IGHID 11417 - The Safety and Efficacy of Fixed Dose Combination Dolutegravir/Abacavir/Lamivudine Initiated During Acute HIV Infection: Impact on the Latent HIV Reservoir and Long-Term Immunologic Effect

NCT number NCT02384395
Document Date 07/26/2021

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Study# 201311

Version 5.1

July 26, 2021

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ACRONYMS

3TC	= lamivudine
ABC	= abacavir
AE	= adverse event
AHI	= acute HIV infection
ALT	= alanine transaminase
ANC	= absolute neutrophil count
ART	= antiretroviral therapy
AST	= aspartate aminotransferase
ATV	= atazanavir
β-HCG	= β human chorionic gonadotropin
BID	= twice daily
CHI	= chronic HIV-1 infection
COBI	= cobicistat
CrCL	= creatinine clearance
DTG	= dolutegravir
EAE	= expedited adverse events
EFV	= efavirenz
EVG	= elvitegravir
FCBP	= females of child bearing potential
FDA	= Food and Drug Administration
FDC	= fixed dose combination
FTC	= emtricitabine
HBcAB	= hepatitis B core antibody
HBsAg	= hepatitis B surface antigen
HBV	= hepatitis B
HCV	= hepatitis C
HLA	= human leukocyte antigen
HSR	= hypersensitivity reactions
IA	= immunoassay
IDS	= Investigational Drug Services
INI	= integrase inhibitor
IRB	= institutional review board
IRS	= immune reconstitution syndrome
IUD	= intrauterine device
LPV	= lopinavir
LFT	= liver function test
MI	= myocardial infarction
NAAT	= nucleic acid amplification test
NRTI	= nucleoside/tide reverse transcriptase inhibitor
NNRTI	= nonnucleoside reverse transcriptase inhibitor
NRTI/nRTI	= nucleoside/nucleotide analogue reverse transcriptase inhibitor
OHRP	= Office for Human Research Protections
PBMC	= peripheral blood mononuclear cells
PEP	= post-exposure prophylaxis
PI	= protease inhibitor
PT	= prothrombin time
PTT	= partial thromboplastin time
QD	= once daily
RCI	= resting cell infection
RTG	= raltegravir
RTV	= ritonavir
S/CO	=signal to cut-off ratio

SCA	= single copy assay
SOE	= schedule of events
SMC	= safety monitoring committee
STAT	= Screening and Tracing Active Transmission Program
TDF	= tenofovir disoproxil fumarate
ULN	= upper limit of normal
UNC	= University of North Carolina
VOR	= vorinostat
VF	= virologic failure
ZDV	= zidovudine

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1. PROTOCOL SCHEMA

Title: The safety and virologic efficacy of fixed dose combination (FDC) dolutegravir/abacavir/lamivudine initiated during acute HIV infection: impact on the latent HIV reservoir and long-term immunologic effect

Purpose:

- To evaluate the safety and virologic efficacy of DTG/3TC/ABC FDC as initial therapy for acute HIV infection (AHI), as well as the feasibility of prompt administration using a rapid HLA-B57 screening antibody assay.
- To seek correlations between low RCI and measures of immune activation.
- Assess long term improvement in T-cell function following early initiation of ART accompanied by rapid vitral suppression.

1.1 Hypotheses:

- The initiation of DTG/3TC/ABC FDC in individuals with AHI will be feasible, safe and will suppress viral replication more rapidly compared to initiation of a NNRTI-based regimen during AHI.
- Rapid reduction in plasma viremia with this integrase-based regimen will limit the area under the pre-ART viral load curve, and thus reduce the latent reservoir size one to two years following ART start.
- Early intiaiton of ART coupled with the rapid reduction in plasma viremia will be associated with better long-term T cell function, specifically better T cell function after 2 years of durable HIV suppression.

Design: This is a multicenter, single arm, open-label study of the safety and virologic efficacy of DTG/3TC/ABC FDC initiated during AHI.

Study Sites: The University of North Carolina, Chapel Hill, North Carolina, USA and Duke University, Durham, North Carolina, USA. The study sites will be members of the Duke-UNC Acute HIV Infection Study Consortium.

Study Population: Men and women $\geq$18 years of age newly diagnosed with AHI, and enrolled within 30 days of their AHI diagnosis.

Sample Size and Study Duration: Projected sample size is 40 participants. These participants will be enrolled in the treatment phase of the study for 96 weeks. The clinical care and HIV-1 RNA and CD4 evaluations, along with the DTG/3TC/ABC FDC will be provided by the study for 96 weeks. After week 96, participants will be followed for longitudinatl assessment of immune cell function through week 240 (year 5), combined with CD4 count and HIV RNA measurements.

Study Objectives:

1.2 Primary Objective: To determine the virologic efficacy of DTG/3TC/ABC FDC given once daily to participants with AHI as determined by the proportion of treated participants with HIV-1 RNA to <200 copies/mL at week 24.

1.3 Secondary Objectives:

- To evaluate the safety and tolerability of DTG/3TC/ABC FDC given once daily in acutely infected participants though 96 weeks of treatment.
- To assess the feasibility of prompt administration of DTG/3TC/ABC FDC using a rapid HLA-B57 screening antibody assay.

- To assess the virologic efficacy of DTG/3TC/ABC FDC given once daily to participants with AHI as determined by the proportion of treated participants with HIV-1 RNA to <50 copies/mL at week 48.
- To compare virologic efficacy of DTG/3TC/ABC FDC to a historical control cohort treated with EFV/FTC/TDF FDC.
- To measure the rate of virologic decline during the first 24 weeks of treatment compared to historical control cohort treated with EFV/FTC/TDF FDC.

1.4 Other Objectives:

- To evaluate immune activation as measured by the proportion CD8+ cells expressing HLA-DR and CD38+ at weeks 0, 24, 48, 96, 120, 144, 192, and 240.
- To assess the effect of the treatment regimen on the latently infected reservoir as measured in PBMCs obtained via leukapheresis at week 48 in a subset of participants with HIV-1 RNA consistently <50 copies/mL (optional repeat at week 96).
- To assess the impact of the treatment regimen on detection of low level plasma viremia as measured by a single copy assay (SCA) at weeks 84 and 96.

2. INTRODUCTION

2.1 Scientific Rationale

Treatment of individuals diagnosed with acute HIV infection (AHI) has important public health implications for HIV transmission, and may result in clinical benefit to individuals. In February of 2013, guidelines in the United States (US) were revised to recommend ART for all HIV-infected individuals, including those diagnosed with AHI [1]. ART treatment during the acute period preserves immune function [2], decreases the latent reservoir [3-5], and essentially halts viral diversification [6]. Accordingly, acutely infected patients suppressed on ART are most likely the population prone to enhanced control of viral replication (and functional cure), and thus, uniquely suited for eradication strategies or immune-based therapy. The Duke – University of North Carolina AHI Research Consortium has accepted AHI referrals from across North Carolina since 1998, allowing for prompt treatment.

To evaluate the efficacy of ART initiated during the period of acute infection, we enrolled 90 acutely infected patients on a treatment study with fixed-dose combination (FDC) efavirenz, emtricitabine, and tenofovir (EFV/FTC/TDF). In interim analysis with 61 of 90 participants, 92% achieved suppressed to <200 copies/mL by week 24 and 85% to <50 copies/mL by week 48 [7]. In sum, virologic efficacy was similar to rates in large treatment trials with recommended first line ART regimens started in individuals with chronic HIV infection (CHI), and was well tolerated. However, integrase inhibitor-based treatment in AHI is enticing given resistance concerns [8] (10% of AHI participants have been shown to have de novo NNRTI resistance [unpublished data, 2012]), fewer metabolic toxicities [9], less central nervous system side effects [10], and rapid viral suppression. In unpublished data, individuals started on an elvitegravir-based regimen (n=16) during AHI suppressed more rapidly to <200 copies/mL at a median of 15 days (range 7-78) compared with 63 days (N=90; range 7-411) with FDC EFV/FTC/TDF.

Time to suppression may be relevant for HIV cure strategies, as our prior work demonstrated a correlation between the size of the latent reservoir and the under the pre-ART HIV RNA curve [11], suggesting that more rapid viral suppression with an integrase-based regimen in AHI could limit the size of the latent reservoir. Further, additional work has shown that ART initiation during AHI decreases, but does not normalize immune activation in all acutely infected patients [12, 13]. However, a shorter time to viral

suppression has been associated with a reduction of CD8+ T cell activation 96 weeks following ART initiation in AHI [13].

Based on this prior data, we propose to employ an integrase inhibitor, dolutegravir (DTG) in fixed dose combination (FDC) with abacavir/lamivudine (ABC/3TC, Epzicom) as initial therapy for AHI. Integrase inhibitor-based treatment combinations have proven to be highly efficacious in the initial treatment of persons with chronic HIV infection (CHI) as demonstrated in STARTMRK (raltegravir) [14] and in ongoing elvitegravir treatment studies [10, 15], suggesting that integrase inhibitor-based regimens may be of value in individuals with AHI. A barrier to prompt administration of this regimen in the setting of AHI includes the need to screen for HLA B*57:01 given the risk of hypersensitivity reactions (HSR) to ABC. Accordingly, we will evaluate the feasibility of rapid screening for this allele using a human leukocyte antigen (HLA) B57 monoclonal antibody, to facilitate the earliest initiation of ART in AHI, given the possible benefit with earlier time to viral suppression.

Effect of early ART on the frequency of RCI: In most patients treated during chronic infection the frequency of RCI in circulating cells is 1000 per billion (1 per million) or greater [16]. We measured resting CD4+ T cell infection (RCI) in 20 AHI participants after stable suppression to <50 cps/ml, using a rigorous limiting-dilution outgrowth assay [17, 18]. We find that immediate ART in AHI limits RCI to a frequency of <0.5 per million [11, 18], in general agreement with work by Chun [19]. In the earlier study by Chun et al. of 7 participants treated in acute or early infection, after 1-2 years of ART, RCI appeared to decay to frequencies similar to our cohort of participants treated in AHI. Whether these kinetics reflect rapid early decay of latently infected cells, or the early clearance of a less stable population of infected cells and persistence of a more rare population of stable cells is unclear. Nevertheless, these findings suggest if residual viral expression and persistent immune dysfunction are related to the burden of the latent viral reservoir (and presumably its periodic activation) these abnormalities should be ameliorated by early ART and rapid viral suppression in AHI. Moreover, the rapid reduction in plasma viremia characteristic of integrase inhibitor-containing therapy may not only limit the latent reservoir size, but will almost certainly rapidly decrease infectiousness, an important issue during AHI [15].

Our painstaking method to reproducibly and accurately measure the frequency of infection within resting CD4+ T cells has been published [17], a modification of the methods originally published by Chun and Siliciano [20, 21]. Typically, 100 million resting CD4+ T cells are assayed, allowing detection of as few as 11 infected resting CD4+ T cells per billion (one of 48 macrocultures positive). Given the low frequency of RCI, we have established that our assay can accurately measure infectious units *per billion* resting cells, estimated by a maximum likelihood method [22]. The method of statistical analysis has been established in our prior work [17, 23]. In the proposed study, the frequency of latent infection will be studies in participants at two occasions approximately 48 weeks apart.

Effect of early and rapid HIV control on long-term immune cell function.

Recent studies have demonstrated that a shorter window between HIV infection and durable viral suppression is associated with lower activation and possibly dysregulation of T cells, relative to non-HIV infected participants (Vinikoor 2013). However, measures of T cell activity suggesting residual T cell activation/ dysfunction were largely performed within 2 years of starting antiretroviral therapy.

In contrast, durable HIV suppression of > 2 years has been associated with restoration of most T cell functions including normal cellular activation (Rehr 2008) (**Figure 1**). We and others have, however, observed ongoing defects in long term suppressed individuals who began ART in the chronic stage of infection, most particularly, poorer T cell proliferation

(**Figure 2).** Accordingly, we propose to assess immune cell function in participants for up to 5 years following the onset of ART treatment.

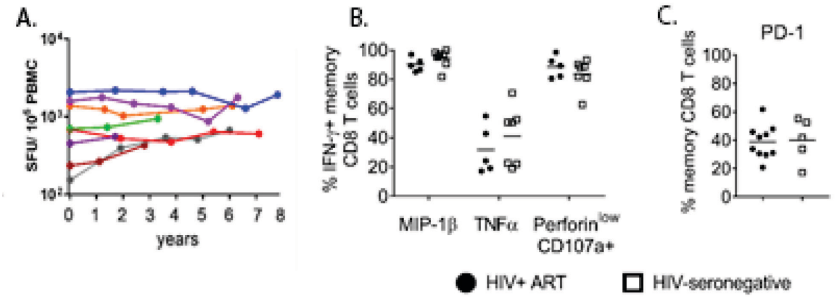

Figure 1 CD8 T cells from HIV+ ART participants on cART treated in chronic infection for > 2 years are stable and by several measures exhibit normal function. A) HIV-specific CD8 T cell responses are stable over time. Interferon-gamma production in response to HIV CD8 T cell (optimal) peptides was quantified by ELISPOT. SFU spot-forming units. T cell responses were measured in HIV+ ART-suppressed participants sampled yearly for up to 8 years. B) Antigen-specific (IFN-γ+) CD8 T cells from HIV+ ART participants can produce multiple cytokines (MIP-1β, TNFα) and degranulate (Perforin^{low} CD107a+). C) Similar expression of PD-1 on memory CD8 T cells from HIV+ and HIV- participants.

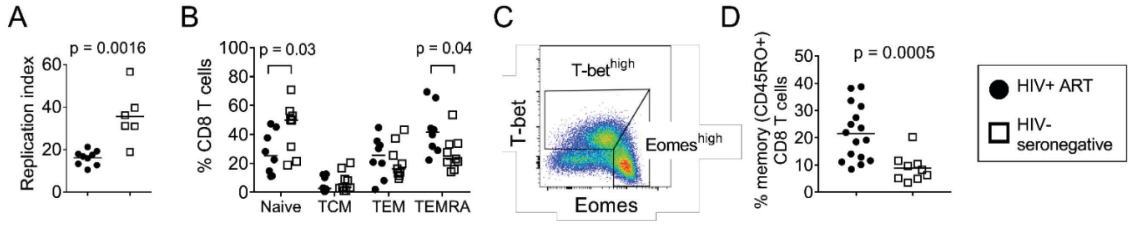

Figure 2 CD8+T cells in long-term ART treated HIV-infected individuals, first treated in chronic infection, exhibit some residual T cell phenotypic and functional dysregulation A) CD8 T cells from HIV-infected ART participants produce fewer daughter cells when they proliferate in response to antigen (replication index; 'flu, EBV, CMV peptide pool) than those from HIV- participants. B) CD8 T cells from HIV+ ART participants display a more terminally-differentiated phenotype than CD8 T cells from HIV uninfected participants. TCM central memory TEM effector memory, TEMRA terminally differentiated. C) Representative plot showing T-bet and Eomes expression in memory CD8 T cells. D) Memory CD8 T cells from HIV-infected ART participants are skewed toward a T-bet^{high} *effector-like* phenotype.

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2.2 Study Treatment

Integrase Inhibitors

HIV integrase inhibitors (INIs) are a promising new class of ART drugs with reported potency and a favorable safety profile. The first two approved integrase inhibitors, raltegravir (RTG) and elvitegravir (EVG) have been shown to be effective and well-tolerated. In the STARTMRK study, RAL was shown to be non-inferior to an efavirenz (EFV) containing standard of care first-line regimen [24]. In the GS-US-236-0102 study, EVG co-formulated with the CYP3A4 inhibitor cobicistat (COBI), tenofovir (TDF), and emtricitabine (FTC) was non-inferior to the co-formulated standard of care regimen EFV/TDF/FTC (Atripla) as first-line treatment [25]. Further, an integrase-based regimen is now a recommended first line regimen for HIV-infected individuals [1].

