Dolutegravir Antiretroviral Strategy to Promote Improvement and Reduce drug Exposure (ASPIRE) Study

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SCHEMA

DESIGN	HIV-1 infected subjects **with** no history of virologic failure and plasma HIV RNA <50 copies/mL for at least 48 weeks while on any United States Department of Health and Human Services (DHHS) recommended, alternative, **or other** three-drug antiretroviral regimen will be randomized to dolutegravir (DTG) plus lamivudine (Arm 1) or continuation of their current regimen (Arm 2) for 48 weeks. The primary endpoint is virologic failure defined as confirmed plasma HIV-1 RNA > 50 copies/mL before or at Week 24 All subjects will undergo routine monitoring including plasma HIV-1 RNA, CD4/CD8 count, hematology, chemistry and fasting lipids. Resistance testing will be done in all patients who experience virologic failure. Single-copy HIV-1 assay will be done to quantify residual viremia. Plasma and serum samples will be stored for possible future exploration of the impact of switching on markers of immune activation, inflammation, bone and renal toxicity. PBMCs will be stored in the subset of patients enrolled at Northwestern University to explore the impact of switching on HIV reservoir size.
DURATION	48 weeks
SAMPLE SIZE	90 subjects
POPULATION	HIV-1-infected men and women, 18 years and older, **with** no baseline **NRTI** resistance, no history of virologic failure, and HIV RNA <50 copies/mL for at least 48 weeks prior to study entry while on any DHHS recommended, alternative, **or other** three-drug regimen
REGIMEN	Subjects will be randomized (1:1) to: Arm 1: dolutegravir 50 mg plus lamivudine 300 mg once daily OR Arm 2: Continue current DHHS recommended or alternative three-drug antiretroviral regimen

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

HIV-infected patients **with** no history of virologic failure, and HIV RNA <50 copies/mL for at least 48 weeks on any DHHS recommended, alternative, **or other** three-drug regimen will maintain viral suppression after switching to DTG + lamivudine.

Note: All DHHS recommended, alternative, **or other** baseline regimens contain a boosted protease inhibitor or non-nucleoside reverse transcriptase inhibitor or integrase inhibitor plus two nucleos(t)ide reverse transcriptase inhibitors, one of them lamivudine or emtricitabine.

1.2 Primary Objective

Among HIV patients **with** no history of virologic failure and HIV RNA <50 copies/mL for at least 48 weeks prior to entry, we will compare virologic failure rate, defined as confirmed HIV RNA >50 copies/mL before or at Week 24 between those who continue their current regimen versus those who switch to DTG + lamivudine

1.3 Secondary Objectives are to determine the impact of switching on:

1.3.1. CD4 count at Weeks 24 and 48

1.3.2 Rates of HIV-1 viremia >20, >50, and >200 copies/mL at Weeks 24 and 48

1.3.2. HIV resistance among those with confirmed viral rebound to > 50 copies/mL

1.3.3. Incidence of clinical and/or laboratory toxicities.
The safety and tolerability measures will include time to discontinuation of any study medication due to adverse events (AEs), proportion of Grade 3 or Grade 4 clinical AEs, proportion of Grade 3 or Grade 4 laboratory abnormalities, and summaries of all treatment-related AEs.

1.3.4. Change in HIV-1 detection by the single-copy assay from baseline to Weeks 24 and 48

1.3.5. To collect and store samples for possible future exploration of the impact of switching on:

a. Other measures of the HIV reservoir size e.g total/integrated DNA and cellular RNA in PBMC (substudy in patients enrolled at Northwestern University)
b. Soluble and cellular markers of immune activation and inflammation: e.g. CRP, IL-6, sCD14, sCD163, d-dimer and TNFR-2
c. Markers of bone turnover and renal tubular toxicity
d. Stored samples may also be used for targeted pharmacokinetic evaluations if needed to explain study results

2.0 INTRODUCTION

2.1 Background and Rationale

Antiretroviral therapy with fewer than three drugs is an option for some HIV-infected patients

Current HIV treatment guidelines recommend the use of three active agents with the goal of maintaining HIV viral suppression below 50 copies/mL (cpm)[1,2] However, long-term combination antiretroviral therapy (ART) has limitations including adverse effects, drug-drug interactions, and cumulative cost. Each constituent compound of ART may have an additive effect on these limitations. For example, two of the most common components of modern ART regimens are the nucleos(t)ide reverse transcriptase inhibitors (NRTI), abacavir and tenofovir, each of which has potential adverse effects. Tenofovir is associated with renal/bone toxicity while abacavir has been associated with hypersensitivity syndrome, and perhaps cardiovascular effects)[3-8]. Adverse effects of NRTIs may overlap with those of protease inhibitors (PI) and/or non-nucleoside reverse transcriptase inhibitors (NNRTI).[4,9,10] The global move towards early ART initiation[11,12]has amplified the impetus to discover novel therapeutic strategies that will avoid long-term toxicity and curtail cost while maintaining virological suppression. One potential strategy is reductive ART, defined as treatment with fewer than three ARV drugs per day in a patient who is virologically suppressed on a three-drug regimen.[13] Other terms that have been used to describe this strategy include ART de-intensification and ART simplification. Crucially, the most successful reductive ART strategies must select both appropriate patient candidates and an optimal ART regimen that provides potential benefits in toxicity and cost while maintaining virologic suppression.

The optimal patients for reductive ART are likely to be those with relatively low viral reservoirs during three-drug ART. Nadir CD4 count may be useful in identifying such patients since CD4 count is readily accessible clinically and has been shown to be predictive of reservoir size during successful ART. This was demonstrated in a study of patients who had been virally suppressed for a mean duration of 3.2 years.[14] In multivariate analysis, only nadir CD4 count was significantly associated with HIV proviral DNA (reservoir size). Duration of viral suppression may also be a useful parameter to identify those likely to have a low reservoir size since longer duration of suppression below 50 cpm has been associated with reduced risk of viral rebound,[15-17] Moreover, viral reservoirs tend to diminish with increased time on ART.[18] In an observational study of 664 patients receiving ritonavir boosted PI (PI/r) monotherapy after initial viral suppression with three agents, both nadir CD4 count <200 cells/mm^3 and a shorter duration of viral suppression prior to regimen simplification were associated with virologic failure.[19] In summary, patients with a higher nadir CD4 count and longer duration of suppressive ART may have lower HIV reservoirs and thus may be more likely to experience a favorable response to a reductive ART regimen.

