™) |
| | |
| Anesthetics | Propofol (Diprivan™) |
| | |
| Anti-arrhythmics | Amiodarone (Cordarone®) |
| | Bepridil (Vascor®) |
| | Disopyramide (Norpace™) |
| | Encainide (Enkaid™) |
| | Lidocaine (Xylocaine™) |
| | Mexiletine (Mexitil™) |
| | Quinidine (Quinidex®) |
| | |
| Anti-convulsants | Carbamazepine (Tegretol™) |
| | Lamotrigine (Lamictal™) |
| | Phenobarbital (Luminal™) |
| | Phenytoin (Dilantin™) |
| | Valproic acid (Depakene™) |
| | |
| Anti-histamines | Chlorpheniramine (Chlor-Trimetron™ and others) |
| | Diphenhydramine (Benadryl™ and others) |
| | |
| Anti-infectives | Acyclovir (Zovirax™) |

| Agent by Class | Precautionary Concomitant Medications |
|---|---|
| | Aminoglycosides |
| | Amphotericin B (Amphocin™, Fungizone™) |
| | Cidofovir (Vistide™) |
| | Clarithromycin (Biaxin™) |
| | Dapsone |
| | Erythromycin (E-mycin™ and others) |
| | Fluconazole (Diflucan™) |
| | Ganciclovir (Cytovene™) |
| | Isoniazid |
| | Systemic Itraconazole (Sporonox®) |
| | Systemic Ketoconazole (Nizoral®) |
| | Ribavirin (Virazole™) |
| | Rifabutin (Mycobutin®) |
| | |
| | Vancomycin (Vancocin™, Vancoled™) |
| | Voriconazole (Vfend) |
| | |
| Beta blockers (selected agents listed, caution should be exercised for the entire class) | Atenolol (Tenormin™) |
| | Metoprolol (Lopressor™, Toprol™) |
| | Propranolol (Inderal™, Inderide™, and others) |
| | |
| Calcium channel blockers (selected agents listed, caution should be exercised for the entire class) | Amlodipine (Norvasc ®) |
| | Diltiazem (Cardizem® and others) |
| | Felodipine (Plendil®) |
| | Isradipine (DynaCirc®) |
| | Lacidipine (Lacipil™) |
| | Nicardipine (Cardene®) |
| | Nifedipine (Adalat™ and Procardia®) |
| | Nimodipine (Nimotop®) |
| | Nisoldipine (Sular®) |
| | Nitrendipine (Nitrendipine™) |
| | Verapamil (Calan™ and Isoptin®) |

| Agent by Class | Precautionary Concomitant Medications |
|---|---|
| | |
| Hormonal agents | Estrogens and Progesterones |
| | Glucocorticoids |
| Hypoglycemics | Pioglitazone (Actos™) |
| | |
| HMG Co Reductase Inhibitors | Atorvastatin (Lipitor®) |
| | Fluvastin (Lescol®) |
| | |
| Psychiatric medications | Bupropion (Wellbutrin®, Zyban®) |
| | Chlorpromazine (Thorazine™) |
| | Clozapine (Clozaril®) |
| | Fluoxetine (Prozac™ and others) |
| | Nefazodone (Serzone®) |
| | Paroxetine (Paxil™) |
| | Risperidone (Risperdal®) |
| | Venlafexine (Effexor®) |
| | |
| Tricyclic Antidepressants (including but not limited to) | Amitriptyline (Elavil™ and others) |
| | Desipramine (Norpramin™ and others) |
| | Imipramine (Tofranil™ and others) |
| | Nortriptyline (Pamelor™ and others) |
| | |
| Sedative/Hypnotics | All benzodiazepines |
| | Alprazolam (Xanax™) |
| | Clorazepate (Tranxene™) |
| | Diazepam (Valium™) |
| | Estazolam (ProSom™) |
| | Flurazepam (Dalmane™) |
| | Oxazepam (Serax™) |
| | Temazepam (Restoril™) |
| | Busprione (Buspar™) |
| | Zaleplon (Sonata™) |
| | Zolpidem (Ambien™) |
| | |
| Other agents | Chlorzoxazone (Parafon Forte™) |

| Agent by Class | Precautionary Concomitant Medications |
|---|---|
| | Cimetidine (Tagamet™) |
| | Naloxone (Narcan™) |
| | Piroxicam |
| | Promethazine (Mepergan™, Phenergan™) |
| | Sildenafil (Viagra®) - see note below |
| | Warfarin (Coumadin™) |

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**

5.3.4.3 Co-administration of Nephrotoxic Agents

Co-administration of agents with nephrotoxic potential (e.g., amphotericin B, aminoglycosides, cidofovir, acyclovir, ganciclovir, vancomycin) or that are renally excreted (e.g., probenicid) may increase serum drug concentrations of TDF and/or increase the concentrations of the other renal-excreted agents. Additional monitoring may be indicated if subjects are placed on these agents while on TDF.

5.3.4.2 Co-administration of Prednisone

Prednisone < 10 mg (or equivalent) is permitted as a stable or tapering dose.

## 5.5 Adherence Assessment

Throughout the study, the documentation of adherence to study drugs is essential. During each visit an adherence diary will be completed by study personal and reviewed with subjects and adherence assessed and clinical importance of strict adherence reinforced. During weekend visits that do not require a study visit, if permitted by patients, subjects should be contacted by phone (at least one attempt) and dose recorded in adherence diary. An adherence questionnaire will be completed during the HAART portion of the study at weeks 8, 24 and 48.