In the BENCHMRK study, patients with three-class antiretroviral resistance (naïve to INIs) received RAL or placebo plus optimized background therapy; 62% of RAL participants (versus 33% of placebo participants) had HIV RNA <50 c/mL at Week 48 [26]. In Study 145 in INI naïve, treatment-experienced participants with at least two-class resistance, EVG once daily was non-inferior to RAL twice daily (BID), each administered with a background regimen that included a ritonavir (RTV)-boosted protease inhibitor (PI) and a second antiretroviral agent. At Week 48 of Study 145, 59% of the EVG group versus 58% of the RAL group achieved virologic response (<50 c/mL) [27].

In addition to providing high rates of virologic suppression in treatment-naïve and treatment experienced patients, INIs have been well-tolerated in clinical trials. In STARTMRK, there were fewer drug-related adverse events (AEs) reported for the RAL group compared with the EFV group, and fewer participants randomized to RAL discontinued from the study due to AEs [28]. In GS-US-236-0102, AEs were similar between the EVG and EFV groups, with the exception of higher rates of nausea in the EVG group; significantly higher rates of dizziness, abnormal dreams, and rash in the EFV group. In this study, a similar percentage of participants in the two groups discontinued treatment because of AEs (4% versus 5%, respectively) [25], and similar findings were observed through 96 weeks [29].

In sum, RAL and EVG are effective, but have some limitations. Although well-tolerated, RAL requires twice-daily doses, has a low genetic barrier to resistance compared with ritonavir-boosted protease inhibitors (PIs) [30], and is currently not available in a FDC regimen. EVG is only available as coformulated EVG/COBI/TDF/FTC (Stribild), and requires co-administration with a pharmacokinetic booster such as COBI [31], which introduces the potential for clinically significant drug-drug interactions with drugs that depend on CYP3A4 for clearance. Further, EVG must be taken with food, and has a low genetic barrier to resistance compared with ritonavir-boosted PIs. EVG also carries a possible increased risk for proximal renal tubulopathy [32, 33], and Stribild is not recommended for patients with creatinine clearance (CrCl) under 70 mL/min. Both RTV and COBI (required in conjunction with EVG) boost TDF concentrations which may increase TDF proximal tubular toxicity [FDA, 2012].

As above, RAL and EVG have relatively low thresholds for resistance development and share resistance pathways; accordingly, a patient who becomes resistant to one is likely resistant to the other. Clinical resistance to both RAL and EVG has been observed in Phase III studies in both treatment-experienced [27, 34] and treatment-naïve participants [24, 25, 35]. In Study 145, comparing EVG- versus RAL-based therapy in treatment-experienced participants who failed therapy, 16/60 (27%) and 15/72 (21%) of patients with integrase genotype data available at the time of virologic failure developed integrase resistance

mutations. Phenotypic cross-resistance to both drugs was typical, preventing sequencing from one drug to the other [27].

Dolutegravir

DTG is a next-generation integrase inhibitor with a plasma half-life of 14 hours, which allows for once-daily dosing without pharmacological boosting [36-38]. No relevant inhibition or induction of cytochrome P450 or food effect has been reported, suggesting low potential for interactions [37, 39]. Most HIV isolates with resistance to RAL and EVG remain susceptible to DTG, making DTG an important option for many treatment experienced patients with multi-class drug resistance and potentially preserving susceptibility to other integrase inhibitor drugs in the event of virologic failure on DTG. Based on in vitro and clinical data, DTG demonstrates excellent antiviral activity and tolerability typical of the integrase inhibitor class, but has a higher barrier to resistance. Dolutegravir is FDA-approved for the treatment of HIV-1 in the US for treatment.

Dolutegravir is being developed as a single-tablet regimen in combination with abacavir-lamivudine (DTG/ABC/3TC). Such a regimen offers the advantage over other single-tablet ART regimens due to the lack of an effect on the cytochrome P450 enzyme CYP3A4, the absence of tenofovir DF (with the possible risk of renal or bone safety), and activity against transmitted viruses with NNRTI resistance. Further, the bioequivalence of DTG/ABC/3TC FDC has been demonstrated without regard to food administration in 62 healthy HIV negative individuals [40].

2.3 Clinical and Safety Data

DTG has been studied in several Phase III clinical trials (SPRING-2 [41], SINGLE [42], SAILING [43], VIKING-3 [44] AND FLAMINGO [45]) and found to be safe and effective.

The SPRING-2 study was a randomized, double-blind trial which showed non-inferior efficacy of once-daily DTG to twice-daily RTG in ART-naïve participants over 96 weeks, with a similar safety profile and no evidence of emergent resistance to DTG in those with virologic failure [41]. DTG was also found to be superior to a PI-based regimen in the FLAMINGO study, in which ART-naïve participants were randomized to either DTG 50mg once daily or darunavir (DRV) 800mg once daily plus ritonavir 100 mg once daily, with investigator-selected TDF-FTC or ABC-3TC. No treatment-emergent resistance was detected in either group, but treatment discontinuation due to adverse events or stopping criteria were less frequent in the DTG versus DRV plus ritonavir group (2% versus 4%).

The SINGLE study of dolutegravir was a blinded comparison of the single-tablet combination of dolutegravir combined with ABC/3TC versus the FDC EFV/TDF/FTC [46]. In this study, 833 ART-naïve participants were randomized to a FDC of dolutegravir at a dose of 50mg plus ABC and 3TC (DTG/ABC/3TC) or EFV/TDF/FTC, a recommended first line regimen [46]. The proportion of participants with HIV RNA levels <50 copies/mL was higher in the DTG/ABC/3TC versus the EFV/TDF/FTC group (88% vs. 81%, p=0.003) and participants receiving DTG/ABC/3TC suppressed more rapidly than those on EFV/TDF/FTC, 28 versus 84 days (p<0.0001), respectively. The safety profile of DTG/ABC/3TC was also better, with fewer discontinuations related to adverse events, and no detectable resistance through 48 weeks. In sum, in each of the 3 large studies (SINGLE [42] and SPRING 2 [41] and FLAMINGO [45]) of DTG in ART naïve patients, no participants developed either integrase or NRTI resistance.

Additional safety data derives from the VIKING study in which twice daily DTG (50mg) in highly treatment-experienced patients was effective in decreasing HIV RNA levels, and only 3% of participants discontinued treatment due to adverse events.

Summary

We propose to evaluate the efficacy and time to viral suppression with DTG/3TC/ABC FDC as initial therapy for AHI, as well as the feasibility of prompt administration using a rapid HLA-B57 screening antibody assay. In addition to validating the restriction of RCI by ART including a DTG-based regimen initiated during AHI, we will seek correlations between low RCI, and measures of immune activation. We hypothesize that rapid reduction in plasma viremia with this regimen will limit the area under the pre-ART viral load curve, and thus reduce the latent reservoir size as measured by a viral outgrowth assay one to two years following ART start, [11] and as compared with the latent reservoir size in acutely infected individuals started on regimens without an integrase inhibitor based regimen. In addition, we will examine the longitudinal impact of the proposed integrase-based regimen initiated during the acute period on immune activation through week 96. If residual viral expression and persistent immune dysfunction is related to the burden of the latent viral reservoir (and presumably its periodic activation) these abnormalities should be ameliorated by early ART with rapid viral suppression. We hypothesize that earlier treatment coupled with more rapid ART-mediated virus suppression will be associated with better long-term T cell function, specifically better T cell function after 2 years of durable HIV suppression.

3. STUDY OBJECTIVES

3.1 Purpose

- To evaluate the safety and efficacy of DTG/3TC/ABC FDC as initial therapy for AHI, as well as the feasibility of prompt administration using a rapid HLA-B57 screening antibody assay.
- To seek correlations between low RCI, and measures of immune activation
- Assess long term improvement in T-cell function following early initiation of ART accompanied by rapid viral suppression.

3.2 Hypothesis

- The initiation of DTG/3TC/ABC FDC in individuals with AHI will be feasible, safe and will suppress viral replication more rapidly compared to initiation of a NNRTI-based regimen during AHI.
- Rapid reduction in plasma viremia with this integrase-based regimen will limit the area under the pre-ART viral load curve, and thus reduce the latent reservoir size one to two years following ART start.
- Early initiation of ART coupled with the rapid reduction in plasma viremia will be associated with better long-term T cell function, specifically better T cell function after 2 years of durable HIV suppression

3.3 Primary Objective

3.3.1 To determine the virologic efficacy of DTG/3TC/ABC FDC given once daily to participants with AHI as determined by the proportion of treated participants with HIV-1 RNA to <200 copies/mL at week 24.

3.4 Secondary Objectives

3.4.1 To evaluate the safety and tolerability of DTG/3TC/ABC FDC given once daily in acutely infected participants though 96 weeks of treatment.

3.4.2 To assess the feasibility of prompt administration of DTG/3TC/ABC FDC using a rapid HLA-B57 screening antibody assay.

3.4.3 To assess the virologic efficacy of DTG/3TC/ABC FDC given once daily to participants with AHI as determined by the proportion of treated participants with HIV-1 RNA to <50 copies/mL at week 48.

3.4.4 To compare virologic efficacy of DTG/3TC/ABC FDC to a historical control cohort treated with FDC EFV/FTC/TDF at weeks 24 and 48.

3.4.5 To measure the rate of virologic decline during the first 24 weeks of treatment compared to historical control cohort treated with DTG/3TC/ABC FDC.

3.5 Other Objectives

3.5.1 To evaluate immune activation as measured by the proportion CD8+ cells expressing HLA-DR and CD38+ at weeks 0, 24, 48, 96, 120, 144, 192, and 240.

3.5.2 To assess the effect of the treatment regimen on the latently infected reservoir as measured in PBMC's obtained via leukapheresis at week 48 in a subset of participants with HIV-1 RNA consistently <50 copies/mL (optional repeat at week 96).

3.5.3 To assess the impact of the treatment regimen on detection of low level plasma viremia as measured by a single copy assay (SCA) at weeks 84 and 96.

4. STUDY DESIGN

This is a multicenter, single arm, 96-week open-label study of DTG/3TC/ABC FDC in AHI. The study will be conducted at the University of North Carolina in Chapel Hill, NC and Duke University in Durham, NC. Both sites are members of the Duke-UNC Acute HIV Infection Study Consortium. All Forty (40) participants will be enrolled in the treatment phase of the study for 96 weeks and will receive DTG/3TC/ABC FDC. The clinical care and HIV-1 RNA and CD4 evaluations, along with the DTG/3TC/ABC FDC will be provided by the study for 96 weeks. After week 96, participants will be followed to allow longitudinal assessment of immune cell function, combined with CD4 count and HIV RNA measurement.

If baseline resistance is detected after treatment begins (e.g. evidence of pre-existing baseline resistance (genotypic or phenotypic) that may adversely affect the efficacy of the study regimen), the study participant will be required to change their treatment regimen as per best clinical practice. The new regimen will not be provided by the study. The participant will obtain new medications via their medical insurance or through available clinical resources.

After individuals are identified with AHI, they will be offered the opportunity to participate in the study. The study consent form(s) will be signed for study participation and these include the screening and main study informed consent as well as the consent for specimen storage.

All participants considered potentially eligible for enrollment and who have signed the screening consent form will have screening lab tests drawn to determine eligibility per lab results.

Completion of all remaining screening evaluations to further determine eligibility will be done after the participant reviews and signs the main study consent. Screening and enrollment will occur on the same day, provided the participant meets the inclusion/exclusion criteria (Section 5.2 and 5.3). Due to the next business day turn around for hepatitis B surface antigen, and the molecular HLA B57 assay (when indicated), potential participants meeting all other inclusion/exclusion criteria but pending these 2 results and who sign the main informed consent will be given 7 days of study treatment, but instructed **NOT** to begin taking until notified by the study team after confirming HLA B*57:01 status and excluding active hepatitis B infection (Reference Appendix 4). Should the person have Hepatitis B or test positive for HLA B57, they will be instructed **NOT** to take study medication and to return to UNC for another ART

regimen. This regimen WILL NOT be provided by the study and the person will be terminated from the study at this time. These people will be replaced on the study.

Participants required to change their regimen due to resistance, adverse events or meeting criteria for virologic failure will be offered the opportunity to switch to the best available regimen as selected by their HIV provider and will be able to remain on study for clinical care and evaluations through week 96. The new regimen will not be provided by the study but obtained via their medical insurance or available clinical resources

5. STUDY POPULATION

5.1 Definitions

5.1.1 For the purpose of this study and to facilitate rapid initation of ART, we will permit inconclusive HIV testing results that are predictive of AHI in the presence of HIV IA laboratory signal to cut-off (S/CO) ratios predictive of AHI.

Acute HIV infection is defined as:

- A negative 4th generation HIV Ag/Ab Combination Assay or any HIV antibody IA test and a detectable HIV-1 RNA (NAAT or Viral load)

OR

- A positive 4th generation HIV Ag/Ab Combination Assay with a S/CO ≥ 1 and a negative or indeterminate HIV confirmatory/differentiating antibody test result with an HIV-1 RNA (qualitative or quantitative) test pending.
    a. Note: Pending HIV RNA test result should be available within 7 working days of study enrollment.

OR

- A positive 4th generation HIV Ag/Ab Combination Assay and a negative or indeterminate HIV confirmatory/differentiating test with a detectable HIV-1 RNA (qualitative or quantitative) test.

OR

- Two different rapid HIV tests with discordant results with HIV serum antibody and/or HIV-1 RNA tests pending.

OR

- A positive HIV antibody test according to standard criteria obtained within 30 days after an initial negative or indeterminate HIV antibody, antigen, or nucleic acid amplification.

5.1.2 Date of HIV diagnosis is defined as:

- Date of blood collection with the first positive HIV test result (standard HIV antibody, rapid HIV antibody or qualitative or quantitative HIV RNA assay).

5.1.3 Virologic Failure is defined as:

a. Failure to achieve HIV-1 RNA <200 copies/mL by wk 24
    or

b. 2 consecutive HIV-1 RNA levels >200 copies/mL at least 1 week apart after week 24.

5.2 Inclusion Criteria

5.2.1 Documentation of Acute HIV infection at or within 30 days of study entry.

5.2.2 Men and women age ≥18 years.

5.2.3 ART naïve, defined as ≤14 days of antiretroviral treatment at any time prior to entry. The only exceptions are:

- Pre-exposure prophylaxis (PrEP) and documented as HIV-1 negative at least 1 month prior to AHI diagnosis during PrEP, and
- Post-exposure prophylaxis (PEP) provided the participant was documented as HIV-1 negative at least 3-6 months following completion of PEP treatment.

5.2.4 Lab values obtained within 30 days prior to study entry:

- Absolute neutrophil count >500/mm3
- Hemoglobin > 8.5 g/dL for men and > 8.0 g/dL for women
- Platelet count >50,000/mm^3
- Lipase ≤ 3 X upper limit of normal (ULN), single repeat test is allowed to determine eligibility
- Calculated creatinine clearance (Cockcroft-Gault formula) ≥ 50mL/min:
  - $CrCl = \frac{(140\text{-age}) \times \text{body weight (kg)} \ (\times 0.85 \text{ if female})}{\text{Serum creatinine [mg/dL]} \times (72)}$

5.2.5 Testing for HBsAg is pending.

Note: Participants who test positive for HBsAg will be terminated from the study prior to starting study treatment.

5.2.6 Testing for HLA-B57 and/or HLA-B*5701 is pending.

Note: Participants who test positive for HLA-B*5701 will be terminated from the study prior to starting study treatment.

5.2.7 A female is eligible to enter and participate in the study if she:

- Is of non-childbearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥ 45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy or bilateral oophorectomy;

  or,

- Is of child-bearing potential, with a negative pregnancy test at screening and at enrollment, who agrees to use one of the highly effective methods of contraception listed below.
  - Complete abstinence from intercourse from 2 weeks prior to administration of study medication, throughout the study, and for at least 2 weeks after discontinuation of all study medication;
  - Approved hormonal contraception - used alone is not considered a sufficient form of contraception for the study - see Appendix 1 for a listing of examples of approved hormonal contraception;
  - Any intrauterine device (IUD) or intrauterine system with published data showing that the expected failure rate is <1% per year; see Appendix 2 for a listing of IUDs meeting this criterion;
  - Male partner sterilization with documentation of azoospermia confirmed ***prior to the female participant's entry*** into the study, and this male is the sole partner for that female participant. The documentation on male sterility can come from the site personnel's review of participant's

medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.;

- Any other method with published data showing that the expected failure rate is <1% per year;
- Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of the study medication.