The integrase strand transfer inhibitor (INSTI) class of antiretroviral drugs has attributes that are desirable in a reductive ART regimen; namely, reliable potency, long-term tolerability, and limited resistance in treatment naïve patients. Dolutegravir (DTG) is especially attractive since resistance to DTG occurs less commonly (discussed in the section below) than resistance to the earlier INSTIs in patients with virologic failure[20-22], suggesting a higher barrier to resistance with DTG. Raltegravir has been studied as part of NRTI-sparing regimens in ART switch studies, demonstrating improvements in som**e** toxicities such as bone mineral density, but with mixed results in terms of virologic efficacy.[20,23-25]. Elvitegravir is less attractive both because it requires pharmacologic boosting and is available in the United States only as a component of a single tablet regimen. We hypothesize that the combination of DTG plus another potent well-tolerated agent will constitute an effective regimen for reductive ART.

Dolutegravir

DTG was FDA approved in 2013 for the treatment of HIV-1 infection in antiretroviral-naïve and experienced patients. In early studies, monotherapy with DTG 50 mg once daily for 10 days resulted in a mean viral load decline of 2.46 $\log_{10}$ and 7/10 (70%) of the subjects achieved viral load < 50 copies/mL .[26] DTG's chiral, non-racemic structure fits loosely into its intasome binding pocket, allowing it to retain binding capacity despite mutational changes in pocket structure, and to dissociate from integrase-DNA complexes more slowly than other members of the INSTI class.[27] Resistance passage experiments demonstrated no development of significant DTG phenotypic resistance after 112 days, whereas >5 fold phenotypic resistance to raltegravir occurred by day 28.[28] As noted above, the resistance profile of DTG appears to be higher than earlier INSTIs, as no mutation emerged in large clinical trials of treatment naïve individuals.[29,30] The R263K mutation was later identified in a few highly treatment experienced patients salvaged with DTG-containing ART. R263K confers very low resistance to DTG but it also compromises viral fitness.[31,32] Other mutations described in association with DTG (e.g G118R and H51Y) also damage viral replicative fitness, which may explain the rarity of DTG-related mutations in clinical trials.[33] The reduced replicative fitness of viruses selected by DTG is consistent with recent findings that integrase mutations selected by DTG impair the emergence of resistance to RTIs such as lamivudine and nevirapine.[31] Furthermore, the metabolic, renal, bone, and drug-drug interaction profile of DTG is highly favorable compared to many antiretroviral agents currently in wide use.[34] DTG is approved for both once- and twice-daily dosing, depending on concomitant medications, or presence of INSTI resistance mutations with or without severe renal disease. The recommended DTG dose in the absence of INSTI mutations or concomitant use of potent UGT1A/CYP3A inducers is 50 mg once daily. Dolutegravir is also available in a fixed- dose combination that includes 50 mg of DTG, 600 mg abacavir, and 300 mg lamivudine, known as Triumeq®**.**

Lamivudine

Lamivudine has long been known to have excellent tolerability, and importantly has low *in vitro* and *in vivo* mitochondrial toxicity.[35] It possesses good CNS penetration,[36] and concentrates in the male and female genital tract.[37] Lamivudine received FDA approval for treatment of HIV-1 infection in 1995 and has remained a core component of many first line ART regimens worldwide.[1,38] The important role of lamivudine in combination ART was recently further demonstrated in the GARDEL study, which found that initial dual therapy with lamivudine plus lopinavir/r was as effective and better tolerated than the combination of lopinavir/r, lamivudine and a second NRTI in treatment naïve patients.[39]

Dolutegravir + lamivudine is an ideal regimen to evaluate for reductive ART

Early trials of reductive ART primarily employed PI/r monotherapy[13]. More recent trials have explored lamivudine plus PI/r including two recent randomized studies (OLE, SALT), which found non-inferiority of regimen simplification from standard three-active drug treatment to PI/r +.lamivudine [40,41] These results differ from those of several PI/r monotherapy switch studies which demonstrated inconsistent efficacy and a higher rate of low-level viremia in those receiving PI/r alone.[42-46] The two-drug regimen of DTG +lamivudine has several potential advantages over PI/r + lamivudine; these include two constituent pharmacologic agents as opposed to three, a lower pill burden, a favorable effect on lipids, reduced drug-drug interactions, and lower rate of gastrointestinal side effects. In addition DTG achieves potent concentrations in the CNS [47] which may not the case for some PIs.[48,49] Taken together, evidence suggests that DTG + lamivudine will be a highly potent and safe regimen with a sufficiently high resistance barrier to maintain virologic suppression, making it an ideal regimen to investigate for reductive ART. This strategy has a high probability of success if utilized in a population of suppressed patients who have clinical parameters associated with relatively low viral reservoirs and long-term adherence.

3.0 STUDY DESIGN

ASPIRE is a prospective, open-label, randomized, multicenter, 48-week study to explore whether HIV-infected subjects **with** no history of virologic failure, and HIV RNA <50 copies/mL for at least 48 weeks on any DHHS recommended, alternative, **or other** three-drug regimen will maintain viral suppression after switching to DTG + lamivudine. **S**ubjects must have a pre-treatment genotype of the reverse transcriptase and protease genes documenting no **NRTI** resistance mutations.

Subjects (N=90) will be randomized to DTG + lamivudine (Arm 1) or continuation of their DHHS recommended, alternative, **or other** regimen (Arm 2) for 48 weeks.

Each subject will be evaluated at screening, entry, and at Weeks 4, 12, 24, 36, and 48. All subjects will undergo routine monitoring including plasma HIV-1 RNA, CD4/CD8, hematology, chemistry, and fasting lipid profiles.

HIV-1 RNA single-copy assay will be performed to quantify changes in residual viremia from baseline to Weeks 24 and 48. Plasma and serum samples will be stored for possible evaluation of changes in soluble and cellular markers of inflammation and immune activation as well as changes in markers of bone turnover and renal tubular toxicity and for targeted pharmacokinetics studies. PBMCs will be stored in the patient subset enrolled at Northwestern University to further explore the dynamics of HIV reservoir size with the experimental reductive strategy.

Subjects with suspected virologic failure (defined as plasma HIV-1 RNA > 50 copies/mL at any time after study entry up to Week 48) will have a confirmatory viral load obtained within 35 days after receipt of the results of the initial sample. Resistance testing will be attempted on the confirmatory HIV RNA in all patients with confirmed virologic failure. Subjects with confirmed virologic failure on the study regimen may be switched to alternative combination ART at the discretion of their HIV care provider. The HIV care provider may elect to continue DTG + lamivudine if there is evidence that virologic failure was caused by a lapse in adherence. At the end of the study, subjects will be managed at the discretion of their primary HIV providers.

All subjects will be followed through Week 48 regardless of treatment modification, discontinuation or adherence.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemoiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load.

NOTE: The term “licensed” refers to a United States FDA-approved kit.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (eg, indirect versus competitive), or a Western blot or a plasma HIV-1 RNA.

4.1.2. HIV-1 RNA <50 copies/mL on all measurements within 48 weeks prior to study entry while on any DHHS recommended, alternative **or other** three-drug antiretroviral regimen. A history of switching for simplification and/or tolerability is allowed.