# 6.0 CLINICAL AND LABORATORY EVALUATIONS

## 6.1 Schedule of Events

| Evaluation | | On-Study Evaluations | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sequence 1 monotherapy | | | | | | | Sequence 2 Dual therapy | | | | | | HAART | TDF switch to 3TC |
| | Screening | Entry | viral dynamic visits: 3 visits between days 2-6 (±1 day) | | | PK | | | ± 1 week | Start | viral dynamic visits: 3 visits between days 43-47 (±1day) | | | PK | PK | ± 3days |
| | Within 30 days of entry | 1 | visit 1 | visit 2 | visit 3 | 7 | 8 | Washout 9-36 | 37 | 42 | visit 1 | visit 2 | visit 3 | 48 | 49 | 63 |
| Informed Consent | X | | | | | | | | | | | | | | | |
| Medical/Medication History | X | | | | | | | | | | | | | | | |
| Documentation of HIV | X | | | | | | | | | | | | | | | |
| Clinical Assessment / AE (include ABC HSR CRF at day 37 for subject restarting ABC) | | X | | | | X | | | X | X | | | | X | | |
| Height, Weight | | X | | | | | | | | | | | | | | |
| EFV prescription given | | | | | | | | | | X | | | | | | |
| Targeted Physical Exam | | X | | | | | | | | | | | | X | | |
| Start Drug | | X | | | | | | | | X | | | | | X | X |
| Observed Dose | | X | X | X | X | X | | | | X | X | X | X | X | | |
| Last dose for Sequence | | | | | | X | | | | | | | | X | | X |
| Complete Adherence Diary | | X | X | X | X | X | | | | X | X | X | X | X | | |

Schedule of Events – Sequence 1 and Sequence 2

| Evaluation | | On-Study Evaluations | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Sequence 1 | | | | | | | Sequence 2 | | | | | | HAART | TDF switch to 3TC |
| | Screening | Entry | viral dynamic visits: 3 visits between days 2-6 (±1 day) | | | PK | | | ± 1 week | start | viral dynamic visits: 3 visits between days 43 -47 (±1 day) | | | PK | PK | ± 3 days |
| | Within 30 days of entry | 1 | visit 1 | visit 2 | visit 3 | 7 | 8 | Washout day 9-36 | 37 | 42 | visit 1 | visit 2 | visit 3 | 48 | 49 | 63 |
| Hematology (local lab) | X | | | | | | | | X | | | | | | | X |
| Chemistry / LFT (local lab) | X | | | | | | | | X | | | | | | | X |
| Urinalysis (local lab) | X | | | | | | | | X | | | | | | | |
| Immunology: CD4+/CD8+ (local lab) | X | X | | | | | | | X | X | | | | | | |
| Pregnancy Testing (local lab) | X | X | Whenever pregnancy is suspected | | | | | | | | | | | | | |
| Virology : (UCSD lab) Plasma HIV-1 RNA PCR | X | X | X | X | X | | X | | X | X | X | X | X | | X | |
| HIV Genotype (UCSD lab) | X | | | | | | | | | | | | | | X | |
| Stored Plasma | X | X | X | X | X | | X | | X | X | X | X | X | | X | |
| Sparse PK sampling (PBMC and Plasma) | | | | | | X | X | | | | | | | X | X | |
| PBMC's for cellular enzymes | | X | | | | | | | | | | | | | | X |
| Shipment to **UCSD** (HIV RNA and genotype) | X | | | | | | X | | | | | | | | X | |
| Shipment to **USC** (All plasma levels, ABC PBMCs, RT-PCR) | | | | | | | X | | | | | | | | X | X |
| Shipment to **Gilead** (TDF PBMCs – not plasma) | | | | | | | X | | | | | | | | X | |

Schedule of Events – HAART portion

| Evaluation | On study Evaluations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Weeks from start of HAART (+/- 1 week) (Weeks post sequence 2 – day 49) | | | | | | Virologic Failure | Regimen Change due to Toxicity | Premature Treatment Discontinuation |
| | HAART week 4 | HAART week 8 | HAART week 16 | HAART week24 | HAART week 36 | HAART week 48 | | | |
| Clinical Assessment / AE | X | X | X | X | X | X | X | X | X |
| Targeted Physical Exam | X | | | | | X | X | X | X |
| Hematology / WBC (local lab) | X | X | X | X | X | X | X | X | X |
| Chemistry / LFT (local lab) | X | X | X | X | X | X | X | X | X |
| Urinalysis (local lab) | X | | | | | X | X | X | X |
| Immunology: CD4+/CD8+ (local lab) | X | X | | X | X | X | X | X | X |
| Plasma HIV-1 RNA PCR (UCSD lab) | | | | X | | X | X | X | X |
| Plasma HIV-1 RNA PCR (local lab) | X | X | X | | X | | | | |
| HIV Genotype (UCSD lab) | | | | | | | X | | |
| Stored Plasma | X | X | X | X | X | X | X | X | X |
| Adherence Questionnaire | | X | | X | | X | X | X | X |
| Shipment to **UCSD** (HIV RNA) | | | | X | | X | X | X | X |

## 6.2 Definitions for Schedule of Events – Timing of Evaluations

### 6.2.1 Prerandomization 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 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 faxed to the UCSD [(619) 298-1379].

Pre-Screening Site Clinical Labs

Plasma HIV RNA and CD4 clinical labs must be available prior to screening and have been obtained no more than 90 days prior to screening.

Screening

Study screening laboratories must be determined within 30 days of study entry (Day 1). Screening and entry evaluations must be separated by at least 48 hours.

Laboratory Results - Screening

All laboratory testing, save the HIV RNA and genotype, will be coordinated through the sites local laboratory and results will be tracked by the CCTG Data Center. The plasma HIV RNA and the genotype will be done centrally and results will be sent back to the sites within the 30 day screening period.

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

The total blood volume for screening labs is 35 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.

Randomization

Upon receipt of the screening laboratory eligibility, the randomization CRF should be completed and faxed to the CCTG Data and Biostatistical Unit at (619-298-1379). This randomization CRF will include PID, patient initials, screening laboratory eligibility sign off, genotype eligibility sign off and study site.