5.2.8 Females who meet the post-menopausal definition, noted in 5.2.7, will have a follicle stimulation hormone (FSH) test to verify menopause,

5.2.9 Ability and willingness of participant to give written informed consent.

5.3 Exclusion Criteria

5.3.1 ALT ≥5 times Upper Limit of Normal (≥5xULN)

5.3.2 AST ≥3x ULN

5.3.3 Bilirubin ≥1.5x ULN (with >35% direct bilirubin)

5.3.4 Weight < 40 kg

5.3.5 Women who are breast-feeding.

5.3.6 Women with a positive pregnancy test on enrollment or prior to study drug administration.

5.3.7 Women and men of child bearing potential unwilling to agree to use an effective method of contraception required by the study.

5.3.8 History or presence of allergy to the study drugs or their components.

5.3.9 Requires or is anticipated to require any of the prohibited concomitant therapy: barbiturates, dofetilide, fampridine (dalfampridine), modafinil, oxcarbazepine, pioglitazone, pilsicainide, pimozide, rifampin, rifapentine, phenytoin, phenobarbital, carbamazepine, and St. John's wort.

- Dofetilide, fampridine, and pilsicainide are prohibited, as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity.

5.3.10 Unable to discontinue any current medications that are excluded during study treatment.

5.3.11 Use of immunomodulators (e.g., interleukins, interferons, cyclosporine), radiation therapy, HIV vaccine, systemic cytotoxic chemotherapy, or investigational therapy within 30 days prior to study entry.

- Prednisone at a daily dose of 10 mg or less (physiologic replacement dose) is permitted.

5.3.12 Treatment with radiation therapy or cytotoxic chemotherapeutics agents within 28 days prior to screening or has an anticipated need for these agents during the study.

5.3.13 Administration of an HIV-1 immunotherapeutic vaccine within 90 days prior to screening.

5.3.14 Prior treatment with any other experimental drug for any indication (within 30 days of initiating study treatment).

5.3.15 Difficulty swallowing capsules/tablets.

5.3.16 Inability to communicate effectively with study personnel.

5.3.17 Incarceration; prisoner recruitment and participation are not permitted.

5.3.18 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements or confound the analysis of study endpoints.

5.3.19 Any condition (including but not limited to alcohol and drug use) or any active clinically significant disease or findings during screening of medical history or physical examination, which, in the opinion of the Investigator would interfere with patient safety or compliance.

5.3.20 Serious illness requiring systemic treatment and/or hospitalization until patient either completes therapy or is clinically stable on therapy, in the opinion of the site investigator, for at least 7 days prior to study entry.

- NOTE: Oral candidiasis, vaginal candidiasis, mucocutaneous herpes simplex, and other minor illnesses (as judged by the site investigator) have no restriction.

5.3.21 A life expectancy less than twelve months.

5.3.22 Acute viral hepatitis, including, but not limited to, hepatitis A, B, or C.

5.3.23 History of myocardial infarction or diagnosis of coronary artery disease.

5.3.24 History of ongoing or clinically relevant pancreatitis within the previous 6 months.

5.3.25 Chronic hepatitis C infection with an anticipated need for treatment during the study period (through week 96).

5.3.26 Chronic hepatitis B infection (see inclusion criteria 5.2.5).

5.3.27 Evidence for moderate to severe hepatic impairment (as defined by the presence of cirrhosis, ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice or Child-Pugh class B or greater hepatic impairment).

5.3.28 Evidence of biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

5.3.29 Any verified grade 4 laboratory abnormality with exception of ALT as defined in exclusion criteria 5.3.1

5.4 Recruitment

Participants for this study are recruited from suspected or confirmed cases of AHI referred to UNC and Duke University ID clinics. Referrals are generated from the North Carolina (NC) Screening and Tracing Active Transmission (STAT) Program [47] and from clinical diagnoses made by both internal and external health care clinics.

The risks and benefits of initiating ART during AHI are discussed with each AHI individual referred to the participating sites as a part of routine evaluation of a new AHI diagnosis. The discussion of initiating ART during AHI is considered an ethical obligation to allow each person to consider all options, and this occurs prior to the discussion of any study participation. Initiation of ART is at the discretion of each person and is entirely voluntary. If AHI individuals are interested in starting treatment, they are offered consideration of participation on a treatment study for acute HIV infected persons.

6. STUDY TREATMENT

6.1. Study Drug

All participants will receive Dolutegravir (DTG 50 mg), abacavir sulfate (ABC 600 mg) and lamivudine (3TC 300 mg) formulated in a single tablet fixed dose combination (FDC) (DTG/ABC/3TC, GSK2619619), administered orally, once daily, with no food or fluid restrictions or requirements.

The medication will be supplied by the study for the 96 weeks. Participants who have evidence of resistance to any of the study medications or develop a hypersensitivity reaction will need to obtain alternative ART medications via their own medical insurance or through available clinical resources, and will be assisted in doing so.

The DTG/ABC/3TC FDC single tablet was approved by the U.S. Food and Drug Administration (FDA) on August 22, 2014 as a fixed dose combination tablet (FDC) for the treatment of HIV-infected adult participants, without clinically suspected resistance to any of the components.

Therapy will be initiated with all drugs simultaneously since co-formulated in a single tablet. Drugs will be given in recommended doses. The timing of doses of study treatment will be left to the individual participants, but should be taken at the same time each day. Study drug will be dispensed in quantities sufficient to last until the next clinic visit with a small excess to accommodate the possibility of a delay in return to scheduled appointments. Study participants will be asked to bring their pill bottles to each visit to assess compliance.

Duration
Participants will participate in the treatment phase of the study for approximately 96 weeks following enrollment.

There will be no study medication administered as part of the study in the long-term longitudinal follow up phase. All participants will access their ART via standard means such as insurance, or medication assistance programs.

Administration and Dispensing
All participants will receive the Alert card for abacavir. As each participant is enrolled, the study site must ensure that:

1) the participant receives the wallet-size warning card;
2) the designated health care provider (e.g., physician, study nurse coordinator, or pharmacist) reviews the signs and symptoms of a HSR with the participant; and
3) the participant verbalizes an understanding of the steps to take in the event of a suspected HSR, including when and how to contact the study site.

6.2. Product Information

Dolutegravir/Abacavir/Lamivudine Tablets, 50 mg/600 mg/300 mg are purple, oval, film-coated, biconvex tablets debossed with '572 Trı' on one side and plain on the other side. The tablets contain 52.62 mg dolutegravir sodium which is equivalent to 50 mg dolutegravir free acid, 702 mg abacavir sulfate, which is equivalent to 600 mg abacavir free base, and 300 mg lamivudine. The tablets are packaged into HDPE bottles with child-resistant closures that include induction seals. The bottles contain a desiccant.

Plasma exposures of DTG, ABC, and 3TC following single-dose administration of this FDC tablet formulation were bioequivalent to those following co-administration of the separate tablet formulations of DTG 50 mg plus EPZICOM (ABC 600 mg/3TC 300 mg) under fasted conditions.

Product Information on the individual components of
Dolutegravir/Abacavir/Lamivudine FDC is provided below:

6.2.1. **Dolutegravir (DTG) - TIVICAY**

In ART-naïve, HIV-infected adult participants, DTG 50 mg once daily was shown to be an efficacious dose, and non-inferior to RAL in combination with a background regimen with dual NRTIs. When used in combination with ABC/3TC,

DTG was shown to be superior to Atripla (EFV/TDF/FTC), a result driven by better tolerability of the DTG-based regimen. DTG was found superior in an open-label, randomized and active-controlled study in which antiretroviral-naïve participants were randomized and received either DTG 50 mg or DRV 800 mg + RTV 100 mg once daily, both administered with dual NRTI therapy (either ABC/3TC or TDF/FTC). The results were largely driven by difference in withdrawals due to adverse events, and withdrawals due to other reasons.

DTG 50 mg once daily has a higher barrier to resistance in INI-naïve patients, as demonstrated in the treatment-experienced (INI-naïve) SAILING study where significantly fewer virologic failures and significantly fewer participants with INI resistance were observed when compared with RAL [43]. Data from three treatment-naïve studies [41, 42, 45] are also supportive of DTG's higher barrier to resistance, given that no participants on the DTG regimen developed resistance to either DTG or the background NRTIs, whereas resistance to both the third agent and the background NRTIs was observed in both the RAL-, EFV-, and DRV+RTV-based comparator arms.

Increases in CD4+ cell counts were observed for participants receiving DTG-containing regimens across all patient populations that were evaluated in the Phase II and III program. These CD4+ cell count increases were similar in comparison with RAL in treatment-naïve and treatment-experienced participants, similar to DRV+RTV in treatment naïve participants, and were greater than those observed with EFV-containing regimens in treatment-naïve participants.

There was no evidence of a diminished response to DTG in specific patient subgroups, such as gender, age (≤ 50 years), race, level of immunosuppression (low CD4+ cell counts or CDC Category C). However, there are limited data in participants aged ≥65 (n=27).

DTG demonstrated a nonpathological effect of increasing creatinine levels due to inhibition of secretion by OCT2 transporter with no effect on GFR and effective renal plasma flow.

6.2.2. **Abacavir (Ziagen®, ABC)**

ABC is a potent NRTI which has been shown to result in similar (non-inferior) virological responses to zidovudine (ZDV) and better CD4+ T-cell responses, when used in combination with 3TC and EFV in antiretroviral-naïve patients. Although ABC has been dosed twice a day, data about the prolonged intracellular half-life of its active moiety (carbovir triphosphate) and from clinical studies suggest once daily dosing is as effective as twice daily dosing when given with 3TC and EFV. This led to the Food and Drug Administration (FDA) approval of a combination tablet of ABC and 3TC given as a single tablet once-daily.

ABC is generally well tolerated. Most clinical adverse events (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 ARV agents (i.e., pancreatitis, peripheral neuropathy, anemia, and neutropenia) have not been commonly seen with ABC therapy. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogues alone or in combination, including ABC, and other ARVs. Exclusive of ABC hypersensitivity reaction (HSR) (see next paragraph), 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.

In clinical studies, approximately 5% of patients receiving ABC develop a HSR that in rare cases has proved fatal. HSR is characterized by the appearance of symptoms indicating multiorgan/body system involvement. Symptoms usually appear within the first 6 weeks of starting treatment with ABC (median time to onset is 9 days), but may occur at any time while on therapy, and most often include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), and lethargy or malaise. Other signs and symptoms may include musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia), headache, paresthesia, and edema. Respiratory tract symptoms have been observed in approximately 20% of patients who experience HSR. Some patients with HSR were initially thought to have respiratory tract disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness. The multisystem nature of the HSR has led to misdiagnosis of the HSR as an intercurrent medical illness or as being related to another medication. Participants who have had an HSR must be advised that they should never take ABC again or any product that contains ABC, such as Trizivir®, as a life-threatening second HSR can occur. Diagnosis and management of HSR is discussed further in sections 6.4.4 and 8.2.1.

Hypersensitivity to abacavir was reported in approximately 206 (8%) of 2,670 patients in 9 clinical trials with abacavir-containing products where HLA-B*5701 screening was not performed. The incidence of suspected abacavir hypersensitivity reactions in clinical trials was 1% when participants carrying the HLA-B*5701 allele were excluded.

ABC is designated as FDA pregnancy Category C.

6.2.3. **Lamivudine (Epivir®, 3TC)**

3TC is a potent NRTI that is widely used in the management of HIV-1-infected participants. Although 3TC is an effective antiviral NRTI, a resistance mutation at codon 184 emerges within weeks of monotherapy and is also seen when 3TC is used as part of any regimen that does not reduce HIV-1 RNA to levels below the assay limit of quantification.

3TC is one of the best-tolerated NRTIs with AEs occurring in less than 5% of participants. Toxicities include headache, nausea and vomiting, malaise, fatigue and sleeplessness, anorexia, dizziness, rash, depression, anemia, neutropenia, and hyperamylasemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogues alone or in combination, including 3TC, and other ARVs.

Participants who are co-infected with hepatitis B virus (HBV) may experience increased liver function tests and exacerbation of hepatitis symptoms when 3TC is stopped. Usually these symptoms are self-limiting; however, death has been reported. The causal relationship to 3TC discontinuation is unknown. HBV-infected participants should be followed closely for the first several months following 3TC discontinuation.

3TC is designated as FDA pregnancy Category C.

6.3. Product Supply, Distribution, and Pharmacy

6.3.1. Acquisition

DTG/ABC/3TC single tablet FDC will be provided by ViiV Healthcare Limited. Study product will be available from the UNC Investigational Drug Services (IDS).

6.3.2. Accountability

The IDS will maintain complete records of all study products received from the ViiV and subsequently dispensed.

6.4. Concomitant Medications

6.4.1. Contraindications

- The DTG/ABC/3TC single tablet FDC is contraindicated in patients with known hypersensitivity to DTG, ABC or 3TC, or to any of the excipients.
- The DTG/ABC/3TC single tablet FDC must not be administered to participants in combination with the antiarrthymic agents dofetilide (Tikosyn®) or pilsicainide
    - Dofetilide is prohibited as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity
- The DTG/ABC/3TC single tablet FDC must not be administered to participant in combination with fampridine (dalfampridine); a potassium channel blocker.

6.4.2. Permitted Medications and Drug Interactions

Caution should be given to co-administering medications (prescription and nonprescription) that may change the exposure of DTG, ABC, 3TC or medications that may have their exposure changed by the DTG/ABC/3TC single tablet FDC.

- DTG should not be given with etravirine (ETR) without the coadministration of atazanavir+ritonavir (ATV+RTV), lopinavir/ritonavir (LPV/RTV) or darunavir + ritonavir (DRV+RTV).
- The following drugs when co-administrated with DTG will cause a decrease in the plasma concentration of DTG and require an increase in dosing frequency to DTG 50mg twice daily: Efavirenz (EFV), Fosamprenavir + ritonavir (FPV+RTV), Tipranavir + ritonavir (TPV+RTV) and rifampin.
- The following drugs when co-administrated of DTG will cause an increase in the plasma concentration of DTG: atazanavir (ATV), atazanavir & ritonavir (ATV & RTV); however, no dosage adjustment to DTG is required.
- Co-administration of DTG/ABC/3TC FDC with nucleoside analogs has the potential to cause lactic acidosis and severe hepatomegaly with steatosis, including fatal cases.
- Co-administration of DTG has the potential to decrease plasma concentrations of Neviripine (NPV), oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St. John's wort.
- DTG should not be co-administered with antacids containing polyvalent cations (i.e. magnesium or aluminum). DTG is recommended to be administered 2 hours before or 6 hours after these agents.
- DTG/ABC/3TC FDC is recommended to be administered 2 hours before or 6 hours after taking calcium or iron supplements, or alternatively, administered with food. Alternatively, DTG/ABC/3TC FDC and calcium or iron containing supplements can be taken together with food.

- Antacids containing polyvalent cations (e.g. Mg, Al) decrease DTG plasma concdentrations. Dolutegravir is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations.
- Metformin concentrations may be increased by DTG/ABC/3TC FDC. Lower metformin doses may be considered for patients treated with DTG and metformin.
- Potential drug-drug interaction between the ABC component of DTG/ABC/3TC and riociguat

6.4.3. **Prohibited Medications**

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Fampridine (see 6.4.1)
- Dofetilide (see 6.4.1)
- Pilsicainide (see 6.4.1)
- Barbiturates
- Carbamazepine
- Cytotoxic chemotherapy
- Hepatitic C treatment
- HIV immunotherapeutic vaccines
- Interferon
- Modafinil
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Pioglitazone
- Pimozide
- Radiation therapy
- Ribavirin
- Rifampin
- Rifapentine
- St. John's wort
- Systemically administered immunomodulators
- Troglitazone
- Other experimental agents and antiretroviral drugs not otherwise specified in the protocol

The following medications or their equivalents may cause decreased concentrations of ABC. Therefore, the following medications must not be administered concurrently with ABC.