At least two measurements within the previous 48 weeks are required prior to study screening.

4.1.3 No history of virologic failure, defined as consecutive HIV RNA > 50 copies/mL after 12 months of initiating ART.

NOTE: An isolated (non-consecutive) HIV RNA > 50 copies/mL (but less than 400 copies/mL) is permitted after 12 months of initiating ART but not in the 48-week window prior to study entry.

4.1.4 Screening plasma HIV RNA < 20 copies/mL using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0, obtained within 45 days prior to study entry

4.1.5. Pretreatment genotype **of the protease and reverse transcriptase genes** documenting no **nucleos(t)ide (NRTI)** mutations according to the 201**4** IAS-USA drug resistance mutations list (available at https://www.iasusa.org/sites/default/files/tam/22-3-642.pdf)

4. 1.6. No known resistance to integrase inhibitors [Note: pre-treatment resistance testing for integrase inhibitors is not required.]

4.1.7. Laboratory values obtained within 45 days prior to study entry:

- ANC ≥750/mm^3
- Hemoglobin ≥10 g/dL
- Platelets ≥50,000/mm^3 .
- Calculated creatinine clearance (CrCl) ≥50 mL/min, as estimated by the Cockcroft-Gault equation

4.1.8 Negative serum or urine pregnancy test at screening and within 48 hours of study entry for women with reproductive potential (defined as women who have not been postmenopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone surgical sterilization [e.g., hysterectomy, bilateral oophorectomy, or salpingectomy]) .The urine test must have a sensitivity of ≤50 mIU/mL.

4.1.9 If participating in sexual activity that could lead to pregnancy, female subjects with reproductive potential must use one form of contraceptive as listed below while receiving protocol-specified medications and for 60 days after stopping the medications. At least one of the following methods MUST be used appropriately:

- Condoms (male or female) with or without a spermicidal agent. Condoms are recommended because their appropriate use is the only contraception method effective for preventing HIV transmission.
- Diaphragm or cervical cap with spermicide
- IUD (intrauterine device)

- Hormone-based contraceptive. Some medications alter the metabolism of hormone-based contraceptives. This interaction may make hormone-based contraceptives less effective. Therefore, an alternative or an additional contraception method may be required. Oral contraceptives containing norgestimate and ethinyl estradiol can be used without an additional contraception method.

Subject-reported history is acceptable documentation of sterilization, other contraception methods, menopause, and reproductive potential.

4.1.10 Men and women age ≥18 years.

4.1.11 Ability and willingness of subject to provide informed consent

4.1.12 Ability to continue current regimen (i.e., have uninterrupted access)

4.1.13 **Negative hepatitis B surface Ag within 45 days of entry**

4.2 Exclusion Criteria

4.2.1 Serious illness or AIDS-related complication within 21 days of screening requiring systemic treatment and/or hospitalization until candidate 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. Need for systemic therapy for malignancy currently or anticipated during the study period.

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

4.2.2 Treatment within 30 days prior to study entry with immune modulators such as systemic steroids, interleukins, interferons, granulocyte colony-stimulating factor (G-CSF), erythropoietin, or any investigational therapy. Vaccination within 7 days

NOTE: Subjects receiving stable physiologic glucocorticoid doses (defined as prednisone ≤15 mg/day [or equivalent] as a stable or tapering dose) are permitted.

4.2.3 Pregnant women or women of childbearing potential who wish to become pregnant during the study period, or Breast-feeding

4.2.4 Active HCV treatment or anticipated need for treatment within study period. HCV infection alone is not exclusionary (see 4.2.5, 4.2.6 and 4.2.9)

4.2.5 Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

4.2.6 Severe hepatic impairment (Class C) as determined by Child-Pugh classification

4.2.7 Known allergy or hypersensitivity to DTG or lamivudine.

4.2.8 Active drug or alcohol use or dependence that could interfere with adherence to study requirements

4.2.9 ALT (alanine aminotransferase) >5 x ULN (upper limit of normal) OR ALT >3 x ULN and total bilirubin >1.5 x ULN (with 35% direct bilirubin) **within 45 days of entry** NOTE: If the potential subject is taking an atazanavir-containing regimen at the time of screening, total bilirubin ≤5 x ULN is acceptable

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, sites must have the protocol and the protocol consent form approved by their local institutional review board (IRB).

Once a candidate for study entry has been identified, details will be carefully discussed with the subject. The subject will be asked to read and sign the approved protocol consent form.

4.3.2 Registration/Randomization

Subjects who meet enrollment criteria will be randomized **on the day of study entry according to the study treatment that has been randomly assigned to the Patient Number on the site-specific Randomization List held by the local site pharmacist.** For subjects from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, **the Eligibility Checklist** must be completed **with the reason(s) for screen failure and faxed to the Data Management Center.**

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

Subjects will be randomized (1:1) to either:

Arm 1: DTG 50 mg orally once daily plus lamivudine 300 mg orally once daily

OR

Arm 2: Continue current DHHS recommended or alternative three- drug antiretroviral regimen

Study treatment duration is 48 weeks.

5.1.1 Regimen

Subjects must begin study treatment within 72 hours after entry (see Section 6.0) and continue on study treatment for 48 weeks.

The pharmacist will dispense the **amount of** study-provided study products at the entry visit (day 0) and Weeks 4, 12, 24, 36 **to last to the next study visit.**

At the Week 48 visit, subjects must return any remaining study-provided study products.

5.1.2 Administration

DTG will be administered orally as one 50 mg tablet once daily with or without food.

DTG should be taken at least 2 hours before or 6 hours after taking cation containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, DTG and supplements containing calcium or iron can be taken together with food.

Lamivudine will be administered orally as one 300 mg tablet once daily with or without food

5.2 Study Product Formulation and Preparation

5.2.1 Dolutegravir (Tivicay) 50 mg tablets. Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°-86°F). **Each bottle contains a 30 day supply.**

Lamivudine (Epivir) 300 mg tablets. Store at 25C (77F); excursions permitted to 15 to 30C (59 to 86F). **Each bottle contains a 30 day supply.**

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply/Distribution

DTG and lamivudine for Arm 1 will be supplied by ViiV.

Subjects must have the ability to continue procuring current regimen if randomized to continue their present treatment (Arm 2)

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received. All unused study products must be returned to the site (or as otherwise directed by the sponsor) after the study is completed or terminated.

5.4 Concomitant Medications

Below are lists of selected concomitant medications. These lists are only current as of the date of this protocol. Therefore, whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, and Investigator's Brochures to obtain the most current information on drug interactions, contraindications, and precautions.

5.4.1 Required Medications: None.

5.4.2 Prohibited Medications

<u>Prohibited medications with DTG</u>

The following are prohibited while the subject is on study drugs:

- Systemic cytotoxic chemotherapy
- Dofetilide (or pilsicainide [available in Japan]) is prohibited as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity

NOTE: Vaccinations are contraindicated within 7 days of study visits in Arms 1 and 2

5.4.3 Precautionary Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medications' and study agents' most recent package inserts, Investigator's Brochures to obtain the most current information on drug interactions, contraindications, and precautions.