The randomization will be done by the Data and Biostatistical Unit and will be faxed to the site within 2 working days of receipt of a correctly completed randomization CRF. Eligible participants will be randomized to one of two mono NRTI therapy arms (TDF alone or ABC alone) for the first sequence.

Entry

The entry evaluation should be scheduled within 30 days of the screening visit. The randomization should be completed and the 7-day supply of treatment for the first sequence should be available. The first dose of study medication should be given and witnessed by the study coordinator **after** drawing the baseline laboratories. A 7-day adherence diary should be completed by study personal for all doses of medication during the 7 day sequence.

6.2.2 On-Study Evaluations

Evaluations should occur after randomization. Ideally, start dates for Sequence 1 (day 1) and Sequence 2 (day 42) should occur on either a Wednesday or Thursday if the patient and site are willing and/or able to have Saturday visits – otherwise on Tuesday. Afterwards 3 viral dynamic visits should occur between days 2 – 6 and days 43-47, respectively, with a visit window of $\pm$ 1 day. Should the start date begin on a Wednesday or Thursday, then the PK visits should occur on days Tuesday-Wednesday or Wednesday-Thursday, respectively. If the start date occurred on a Tuesday then the PK visits would occur the following Monday-Tuesday. Thereafter, while on HAART therapy, study evaluations will occur on day 63 (week 2 from day 49) and weeks 4, 8, 16, 24, 36 and 48 or as needed. In instances of virologic failure and/or premature treatment discontinuation evaluations would also need to occur.

Total blood volume for laboratory evaluations from days 1 – 49 will be approximately 448 mL.

On day 37, prior to Sequence 2, those patients that were randomized to ABC monotherapy during Sequence I should be evaluated for evidence of potential ABC hypersensitivity at any time since study initiation. If a patient has evidence of ABC hypersensitivity symptoms all study medication should be held and the protocol team notified.

6.2.3 Evaluations for randomized or registered subjects who do not start study treatment:

No follow-up evaluations will be required for subjects that are not randomized and/or do not start study treatment.

6.2.4 Treatment Discontinuation Evaluations

1. Subjects on either Sequence 1 or Sequence 2 portion of the study, who discontinue treatment regimen before the end of Sequence 2 will be removed from the study.
2. Subjects that miss more than one scheduled visit during the viral dynamics portion will need to be removed from the study.
3. Subjects that miss either of the PK visit days (there is no visit window period for PK visits) will need to be removed from the study.

Subjects should have a Premature Treatment Discontinuation visit (see section 6.1) within 14 days after stopping their antiretrovirals.

Subjects on the HAART therapy portion of the study, who discontinue their study regimens at day 63 or before the end of the study will not be followed until study completion. They will return for a Premature Termination Visit.

6.2.5 Change in Antiretrovial Regimen

Subjects on the HAART therapy portion of the study, who change their treatment regimen before the end of the study and who choose to be followed on the study, will come in for a visit for therapy change and the new regimen should be initiated within 72 hours.

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 during HAART portion of study

Virologic failure will be decided on a case by case basis by the local site's study investigator in collaboration with the protocol team. Suggested criteria include: a < 2.0 log drop in plasma HIV RNA by week 8 from day 49 and/or a $\geq$ 0.5 log increase from nadir. For subjects who reach a plasma HIV-1 RNA failure, a 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 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 HAART.

6.2.7 Post-Treatment Evaluations

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

6.2.7 Premature Treatment Discontinuation

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

6.2.8 Pregnancy

Women who become pregnant during the study will be required to permanently discontinue their study regimens. 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

Include antigen, antibody, or other recognized methods of documenting HIV infection from subject's source documentation.

If the subject has evidence of recent HIV infection, defined by infection within 24 months, a resistance assay (either genotype or phenotype) from any laboratory must be obtained and made available for review by the protocol team prior to screening. Obtaining resistance testing for patients with suspected recent HIV infection is part of standard medical care according to current guidelines. (The protocol will not provide the resistance assay.) The protocol team will make the decision on whether significant resistance is present that might make entry into the study a potential risk for the subject. If the patient is allowed to enter the study, another genotypic analysis will be provided by the study. Note: this resistance assay is different than the one obtained at screening which is provided by the study.

Recent HIV Infection

The following are possible laboratory and clinical symptoms that should prompt consideration of recent or acute HIV infection: (This is not intended to be a complete list, but should help the investigator consider recent HIV infection)

Negative HIV ELISA (or other screening test) within the past 24 months.

Positive ELISA or other screening test with negative or indeterminate (≤ 2 bands) Western blot in the past 24 months.

Detuned HIV ELISA with an OD reading < 0.75 with a positive standard HIV ELISA in the past 6 months

A history consistent with acute retroviral syndrome (HIV seroconversion illness) in the past 24 months and no previous HIV ELISA in the past 24 months (in a subject who has not had a previous HIV test). Seroconversion symptoms, in the absence of other defined etiology, include the following:

- Fever
- Sore throat
- Fatigue
- Headache
- Nausea
- Weight loss
- Myalgia
- Rash
- Diarrhea
- Vomiting

6.3.2 Medical 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.

6.3.3 Medication History

At screening, a medication history will be obtained and must be recorded in the source documents, including:

Complete history of any prescription medications taken for the treatment or prophylaxis of opportunistic infections, including actual or estimated start and stop dates in the past 30 days. This will be recorded in the concomitant medication form.

All prescription medications in addition to those noted taken within 30 days of entry, including actual or estimated start and stop dates.

Nonprescription medications taken within 30 days of entry. Include actual or estimated start and stop dates.

Alternative therapies and/or dietary supplements taken within 30 days of entry or since the last clinic visit. Include actual or estimated start and stop dates.

Allergies to any medications and their formulations must be documented.