- Riociguat

Chronic use of oral glucocorticoids must be avoided; however, short treatment courses (for example, 10 days or less) and topical, inhaled, or intranasal use of glucocorticosteroids will be allowed.

6.4.4. **Prohibited Medications During the Longitudinal Phase of the Study**

Participants will not receive any ART via the study while in the longitudinal phase of the study. There is no concomitant medication which would preclude a participant from participating in the study after Week 96.

6.4.5. **Hypersensitivity Reactions**

Abacavir

The HLA-B*5701 allele is associated with a significantly increased risk of a hypersensitivity reaction to abacavir. The PREDICT-1 study demonstrated that prospective HLA-B*5701 screening decreased the incidence of ABC-related HSR from 7.8% to 3.4% [48]. Screening for carriage of the HLA-B*5701 allele is recommended prior to initiating treatment with ABC, and for those testing positive, initiating an ABC-containing regimen is not recommended.

Almost all patients developing a hypersensitivity reaction will have fever and/or rash (usually maculopapular or urticarial) as part of the syndrome, however reactions have occurred without rash or fever.

Symptoms can occur at any time while being treated with abacavir, but usually appear within the first six weeks of initiation of treatment (median time to onset 11 days).

The signs and symptoms of this hypersensitivity reaction are listed below.

Symptoms reported in at least 10% of patients with a hypersensitivity reaction are in bold text.

Skin	**rash** (usually maculopapular or urticarial)
Gastrointestinal	**nausea, vomiting, diarrhea, abdominal pain**, mouth ulceration
Respiratory Tract	**dyspnea, cough**, sore throat, adult respiratory distress syndrome, respiratory failure
Miscellaneous:	**fever, fatigue, malaise,** edema, lymphadenopathy, hypotension, conjunctivitis, anaphylaxis
Neurological/Psychiatry:	**headache**, paresthesia
Hematological:	Lymphopenia
Liver/pancreas:	**elevated liver function tests**, hepatic failure
Musculoskeletal:	**myalgia**, rarely myolysis, arthralgia, elevated creatine phosphokinase
Urology:	elevated creatinine, renal failure

Some patients with hypersensitivity presented symptoms associated with a flu-like illness, gastroenteritis or reactions to other medications. Delaying diagnosis of hypersensitivity 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 participants presenting with symptoms of these diseases and is a clinical diagnosis. If hypersensitivity reaction cannot be ruled out, the DTG/ABC/3TC single tablet FDC, or any other medicinal product containing abacavir (e.g. ZIAGEN, EPZICOM, KIVEXA, TRIZIVIR) should not be restarted.

The symptoms related to this hypersensitivity reaction worsen with continued therapy, and usually resolve upon discontinuation of abacavir.

Restarting abacavir 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. Regardless of their *HLA-B*5701* status, participants who develop this hypersensitivity reaction must discontinue the DTG/ABC/3TC single tablet FDC and must never be re-challenged with the DTG/ABC/3TC single tablet FDC, or any other medicinal product containing abacavir (e.g. ZIAGEN, EPZICOM, KIVEXA,TRIZIVIR).**

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 restarted therapy, and who had no preceding symptoms of a hypersensitivity reaction.

An Alert Card with information for the participant about this hypersensitivity reaction will be provided to the participant at enrollment on the study.

See Appendix 3 for Essential Patient Information that will be reviewed and then provided to each participant at the screening and enrollment visits.

Dolutegravir

Hypersensitivity reactions have been reported with integrase inhibitors, including DTG, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. Mild to moderate rash is an expected adverse reaction for DTG-containing antiretroviral therapy. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy, and tend to resolve within two to three weeks. The index case of a hypersensitivity reaction with DTG involved a profuse, purpuric, and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported for DTG in clinical trials.

DTG/ABC/3TC single tablet FDC and any other suspect agent should be discontinued immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema). Clinical status including liver aminotransferases should be monitored and appropriate therapy initiated. Delay in stopping treatment with the DTG/ABC/3TC single tablet FDC or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction.

6.5. Potential Risks and Benefits

- **Immune Reconstitution Syndrome (IRS)**
  In HIV-infected patients with severe immune deficiency at the time of initiation of antiretroviral therapy (ART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise and cause serious

clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART.

Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some hepatitis B and/or C co-infected patients at the start of DTG therapy. Monitoring of liver chemistries is recommended in participants with hepatitis B and/or C coinfection

- **Lactic Acidosis and Severe Hepatomegaly with Steatosis**
  Treatment with the DTG/ABC/3TC single tablet FDC should be suspended in any participant who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity, with or without hepatitis, which may include hepatomegaly and steatosis even in the absence of marked transaminase elevations. Symptoms associated with lactic acidosis include: generalized weakness, anorexia and sudden unexplained weight loss, gastrointestinal and respiratory symptoms. Female sex and obesity may be risk factors for the development of lactic acidosis and severe hepatomegaly.

- **Acute Hepatic Failure**
  Hepatotoxicity may develop in participants receiving dolutegravir-containing regimens. Participants with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Participants with an acute diagnosis of hepatitis A, B, or C as well as those with a chronic diagnosis of hepatitis B or C are excluded from study participation. Liver function is monitored regularly throughout the study.

- **Pregnancy and Lactation**
  The safe use of the DTG/ABC/3TC single tablet FDC in human pregnancy has not been established. DTG, ABC and 3TC have been shown to cross the placenta in reproductive toxicity studies in animals. 3TC and ABC, but not DTG, have been associated with findings in animal reproductive toxicity studies. In one study, approximately 0.9% of women taking DTG when they became pregnant had babies with serious brain and spine defects. These defects happened early in pregnancy, before many women knew they were pregnant. For this reason, females of childbearing age should avoid getting pregnant while in the study and if this is not an option, an alternative treatment should be considered. Therefore, administration of DTG/ABC/3TC FDC in pregnancy should be considered only if the benefit to the mother outweighs the possible risk to the fetus.

  There is no requirement to exclude females of child bearing potential (FCBP) from this study based on reproductive toxicity findings for DTG, ABC and 3TC available to date. FCBP will be required to have a negative pregnancy test (serum β human chorionic gonadotropin [β-hCG]) at screen and a negative pregnancy test at enrollment (section 5.3.6). FCBP must agree to use one of the highly effective methods of contraception listed in the inclusion and exclusion criteria for this study (sections 5.2.7 and 5.3.7) In addition, FCBP will be assessed for pregnancy and their current birth control methods at each study visit and a urine pregnancy test will be performed at each visit. A serum pregnancy test will be performed at any visit when pregnancy is suspected based on participant report or reported date of LMP. The investigator or study coordinator will check and confirm at every visit that FCBP are avoiding pregnancy. (Reference SOE.)

Women, who met the definition of menopause, per inclusion criteria 5.2.7 and 5.2.8, will have an FSH Level done to confirm menopause.

Health experts recommend that where possible HIV infected women do not breast feed their infants in order to avoid transmission of HIV. It is expected that dolutegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Lamivudine is present in human milk. There is no information on the effects of lamivudine on the breastfed infant or the effects of the drugs on milk production. Because of the potential for (1) HIV-1 transmission (in HIV-negative infants), (2) developing viral resistance (in 3 HIV-positive infants), and (3) adverse reactions in a breastfed infant, mothers should be instructed not to breastfeed if they are receiving EPIVIR. For these reasons, women who are breastfeeding will be excluded from participating in this study (section 5.3.5).

- **Embryo-fetal Toxicity**
  Embryo-fetal toxicity may occur when dolutegravir is used at the time of conception and in early pregnancy. Dolutegravir should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus. FCBP should be informed about the potential risk of neural tube defects with DTG and counselled about the use of effective contraception. It is recommended that pregnancy testing is conducted prior to initiation of DTG. If there are plans to become pregnant, or if pregnancy is confirmed within the first trimester while on DTG, the risks and benefits of continuing DTG versus switching to another antiretroviral regimen should be discussed. Factors to consider should include feasibility of switching, tolerability, ability to maintain viral suppression, actual gestational age, risk of transmission to the infant, and the available data around the potential risk of neural tube defects and other pregnancy outcomes for dolutegravir and alternative antiretroviral drugs.

  A causal relationship of these events to the use of DTG has not been established. The incidence of neural tube defects in the general population ranges from 0.5-1 case per 1,000 live births. As most neural tube defects occur within the first 4 weeks of fetal development (approximately 6 weeks after the last menstrual period), this potential risk would concern women exposed to DTG at the time of conception and in early pregnancy.

  Dolutegravir use during pregnancy has been evaluated in the Antiretroviral Pregnancy Registry (APR) in over 800 pregnancies (as of January 2020). Available human data from the APR do not show an increased risk of major birth defects for DTG compared to the background rate.

- **Hypersensitivity reactions**
  See Section 6.4.5 above.

- **Hepatitis B**
  In clinical trials of non-HIV-1-infected patients treated with 3TC for chronic hepatitis B virus (HBV), clinical and laboratory evidence of exacerbations of hepatitis have occurred after discontinuation of 3TC. Exacerbations have been detected primarily by serum ALT elevations in addition to re-emergence of HBV DNA. Although most events were self-limited, fatalities have been reported in some cases. Post-marketing data also describes similar events after changes from 3TC-contining HIV regimens to regimens without 3TC in patients co-infected with HIV and HBV. Accordingly, patients co-infected with hepatitis B are excluded from participation in this study.

- **Psychiatric Diagnosis**
  Depression, Suicidal Thoughts/Behaviors, and Anxiety
  DTG demonstrated that some patients, mostly those who had mental health problems before taking dolutegravir, experienced feelings of deep sadness and unworthiness (depression), suicidal thoughts, and suicidal behaviors.

  The adverse drug reaction of anxiety has been added to the company Global Data Sheet (GDS) and clinical trial reference safety Information for DTG, Triumeq (DTG,/ABC/3TC FDC), and DTG + RPV.

- **Myocardial Infarction**
  In a prospective, observational study designed to evaluate the rate of myocardial infarction (MI) in patients on ART, the use of ABC within the prior 6 months was correlated with an increased risk of MI [49]. In a sponsor-conducted pooled analysis of clinical trials, no excess risk of MI was observed in ABC-treated participants as compared with control participants. Altogether, 10 studies have evaluated the association between abacavir and the risk of MI; among the five larger studies, three conclude there is an association and two reports the association is not robust [50]. In totality, the available data from the observational studies and from controlled clinical trials show inconsistency; therefore, evidence for a causal relationship between abacavir and the risk of MI is inconclusive..

- **Elevations in serum lipids and blood glucose**
  Serum lipid and blood glucose levels may increase during antiretroviral therapy. Disease control and life style changes may also be contributing factors.

- **Adverse Reactions or Events and associated Sign and Symptoms**
  The DTG/ABC/3TC single tablet FDC contains DTG, ABC and 3TC; therefore the adverse events associated with these may be expected. For many of the adverse events listed it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

- **Other potential adverse events**
  Many of the adverse events listed occur commonly (nausea, vomiting, diarrhea, fever, lethargy, rash) in patients with ABC hypersensitivity. Therefore, participants with any of these symptoms should be carefully evaluated for the presence of this hypersensitivity reaction. If the DTG/ABC/3TC single tablet FDC has been discontinued in participants due to experiencing any one of these symptoms and a decision is made to restart ABC, this must be done only under direct medical supervision.

Clinical safety data with DTG/ABC/3TC FDC are limited. The adverse reactions observed for the combination of DTG + ABC/3TC were generally consistent with the adverse reaction profiles for the individual components dolutegravir, abacavir and lamivudine.

Summary of adverse reactions associated with the combination DTG+ABC/3TC

Gastrointestinal disorders	**Common**: abdominal distension, gastroesophageal reflux disease, dyspepsia
Nervous System disorders	**Common:** somnolence
Musculoskeltal and connective tissue disorders	**Uncommon: arthralgia and myalgia**
Psychiatric disorders	**Common:** depression, nightmare and sleep disorder **Very Common:** Insomnia
Metabolism and nutrition disorders	**Common:** hypertriglyceridemia and hyperglycemia
General disorders	**Very Common:** fatigue

Note: Frequencies are defined by MedDRA system organ class as very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

Summary of adverse reactions associated with the individual components of the DTG+ABC/3TC

System Organ Class	DTG	ABC	3TC
Blood and lymphatic system disorders			**Uncommon**: neutropenia, anemia, thrombocytopenia
Immune System Disorders	**Uncommon:** hypersensitivity, IRS	**Common:** drug hypersensitivity	
Metabolism and nutrition disorders		**Common:** anorexia	
Psychiatric disorders	**Common:** Insomnia[1], abnormal dreams		
Nervous System disorders	**Very Common**: headache **Common:** dizziness		
Gastrointestinal disorders	**Very Common:** nausea, diarrhea **Common:** vomiting, flatulence, abdominal pain, upper abdominal pain, abdominal discomfort		
Hepatobiliary disorders	**Uncommon:** hepatitis		**Uncommon:** transient elevations in AST and ALT
Skin and subcutaneous tissue disorders	**Common:** rash, pruritus		**Common:** rash
General disorders and administration site conditions	**Common:** fatigue[2]	**Common:** fever, lethargy, fatigue[2]	Common: fatigue[2], malaise, fever
Laboratory	**Uncommon**: elevations in CPK[2], creatinine and total bilirubin		

Note: Frequencies are defined by MedDRA system organ class as very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1,000 and <1/100), rare (≥1/10,000 and <1/1,000) and very rare (<1/10,000), including isolated reports.

[1] Insomnia was observed at a greater frequency with the combination DTG + ABC/3TC (i.e., very common) when compared to the individual component DTG
[2] These were asymptomatic and mainly in association with exercise

7. Study Procedures

7.1. Schedule of Events

A detailed Schedule of Events (SOE) is provided at the end of the protocol.

The SOE represents all possible study visits through End of Study (EOS). Exceptions to specific events are noted.

After enrollment, study windows will span half the time between visits.
Examples: 1) Week 2 visit is + or – 1 week of enrollment and Week 4 visit
2) Week 8 visit is + or – 2 weeks of Week 4 visit and Week 12 visit
3) Week 36 visit is + or – 6 weeks of Week 24 visit and Week 48 visit
4) Week 120 visit is + or – 3 months of Week 96 and Week 144 visit

7.1.1. Screening and Enrollment Visit

All participants considered potentially eligible for enrollment will complete the main study consent and when applicable, a screening consent prior to the main consent to facilitate the ascertainment of eligibility labs required for study entry. All participants who signed a screening consent will undergo screening evaluations to determine eligibility. Screening and enrollment can occur on the same day, provided the participant meets the inclusion/exclusion criteria (Section 5.2 and 5.3).

Screening labs that are standard of care may be obtained after signing the screening consent and prior to signing the study's main informed consent. These tests, although part of study screening, are standard of care for clinical evaluation of newly diagnosed patients. Obtaining these labs immediately following the clinical evaluation and after signing the study screening ICF will facilitate the ability to prescribe medication sooner, including on the same day as the visit, should the participant decide against study participation or fail to meet eligibility.

The following study screening labs will be obtained after the screening consent is obtained.

CBC with differential	Lymphocyte markers
Chemistries: (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, creatinine clearance)	Hepatic function tests: (ALT, AST, alk phos, total bilirubin, direct bilirubin and lipase)
HIV antibody test	HIV-1 RNA
Serum pregnancy test (females)	Follicle stimulating hormone level (optional - to confirm menopause only)
Hepatitis B surface antigen	Hepatitis C antibody/refex RNA
STD screening (RPR, CT, GC)	HLA B*57:01 screening
Genotype and integrase genotype	Immunology samples for study

Enrollment can occur pending the HLA B57 and hepatitis B surface antigen test results. Due to the next business day turn around for hepatitis B surface antigen, and the molecular

HLA assay (when indicated), potential participants meeting all other inclusion/exclusion criteria but pending these 2 results and who sign informed consent will be given 7 days of study treatment, but instructed **NOT** to begin taking until notified by the study team after confirming HLA B57 or HLA B*57:01 status (when indicated) and excluding active hepatitis B infection (Reference Appendix 4). Should the person have Hepatitis B or test positive for HLA B*57:01, they will be instructed **NOT** to take study medication and to return to UNC or Duke for another ART regimen. This regimen WILL NOT be provided by the study and the person will be terminated from the study at this time. These people will be replaced on the study. The PID and SID will not be re-assigned.