Precautionary medications with DTG

• antacids or laxatives that contain aluminum, magnesium, sucralfate (CARAFATE®), or buffered medicines. DTG should be taken at least 2 hours before or 6 hours after these medicines are ingested.
• iron or calcium supplements. Supplements including multivitamins containing calcium or iron may be taken at the same time with DTG if taken with food. Otherwise, DTG should be taken at least 2 hours before or 6 hours after these medicines.
• anti-seizure medicines: oxcarbazepine (TRILEPTAL®), phenytoin (DILANTIN®, DILANTIN®-125, PHENYTEK®), phenobarbital (LUMINAL®), carbamazepine (CARBATROL®, QUETRO®, TEGRETOL®, TEGRETOL®-XR, TERIL®, EPITOL®)
• St. John's wort (*Hypericum perforatum*)
• a medicine that contains metformin
• rifampin (RIFATER®, RIFAMATE®, RIMACTANE®, RIFADIN®) as DTG dose must be adjusted

5.5 Adherence Assessment

Adherence to all study drugs will be monitored by self-report. Sites will provide adherence reinforcement, according to local standard practice, throughout the study. Subjects with poor adherence will be provided counseling by the site.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Events

Evaluation	VISITS								
	Screening	Entry	Wk 4	Wk 12	Wk 24	Wk 36	Wk 48	Confirmation of Virologic Failure	Premature Study or Treatment Discontinuation
Complete Physical Exam		X							
Targeted Physical Exam, Adverse Event Assessment	X		X	X	X	X	X	X	X
Informed Consent, Medical History, Eligibility Criteria Review	X								
Study Evaluations (Clinical Assessment, Concomitant Medications)	X	X	X	X	X	X	X	X	X
Pharmacy Dispensing		X	X	X	X	X			
Adherence Assessment			X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X		X
Chemistry and Liver Function Tests	X	X	X	X	X	X	X		X
Fasting Lipid Panel		X			X		X		
Pregnancy Testing	X	X	If pregnancy is suspected						
Hepatitis B Surface **Antigen**	X								
Hepatitis C Antibody		**X**							
CD4/CD8		X			X		X		X
CD4 Nadir		**X**							
HIV-1 RNA (Cobas Taqman v2)	X	X	X	X	X	X	X	X	X
Urinalysis	X								
PBMC Processing and Storage (Northwestern only)		X			X			X	X
Plasma Storage	X	X	X	X	X	X	X	X	X
Serum Storage		X					X	X	X
Single-copy HIV 1 RNA		X			X		X		X
HIV Genotype								X	

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the subject starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 45 days prior to study entry, unless otherwise specified. The site may use documentation of HIV infection and the HIV resistance genotype obtained pre-treatment.

In addition to data being collected on subjects who enroll into the study, **reason(s) for** screening failures will be captured **on the Eligibility Checklist and faxed to the Data Management Center (will not be entered directly in REDCap).**

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluation and be completed prior to the initiation of study medications.

6.2.3 Post-Entry Evaluations

On-Treatment Evaluations
Evaluations should occur +/- 14 days of the scheduled visit.

Visit to Confirm Virologic Failure
Subjects with a suspected virologic failure should have a sample for confirmatory viral load obtained within 35 days after receipt of the results of the initial sample **and other Confirmation of Virologic Failure visit evaluations**. If the initial sample was collected during a treatment interruption, sites are encouraged to address toxicity or adherence issues before taking the confirmatory sample

NOTE: Virologic failure **is** defined as **confirmed** plasma HIV-1 RNA > 50 copies/mL at any time after study entry up to Week 48

If the Confirmation of Virologic Failure visit coincides with a regularly scheduled visit, the evaluations should be combined.

If virologic failure is confirmed, sites must inform the protocol team by sending an email to **aspire-team@googlegroups.com** . Management of subsequent ART will be left to the discretion of the site investigator. If stopping study treatment, the subject will complete the Premature Treatment Discontinuation evaluations per section 6.2.4 and continue to be followed on study/off study treatment. .

6.2.4 Discontinuation Evaluations

Evaluations for Registered Subjects Who Do Not Start Study Treatment

Subjects who do not begin study treatment should have screening and entry forms completed and entered in the database. Beyond the entry visit, no further evaluations are required. These subjects will be replaced.

Premature Treatment Discontinuation Evaluations
Subjects who discontinue the study medications before the end of the study (Week 48) should have the Premature Treatment Discontinuation evaluations done within 14 days after stopping study drugs. They will be encouraged to continue to attend all study visits and receive study evaluations as per section 6.1 through Week 48.

Premature Study Discontinuation Evaluations
All subjects who prematurely discontinue participation in the study should have the Premature Study Discontinuation evaluations done.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol must be present in the source documents.

All stated evaluations are to be recorded on the CRF and keyed into the REDCap database unless otherwise specified.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the CRF.

6.3.2 Medical History

The medical history must include all diagnoses identified by the ACTG criteria for clinical events and other diagnoses. In addition to reporting all diagnoses within the past 30 days prior to study entry, the following diagnoses should be reported regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis

Any allergies to any medications and their formulations must also be documented.

6.3.3 Medication History

A medication history must be present in the history and recorded in the source documents:

Medication History Table

Medication Category	Complete History or Timeframe	Record in CRFs
Antiretroviral therapy	Complete **(start date of initial ART regimen, estimated time on each drug)**	Yes
Immune-based therapy	Within 30 days prior to entry	Yes
Prescription drugs for treatment or prophylaxis of opportunistic infections (OIs)	**Within 30 days prior to entry**	Yes
Other prescription drugs	Within 30 days prior to entry	Yes
Non-prescription drugs	Within 30 days prior to entry	No
Complementary and alternative medicines	Within 30 days prior to entry	No

6.3.4. Nadir CD4+

The subject's prior nadir CD4+ cell count (absolute value and date) should be documented with a copy of the nadir CD4+ cell count report or clinician's documentation of the CD4 nadir in the subject's medical record**. If documentation is not available, patient's recall of CD4 nadir can be recorded.**

6.3.5 Clinical Assessments

Complete Physical Exam
A complete physical examination performed at **any time between screening and** the entry evaluation is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; and examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, height, weight, and vital signs (temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Exam
A targeted physical examination is to be performed at screening and after the entry visit and will be driven by any previously identified or new signs or symptoms including diagnoses that the subject has experienced since the last visit. This examination includes weight and vital signs (temperature, pulse, respiration rate, and blood pressure).

Signs and Symptoms
At entry, record on the CRFs all signs/symptoms occurring within 30 days prior to entry.