6.3.4 Concomitant Medications

The following medications should be recorded on the case report forms (CRFs):

Exclusionary medications (Section 5.4.2)

Precautionary Medications (Section 5.4.3)

Please refer to the most recent study medication's package insert or investigator's brochure to access additional current information on prohibited and precautionary medications.

At the following study visits all concomitant medications taken since the last visit will be recorded in the source documentation and entered into the concomitant medication CRF (log): screening,

entry to sequence 1, entry to sequence 2 and at each study visit during the HAART treatment period. A copy of the concomitant medication log should be faxed to the CCTG Data Center at the end of study. The following medications and/or class of medications should be included on the CRFs: all prescription medications.

During the study, all modifications to study drugs including subject-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation of treatment will be recorded on the CRFs at each visit. Subject-initiated and protocol-mandated interruptions include both inadvertent and deliberate interruptions of study drug(s) dose(s) for a period of > 1 day.

6.3.5 Study Treatment Modifications

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

6.3.6 Nadir CD4+

The subject's prior nadir CD4+ cell count (absolute value and date) should be documented during screening and, when possible, a copy of the nadir CD4+ 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.

6.3.7 Clinical Assessments

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 entry, at completion of sequence 2, at weeks 4 and 48 of HAART therapy and in instances of virologic failure or premature treatment discontinuation if they should occur. Documentation must include any HIV-related, toxicity-related, or AIDS-defining events.

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 $\geq$ 2 signs and symptoms, HIV-related and AIDS-defining events and deaths on the CRFs. That have occurred since the last visit. CRFs should be completed within 48 hours of a 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, HIV-related 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 other visits, record all Grade ≥ 2 laboratory toxicities 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, phosphorous, blood urea nitrogen, creatinine, glucose, AST/ALT, alkaline phosphatase, total bilirubin.

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, electrolytes (sodium, potassium, chloride, and bicarbonate), calcium, and phosphate will be performed in real time at the site's local laboratory.

Blood volume: 7 mL

Urinalysis Test

Specific gravity, pH, protein and blood will be performed in real time at the site's local laboratory.

5 ml urine

Pregnancy Test

For women with reproductive potential: Urine β-HCG (urine test must have a sensitivity of 25-50 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

CD4/CD8

Obtain absolute CD4/CD8 count and percentages within 30 days of 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.

CD4+ and CD8+ cell counts and percentage evaluations should be performed at the same local laboratory for baseline calculation and throughout the course of the study.

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

Blood volume: 5 mL

6.3.10 Virologic Studies

Plasma HIV-1 RNA

Screening HIV-1 RNA must be performed at a central lab within 30 days prior to study entry.

CD4 and HIV RNA eligibility will be determined by laboratories obtained from patient's provider as part of standard of care within 90 days of screening (prior to screening). The calculated baseline value (used for analysis) will be the mean of the pre-entry and entry determinations, which must have been obtained at least 48 hours apart.

Plasma HIV-1 RNA should be collected at every study visit, except day 7 and day 48, during Sequence 1 and 2 and during scheduled visits of HAART therapy. HIV RNA samples for screening, Sequence 1, Sequence 2 and weeks 24 and 48 of HAART will be performed at a central laboratory – all other HIV RNA testing during the HAART portion of the study will be done at the site's local laboratory.

Genotype Resistance Assay

Samples for genotypic analysis of plasma HIV-1 RNA obtained at screening and day 7. The screening sample will be run in real-time, while day 7 sample will be stored for possible future analyses.

An HIV genotype will be performed in real time at day 49, but will not be available until after patient begins EFV. Any identification of new resistance mutations will prompt a retrospective evaluation of stored plasma from day 7. And any evidence of virologic failure will also prompt a genotype evaluation.

Samples for genotypic analysis obtained at the time of virologic failure will be tested in real time for subject management by a central laboratory**.**

Stored Plasma

Stored Plasma will be collected at study entry and during every visit during Sequence I and II (except days 7 and 48) and HAART therapy and in cases of virologic failure and/or premature treatment discontinuation for future studies. Specimens will be batched and stored in the central CCTG specimen repository.

Blood volume: 20 mL – for screening
Blood volume: 15 mL – for all other virology collections

6.3.11 Pharmacokinetic Studies

Sequence 1 (monotherapy)

At day 7 of Sequence 1 a sparsely populated pharmacokinetic profile will be collected from all patients. This includes a pre-dose intracellular (PBMC) and plasma trough level (time 0) of TDF or ABC monotherapy followed by a witnessed dose of study medication and two additional intracellular (PBMC) and plasma samples collected 3 and 6 hours post witnessed dose. Additional plasma-only samples should be collected at 30 minutes, 1-hr and 2-hr post dose. After each sample is collected PBMC and plasma separation should be done immediately after collection and stored for shipping the next day.

At day 8 of Sequence 1, a 24-hour post dose intracellular (PBMC) and plasma sample should be collected before any dose of study medication is given. All 7 samples from the sparse PK (time 0, 30-

min, 1-hr, 2-hr, 3-hr, 6-hr and 24-hr post dose) should be sent **overnight** to the appropriate off-site lab for analysis. If the patient is on the ABC arm then both PBMCs and plasma specimens should be sent to USC (one shipment). If the patient is on the TDF arm then the PBMCs should be sent to Gilead **AND** the plasma should be sent to USC (two separate shipments).

Blood volume (PBMC-plasma): 20 mL – each draw
Blood volume (plasma only): 3 mL – each draw
Blood volume: 89 mL- over 2 days

Sequence 2 (dual-therapy)

At day 48 of Sequence 2, a sparsely populated pharmacokinetic profile will be collected from all patients. This includes a pre-dose intracellular (PBMC) and plasma trough levels (time 0) of TDF + ABC dual-therapy followed by a witnessed dose of study medication and two additional intracellular (PBMC) and plasma samples collected 3 and 6 hours post witnessed dose. Additional plasma-only samples should be collected at 30 minutes, 1-hr and 2-hr post dose. After each sample is collected PBMC and plasma separation should be done according to PBMC processing protocol after collection and stored for shipping the next day.