The screening/enrollment visit must occur within 30 days of the date of AHI diagnosis (Section 5.1.)

During the main study consent process, all participants will be offered the opportunity to participate in the leukapheresis sub-study. Participants may elect to participate in the sub-study at screening/enrollment in the main consent or they may choose to participate later in the study and resign a new consent at that time.

Enrollment occurs on the same day as screening. Participants with AHI who are eligible, have had the study explained to them and have signed the main study consent will be enrolled if therapy is initiated within 30 days of their diagnosis with AHI. Efforts will be made to initiate therapy as soon as possible.

The study drug and study commitment will be reviewed at the time of enrollment.

Prior to enrollment the following will be completed:

- Depression Assessment (PHQ-9)
- Screening Informed consent (completed prior to screening laboratory assessments)
- Main study Informed Consent
- Inclusion/exclusion criteria
  - Clinical laboratory evaluations within acceptable parameters
- Pending confirmation of HLA and hepatitis B status
- Adherence counseling

The date that participants start therapy will be considered study day 0. The participant will be considered enrolled on the study the day he/she screens and is sent home with the study medications. Should participant test HLA B*57:01 positive, he/she will be terminated from the study.

The following procedures and laboratory tests will be completed during the screening/enrollment evaluation after the participant has signed all applicable (screening and main) informed consents.

- Medical history – inclusive of all concomitant meds within last 30 days.
- Complete physical examination - inclusive of Vital Signs, height, & weight
- Acute HIV assessment – questionnaire administered by study coordinator which explores HIV and STI testing history, drug and alcohol use and HIV acquisition risk.
- Depression Assessment (PHQ-9 questionnaire)
  Note: Most participants will have a depression assessment done as part of the standard initial ID clinical evaluation done on the same day as their consent, screening/enrollment. These assessments, done by ID clinic social workers, will be used as the baseline assessment and may be obtained prior to the study consent.
- Females: Serum Pregnancy test
  Note: Pregnancy test must be verified as negative within 72 hours of study entry.

- Females: FSH level to document menopause
- Clinical laboratory evaluation or documentation of below within prior 30 days:
    - Chemistries – sodium, potassium, chloride, bicarb, gluc, BUN, creatine and creatinine clearance
    - Hepatic Function Test (or LFTs) – AST, ALT, Alk phos, T. Bili
    - Direct bilirubin – obtained at screening only
    - Lipase
    - CBC with differential
    - Lipid*, preferred fasting and can be obtained at visit 2 if not fasting at blood draw.*
- Urine Testing
    - Urinalysis macro
    - GC and CT testing *(not required if done within 30 days of visit and documentation of results (and treatment, if applicable) available)*
- HIV-1 RNA PCR
- Lymphocyte Markers (CD4/CD8)
- HIV-1 Combo Ag/Ab with confirmatory/differential test (if the test is not positive, meaning the differential test results are negative or indeterminate, the test will be repeated at week 12)
    - AHI testing results based on SCO values will be obtained from the testing lab at the time of the indeterminate differentiating test result and prior to the HIV RNA confirmation test availability.
    - AHI criteria based on the use of SCO with 4th generation HIV test and/or Geenius HIV-1/HIV-2 Supplemental Assay banding patterns can be found in study specific standard operating procedures.
- HIV Genotype and Integrase Resistance Genotype testing
- RPR serology *(not required if done within 30 days of visit and documentation of results (and treatment, if applicable) available)*
- Hepatitis B antibody and surface antigen (HBsAg)
    - Results available next business day.
    - Refence Appendix 4 - participants given a 7 day starter pack of study treatment at enrollment, will be instructed NOT to begin until contacted by study staff and notified of a negative result.
- Hepatitis C antibody test – if positive, reflex to HCV RNA test
- HLA B57/58 flow cytometry antibody assay
    - If the HLA B57/58 flow cytometry assay is negative, the participant can be enrolled and immediately start study treatment.
    - A positive result on the HLA B57/58 flow cytometry assay will be reflexed to a molecular HLA test to specifically detect B*57:01, with results anticipated the next business day. Reference Appendix 4 for dispensing study medications. Participants will be given a 7 day starter pack of study treatment at enrollment, but instructed NOT to begin until contacted by study staff and notified of a negative result.
- Research Assay Collections
    - HIV-1 T lymphocyte studies and plasma and serum for storage

All participants will be counseled on the signs and symptoms of hypersensitivity associated with Abacavir and given the "Alert Card" containing information about this hypersensitivity reaction (see Attachment 3).

All persons agreeing to participate in the study and having signed the study consent, will be counseled on the practice of safer sexual practices including the use of effective barrier methods.

7.1.2. **Weeks 2, 8, 16, 36, 60, and 84**

The following evaluations will be performed:

- Targeted physical exam
- For females of child bearing potential (FCBP) – urine pregnancy test and assess date of LMP[1] and birth control measures[2]
- ART adherence reviewed
- Concomitant medications reviewed
- Adverse Event Assessment
- Research Assay Collections
    - HIV-1 T lymphocyte studies & plasma and serum for storage (week 2 only)
    - Single copy assay (week 84 only)
- Clinical Laboratory Evaluations
    - Serum pregnancy test[1] (if >35 days since first day of last menstrual period in women pre-menopause)
    - HIV-1 RNA PCR
    - APTT/PT & INR (at ***week 36 and week 84*** if plan to do leukapheresis optional procedures)

[1]Females of child-bearing potential will have serum pregnancy testing as clinically indicated at any time point during the course of the study through Week 96.
[2]Females of child-bearing potential (FCBP) will be terminated or withdrawn from study if inadequate birth controls measures are assessed or the female participant indicates that she changed her mind and would like to be pregnant at any time point during the course of the study through Week 96.

7.1.3. Week 4

The following evaluations will be performed:

- Targeted clinical exam and physical
- ART adherence reviewed
- Concomitant medications reviewed
- Adverse Event Assessment
- Clinical Laboratory Evaluations
    - Urine pregnancy test (all FCBP)
    - Assess date of LMP and Birth Control Measures
        - Serum pregnancy test (if >35 days since first day of last menstrual period in women pre-menopause)
    - HIV-1 RNA PCR
    - Chemistries (sodium, potassium, chloride, bicarb, gluc, BUN and creatinine and creatinine clearance)
    - LFTs (AST, ALT, Alk phos, T. Bili)
    - CBC with diff

7.1.4. Weeks 12, 24, and 72

The following evaluations will be performed:

- Targeted clinical exam and physical
- ART adherence reviewed
- Concomitant medications reviewed
- Adverse Event Assessment
- Clinical Laboratory Evaluations
    - Urine pregnancy test (all FCBP)
    - Assess date of LMP and Birth Control Measures

        - Serum pregnancy test (if >35 days since first day of last menstrual period in women pre-menopause)
    - HIV-1 RNA PCR
    - Chemistries (sodium, potassium, chloride, bicarb, gluc, BUN & creatinine and creatinine clearance)
    - LFTs (AST, ALT, Alk phos, T. Bili)
    - CBC with diff
    - Lymphocyte Markers (CD4/CD8)

- ***Week 12 only:***
  HIV-1 Combo Ag/Ab with confirmatory/differentiating test (only obtained on participants who had a negative or indeterminate confirmatory/differentiating test at enrollment). The study can perform the HIV1/2 confirmatory/differentiating without the HIV-1 Comb Ag/Ab test if the Combo test was positive at baseline.

- ***Weeks 12 and 24 only:***
  Research Assay Collections
    - HIV-1 T lymphocyte studies, serum and plasma storage

- ***Weeks 24 and 72***
  Depression Assessment (PHQ-9)

7.1.5. **Weeks 48 and 96**

The following evaluations will be performed:
- Targeted clinical exam and physical
- ART adherence reviewed
- Concomitant medications reviewed
- Depression Assessment (PHQ-9)
- Adverse Event Assessment
- Clinical Laboratory Evaluations
    - Urine pregnancy test (all FCBP)
    - Assess date of LMP and Birth Control Measures
        - Serum pregnancy test (if >35 days since first day of last menstrual period in women pre-menopause)
    - HIV-1 RNA PCR
    - Chemistries (sodium, potassium, chloride, bicarb, gluc, BUN & creatinine and creatinine clearance and Lipase)
    - LFTs (AST, ALT, Alk phos, T. Bili)
    - Fasting Lipids
    - CBC with diff
    - CD4/CD8
- Research Assay Collections
    - HIV-1 T lymphocyte studies, serum and plasma storage
    - Single copy assay (week 96 only)
- Optional Procedures:
    - Leukapheresis

7.1.6. **Weeks 120, 144, 192, 240**

Once participants complete Week 96, they will be followed for up to 3 years. Subsequent visits will occur at Weeks 120, 144, 192 and 240. At each visit, participants will have research samples collected and the following evaluations will be obtained from chart abstraction of the clinical provider's evaluations done during the window period of the visit:

- Update medical history documenting new diagnosis since the last clinical appointment.
- Update concomitant medications to include all meds taken at the time of the office visit or within the last 30 days, if available.
- Update ART medication Note all ART changes along with the date and reason for the change.
- Adverse Event Assessment per longitudinal follow-up (see protocol section 8.2.13.1)
- Obtain medical release, as necessary, for participants who have medical care provided outside the UNC or Duke Hospital Centers.
- Clinical Laboratory Evaluations - collect as part of study to supplement clinical assessment. If already drawn as part of the provider visit, do not repeat. Use the values obtained at the clinical visit.
    - HIV-1 RNA PCR
    - CBC with diff
    - CD4/CD8
- Research Assay Collections
    - HIV-1 T lymphocyte studies, serum and plasma storage

7.2. Optional Procedures

Due to practical considerations, leukapheresis procedures to collect specimens will be optional for enrollees, and performed as agreed upon by each individual participant. Efforts will be made to obtain consent for both leukapheresis procedures as possible, and to perform both on at least 10 participants. Once optional leukapheresis procedure have been completed on at least 10 participants, each additional participant (above the initial 10) who agrees to these optional procedures will be explained that some or all of the procedures may not be performed since collection of the samplemay not provide information to change or impact the study and thus justify them undergoing the risk of the procedure.

Participants will be asked to participate in the following optional sub-study:

7.2.1. Leukapheresis

The first leukapheresis sample will be obtained between weeks 36-48, preferably as close to week 48 as possible and the participant must have an undetectable HIV-RNA. The second time point will occur between weeks 84-96, preferably as close to week 96 as possible. For the second time point, participants must have an undetectable HIV-1 RNA.

- Additional criteria for leukapheresis:
    - Prothombin time (PT): < 1.2 x ULN
    - Partial thromboplastin time (APTT): < 1.5 x ULN
    - Platelets: > 100,000/mm3
    - Adequate venous access

7.3. Screen Failures

Participants can have abnormal labs repeated once to be eligible for study participation**.**

Participant with a positive HLA B*57:01 PCR-SSP or Hepatitis B test will be terminated from study. These participants would not be considered screen failures as they were enrolled pending these results.

7.4. Study Treatment Stopping Rules

7.4.1. HLA B*57:01 or Hepatitis B surface antigen positive

Any enrolled participant found to be positive for the HLA B*57:01 allele or for Hep B sAg will be terminated from the study prior to starting study treatment, and will be prescribed another ART regimen. This regimen would not be covered by the study and would be the responsibility of the participant. This participant would not be allowed to continue on the study and would be replaced. This participant would be asked to return the 7 day supply of study treatment administered while confirmation of HLA B*57:01 and hepatitis B status was pending and would be referred for initiation of ART per routine clinic procedures.

7.4.2. Baseline Resistance

Any enrolled acutely infected participant with evidence of baseline resistance will be continued on study and ART optimized using genotype results. Descriptive results will be reported but will not be included in the efficacy portion of the data analysis.

7.4.3. Potential Hepatotoxicity

Stopping criteria for elevated transaminases are delineated below.

- ALT ≥3XULN and bilirubin ≥2xULN (>35% direct bilirubin; bilirubin fractionation required)
- ALT ≥8xULN;
- ALT ≥3xULN (if baseline ALT is < ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR:
- ALT ≥3x baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such a fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8xULN that persists > 2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks;

Participants with ALT ≥5xULN should be followed weekly until resolution or stabilization (ALT <5xULN on 2 consecutive evaluations).

When liver chemistry stopping criteria above is met, do the following:

- Immediately discontinue DTG and withdraw the participant from the study. Participants should not restart DTG due to the risk of a recurrent reaction. Report the event to the study sponsor within 24 hours of learning its occurrence.
- Make every reasonable attempt to have the participants return for evaluation within 24 hours for repeat chemistries and evaluation;
- Consider a hepatology consultation
- Monitor participants twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline value

In the event that liver stopping criteria are met, the PI will consider the following additional tests to further evaluate the liver event. However any

additional evaluations will be charged to the participant or the participants health care insurance:

- Viral hepatitis serology including:
    a) Hepatitis A IgM antibody;
    b) HBsAg and Hepatitis B Core antibody (IgM)
    c) Hepatitis C RNA;
    d) Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening
- Drugs of abuse screen including alcohol
- Serum acetaminophen test (APAP adduct test)
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Fractionate bilirubin, if total bilirubin is > 1.5XULN:
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, or other over the counter medications or putative hepatotoxins at every study visit to monitor elevated ALT/AST.

7.4.4. Virologic Failure

For the purpose of clinical management in this study, virologic failure must be confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between one to four weeks after the initial suspected virologic failure sample.

Individual participants who meet the VF definition will be continued on study follow-up as per protocol, will have therapy optimized or discontinued per best clinical practice, and may continue on study therapy if clinically indicated. ART-adherent participant is defined as a participant that has ≥ 95% adherence by pill counts.

The following guidelines will be followed for scheduling confirmatory HIV-1 RNA testing in the setting of concurrent illness, immunization within the prior 4 weeks or ART interruption (per below) in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2-4 weeks following resolution of any intercurrent illness.
- Confirmatory testing should be scheduled at least 4 weeks following any immunization.

- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2-4 weeks following resumption of full dose of study medication.

7.5. Early Discontinuation or End of Study

Participants who do not complete at least the first 12 weeks of the study will be replaced.

Participants who elect to terminate the study at any time after 12 weeks of therapy, but before the week 96 visit, will have a study termination visit completed which will be identical to the week 96 visit as outlined in the SOE.

Participants will be terminated from the study if they are positive for HLA B57/58 or Hepatitis B.

7.6. Withdrawal of a Participant from Study

Participants will be withdrawn from further study evaluations for any of the following reasons:

- Withdrawal of informed consent (participant's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued study treatment and participation in the trial is not in the best interest of the participant.
- Participants who become prisoners or become involuntarily incarcerated for treatment of either a psychiatric or physical (e.g. infectious disease) illness.
- Pregnancy or females of reproductive potential who changed their minds and desire to be pregnant
- Requires the use of long-term, unacceptable concomitant medications.
- Gross noncompliance with administration of the study medication(s) or with completion of protocol procedures such that reliable safety assessments (clinical and laboratory) are jeopardized.
- Confirmed virologic failure (VF) as defined in section 5.1.3
- Confirmed creatinine clearance (Cockcroft-Gault formula) below 50 mL/min while on treatment.
    - Due to required dose reduction of 3TC due to decreased clearance.

7.7. Reimbursement

For each study visit, participants will receive a stipend to help cover travel costs. For participants co-enrolled on other studies with study visits occurring at the same time as this study, the participant will receive compensation once for travel. If the participants receive their travel reimbursement from the other study, they will receive a stipend at the visits that immunology labs are collected specifically for analysis on this study (weeks 0, 12, 24, 48, and 96).