After entry, **record** all Grade ≥3 signs/symptoms, any signs/symptoms regardless of grade that lead to a change in treatment, or that meet EAE, SAE, or ICH guidelines.

Diagnoses
At screening, record diagnoses in the medical history per section 6.3.2. At study entry and thereafter, record all new diagnoses since the last study visit identified by the ACTG criteria for clinical events and other diseases.

Concomitant Medications
Record any immune-based therapies and other prescription medications taken since the last study visit, including actual or estimated start dates and stop dates in the CRF. Current non-prescription, alternative and traditional medications are recorded in the source documents only.

Study Treatment
Record all study treatment (DTG + lamivudine or continued ART) modifications, including initial doses, subject-initiated and/or protocol-mandated modifications, and inadvertent and deliberate interruptions of more than 7 days total or 3 or more consecutive days since last visit. Record any permanent discontinuation of treatment.

6.3.6 Laboratory Evaluations

Sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version **2.0, November 2014**, which can be found **at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.**

Record all protocol-required laboratory values, regardless of grade, obtained at screening and entry on the CRFs.

After entry, record all laboratory values Grade ≥3. All laboratory values that lead to a change in study treatment, and all renal (serum creatinine and blood urea nitrogen) and liver function tests (AST, ALT, alkaline phosphatase, total and direct bilirubin) regardless of grade, must be recorded. Also record all lipid values regardless of grade on the CRF.

Hematology
Hemoglobin, hematocrit, white blood cell count (WBC), with differential, absolute neutrophil count (ANC), and platelet count.

Liver Function Tests
AST (SGOT), ALT (SGPT), alkaline phosphatase, total and direct bilirubin

Blood Chemistries
Electrolytes (Na+, K+, Cl-, HCO_3/CO_2), glucose, creatinine, phosphate, and blood urea nitrogen,

Fasting Lipids
Total, HDL, and LDL cholesterol, triglycerides.

Subjects should be instructed to fast for 8 hours prior to this test. Fasting is defined as no food or drink, except for sips of water with medications. If the subject has not been fasting, the visit does not need to be rescheduled. Record the non-fasting status on the CRF.

Hepatitis B Surface Antigen
Documentation of **negative** hepatitis B surface **antigen** within **45** days prior to study entry

Hepatitis C Antibody
Documentation of hepatitis C antibody status
NOTE: HCV antibody testing is not needed if there is documented positive HCV antibody status ANY TIME prior to study entry OR a negative HCV antibody test within 90 days prior to study entry

Urinalysis
Dipstick or microscopic exam may be done; if dipstick results are abnormal, microscopic exam is required.

Pregnancy Test
All women with reproductive potential must have a negative serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test result at screening and within 48 hours prior to initiating protocol-specified medications and any time thereafter when pregnancy is suspected. (The urine test must have a sensitivity ≤50 mIU/mL).

6.3.7 Immunologic Studies

CD4+/CD8+

Evaluations for CD4+/CD8+ cell counts and percentages should be performed at the same laboratory, if possible, for all on-study evaluations. The laboratory must have CLIA certification, or its equivalent.

Because of the diurnal variation in CD4+/CD8+ cell counts, determinations for individual subjects should be obtained consistently in either the morning or the afternoon throughout the study, if possible.

6.3.8 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 45 days prior to study entry. All on-study HIV-1 RNA assays including the screening measurement must be done using the COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, v2.0, lower quantification limit of 20 copies/mL (Roche Molecular Systems, Inc.) at a CLIA certified local laboratory as specified in the Laboratory Processing Chart.

Subjects with suspected virologic failure should have a sample for confirmatory viral load obtained within 35 days after receipt of the results of the initial sample.

Genotype

Pre-treatment - Pre-treatment RT/protease genotype must be documented prior to study entry. [Note: pre-treatment integrase genotype is not required]

Virologic failure - When a subject is suspected to have virologic failure, a confirmatory plasma HIV-1 RNA **and a plasma sample for genotyping will be collected.** If failure is confirmed, plasma from the Virologic Failure Confirmation Visit should be sent **to Northwestern** for real-time genotyping at Quest Diagnostics. RT/protease + integrase if in Arm 1; RT/protease only if in Arm 2. See details in the Laboratory Processing Chart (LPC).

Stored Plasma for Virology: Single Copy HIV-1 Assay:
Plasma samples will be stored to measure HIV-1 by single copy assay at Entry, Week 24, Week 48, and at time of study premature discontinuation. HIV-1 single copy assay will be performed at premature discontinuation only if HIV RNA is < 20 copies/mL

Samples should be stored at each site and batch shipped to the laboratory of Dr. Jonathan Li at two time-points: 1) after all subjects at the site complete Week 24 and; 2) after all subjects at the site complete Week 48. **See details in the LPC**.

PBMCs (Substudy in patients enrolled at Northwestern University)
PBMCs will be processed and stored for possible evaluation of HIV reservoir dynamics e.g by measuring changes in total and integrated DNA in PBMC

6.3.9 Adherence Assessment

Adherence to all study medications will be assessed by self-report. Sites will provide adherence reinforcement, according to local standard practice throughout the study. Subjects with poor adherence will be provided counseling by the site.

Time of last dose of study medications and time of plasma collection will be recorded at the study visits where adherence assessments are completed.

6. 3.10 Storage of Plasma and Serum for potential future studies

Plasma and serum samples will be stored for possible evaluation of changes in soluble and cellular markers of inflammation, immune activation, bone turnover and renal tubular toxicity, and for possible targeted pharmacokinetic studies. The specific biomarkers are to be determined. Date and time of samples collected and last dose of study drugs will be recorded. The samples will be shipped and stored at the study repository at Northwestern University**.**

7.0 CLINICAL MANAGEMENT ISSUES

7.1 Toxicity Management

Criteria for subject management, dose interruptions, modifications, and discontinuation of study treatment will be mandated only for toxicities attributable to study-provided drugs (i.e., DTG and lamivudine in Arm 1). If any individual study-provided drug must be interrupted or discontinued due to toxicity, then the entire regimen must be interrupted or discontinued. Toxicities that occur in subjects randomized to continuation of their ART regimen (Arm 2) will be managed according to standard practice by the site investigator. If the site investigator intends to substitute one or more drugs in Arm 2 for toxicity management, the ASPIRE study team must be consulted for approval at **aspire-team@googlegroups.com** ,

The grading system for drug toxicities is the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version **2.0, November 2014, located at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.** NOTE: The ASPIRE protocol team must be notified by e-mail regarding toxicities that result in regimen interruption or discontinuation. Email: **aspire-teamgooglegroups.com.**

The general guidelines presented in sections 7.1.1 to 7.1.3 apply to toxicities that are not specifically discussed further below. Subjects randomized to continuation of their current regimen should be managed according to standard practice by the site investigator.