At day 49 of Sequence 2 a 24-hour post dose intracellular (PBMC) and plasma sample should be collected and processed. All 7 samples from the sparse PK (time 0, 30-min, 1-hr, 2-hr, 3-hr, 6-hr and 24-hr post dose) should be sent **overnight** to appropriate off-site lab for analysis. Since the patient is on dual therapy and the each drug is measured in separate labs each PBMC samples should be split at each time-point with half of the samples shipped to Gilead and half shipped to USC (two separate shipments). **ALL** plasma samples should be sent to USC. Since samples have to be split we will need to collect double the blood for the intracellular (PBMC) PK:

Blood volume (PBMC-plasma): 40 mL – each draw
Blood volume (plasma only): 3 mL – each draw
Blood volume: 169 mL- over 2 days

### 6.3.12 PBMCs for RT-PCR

At day 1 and day 63 a PBMC sample for RT-PCR of nucleoside analogue transport enzymes (enzymes for efflux, influx) will be collected. The day 1 specimen should be stored and sent with day 8

PK specimens to USC. Day 63 specimen should be sent to USC after collection and processing.

Blood volume: 20 mL

6.3.17 Adherence Questionnaires

Adherence questionnaires will be conducted by study personal during sequence 1 and 2. Adherence questionnaires will also be conducted on weeks 8, 24, and 48 of HAART 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 TOXICITY MANAGEMENT

Specific management of toxicity will be discussed only to those medications thought to be related to any of the study-provided medications (include: TDF, ABC, 3TC and EFV). 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.

7.1 Criteria for subject management

The toxicities expected to be attributed to one or more study medications may have one or more of the following dosing modifications:

a. all study drugs may be held;

b. if during the Sequence 1 or Sequence 2 of the study a toxicity thought to be related to one of the NRTI's occurs that results in the need to switch or discontinue study medications, then that subject would be removed from study;
c. if after the Sequence 2 of the study a toxicity thought to be related to one of the NRTI's occurs, the regimen may be switched to an alternative NRTI;
d. if after Sequence 2 of the study a toxicity thought to be related to EFV occurs, then best available therapy as recommended by the site investigator may be offered and the patient may continue on the study.

NOTE: The protocol endpoint must be notified by e-mail of all toxicities that result in a change (temporary hold or discontinuation) in regimen. Patients that develop limiting toxicities after Sequence 2 thought to be related to study medications should continue to receive follow up for 48 weeks.

## 7.2 Commonly occurring adverse events

### 7.2.1 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 $\geq$ 2 creatine in subjects receiving TDF (See section 7.2.14). 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.

However, in the event that a subject develops a Grade 1 or 2 reaction considered to be drug-related to either NRTI's during Sequence 1 or Sequence 2 of the study, then this subject should be removed from the study **only if** this results in a need to discontinue or substitute any of the study drugs. Otherwise study subject may continue in study.

### 7.2.2 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** to an NRTI should have all medications held or have their NRTI regimen switched for an alternative NRTI regimen. 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 and laboratories repeated within 2 weeks.

Likewise if the Grade 3 adverse event is thought to be related to EFV then an alternative therapy may be offered at the discretion of the site investigator. 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.

However, in the event that a subject develops a symptomatic Grade 3 reaction considered to be **study drug-related** to either the NRTI's during Sequence 1 or Sequence 2 of the study, then this subject should be removed from study.

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.

7.2.3 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. 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 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. A new regimen may be chosen at the discretion of the local investigator. Subjects experiencing Grade 4 adverse events requiring permanent discontinuation of study drug therapy 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.

However, in the event that a subject develops a symptomatic Grade 4 reaction considered to be study drug-related to either the NRTI's during Sequence 1 or Sequence 2 of the study, then this subject should be removed from study.

7.2.4 Rash

Subjects receiving ABC who develop rash of any grade should be evaluated for the possibility of an HSR or a serious skin reaction such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme and managed appropriately as outlined below. 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. The 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.

Grade 1 or 2

Study treatment should continue without interruption (assuming no evidence of ABC hypersensitivity reaction is present). Subjects with a Grade 1 or 2 rash may be treated symptomatically with permitted antipyretic, antihistamine, and/or non-steroidal anti-inflammatory medications, but should be monitored closely by the local investigator.

Grade 3 or 4

A rash of Grade 3 or 4 necessitates that all study medications should be held for any Grade 3 or 4 rash unless the rash is determined to be unrelated to study medications. Upon resolution to Grade $\leq 1$, the site investigator should discuss alternative regimens with the protocol chairs.

### 7.2.5 Hypersensitivity Reaction (HSR) with ABC

All suspected cases of ABC HSR should be considered serious adverse experiences. The diagnosis of hypersensitivity to ABC remains a clinical diagnosis. There is no pathogenomonic clinical sign or laboratory finding that renders the diagnosis.

Fatal HSRs have been associated with ABC therapy. ABC therapy SHOULD NOT be restarted following an HSR, because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Subjects who develop signs or symptoms of hypersensitivity should discontinue treatment as soon as an HSR is first

suspected and should seek medical evaluation immediately, preferably on the same day that symptoms are reported.

Management of HSR

All subjects that receive ABC will be given a wallet-sized card of common ABC HSR symptoms.

**Patients developing signs or symptoms of hypersensitivity MUST contact their doctor immediately for advice. If a hypersensitivity reaction is diagnosed the abacavir-containing product MUST be discontinued immediately.** The patient should be asked to return all unused supplies of the abacavir-containing product for disposal to prevent an accidental re-challenge.