Participants will receive an additional stipend when they participate in the optional leukapheresis procedure.

7.8. Treatment at the End of the Study

Following Week 96 all participants will need to make alternative arrangements for independent access to all other antiretroviral therapy.

7.9. Description of Evaluations

7.9.1. Clinical Evaluations and Procedures

Participants will be evaluated by physical examinations, medical history, clinical laboratory tests, vital sign measurements, and AE evaluations. Safety assessments will include grading of the frequency and severity of AEs associated with the treatment including clinical laboratory values. Participants and/or their primary care provider will be informed of any clinically significant laboratory test result or clinical event that occurs throughout the study. Participants will be referred for care where appropriate. Clinical labs will be collected and processed at UNC McLendon Lab, UNC CFAR HIV/STD Laboratory Core (CHSLC), Duke Hospital Lab, or Lab Corp.

- Informed Consent
  Prior to performing any study-related procedure or assessments, the study coordinator will discuss the study with the potential participant and obtain signed informed consent. This communication should be documented.

- Completed medical histories
  Medical histories will be obtained at screening and should include demographic information (date of birth, gender, race, ethnicity), participant's medical history, and medication history.

- Updates to medical histories at all clinical visits

- Complete Physical Exams
  A complete physical examination (PE) is done at the following visits:
  - Screening
  - Early Termination
  - Week 96 or End of Study (EOS)

  The PE will include a complete review of systems, vital signs, and weight. Height will be measured at the Screening Visit only. The complete physical exam also includes signs and symptoms, and diagnoses.

- Directed or targeted medical histories and physical exams
  A targeted physical examination is done at all other designated visits and includes vital signs and is to be driven by any previously identified or new event that the participant has experienced since the last study visit or any unresolved signs or symptoms experienced previously. This assessment will include weight, vital signs, a signs and symptoms update, and clinical assessment of HIV disease.

- Vital Signs - Temperature, respiration, pulse, and blood pressure and weight at each study visit.

- Height - Required at study screening visit only

- Concomitant Medication History
  - Include all current medications and any PRN medications used within the past 30 days.
  - All medication, over the counter (OTC) and herbal supplements taken within 30 days of study entry
  - After study entry, only new and discontinued prescription medications will be recorded.

- Signs, symptoms and diagnosis of illnesses and disease

- At entry, record all grades of signs and symptoms that occurred 30 days prior to study entry.
- After study entry, grade ≥3 signs and symptoms must be recorded.
- Record all signs and symptoms that lead to a change in treatment, regardless of grade.

- Blood Collection - Please reference SOE.

- Acute HIV Assessment.
  The study coordinator will administer this IRB approved assessment to participants at the enrollment visit and/or Week 2 visit (if unable to complete at enrollment). This assessment will be completed as close as possible to enrollment and will assess participant demographics, risk associated with HIV acquisition, and sexual, alcohol and drug preferences and usage in relation to date of HIV acquisition.

- Depression Assessment
  Participants will be assessed every 6 months for depression as well as suicidal thoughts or ideation. The PHQ-9 form will be used to document the assessment. This form is completed at the initial clinical evaluation by the ID clinic social worker. The study coordinator will administer this form every 6 months while a participant is on study. The PHQ-9 form will be reviewed by the study PI. Any changes in the PHI-9 assessment that indicate the development of depression, increased severity of depression or suicidal thoughts will be addressed immediately with the study PI and the participant's primary ID provider in collaboration with other necessary psycho-social counselors per established protocol for management of suicidality/severe depression in the UNC ID Clinic.

- Assessment of Adverse Events - Please reference protocol section 8.2.

- Assessment of Pregnancy Status which includes the date of last menstrual period (LMP) and birth control measures. Women with > 35 days since the LMP will have a serum pregnancy test done to confirm negative status.

  POCT urine pregnancy test will be completed at all study visits.

  Female participants indicating that they changed their mind and desire to become pregnant will be withdrawn from the study.

- HLA B57/58 flow cytometry assay
  In order to allow prompt initiation of DTG/3TC/ABC FDC, we will employ a flow cytometry assay using an HLA-B57/58 reactive monoclonal antibody as a screening test. This assay has been validated for this study in the UNC Center for AIDS Research (CFAR) HIV/STD Laboratory Core (CHSLC).

  A negative result will be reported negative for HLA-B57, and the individual may enroll on study and start treatment.

  A positive HLA-B57 result will be reflexed to a molecular HLA test to specifically detect B*57:01, with results available same day or next business day (if received in lab after 11:00am). The confirmatory molecular HLA test will confirm if reactivity in the flow cytometry assays is due to the presence of HLA-B*57:01 or to other cross-reactive HLA alleles. Studies have reported a

prevalence of the HLA-B*57:01 allele of 5-6% among HIV-infected patients [40, 41]. Because of cross-reactivity, confirmatory testing will be required in a few more individuals than the expected 1-3 B*57:01 positive participants during the study.

- Longitudinal follow-up will include an extended study schedule:

  Study research sample collection and abstracted medical record updates for PHI 05 participants will be extended to 5 years in accordance with the following schedule:

	Week 120 (2.5 years)	Week 144 (3 years)	Week 192 (4 years)	Week 240 (5 years)
Clinical Updates	X	X	X	X
Blood collection for:				
- CD4 count	X	X	X	X
- HIV viral load	X	X	X	X
- Immune Assays	X	X	X	X

  Note: The clinical labs for CD4 and HIV RNA PCR values can be obtained from medical record if clinical appointment is done separately from the research collection. The clinical labs need to be obtained within the study visit window.

- Leukapheresis

  This is an optional sub-study. Participants can undergo 2 resting cell assessment leukaphereses at one of the following locations: 1) the UNC's Apheresis Lab located on the 1st floor of UNC Hospitals, or 2) the American Red Cross (ARC) Apheresis Lab located in Durham, NC. Participant's enrolled at Duke University will have the procedure completed in the Apheresis Lab located at Duke University.

  These optional leukapheresis products will be transported on the day of collection to the Margolis Laboratory on the UNC campus.

  Leukapheresis is a procedure in which white blood cells are donated for research. Only white blood cells are removed in this process, and red blood cells and blood plasma (liquid) is not removed. During leukapheresis, the blood is removed through a needle inserted in a vein in one arm and it will pass through sterile disposable centrifuge tubing to a leukapheresis machine, which separates blood into plasma, red blood cells, platelets and white blood cells. The red cells and most of the plasma will be returned through a needle in the other arm or to the same arm, a total loss of red blood cells of only 15 mL. White cells, some platelets and a small amount of plasma will be retained for use in research. Each donation takes between 2 to 4 hours. The mild reduction in white blood cell and platelet counts is only temporary and is not hazardous to the participant's health. No sedation is required with this procedure

  Note: Refer to the UNC Apheresis or the ARC SOPs and Study Specific Lab Manual for procedures specific to this study.

  Participants who experience a Grade 3 or higher toxicity related to the first leukapheresis procedure at Week 48, will not be asked to complete the 2nd procedure at Week 96 of the study. The exception would be in the case of ≥

Grade 3 blood pressures (BP). Elevated BP observed during the leukapheresis procedure will be monitored via Apheresis Lab policies. These will be noted and documented but Grade 3 or higher BPs will not be used to discontinue study participation from a future leukapheresis as Grade 2 and 3 BPs are frequently observed during this procedure secondary to the BP cuff placement and nervousness of the participant.

7.9.2. **Clinical Laboratory Evaluations**

Labs utilized for the clinical evaluations will be UNC McLendon Lab or LabCorp with HLA testing conducted in the UNC CFAR HIV/STD Laboratory Core (CHSLC). Details of specimen collection are found in the Lab Procedures Manual for this study**.**

The results of clinical laboratory tests will be assessed by the investigator to determine the participant's continuing eligibility at specified visits. If values are outside the normal reference range, the investigator will determine whether or not the abnormal value is clinically significant. All confirmed abnormal laboratory values that the investigator deems clinically significant must be reported as AEs. Participants and/or their primary care provider will be informed of any clinically significant laboratory test result or clinical event that occurs throughout the study. Participants will be referred for care where appropriate.

- Clinical Chemistries
  Includes sodium, potassium, chloride, bicarb, glucose, BUN, creatinine, and creatinine clearance. Lipase will be done a screening and weeks 48 and 96.

- Hepatic Function Tests
  Includes ALT, AST, alkaline phosphatase and total bilirubin. A direct bilirubin will be done at screening only.

- Hematology
  CBC with WBC differential

- Fasting Lipids

- Prothrombin time (PT) and PTT, and INR
  Evaluation based on selection of optional procedure(s) and performed at or around the Week 36 and 84 Visit.

- HIV EIA Combo Ag/Ab Testing with differentiating/confirmatory test
  This testing will be repeated at Week 12 if the differentiating/confirmatory test is not positive at enrollment visit. It is not required to repeat the HIV EIA Ag/Ab test if positive at enrollment.

- HLA B57 Assays
  Peripheral blood samples collected in EDTA will be screened for HLA-B*57:01 using a flow cytometry assay with a HLA-B17 specific monoclonal antibody. In this assay, cells are stained with monoclonal antibodies to CD3-APC and HLA-B17-biotin. After incubation and lysis of red blood cells, streptavidin –PE is added. After an additional wash and paraformaldehyde fixation, CD3 positive T cells are assessed for expression of HLA-B17 related HLA antigens.

HLA-B*57:01 (a B17 related HLA molecule) is excluded if no B17 staining is observed. Samples that demonstrate HLA-B17 antibody binding will be reflexed for further testing on the same day with an HLA-B*57:01 PCR-SSP assay to determine if HLA-B*57:01 is present or if positive staining is due to a cross-reactive (related) HLA antigen (such as B58 or B*57:03). Results from the HLA-B*57:01 PCR-SSP assay would be available same day if samples are received early in the day, or on the next business day.

- HIV RNA
  Performed at all study visits.

- CD4+ T cell differential panel

- FSH Level – follicle stimulating hormone level will be done on all women at screening who indicate menopause per definition in 5.2.7.

- Serum pregnancy test
  For females of child bearing potential, ascertainment of a negative result will be required for study enrollment and at any visit if pregnancy is suspected. Documentation of the date of last menstrual period (LMP) required at all study visits through Week 96 to rule out suspicion of pregnancy. Additionally, review and documentation of birth control methods will be done at each study visit through Week 96.

- POCT urine pregnancy
  For FCBP, this test will be performed at each study visit. Serum pregnancy test will be performed at any visit where pregnancy is suspected.

- Hepatitis B antibody and surface antigen (HBsAg) at screening

- Hepatitis C antibody test – reflex HCV RNA if positive at screening

Labs that are abnormal and meet grading standards per DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, will be reassessed.

Labs utilized for the clinical evaluations will be performed at the Duke University Lab, UNC McLendon Lab or LabCorp.

Blood collected for research will be studied primarily at one of the following laboratories: Margolis Lab, Goonetilleke Lab, and UNC CFAR HIV/STD Laboratory Core (CHSLC).

These research laboratory evaluations include:

- HIV-1 infection of resting CD4+ T cells, VIA, and Latency Clearance Assay;
- CD4/CD8 Immunology Processing;
- Single Copy HIV RNA Assay;
- HIV-1 T-Cell Lymphocyte Studies.

7.10. **Stored Samples**

A separate IRB application will be submitted for future analysis involving these blood samples. These stored samples will only be used for research including genetic studies of the stored samples, after specific further review and approval by the UNC IRB.

Stored Specimens

Any remaining specimens that will be stored for future research will be stored safely and securely in a research specimen storage laboratory at the University of North Carolina at Chapel Hill (UNC-CH). No protected health information (PHI) is included with the samples. The samples will be identified by coded number to maintain participant confidentiality. The link between Participant Identifier Code (PID) on the samples and PHI is maintained in a secured file on a secured server in the control of the principal investigator at UNC-CH. Future researchers would not have access to this link. Only study personnel, people who work at the research specimen storage laboratory at UNC-CH and IRB approved researchers will have access to the participants' samples. Since all the stored specimens are de-identified, the people who work at the research specimen storage laboratory will not have any personally identifying information that would link to a participant. The researchers who receive the specimens may receive information pertaining to lab assay values, age, and sex of the specimen donor, but will not be given the name or any other information that identifies the participant. These samples will be stored indefinitely.

8. CLINICAL MANAGEMENT ISSUES

8.1. Toxicity

Only toxicities considered to be possibly, probably or definitely related to DTG/ABC/3TC FDC will be managed directly by this protocol.

8.2. Toxicity Management

Adverse events that occur during the trial should be evaluated by the Investigator or their designee. The grading system for drug toxicities is located in the U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014], which can be found on the DAIDS RSC Web site:
http://rsc.tech-res.com/safetyandpharmacovigilance/.

Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 8.2.2.

NOTE: In the event of a discontinuation of DTG/ABC/3TC FDC for any reason, re-initiation of this drug should be undertaken with caution. The investigator or their designee must obtain a complete history of the events surrounding the discontinuation of DTG/ABC/3TC FDC, evaluate for the possibility of a clinically suspected hypersensitivity reaction (HSR), and initiate participant management as outlined below, regardless of a participant's HLA-B*5701 status.

8.2.1 Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study medication at the discretion of the Investigator or their designee. (NOTE: see Section 6.4.5 "Specific Toxicities/Adverse Event Management" for exceptions to this

guideline). Participants who choose to withdraw from study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

8.2.2 Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

If the Investigator or their designee has compelling evidence that the Grade 3 AE or toxicity has not been caused by the study medication, dosing may continue after discussion with the study management team.

Participants who develop a Grade 3 AE or toxicity, which the Investigator or their designee considers related or possibly related to the study medication, the medication should be withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, study drug may be re-started, with the exception of suspected HSR due to abacavir.

Should the same Grade 3 AE recur within 28 days in the same participant, the study drug should be permanently discontinued and the participant withdrawn from study. Participants experiencing Grade 3 AEs requiring permanent discontinuation of the study drug should be followed weekly until resolution of the AE and encouraged to have withdrawal study evaluations completed. A Follow-Up visit should be performed 4 weeks after the last dose of the study medication.

Participants with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the study management team, may continue the study drug if the Investigator or their designee has compelling evidence that the toxicity is not related to the study medication.

Exceptions are noted below for lipid abnormalities.

8.2.3 Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have the study drug permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the study drug, dosing may continue after discussion with and agreement from the study management team. Participants should be rechecked each week until the AE returns to Grade 2.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above.

Participants with Grade 4 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the study management team, may continue therapy if the Investigator has compelling evidence that the toxicity is not related to the study drug. Exceptions are noted below for lipid abnormalities.

A follow-up visit should be performed 4 weeks after the last dose of study medication if AEs or laboratory abnormalities are ongoing.

8.2.4 Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to IP are provided below. Toxicities that the Investigator considers related or possibly related to one of the background ART medications may be addressed by substitution of the medication for another approved HIV medication.

The DTG/ABC/3TC single tablet FDC contains DTG, ABC and 3TC; therefore the adverse events associated with these individual components may be expected. For many of the adverse events listed it is unclear whether they are related to the active substance, the wide range of other medicinal products used in the management of HIV infection, or whether they are a result of the underlying disease process.

Participants who permanently discontinue study medications for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-Up study evaluations.

8.2.5 **Hypertriglyceridemia/Hypercholesterolemia**

Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study medications. A confirmatory fasting triglyceride and/or cholesterol level should be obtained prior to the institution of medical therapy for hyperlipidemia.

8.2.6 **Lipase Elevations and Pancreatitis**

Participants with asymptomatic Grade 1 or 2 elevations in lipase may be followed closely for the development of symptoms.

Participants with asymptomatic Grade ≥3 elevations in lipase that are considered possibly or probably related to the study drug should have the study drug interrupted until serum lipase returns to Grade ≤2. Repeat lipase testing within 2 weeks of any Grade ≥3 result. Participants with persistence of Grade ≥3 lipase in the absence of other diagnoses or reoccurrence of lipase elevation (at Grade ≥2) following reintroduction of the study drug should permanently discontinue the study drug.