7.1.1 Grade 1 or 2 Toxicity

Subjects who develop a Grade 1 or 2 adverse events (AE) or toxicity may continue DTG and lamivudine without alteration of the dosage. If a subject chooses to discontinue study treatment, the site should complete the Premature Treatment Discontinuation evaluations, notify the ASPIRE protocol team, and encourage the subject to attend all remaining study visits.

7.1.2 Grade 3 Toxicity

Asymptomatic Grade 3 abnormalities must be evaluated and managed by the site investigator. It may be necessary to hold all study drugs. Consultation with the ASPIRE protocol team is encouraged. The ASPIRE protocol team must be notified by e-mail regarding toxicities that result in a change in regimen. Asymptomatic elevations of triglycerides or cholesterol do not require treatment discontinuation. If the site investigator has compelling evidence that the AE was NOT caused by a study drug, dosing may continue. If study drugs are held, the subject should be re-evaluated closely until the AE returns to Grade $\leq$2, at which time study treatment may be reintroduced at the discretion of the site investigator or according to standard practice.

If the site investigator determines that a Grade 3 AE or toxicity is an isolated event, the site has the option of confirming the toxicity before holding study treatment.

If the same Grade 3 AE recurs within 4 weeks or reintroducing study drugs, the implicated study regimen must be permanently discontinued. If the same Grade 3 AE recurs after 4 weeks, but is not thought to be related to DTG or lamivudine, the management scheme outlined above may be repeated.

Subjects who develop symptomatic Grade 3 AE or toxicity thought to be related to study treatment should have both DTG and lamivudine discontinued. If the site investigator has compelling evidence that the AE has NOT been caused by DTG or lamivudine, dosing may resume when the AE has resolved to Grade ≤2. The ASPIRE protocol team must be consulted.

Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed closely until resolution of the AE. The ASPIRE protocol team must be notified and the subject should be encouraged to attend all remaining study visits and continue other study evaluations according to the protocol.

7.1.3 Grade 4 Toxicity

Subjects who develop a Grade 4 AE or toxicity thought to be related to study treatment will have both DTG and lamivudine discontinued. If the site investigator has compelling evidence that the AE has NOT been caused by DTG or lamivudine, dosing may resume when the AE has resolved to Grade ≤2. The ASPIRE protocol team must be consulted.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study treatment should be followed closely until resolution of the AE to Grade ≤2, and the protocol team must be consulted. The subject should be encouraged to attend all remaining study visits and continue other study evaluations according to the protocol.

7.1.4 Discontinuation of DTG

Discontinuation of DTG for suspected drug induced liver injury (DILI), other clinically significant liver chemistry elevations, severe skin reaction or hypersensitivity reaction, subjects should not restart DTG due to the risk of a recurrent reaction; such subjects should be withdrawn from the study treatment and be reviewed for alternative antiretroviral therapy. The subject should be encouraged to attend all remaining study visits and continue other study evaluations according to the protocol.

7.2 Rash

Mild to moderate rash may occur with DTG-containing ART, generally occurring within the first ten weeks of therapy, and only rarely requiring discontinuation of therapy. The rash tends to resolve within two to three weeks. The index case of DTG hypersensitivity, which is the only case reported to date, 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 (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme, have been reported for DTG in clinical trials. The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings). If the etiology of the rash can be definitely diagnosed as being unrelated to study drugs and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

7.2.1 Grade 1

Subjects with an isolated Grade 1 rash may continue DTG at the Investigator's discretion. The subject 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.

7.2.2 Grade 2 .
Subjects may continue study drugs for an isolated Grade 2 rash. However, study drugs (and all other concurrent medication(s) suspected in the investigator's causality assessment) should be discontinued for any Grade 2 rash that is associated with an increase in ALT. The subject 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.

7.2.3 Grade 3 or 4
Subjects should permanently discontinue study drugs (and all other concurrent medication(s) suspected in the investigator's causality assessment) for an isolated Grade 3 or 4 rash. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

7.3 Nausea/Vomiting

Nausea/vomiting of any grade may be treated symptomatically with oral antiemetics or antiemetic suppositories. For Grade ≥3 nausea or vomiting thought to be secondary to study drugs that fails to improve on antiemetics to Grade ≤2, all study drugs must be held until Grade ≤2. If Grade ≥3 nausea or vomiting recurs with reinstitution of study drugs or persists beyond 14 days despite symptomatic management, then study treatment must be discontinued and the protocol team consulted.

7.4 AST/ALT Elevations

7.4.1 Grade 1 or 2

Study treatment may be continued for asymptomatic, isolated Grade 1 or 2 AST/ALT elevations, at the discretion of the site investigator.

Careful assessments should be done to rule out the use of alcohol, non-study drug-related drug toxicity or viral hepatitis as the cause of liver chemistry elevation. Evaluations to be considered (but are not required) include: Viral hepatitis serology including: Hepatitis A IgM antibody; Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; 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; Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies; Liver imaging (ultrasound, magnetic resonance, or computerized tomography)

7.4.2. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology. Study drugs will be stopped if any of the following

liver chemistry criteria are met:

- ALT ≥3 x ULN and bilirubin ≥2 x ULN (>35% direct bilirubin; bilirubin fractionation required)
  - NOTE: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver stopping criteria;
- ALT ≥8 x ULN;
- ALT ≥3 x ULN (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 ≥3 x baseline ALT with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5 x ULN and <8 x ULN that persists > 2 weeks (with bilirubin <2 x ULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5 x ULN but <8 x ULN and cannot be monitored weekly for >2 weeks;

Subjects who develop ALT ≥5 x ULN should be followed weekly until resolution or stabilization (ALT <5 x ULN on 2 consecutive evaluations).

When liver chemistry stopping criterion is met, do the following:

- Immediately discontinue DTG. Subjects should not restart DTG due to the risk of a recurrent reaction.
- Report the event to the study team within 24 hours of learning its occurrence
- Complete the GSK Liver Event CRF and SAE CRF where applicable
- Complete the GSK Liver Imaging and/or Liver Biopsy CRFs if these tests are performed;
- Perform liver event follow up assessments, and monitor the subject twice weekly until liver chemistries resolve, stabilize, or return to baseline values;
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments, and close monitoring;
- A specialist or hepatology consultation is recommended;
- Subjects should continue to be followed off study treatment for the duration of the study. The subject should be encouraged to attend all remaining study visits and continue other study evaluations according to the protocol

Consider the following to further evaluate the liver event:

- Tests listed in section 7.4.1 above
- 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, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the GSK Liver Event Alcohol Intake CRF.

7.5 Creatinine

DTG initiation is typically associated with an increase in serum creatinine levels of approximately 0.11-0.14 mg/dL, which is attributable to DTG's inhibition of tubular secretion of

creatinine. As this change is not associated with an actual decline in glomerular filtration rate as measured by iohexol clearance, no treatment change is indicated. Subjects should be counseled about this expected increase before initiating study medications. Lamivudine requires dose adjustment for calculated creatinine clearance (CrCl) <50 mL/min

Subjects who have an increase in creatinine of one grade should be carefully evaluated for causes of change in renal function but may continue on study treatment.