**An abacavir containing medicinal product (Ziagen, Trizivir or the abacavir/lamivudine fixed dose combination, Epzicom), MUST NEVER be administered following a hypersensitivity reaction, as more severe symptoms will recur within hours and may include life-threatening hypotension and death.**

To avoid a delay in diagnosis and minimise the risk of a life-threatening hypersensitivity reaction, the abacavir-containing product should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible (respiratory diseases, flu-like illness, gastroenteritis or reactions to other medications).
Symptomatic support for abacavir hypersensitivity may be indicated. This should include, for example, administration of intravenous fluids to patients who develop hypotension. Antihistamines or corticosteroids have been used in cases of abacavir hypersensitivity, however there are no clinical data demonstrating the benefit of these in the management of the reaction.

Laboratory and other investigations which may be useful in the evaluation and treatment of abacavir hypersensitivity include, but may not be limited to, measurement of ALT, AST, creatine phosphokinase, serum creatinine and white blood cell differential count and chest x-ray, if respiratory symptoms are present.

If a subject reports symptoms suggestive of hypersensitivity, s/he should be instructed not to take any additional doses and should be evaluated at the clinic. The evaluation should consist of a careful history and physical examination. Laboratory studies should be obtained as clinically indicated. There is no diagnostic test available to confirm the clinical diagnosis. If upon evaluation the subject does have a presentation consistent with

hypersensitivity, therapy with ABC must be permanently discontinued and the protocol team informed.

Discontinuation and Reintroduction of ABC Therapy

Subjects who discontinue ABC for any reason should be queried regarding signs and symptoms of HSR. This should be done at the beginning of Sequence 2 (day 37) for those patients randomized to ABC during Sequence 1. An ABC HSR checklist will be completed on day 37 and whenever symptoms of ABC HSR are suspected. Patients will be given a wallet-sized ABC HSR symptom card to carry when they receive ABC medication.

If therapy with abacavir has been discontinued and restarting therapy is under consideration, the reason for discontinuation should be evaluated to ensure that the patient did not have symptoms of a hypersensitivity reaction. **If hypersensitivity reaction cannot be ruled out, no medicinal product containing abacavir (Ziagen, Trizivir or the abacavir/lamivudine fixed dose combination) should be restarted.**

There have been infrequent reports of hypersensitivity reaction following reintroduction of an abacavir-containing product where the interruption was preceded by a single key symptom of hypersensitivity (rash, fever, malaise/fatigue, gastrointestinal symptoms or a respiratory symptom). If a decision is made to restart any abacavir-containing product in these patients, this should be done only under direct medical supervision.

On very rare occasions hypersensitivity reactions have been reported in patients who have re-started therapy, and who had no preceding symptoms of a hypersensitivity reaction. If a decision is made to re-start an abacavir-containing product, this must be done only if medical care can be accessed readily by the patient or others.

If symptoms consistent with HSR are **not** identified, reintroduction of ABC can be undertaken with caution. This will be done for all patients randomized to ABC on Sequence 1 who then start Sequence 2. Patients will be seen 4 out of 7 days after starting ABC in Sequence 2. Reintroduction of the drug must occur in a setting where the subject can readily access medical care.

After Sequence 2, the physician may deem that reintroduction of ABC is medically advantageous or necessary in a subject who had a documented intercurrent medical illness, which included one or more symptoms that could have also represented an ABC HSR. The primary responsibility for the decision to restart ABC in this setting rests with the site principal investigator or his/her physician designee. The subject must be informed

of the possibility of rapid onset HSR. Reintroduction in these circumstances must be done under close medical supervision.

Essential patient information

***Investigators must ensure that patients are fully informed regarding the following information on the hypersensitivity reaction:***

- Patients must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life threatening reaction or death.

- Patients developing signs or symptoms possibly linked with a hypersensitivity reaction **MUST CONTACT their doctor IMMEDIATELY**.

- Patients who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal product (Ziagen, Trizivir or the abacavir/lamivudine fixed dose combination) again.

- In order to avoid restarting the abacavir-containing product, patients who have experienced a hypersensitivity reaction should be asked to return the remaining tablets or oral solution to the pharmacy.

- Patients who have stopped an abacavir-containing product for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting.

- Each patient should be reminded to read the Package Leaflet included in the pack.

- Patients should be reminded of the importance of removing the Alert Card (wallet size card) and keeping it with them at all times.

Reporting of Hypersensitivity Reactions

All cases of potential abacavir hypersensitivity should be reported as Serious Adverse Events (SAE).

Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme

Serious skin reactions such as Stevens Johnson Syndrome, Toxic Epidermal Necrolysis or Erythema Multiforme have been reported very rarely in patients taking abacavir-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the abacavir hypersensitivity reaction, but they do have features typical of these serious skin reactions.
If a serious skin reaction develops, the abacavir-containing product should be discontinued, and the patient should not be rechallanged with any abacavir-

containing medicinal product (Ziagen, Trizivir or the abacavir/lamivudine fixed dose combination).
As many products other than abacavir also cause these serious skin reactions, all other medicinal products that the patient is receiving should also be reviewed and discontinued as appropriate.

7.2.6 Nausea and Vomiting

Grade 1 or 2

Study treatment should continue without interruption. Subjects with Grade 1 and 2 nausea or vomiting may be treated symptomatically with permitted oral antiemetic therapies or antiemetic suppositories. Subjects should be instructed to take medications with food.

Grade 3 or 4

Subjects with Grade 3 or 4 study-related nausea and vomiting should interrupt all study drugs until the toxicity grade returns to Grade $\leq 2$ or to baseline and be treated symptomatically. If Grade $\geq 3$ nausea and vomiting recurs upon the resumption of study medications despite symptomatic treatment, these should again be interrupted and the protocol team notified for possible alternative antiretroviral agents.

7.2.7 Diarrhea

Grade 1 or 2

Study treatment should continue without interruption. Subjects with diarrhea of any toxicity grade may be treated symptomatically with permitted antimotility agents.