The study drug should be held in all participants with a confirmed diagnosis of clinical pancreatitis that is considered possibly or probably related to the study medication. After complete resolution of the episode, participants may be re-challenged with the study drug, only if the Investigator has compelling evidence that the event was not caused by study drug. Upon rechallenge, lipase determinations should be performed every 2 weeks for at least 6 weeks after re-initiation of treatment. With any elevation of lipase of Grade ≥2 or any recurrence of symptoms, the participant should discontinue study drug and be withdrawn from study.

8.2.7 **Decreased Renal Function**

Participants who have a decline in creatinine clearance of >50% must return for a confirmatory assessment as soon as possible.

If development of a creatinine clearance measuring <50 mL/min via Cockroft-Gault method, participant must return for a confirmatory assessment as soon as possible.

8.2.8 **Allergic Reaction**

Participants may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study drug should permanently discontinue the medication regimen and the participant may continue on study off study drug. Participants should be treated as clinically appropriate and followed until resolution of the AE.

Participants should be managed in terms of a clinically suspected ABC Hypersensitivity.

8.2.9 **Abacavir Hypersensitivity Reaction (HSR)**

The most significant toxicity associated with ABC is the well-characterized drug-related hypersensitivity.

The diagnosis of HSR to ABC remains a clinical diagnosis. There is no pathognomonic clinical sign or laboratory finding that renders the diagnosis. In clinical studies, approximately 5-6% of participants receiving ABC develop an HSR that in rare cases has proved fatal. HSR is characterized by the appearance of symptoms indicating multiorgan/body system involvement.

Symptoms usually appear within the first 6 weeks of starting treatment with ABC (median time to onset is 9 days), but may occur at any time while on therapy.

Symptoms most often include fever, rash, gastrointestinal symptoms (nausea, vomiting, diarrhea, or abdominal pain), respiratory symptoms (dyspnea, sore throat, cough), and lethargy or malaise. Other signs and symptoms may include musculoskeletal symptoms (myalgia, rarely myolysis, arthralgia), headache, paresthesia, and edema. Respiratory tract symptoms (dyspnea, sore throat, cough) have been observed in approximately 20% of participants who experience HSR. Some participants with HSRs were initially thought to have respiratory tract disease (pneumonia, bronchitis, pharyngitis) or a flu-like illness.

Physical findings may include lymphadenopathy and, occasionally, mucous membrane lesions (conjunctivitis and/or mouth ulceration). The rash is variable and may be absent, but often appears maculopapular or urticarial. Laboratory abnormalities that may accompany ABC hypersensitivity include elevated transaminases, CK, or creatinine or lymphopenia.

The misattribution of the symptoms of HSR to another medical condition or delay in diagnosis of hypersensitivity has resulted in ABC being continued or reintroduced, leading to more severe presentation or rapid (within hours) onset of HSR or death. Therefore, the diagnosis of HSR should be carefully considered for participants presenting with symptoms of these diseases, even if another medical

diagnosis seems likely. Reintroduction of ABC in participants after treatment interruption, with no preceding symptoms of HSR, has rarely resulted in HSR.

Symptoms related to HSR worsen with continued therapy and usually resolve upon discontinuation of ABC. Restarting ABC following an HSR results in a prompt return of symptoms within hours. This recurrence of the HSR may be more severe than on initial presentation and may include life-threatening anaphylaxis; hypotension; liver, renal and respiratory failure; and death. Participants who develop an HSR must discontinue ABC and MUST NOT be rechallenged with ABC.

Management of HSR

In any participant treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the Local Country Prescribing Information) must remain the basis of clinical decision making. Regardless of HLA-B*5701 status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., DTG/ABC/3TC, ZIAGEN™, EPZICOM/KIVEXA™ or TRIZIVIR™) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

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

In order to avoid restarting the ABC-containing product, participants who have experienced an HSR reaction should be asked to return the remaining tablets to the pharmacy.

Participants who have had an HSR must be advised to never take an ABC-containing product (Ziagen®, Trizivir®, or the ABC/3TC fixed-dose combination). ABC therapy SHOULD NOT be restarted following a HSR, because more severe symptoms will occur within hours and may include life-threatening hypotension and death. Fatal HSRs have been associated with re-initiation of ABC therapy. Participants who develop signs or symptoms of HSR, MUST contact their doctor immediately for advice. The site investigator must be notified and provide sign-off for those participants who discontinue ABC due to HSR.

Study Drug will be held for all incidences of suspected ABC HSR.

8.2.10 Skin reactions without other symptoms typical of ABC HSR

Participants should be instructed to contact the Investigator or study coordinator as soon as possible if they develop a rash while on study.

Participants who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN and

Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, the study drug (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the participant should not be re-challenged with any ABC-containing medicinal product (i.e. ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

The following guidance is provided for clinical management of participants who experience rash alone in the absence of accompanying diagnosis of ABC HSR, systemic or allergic symptoms or signs of mucosal or target lesions.

- Participants with an isolated Grade 1 rash may continue the study drug at the Investigator's discretion. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.
- Participants may continue study drug for an isolated Grade 2 rash. However, the study drug (and all other concurrent medication(s) suspected) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The participant should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.
- Participants should permanently discontinue the study drug (and all other concurrent medication(s) suspected) for an isolated Grade 3 or 4 rash, and the participant should be withdrawn from the study. Participant should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as adverse events (see section 8.2.2) and appropriate toxicity ratings should be used to grade the events.

If the etiology of the rash can be definitely diagnosed as being unrelated to the study drug and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

8.2.11 Adverse Events (AEs)

Reports of AEs will be elicited by verbally questioning the participant at all visits. The study coordinator will also telephone the participant approximately 2 to 3 days after initiation of medications. The participant will be instructed to contact the study coordinator or investigator if such events occur at any point during the study.

Any events spontaneously reported by the participant or observed by the study team will be recorded.

If an AE occurs, the study coordinator, in collaboration with the investigator or their designee, will evaluate the severity and seriousness of the AE and the relationship to the study product, and will document the findings as outlined in section 8.2.5. Appropriate countermeasures, including medical intervention or procedures, must be instituted if indicated clinically.

All reactions will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014]. Available from: http://rsc.techres.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf

8.2.12 Definition of an Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable or unintended sign (including an abnormal lab finding, for example), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

1. An AE does include a/an
    - Exacerbation of a pre-existing illness;
    - Increase in frequency or intensity of a pre-existing episodic event or condition;
    - Condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study; and
    - Continuous persistent diseases or symptoms present at Baseline that worsen following the start of the study

2. An AE does not include a/an:
    - Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); however, the condition that led to the procedure is an AE;
    - Pre-existing diseases or conditions present or detected at the start of the study that do not worsen;
    - Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social or convenience admissions);
    - The disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition; and
    - Overdose of either the study medication or concurrent medications without any signs or symptoms.

3. Recording the AE
   In general, abnormal laboratory findings (e.g., clinical chemistries, hematology, urinalysis) or abnormal assessments (e.g., vital signs, EKGs) are not recorded as AEs unless they are considered clinically significant by the investigator. If an abnormal lab finding is considered clinically significant, it must be recorded in the AE log as:
    - If it contributes to a clinical diagnosis, the diagnosis must be recorded as the AE (e.g., a clinically significant elevation in blood

glucose must be recorded as "diabetes" if a clinical diagnosis is made); OR
- If an abnormal finding does not indicate a clinical diagnosis, the abnormality itself must be recorded.

8.2.13 Adverse Event Reporting Period

The AE reporting period for each participant begins from the time of signing the informed consent and lasts until the final treatment visit (Week 96) for each participant.

AEs leading to discontinuation, AEs of ≥Grade 3 severity, related adverse events, and lab abnormalities as well as safety concerns will be communicated in a timely manner to ViiV Healthcare, and the UNC IRB. The Sponsor of this study is ViiV Healthcare. The principal investigator (Cynthia Gay, MD, MPH) or her designee at UNC-CH will be responsible for reporting to the UNC IRB and ViiV Healthcare.

8.2.13.1 Adverse Event Reporting after Week 96 (Longitudinal Phase)

This is the longitudinal phase of the study. The study will no longer provide medication. Adverse events reporting will be restricted to the following:

- Any adverse event occurring as a consequence of procedures required by the longitudinal follow-up will be followed and documented in accordance with provisions outlined below.

For the purpose of this follow-up phase - an AE is any untoward medical occurrence in a participant associated with procedures required for the follow up. An AE can therefore be an unfavorable and unintended sign, symptom, or disease temporarily associated with procedures required in the longitudinal phase (i.e., hematoma following venipuncture).

An AE does not include the following for the Longitudinal phase

- Any medical condition or clinically significant laboratory abnormality with an onset date after week 96 is not an AE.
- Any medical condition or clinically significant laboratory abnormality occuring after week 96 and which is attributed to the initial treatment phase of the protocol by the PI will be followed according to the treatment AE guidelines.

New medical diagnosis occurring after Week 96 and not related to the initial treatment phase will be captured as part of the medical history but will not be reported as an AE.

8.2.14 Documentation of Adverse Events

Throughout the trial, the study coordinator will monitor closely for the development of AEs and the investigator or their designee will determine clinical significance of AEs, and medical interventions will be initiated if required.

1. Chart documentation will include:
   - Concise diagnosis
   - Onset date
   - Criterion for regarding as an AE;
   - Setting;
   - Resolution date;
   - Severity (per DAIDS toxicity grading table)

2. Relation to the study product (unrelated, unlikely, possibly, probably, definitely); an AE may be considered related if it follows a reasonable temporal sequence from administration of the study drug product, confirmed by improvement when the product is stopped and re-appears on repeated exposure.
3. Study drug product change (interrupted or discontinued); and
4. Seriousness (not serious, fatal, life threatening, leads to or prolongs hospitalization, results in persistent or significant disability or incapacity, congenital anomaly or birth defect, important medical event).

8.2.15 Definition of a Serious Adverse Event

As provided in Title 21 CFR part 312, an SAE is an AE occurring at any dose that results in any of the following outcomes;

1. Death;
2. A life-threatening AE;
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. A persistent or significant disability or incapacity;
5. A congenital anomaly or birth defect; and

Important medical event that may not result in death, be life-threating, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical and surgical intervention to prevent one of the outcomes.

8.2.15.1 Definition of a Serious Adverse Event after Week 96 (Longitudinal Phase)

Any SAE occurring during the initial treatment phase will be followed, documented and reported under the treatment phase of the protocol. Similarly any new SAEs occurring before week 96 and considered related to the study drug administered or procedure completed in the treatment phase will be followed, documented and reported per protocol.

The only SAE which will be reported after Week 96 are events considered to be related to the procedures required in the follow up visits after week 96. The definition of SAE is in section 8.2.15.

The relationship to the study procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following consideration

- NO: Evidence exists that the AE has an etiology other than the study procedure
- YES: the AE occurred as a result of a protocol-required procedure such as venipuncture.

8.2.16 Definition of a Serious Unexpected Adverse Event

A serious unexpected adverse event is defined as an SAE that is not identified in the IB.

8.2.17 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator or their designee are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator or their designee to be more severe than expected for the participant's condition, are not to be reported as AEs or SAEs.

8.2.18 Reporting of Serious Adverse Events

All SAEs occurring during the study will be reported to the UNC IRB per the UNC IRB reporting requirements and ViiV Healthcare within 24 hours of knowledge of the occurrence. A written report (Serious Adverse Event Report Form) will be faxed or sent within 72 hours. Additional information will be supplied upon as requested. The Sponsor of this study is ViiV Healthcare. The principal investigator (Cynthia Gay, MD, MPH) or her designee at UNC-CH will be responsible for reporting to the UNC IRB and ViiV Healthcare.

8.2.18.1 Any SAE deemed by the investigator or their designee to be related to a protocol related procedure after Week 96 should be collected and reported using the ViiV Healthcare SAE report form.

8.2.19 Follow-Up of AEs and SAEs

All AEs and SAEs must be followed until resolution, become chronic, or stable. The resolution status of such an event must be documented. In addition, the investigator should report all follow-up for reportable SAEs to the IRB.

8.3 Pregnancy and Breastfeeding

8.3.3 Screening

If the pregnancy test is positive at screening, the potential participant will not be allowed to enroll on the study and start study treatment. No further evaluations are necessary.

Females and males of reproductive potential will be required to use effective contraception while on study. Men or women refusing to use study-required contraception will not be allowed to enroll on the study or continue on the study. No study medication will be provided.

Breastfeeding excludes a woman from participation due to the potential for HIV-1 transmission.

8.3.4 Pregnancy during study participation

The study will assess women for the date of their last menstrual period and perform a POCT urine pregnancy test at each study visit. A serum pregnancy test will be done for any suspected pregnancy based on clinical assessment or date of LMP. If the participant becomes pregnant during the study then study medication must be changed immediately to a regimen that would be safe and effectively control viral replication in a pregnant woman. The participant may continue in the study in an

off study treatment/on study status. The participant will be followed until the pregnancy outcome.

Participants who become pregnant will be seen monthly until week 12/16 of pregnancy and every 3 months thereafter.

8.3.5 Reporting Requirements

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a participant or a participant's partner (spontaneously reported to them) that occurs during the study.

Any pregnancy that occurs in a female participant or a partner of a male participant during study participation will be reported using a clinical trial pregnancy form. The participant will be informed that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to dolutegravir during pregnancy. The pregnancy will be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

If the pregnancy continues to term, the outcome (health of infant) must also be reported the UNC IRB and ViiV Healthcare.

8.3.6 The Sponsor of this study is the University of North Carolina at Chapel Hill. The principal investigator (Cynthia Gay, MD, MPH) at UNC-CH will be responsible for reporting to the UNC IRB and ViiV Healthcare.

8.3.7 We will obtain a medical release or separate consent granting permission to follow the health of both the pregnant partner and her unborn child. We will conduct a post-delivery interview and complete a CRF to collect the data related to the pregnancy outcome.

9 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

Study treatment should be discontinued if:

- A Grade 3 or 4 reaction occurs that is definitely, probably or possibly related to study treatment.
- Hypersensitive reaction to Abacavir cannot be ruled out.
- Completion of treatment as defined in the protocol.
- Request by participant to terminate treatment.
- Pregnancy
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

9.2 Premature Study Discontinuation

Every effort should be made to retain participants on study to assess safety outcomes. Participants should discontinue study if:

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.

- Participant 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 IRB, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

This is a multicenter, single arm, open-label study of the safety, virologic efficacy, feasibility, and impact of DTG/3TC/ABC FDC initiated during the period of AHI on resting cell infection, and immune activation. Participants will be followed for 96 weeks. The primary objective is virologic efficacy as determined by the measurement of plasma HIV-1 RNA levels at Week 24.

10.2 Primary Endpoint

10.2.1 Efficacy – Virologic

Virologic failure (VF) is defined as:

- failure to achieve HIV-1 RNA <200 copies/mL by week 24, **or**
- consecutive HIV-1 RNA levels >200 copies/mL at least 1 week apart after week 24

10.3 Secondary Endpoints

10.3.1 Safety

Occurrence of a Grade ≥ 3 AE, including sign/symptom, lab toxicity, or clinical event, or Grade ≥ 1 AE that is definitely, probably, or possibly related to study treatment any time from study treatment initiation through week 96.

Safety data will include local and systemic signs and symptoms, laboratory measures of safety/toxicity, and all adverse and serious adverse events. Safety data will be routinely collected throughout the duration of the study. Relationship to study treatment will be judged by the protocol team.

10.3.2 Feasibility of using a rapid HLA-B57 screening antibody assay

Time from date of sample collection for testing with the HLA-B57 assay to date of result and date of initiation of study treatment.