The protocol team must be consulted if a subject has an increase in creatinine of 2 grades or more. If the increase in creatinine is considered to be due to causes other than study treatment, study treatment may be continued after approval by the team.

If lamivudine is continued despite confirmed calculated CrCl <50 mL/min, dosing will be adjusted per the package insert. The protocol team must be consulted if a subject requires dialysis while on study. The subject must permanently discontinue study treatment and will be encouraged to remain on study/off study treatment. Further evaluation and management should proceed at the discretion of the site investigator.

7.6 Allergic Reaction

Subjects may continue study medication for Grade 1 or 2 allergic reactions at the discretion of the site investigator. The subject 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 at the discretion of the site investigator.

Subjects with ≥Grade 3 allergic reactions that are considered to be possibly or probably related to the study medications should permanently discontinue study medications and continue to be followed off-study medications, on-study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

7.7 Suicidal Ideation or Behaviors

If any subject experiences a possible suicidality-related adverse event while participating in this study that is considered by the Investigator to meet International Conference on Harmonization (ICH)-E2A definitions for seriousness, the Investigator will collect information using a GSK Possible Suicidality Related Adverse Event (PSRAE) CRF form in addition to reporting the event on an Event CRF form. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported within one week of the investigator diagnosing a possible suicidality-related adverse event.

7.8. Pregnancy

If a subject becomes pregnant after study entry, the IND Sponsor (Dr. Babafemi Taiwo) should be notified as soon as the site investigator becomes aware of this development using the GSK Pregnancy Notification Form. The IND Sponsor will forward the completed GSK Pregnancy Notification Form to ViiV within 7 days of receipt. Study medications must be discontinued and arrangements made for alternative ART, which should be prescribed at the discretion of the

site investigator. The pregnant subject should come in for a premature discontinuation of study treatment visit within 14 days after stopping study medications. Pregnant subjects who choose to stay on study will continue to be followed on study/off study treatment, but do not require blood draws for stored samples. They also will not have to complete the adherence questionnaire.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the IND Sponsor using the GSK Pregnancy Follow-up Form. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or EAE. Spontaneous abortions must be reported as an EAE. Any EAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the IND Sponsor.

If a woman has completed the study or chooses to discontinue from the study before the end of the pregnancy, site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on a CRF at the end of the pregnancy.

Pregnancies that occur on study should be reported to The Antiretroviral Pregnancy Registry as well. Intrapartum complications and/or pregnancy outcome should be recorded on the CRFs up to week 48 and also reported to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-1052.

8.0 CRITERIA FOR DISCONTINUATION

8.1 Permanent Study Treatment Discontinuation

- Drug-related toxicity requiring permanent study treatment discontinuation (see section 7.0)
- Requirement for prohibited concomitant medications (see section 5.4)
- Requirement to start hepatitis C treatment
- Pregnancy
- Breast-feeding
- Completion of treatment as defined in the protocol
- Request by subject to terminate treatment
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol
- Failure by the subject to attend 2 consecutive clinic visits

8.2 Premature Study Discontinuation

- Request by the subject to withdraw
- Request of the primary care provider or investigator if s/he thinks the study is no longer in the best interest of the subject
- Subject judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results
- At the discretion of the IRB, FDA, IND sponsor, or pharmaceutical supporters

9.0 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

ASPIRE is a prospective, open-label, randomized, multicenter, 48-week study to explore whether HIV-infected subjects **with** no history of virologic failure, and HIV RNA <50 copies/mL for at least 48 weeks on any DHHS recommended, alternative, **or other** three-drug regimen will maintain viral suppression after switching to DTG + lamivudine. Subjects must have plasma HIV-1 RNA levels less than 20 copies/mL within 45 days of study entry and a pretreatment genotype documenting absence of any **NRTI** mutation. **.**

9.2 Endpoints

9.2.1 Primary Endpoint:

Virologic failure defined as confirmed viral load >50 copies/mL before or at Week 24

.

9.2.2 Secondary Endpoints

9.2.2.1 Change in CD4 count from baseline to Weeks 24 and 48.

9.2.2.2 Confirmed viral rebound to >20 copies/mL, >50 copies/mL and >200 copies/mL at any time up to or including Week 48

9.2.2.3 Drug resistance associated mutations in subjects with virologic failure

9.2.2.4 Laboratory Toxicities or clinical adverse events of Grade 3 or higher, or of any grade which led to a permanent change or discontinuation of study treatment regimen.

9.2.2.5. Change in residual viremia as measured by single copy assay

9.2.2.6 Adherence measured by self-report of missed doses

9.2.2.7 Potential exploratory studies if primary hypothesis is proven:
-Change in markers of inflammation/activation.
-Change in reservoir size
-Change in markers of bone turnover and renal tubular toxicity

9.3 Randomization and Stratification –

Subjects will be randomized 1:1 to DTG plus lamivudine (Arm 1) or continuation of their current regimen (Arm 2) for 48 weeks.

9.4 Sample size and Accrual

With a sample size of 41 subjects/arm, the study will have 80% power to show non-inferiority of DTG + lamivudine compared to DHHS regimen using a 12% non-inferiority margin. The following assumptions are used in the sample size calculation:

I. Non-inferiority will be assessed with a one-sided 5% type I error rate.

II. The cumulative probability of virologic failure by Week 24 is estimated to be 5% for both arms.

Assuming a lost to follow-up rate of 10% for each arm, the target sample size is 45 subjects/arm or 90 in total.

It is anticipated that the study will meet its accrual target in 3 to 6 months.

9.5 Monitoring

An independent Data Monitoring Committee will evaluate virologic and safety data after the first 45 patients reach week 12.

9.6 Analyses

9.6.1 Primary Anaysis

Among suppressed HIV patients **with** no history of virologic failure, and HIV RNA <50 copies/mL for at least 48 weeks on any DHHS recommended, alternative, **or other** three-drug regimen, we will compare virologic failure rate, defined as confirmed HIV RNA >50 copies/mL by week 24 between those who continue their DHHS regimen versus those who switch to DTG + lamivudine

For primary analysis, we will use the FDA snapshot approach in which a subject is considered a failure if any of the following occurs during the analysis period: virologic failure (i.e., confirmed viral load > 50 copies/mL); loss to follow up; or discontinuation/modification of randomized treatment. A secondary analysis will also be conducted, wherein a subject is considered censored at the time of loss to follow-up or discontinuation/modification of study treatment.