Grade 3 or 4

For 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. 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.

7.2.8 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 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.

7.2.9 AST/ALT Elevations

Grade 1 or 2

Study medications may be continued.

Grade 3

Study medications may be continued for 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.

Grade 4

All study medications should be held for AST or ALT Grade 4 elevations until the toxicity returns to Grade $\leq 2$. If the Grade 4 elevation in AST or ALT recurs, alternative ARV therapy should be considered in consultation with the protocol team.

7.2.10 Lactic Acidosis

Symptomatic Hyperlactatemia

If symptoms develop suggestive of hyperlactatemia, the site should perform a lactate level.

Symptomatic hyperlactatemia will be defined as new, otherwise unexplained and persistent occurrence for > 2 weeks of one or more of the following:

- nausea and vomiting
- abdominal pain or gastric discomfort
- abdominal distention
- increased LFTs

- unexplained fatigue
- dyspnea

PLUS a confirmed lactate level > 2 x ULN.

If the lactate value is > 2 x ULN, obtain a confirmatory lactate value as soon as possible, preferably within 1 week. Antiretroviral therapy should be interrupted immediately if the confirmatory value remains > 2 x ULN or if the site is unable to obtain a confirmatory value within 1 week. Determine lactate levels every 4 weeks until the lactate value returns to normal, at which time a new antiretroviral regimen may be constructed in consultation with the protocol team.

Management of symptomatic lactate value ≤ 2 x ULN will precede at the discretion of the local investigator. However, any modification of a subject's antiretroviral regimen should be made in consultation with the protocol team. Since some of the symptoms of hyperlactatemia are vague and may be present in many subjects (e.g., fatigue), repeated lactate determinations are advised.

NOTE: See the AACTG Web site for guidelines for the collection of lactate specimens: (http://aactg.s-3.com/members/download/other/Metabolic/LacAcid.doc).

Asymptomatic Hyperlactatemia

If the lactate value is > 2 x ULN, a confirmatory lactate value must be obtained as soon as possible, preferably within 1 week. Subjects should be evaluated for any of the symptoms or findings listed above in Symptomatic Hyperlactatemia. Study medications must be discontinued for all subjects with a confirmed lactate value of > 4 x ULN, whether or not the subject has any symptoms listed above. Lactate levels should be obtained every 4 weeks until the level returns to < 2 x ULN, at which time a new antiretroviral regimen may be initiated in consultation with the protocol team.

If a lactate level of Grade > 2 to 4 x ULN is confirmed and the subject remains asymptomatic, the subject should be followed with repeat lactate levels every 4 weeks. Serial monitoring may be discontinued if two or more lactate measurements are ≤ 2 x ULN and the subject remains asymptomatic.

### 7.2.11 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.

7.2.12 Anemia/Neutropenia

Subjects with Grade 3 or 4 anemia or neutropenia attributed to any of the NRTI's should have all study treatment interrupted until the abnormality returns to Grade ≤ 2. Therapy may be resumed after the anemia or neutropenia has returned to Grade ≤ 2 using the same dual-NRTI regimen. Recurrent Grade 3 or 4 anemia or neutropenia attributed to any of the NRTI's after should prompt a change in dual-NRTI regimen in consultation with the protocol team.

Subjects with anemia or neutropenia may be treated with blood transfusion and/or erythropoietin (Epogen®, Procrit®) or G-CSF (Neupogen®) at the discretion of the site investigator.

7.2.13 CK Elevations

Asymptomatic elevations in CK or elevations due to exercise **should be repeated (within 2-4 weeks) to assure that they are transient or due to exercise and** will not require a change in study treatment. Elevations in CK > 20 X ULN should be repeated after the subject has abstained from exercise for ≥ 24 hours. For persistent CK elevations >20 x ULN should prompt a change in dual-NRTI regimen and the protocol team should be notified.

7.2.14 Hypophosphatemia (for TDF)

For Grades 1 and 2 hypophosphatemia, the phosphate should be repeated within 2 weeks and TDF may be continued. For Grades 3 and 4 hypophosphatemia, the phosphate should be repeated within 1 week. Supplemental phosphate should be given and other causes of low phosphate should be investigated. Persistent hypophosphatemia (Grade 3 or 4) should lead to permanent discontinuation of TDF and notification of the protocol team.

# 8 CRITERIA FOR TREATMENT DISCONTINUATION

8.1 Criteria for Treatment Discontinuation

- Drug-related toxicity (see section 7, Toxicity Management).
- Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.
- Requirement for prohibited concomitant medications (see section 5.4.2)
- Pregnancy or breast-feeding.

8.2 Criteria for Discontinuation from the Study

- Failure to complete Sequence 1 or 2 whether due to toxicity, poor adherence or need to stop drug.
- If the subject misses more than 1 visit during the viral dynamics portion of Sequence I and II
- Failure to complete both PK visits in Sequence I and II as scheduled
- Failure by the subject to attend three consecutive clinic visits during the HAART 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 randomized comparative, open-labeled study of potency and pharmacokinetics of two antiretroviral agents, TDF and ABC. Eligible patients will be randomized into two monotherapy arms (TDF and ABC) for a short (one week) viral dynamics and pharmacokinetics evaluation to determine their potency. After a one-month washout period, all patients will start a dual-therapy of ABC+TDF. Viral dynamics and pharmacokinetics of the dual-therapy will be evaluated during the first week of the treatment. EFV will be added to the regimen after one week of the dual-therapy administered. Two weeks later,

3TC will be used to replace TDF in this HAART regimen, and continue this treatment up to 46 weeks.