10.3.3 Time to HIV-1 RNA levels <200 and <50 copies/mL

10.3.4 HIV-1 RNA level at week 48

10.4 Other Endpoints

10.4.1 Detection of low level viremia as measured by single copy assay at weeks 84 and 96

10.4.2 Proportion CD8+ cells expressing HLA-DR and CD38+ at weeks 0, 24, 48, 96, 120, 144, 192, and 240.

10.4.3 Frequency of resting cell infection at week 48

10.5 Sample Size and Accrual

The total sample size is 40 participants. The samples size for this pilot study is primarily determined by practical considerations. Participants who do not start study treatment or discontinue study prior to week 12 will be replaced. Enrollment will continue until the proposed 40 participants have been enrolled. Based on prior experience within the Duke-UNC Acute HIV Consortium, the team expects that 1-2 participants will accrue into the study per month, inclusive of both sites.

10.5.1 Efficacy

The primary virologic assessment will be the proportion of participants with HIV RNA levels <200 copies/mL at week 24. Assuming 10% of drop out of participants, the 95% confidence interval for the result of 28 of 36 (or 77.8%) completed participants suppressing viremia to < 200 copies/ml would be 64 to 91.4%.

10.6 Monitoring

Accrual, baseline characteristics, conduct of the study (including premature study discontinuations), any interruptions of ART, virologic failures, and all reported toxicities and AEs will be monitored during the study by the protocol team on a regular basis.

It will be the responsibility of the protocol team to interpret the toxicity data, make decisions needed to protect participants from undue risk that may require enrollment suspension or study termination or possible modifications to the study for safety concerns, and determine whether or not participant replacements are needed.

Study Wide Stopping Rules

- If the study experiences 3 failures, in the first 10 participants or 5 total virological failures that are not clearly due to non-adherence, the study will be stopped**.**

10.7 Analyses

10.7.1 Primary Analyses

As this is a pilot study, statistics for the primary analysis will be primarily descriptive. The proportion and 95% confidence intervals of participants with plasma HIV-1 RNA < 200 copies/mL and <50 copies/mL at Weeks 24 and 48, respectively, will be tabulated and presented.

10.7.2 Secondary Analyses

10.7.2.1 Safety and feasibility

- Descriptive summary (proportions and 95% confidence intervals) of all adverse events (AEs), all drug-related AEs, and any grade 3/4 AEs will be generated.

- The feasibility of using a rapid HLA B57 antibody test to allow prompt initiation of an ABC-containing regimen will be assessed by

calculating the time (median and range in days) from the date of sample collection for testing to date of result and date of initiation of study treatment.

10.7.2.2 Virologic

- Longitudinal presentation of median plasma HIV-1 RNA (log10 copies/mL scale) and CD4 cell count will be presented by visit during the 96 weeks of follow-up.

- Time-to-viral-suppression will be examined among enrolled patients in relation to baseline characteristics using the Kaplan Meier method and multivariate Cox proportional hazards regression. Time-to-viral-suppression will be defined as the time to HIV RNA <200 copies/mL or <50 copies/mL after ART initiation. Potential exposures will include duration from estimated-date-of-infection until treatment, baseline CD4 count, baseline HIV RNA level, and age. The Kaplan Meier method and log-rank tests will be used to compare time-to-viral-suppression between participants and our acute HIV cohort of 90 individuals who initiated FDC EFV/FTC/TDF within 30 days of AHI diagnosis. Multivariate proportional hazards regression will be used to estimate hazard ratios, controlling for baseline variables. The final model will be built using backwards elimination with a 10% change in estimate criteria for retaining confounding variables.

- Differences in time-to-viral-suppression will be compared between enrollees on this study and our acute HIV cohort (n=90) who initiated FDC EFV/FTC/TDF within 30 days of AHI diagnosis to assess virologic efficacy at weeks 24 and 48 using log-rank tests and Kaplan-Meier methods.

- Virologic Failures will be presented and separated into two types, (A) VF without resistance (likely due to markedly inadequate adherence) and (B) VF with resistance. The proportion and 95% confidence intervals of participants exhibiting each type of VF will be presented.

10.7.2.3 Other Analaysis

- The frequency of CD8+ cells expressing HLA-DR and CD38+ will be compared with levels of immune activation in seronegative patients and those on the acute HIV cohort who initiated FDC EFV/FTC/TDF during AHI using one way analysis of variance tests at baseline, and weeks 24, 48, and 96.

10.7.2.4 Immune Cell Function

- Longitudinal assessments of T cell phenotype and function will be performed. Data will be compared with cross-sectional data generated from sampling of HIV-1 seronegative individuals.

- Standardized cellular assays will focus on i) measuring both CD4 and CD8 T cell proliferation to viral antigens (HIV, EBV, Influenza and CMV) and mitogenic stimulation (Figure 2A) ii) phenotypic and memory status of CD8 T cells, particularly expression of T-cell master regulators T-bet and Eomes (Figure 2B,C) iii) activation markers including PD-1, CD160, CD38 and HLA-DR (Figure 1C, Clutton 2016) and iv) measurements of cellular metabolism, specifically

measures of aerobic glycolysis and mitochondrial mass and polarization (Henson 2014, Bengsch 2016).

- Statistical analysis of data will be performed in conjunction with the UNC CFAR Biostatistics Core.

11. DATA COLLECTION, MONITORING, AND ADVERSE EVENT REPORTING

11.1. Records to Be Kept

Source documents will be provided for each participant. Participants will be identified by name in the source documents but will not be identified by name in the database or on any report associated with the study. Participants will be identified by the participant identification number (PID) and study identification number (SID) provided by the study database upon screening.

11.2. Role of Data Management

It is the responsibility of the study site to assure the quality of data for this study. This role extends from protocol development to generation of the final study databases.

11.3. Clinical Site Monitoring and Record Availability

The site investigator or their designee will make study documents (e.g., consent forms, study drug product, distribution forms, source documents) and pertinent hospital or clinic records readily available for inspection by the local IRB, site monitors, the FDA, and the industry supporters or designee for confirmation of the study data.

11.4. Expedited Adverse Event Reporting to FDA

11.4.1. Adverse Event Reporting

Adverse events involving investigational (study) drugs, such as those relating to Investigational New Drug (IND) applications, including those for cellular products administered under IND, should be reported as required in the study protocol and sent to the FDA.

11.4.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used in this study.
- The study product, for which expedited reporting is required, is: DTG/3TC/ABC FDC.

11.4.3 Grading Severity of Events

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014] , must be used and is available on the DAIDS RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/.

All confirmed ≥ grade 3 lab results and serious adverse events occurring during clinical studies must be reported to the appropriate ViiV healthcare Clinical contact person by the research staff within 24 hours of their knowledge of the event. AEs occurring after Week 96 will be reported as described in protocol sections 8.2.13.1 and 8.2.15.1.

11.4.4 Expedited AE Reporting Period

- The expedited AE reporting period for this protocol is the entire study duration for an individual participant (from study enrollment until study completion or discontinuation of the participant from study participation for any reason).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to the FDA if the study staff become aware of the events on a passive basis (from publicly available information).

12. EXTERNAL SUPPORT/COLLABORATION/FUNDING

12.1. National Cancer Institute, Frederick, MD
12.1.1. Single Copy HIV RNA assay

12.2. ViiV Healthcare

13. HUMAN PARTICIPANTS

13.1. 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 responsible for oversight of the study. A signed consent form will be obtained from each participant. 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 participant, and this fact will be documented in the participant's record.

13.2. Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked in a secure area accessibly only to research study personnel. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by IRB, or the industry supporters or designee.

13.3. Study Discontinuation

The study may be discontinued at any time by the IRB, the industry supporters or other government agencies as part of their duties to ensure that research participants are protected.

14. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the industry supporters prior to submission.

15. 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 dangerous goods materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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Appendix 1

List of Highly Effective Birth Control Methods for Avoidance of Pregnancy in Females of Childbearing Potential

- Abstinence
- Contraceptive subdermal implant
- Combined estrogen and progesterone oral contraceptive
- Injectable progestogen
- Implants of levonorgestrel
- Contraceptive (Estrogenic) vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with published data showing an expected failure rate of <1% per year
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female participant's entry into the study, and this male is the sole partner for that participant. The documentation on male sterility can come from the site personnel's review of participant's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

Appendix 2

Examples of Intrauterine Devices (IUDs) with published data showing an expected failure rate of <1% per year

This list is not all inclusive and IUDs not included on this list may meet this protocol-required definition. Check the product labeling carefully for any IUD.

- Paragard T380A
- Mirena
- Flexigard 330
- Ombrelle 380
- Cu-Safe 300
- Cu-Fix 390
- TCu380Ag
- TCu380S

Supporting References

Paragard T380A Prescribing Information (May 2006)

Mirena Prescribing Information (Oct 2009)

Kulier R, Helmerhorst FM, O'Brien P, et. al. Copper containing, framed intra-uterine devices for contraception. Cochrane Database Syst Rev 2006;CD005347

Boateng J, Chi I-c and Jones DB. An evaluation of six new intrauterine devices. *Advances in Contraception*. 1994;10:57-70.

Appendix 3
Essential Participant Information

1. Participants must be made aware of the possibility of a hypersensitivity reaction to abacavir that may result in a life-threatening reaction or death and that the risk of a hypersensitivity reaction is increased if they are HLA-B*5701 positive.

2. Participants must also be informed that HLA-B*5701 negative individuals can also experience abacavir hypersensitivity reaction. Therefore, ANY participant who develops signs or symptoms consistent with a possible hypersensitivity reaction to abacavir MUST CONTACT their doctor IMMEDIATELY.

3. Participants who are hypersensitive to abacavir should be reminded that they must never take the DTG/ABC/3TC single tablet FDC or any other medicinal product containing abacavir (e.g. ZIAGEN, EPZICOM, KIVEXA, TRIZIVIR) again, regardless of their HLA-B*5701 status.

4. In order to avoid restarting the DTG/ABC/3TC single tablet FDC, participants who have experienced a hypersensitivity reaction should be asked to return the remaining DTG/ABC/3TC FDC tablets to the Investigator or site staff.

5. Participants who have stopped the DTG/ABC/3TC single tablet FDC for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting

6. Each participant should be reminded to read the package leaflet included in the DTG/ABC/3TC single tablet FDC pack. They should be reminded of the importance of removing the Alert Card included in the pack, and keeping it with them at all times.

Appendix 4

Study Drug Dispensing Options at Enrollment

1. Options for drug dispensing at the study sites: Duke University (Duke) and the University of North Carolina at Chapel Hill (UNC):
    a) Send the participant home with a 7 day supply of FDC dolutegravir/abacavir/lamivudine. The participant is instructed to start the medication ONLY after confirmation of the HLA and Hepatitis B testing results. The remainder of the 30 day supply of medication will be picked up by the participant or can be mailed to the participant after confirmation of negative testing results. (Offered only at UNC).
    b) Mail the participant 30 days of medications after the HLA and Hepatitis B testing results are confirmed (Duke and UNC)
    c) Bring the participant back after confirmation of HLA and Hepatitis B testing results to get 30 days of the medication (Duke and UNC)

Schedule of Events Evaluations	Combined Screen and Enrollment	Treatment Phase											Early Discontinuation or End-of-Study
Study Weeks	**0**	**2**	**4**	**8**	**12**	**16**	**24**	**36**	**48**	**60**	**72**	**84**	**96**
Clinical Procedures													
Consent, Eligibility, Demographics,	X												
Complete Physical Examination[1] (vital signs, height & weight) and medical history[2]	X												X
Targeted Clinical Assessments[3]		X	X	X	X	X	X	X	X	X	X	X	
Acute HIV Assessment	X*												
Depression Assessment (PHQ-9)	X#						X		X		X		X
Assessment of Pregnancy and Birth Control	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
ART & Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures													
Chemistries[4]	X		X		X		X		X		X		X
Liver Function Labs[5]	X		X		X		X		X		X		X
CBC with differential	X		X		X		X		X		X		X
Serum Pregnancy Test	X												X
Urine Pregnancy Test		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	
Follicle Stimulating Hormone[∞]	X												
Fasting Lipids	X[7]								X				X
Lipase	X								X				X
HLA B57 Rapid test	X												
HIV-1 Combo Ag/Ab test	X				X[8]								
HBV AB, HBVsAg and HCV AB[±]	X												
RPR[9]	X												
HIV-1 RNA PCR	X	X	X	X	X	X	X	X	X	X	X	X	X
HIV Genotype	X												
CD4+ T Cell Differential Panel	X				X		X		X		X		X
Urine for GC and Chlamydia[9]	X												
Urinalysis macro	X												
Lymphocyte Activation Studies[10, 12]	X				X		X		X				X
Serum and PBMCs for storage[10]	X	X			X		X		X				X
Single Copy Assay[13]												X	X
Optional Procedures													
PT and APTT								X				X	
Resting Cell Infection Measurement[11]									X				X
Leukapheresis[11]									X				X

[1] The Complete PE will include a complete review of systems, vital signs, and weight. Height will be measured at the Screening Visit only. The complete physical exam also includes signs and symptoms, and diagnoses.
[2] Medical histories will be obtained at screening and should include demographic information (date of birth, gender, race, ethnicity), participant's medical history, and medication history.
[3] A targeted physical examination is done at all other visits and includes vital signs and is to be driven by any previously identified or new event that the participant has experienced since the last study visit or any unresolved signs or symptoms experienced previously. This assessment will include weight, vital signs, a signs and symptoms update, and clinical assessment of HIV disease.
* The acute HIV assessment will be initiated at screening/enrollment visit but may be completed at the Week 2 visit if required.
# The baseline depression assessment (PHQ-9) may be completed prior to consent as this assessment is a standard of care assessment done on all new ID clinic patients.
[4] Chemistries includes sodium, potassium, chloride, bicarb, glucose, BUN,creatinine and calculation of creatinine clearance.
[5] Includes ALT, AST, alkaline phosphatase and total bilirubin. A direct bilirubin will be done at screening only.
[6] For females of child bearing potential, ascertainment of a negative POCT urine pregnancy test result will be required at all study visits. Suspicion of pregnancy based on clinical assessment or date of LMP will require a serum pregnancy test at the study visit. (reference protocol section 7.9.1.)
[∞]Optional test – complete on any women who meet the definition of menopause as described in protocol section 5.2.7, to confirm menopause.
[7] Fasting and can be obtained at visit 2 if not fasting at screen/enrollment visit.
[8] Repeat HIV-1/2 confirmatory/differentiating testing at week 12 if the enrollment test is negative or indeterminate. Only repeat HIV -1 Combo Ab/Ab test with differentiating test if the Combo Ag/Ab test was negative at enrollment. Completion of both test acceptable if exact testing results not available at enrollment.
[±] Reflex to HCV RNA test, if positive
[9] Testing not required if done within 30 days of visit and documentation of results (and treatment, if applicable) are available.
[10] Processed and stored at UNC CFAR HIV/STD Laboratory Core (CHSLC). Analysis to be completed in the Goonetilleke Lab at UNC.
[11] Processed in the Margolis Lab
[12] Includes serum, plasma and PBMCs for storage - (1) 3.5 mL SST and (4) 8.5 mL ACD
[13] Processed and stored at UNC CHSLC. Batched and shipped to National Cancer Institute (NCI) in Fredericksburg, MD
[14] In situations where the CBC with differential is not required to run the CD4 test, the CBC is optional.
[15] Abstract from clinical record. Clinical lab testing can be abstracted from clinical record if testing completed within visit window and separate from research samples collection. Complete clinical labs at UNC McLendon Lab for provider availability in UNC EMR.

Schedule of Events	**Longitudinal Follow -Up Phase**			
Study Weeks	**120**	**144**	**192**	**240**
ClinicalAssessment per chart abstraction[15]				
Consent, Demographics, and/or Medical Release (as required)[15]	X	X	X	X
Update medical history[15]	X	X	X	X
Adverse Event Assessment[15]	X	X	X	X
Update ART & Concomitant Medication[15]	X	X	X	X
Clinical Laboratory Procedures or documentation per chart abstraction				
CBC with differential[14, 15]	X	X	X	X

HIV-1 RNA PCR[15]	X	X	X	X
CD4+ T Cell Differential Panel[15]	X	X	X	X
Research Assay				
Lymphocyte Activation Studies[10,12]	X	X	X	X