## 9.2 Endpoints

### 9.2.1 Primary Endpoint

1. Slope of Phase I HIV RNA dynamics and plasma HIV RNA change from baseline to Day 7.

2. Plasma TDF and ABC concentrations; intracellular CBV-TP and TDF-DP concentrations.

### 9.2.2 Secondary Endpoints

1. Plasma HIV RNA < 50 copies/mL at week 24 and 48

2. Change in CD4 count from baseline at week 24 and 48

3. New reverse transcriptase mutations assessed by genotype (IAS-USA mutation list) at day 48.

4. Change in expression of nucleoside transport expression as assessed by specific mRNA transcript expression.

5. Treatment related toxicity between regimens.

## 9.3 Sample Size and Accural

Our sample size is determined based on one of the primary endpoints, the viral dynamic endpoint. Notermans et al. [31] presented the phase 1 decay rates for two groups: Group A (ritonavir, AZT, 3TC): d1 (slope of the phase 1 decay) mean=0.56, standard deviation =0.17 (CV=30%) and Group B (ritonavir given alone for 21 days, added AZT and 3TC on Day 21): d1 mean=0.46, standard deviation =0.13 (CV=28%). More recent data for phase 1 decay for TDF monotherapy yielded a mean value of 0.4 and standard deviation of 0.1 (5), i.e. CV=25%.

If we accept a type I error alpha=0.05 and a minimum of 80% power, the following table gives the sample sizes per arm required to detect the percentage differences of two sample means using a two-sided, two-sample test under the normality and between-group equal variance assumptions:

Sample Size Per Arm (N1=N2)
==========

| CV | Difference (%) in Means | | |
|---|---|---|---|
| | **20%** | **30%** | **40%** |
| **25%** | 25 | 11 | 7 |
| **30%** | 36 | 16 | 9 |
| **35%** | 49 | 22 | 13 |

With a sample size of 10 subjects per arm, we can detect a 30% difference in Phase I viral decay rates with a power of 80% and significance level of 0.05 if the CV=25%; and a 40% difference if the CV=30%. Since we expect a smaller within-subject variation in viral decay rates, we may be able to detect a smaller difference in viral decay rates between the monotherapy and dual-therapy.

Additionally, sample size determinations were done for pharmacokinetic parameters. Assuming an intra-patient coefficient of variation (CV) of 20%, a sample size of 10 should be able to detect a 30% difference in intracellular concentrations between mono and dual NRTI therapy sequences. If the intra-patient CV is higher, only larger differences between mono or dual therapy would be detectable.

## 9.4 Monitoring

The safety and tolerability of the study medications will be monitored by means of adverse event reports (AER) and biweekly toxicity reports presenting laboratory and clinical data. It is required that these data be entered into the database within 48 hours of the time at which the results of the laboratory tests or clinical examinations become available. These reports will be discussed by the protocol team on biweekly or monthly conference calls. Since Phase I studies are not routinely reviewed by the Data and Safety Monitoring Board, it is the responsibility of the Principal Investigator and the CCTG protocol team to interpret the toxicity data and make any decisions needed to protect patients from undue risk. Accrual and toxicity summaries will be provided to the Protocol Chairs and CCTG Investigators by the Data Manager and Biostatistician.

The protocol team will review all screening genotypes in order to assure eligibility prior to randomization. The day 49 genotype will be run in real time and reviewed by the protocol team as soon as it is available. If more than one patient develops a new (i.e. not present on screening genotype) genotypic mutation in reverse transcriptase at day 48, an independent interim review committee will be established to review the study results to date. The interim 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.

## 9.5 Analysis

### 9.5.1 Primary Objective Analysis

1) Viral decay rates will be estimated using the least squared methods and mixed-effects model approach. The comparisons of viral decay rates between mono and dual NRTI treatment groups will be performed based on the estimated viral decay rates (derived variable approach)using Wilcoxon rank tests [23, 32, 33].

2) The plasma pharmacokinetic parameters (AUC, Cmin, Cmax, $T_{1/2}$, etc.) will be calculated using non-compartmental method (trapezoidal rule), and two arms will be compared using the nonparametric Wilcoxon rank sum test.

Plasma concentrations of TDF and ABC alone and in combination with each other will be fit to compartmental pharmacokinetic models using a non-parametric population-modeling program (NPEM2, USC*PACK software, Laboratory of Applied Pharmacokinetics, University of Southern California). Intracellular levels will be assessed in relationship to viral plasma kinetics.

Plasma TDF and ABC concentrations will be weighted according to the inverse of the assay error variance. Model discrimination will be determined based on Akaike information criteria and log-likelihood values.

Subjects will be randomized to either TDF or ABC PO route for 7 days, which involves a fixed number of subjects. A sample size of 20 subjects (10 ABC and 10 TDF monotherapy and 20 ABC+TDF dualtherapy in HIV-positive patients). A 15% difference in plasma concentration will be considered to be clinically significant. Unpaired t-test or Mann-Whitney rank sum test, whenever appropriate, will be utilized for the comparison of demographic characteristics as well as PK parameters between the two studied groups. Selection of parametric or nonparametric will be determined after completion of tests for normality.

### 9.5.2 Secondary Objective Analysis

1) The number of subjects whose plasma HIV RNA < 50 copies/mL at weeks 24 and 48 will be descriptively summarized and reported.

2) The change in CD4 count from baseline at weeks 24 and 48 will be summarized tabulated.

3) The new reverse transcriptase mutations assessed by genotype (IAS-USA mutation list) at day 48 will be summarized by Arms A and B. A comparison between the two arms will be conducted using the exact Fisher test.

4) The change in expression of nucleoside transport expression as assessed by specific mRNA transcript expression will be summarized by Arms A and B. A comparison between the two arms will be conducted using Wilcoxon rank test.

5) The treatment related toxicities will be summarized by Arms A and B. A comparison between the two arms will be conducted using the exact Fisher test.

## 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 **C**CTG Data and Biostatistical Unit.

10.2.2 It is the responsibility of the **C**CTG 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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