9.6.2 Secondary Analyses

For secondary analyses, we will compare between Arm 1 and Arm 2:

9.5.2.1 Change in CD4 count from baseline to weeks 24 and 48

9.5.2.2 Proportion of subjects with HIV RNA >20, >50, and >200 copies/mL at weeks 24 and 48. The proportion of subjects with these levels of viremia will be plotted by time over the course of the study

9.5.2.3 HIV resistance among those with confirmed viral rebound to > 50 copies/mL

9.5.2.4 Incidence of clinical and/or laboratory toxicities.
The safety and tolerability measures will include:
- Time to discontinuation of any study medication due to adverse events (AEs), -- Proportion of Grade 3 or Grade 4 clinical AEs,
- Proportion of Grade 3 or Grade 4 laboratory abnormalities,
- Summaries of all treatment-related AEs.

9.5.2.5 Subject-specific changes in HIV-1 viremia using single-copy assay from baseline to weeks 24 and 48. Correlations between viremia detected by the single copy assay and protocol defined virologic failure as well as viral rebound to >20 copies/mL,

20-50 copies/mL and > 200 copies/mL will be determined

9.5.2.6 Descriptive statistics of the number of missed doses (over the past 4 days) at weeks 4, 12, 24, 36, 48

9.5.2.7 (Possible future analyses)

a. Other measures of the HIV reservoir size
b. Soluble and cellular markers of immune activation and inflammation
c. Markers of bone turnover and renal tubular toxicity

10.0 PHARMACOLOGY PLAN

Not applicable.

11.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1 Records to Be Kept

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by the **Patient Number** and **Screening Number** provided upon registration.

11.2 Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the central data management team at Northwestern University. The Research Electronic Data Capture (REDCap) data management system will be used.

11.2.2 It is the responsibility of the central data management team to assure the quality of computerized data for the study. This role extends from protocol development to generation of the final study databases. The REDCap data management system will be used for data entry, data queries, and data reports.

11.3 Clinical Site Monitoring and Record Availability

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

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

11.4 Expedited Adverse Event Reporting

The adverse events (AEs) that must be reported in an expedited fashion to the IND Sponsor (Dr. Babafemi Taiwo at Northwestern University) are all serious adverse events (SAEs) as defined by International Conference on Harmonization (ICH) guidelines regardless of relationship to the study agent(s).

SAEs as defined by ICH guidelines are: deaths, life-threatening events, events that require hospitalization or prolongation of hospitalization, events that result in persistent or significant disability or incapacity, and congenital anomalies or birth defects. Important medical events as assessed by medical and scientific judgment may also be considered SAEs by the investigator and should be reported in an expedited fashion. Possible drug-induced liver injury is also considered an SAE in this study and requires expedited reporting.
The study agents that must be considered in determining relationships of AEs requiring expedited reporting to the IND Sponsor are DTG and lamivudine.

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version **2.0, November 2014,** must be used and is available **at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx**.

Any SAE occurring during the study up to 28 days post the last dose of study drug must be documented on the GSK Serious Adverse Events Form with Toxicity Grading and faxed to the IND Sponsor, Dr. Babafemi Taiwo, at 1-312-695-5088 within 24 hours of awareness. The IND Sponsor and the ASPIRE Research Manager should be alerted about the faxed form by sending an email to b-taiwo@northwestern.edu and baiba@northwestern.edu with the title: ASPIRE SAE REPORT. The IND Sponsor will forward the completed SAE Form to ViiV immediately upon receipt.

The FDA also requires sponsors to submit a written Safety Report of all serious and unexpected AEs to all participating investigators of a trial. All participating investigators, at all sites, will be notified of any unexpected SAEs occurring at other sites, in an IND Safety Report from the IND Sponsor. The IND Sponsor will also notify investigators of any revisions to the protocol or to the consent, or study closure. The study investigators in this study have the responsibility of promptly reporting all SAEs so that IND Sponsor can comply with these regulations.

The protocol-defined expedited event reporting period for this protocol is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

After the end of the protocol-defined reporting period stated above, sites must report serious, unexpected, suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

12.0 HUMAN SUBJECTS

12.1 Institutional Review Board (IRB) Review and Informed Consent

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

(or legal guardian or person with power of attorney for subjects who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject or legal guardian, and this fact will be documented in the subject's record.

12.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All records will be kept locked. All REDCap entry will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the FDA, or the IND sponsor.

12.3 Study Discontinuation

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

13.0 PUBLICATION OF RESEARCH FINDINGS

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

14.0 BIOHAZARD CONTAINMENT

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

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 I: SAMPLE INFORMED CONSENT: Version 2.0, dated 6/15/2015

Protocol Title:
Dolutegravir **A**ntiretroviral **S**trategy to **P**romote **I**mprovement and **R**educe drug **E**xposure (ASPIRE) Study

Principal Investigator and IND Sponsor:
Babafemi Taiwo, M.B.B.S.
Northwestern University

Financial Support provided by: ViiV Healthcare

INTRODUCTION

You are being asked to take part in this research study because you have human immunodeficiency virus (HIV), the virus that causes AIDS, and are on HIV treatment that is keeping the virus well controlled. Dr. Babafemi Taiwo at Northwestern University is the study sponsor with financial support provided by ViiV. The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

Recommended treatment regimens for a person with HIV infection contain three active HIV drugs. Most people who take these medications regularly have a good result, which is usually determined by measuring the amount of HIV in the blood (viral load). The desired response is when the level of HIV is reduced to very low levels in the blood. Treatment of HIV is life-long. Since some HIV medications have side effects and are costly, there is interest in whether HIV can be successfully controlled with fewer than three HIV drugs.

The main purpose of this study is to evaluate how well a combination of two study drugs (DTG plus 3TC) will keep HIV suppressed in the blood of patients who are currently taking three HIV drugs and have a very low viral load. The study will also look at the safety and tolerability of this study drug combination, and how well patients are able to take the study drugs on schedule. In addition to a standard test used to measure blood HIV levels in the clinic, the study will use a very sensitive research test that can detect as little as one HIV virus in each milliliter of blood. This test is called the single copy assay and is currently used for research only. This very sensitive test will help to better see the effect that changing from three active HIV drugs to the two study drugs has on very low levels of HIV in the blood.

The drugs used in this study are dolutegravir (DTG, Tivicay) and lamivudine (3TC, Epivir). DTG is an integrase inhibitor (a type of HIV drug) and is approved by the Food and Drug Administration (FDA) for HIV treatment. 3TC is a nucleoside reverse transcriptase inhibitor (another type of anti-HIV drug) that is also approved by the FDA for HIV treatment. Both DTG and 3TC are

currently part of recommended regimens for treatment of HIV along with a third active drug. However, the two-drug combination has not been tested before, and this is the purpose of this study.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you agree to join this study, you will be asked to sign this consent form. After you have signed the form, you will be asked some questions and will undergo some tests at a screening visit to see if it is safe for you to join the study. The screening visit will take about 30-60 minutes.

Screening

You will have a clinical assessment that will include questions about your health and any medicines you have taken in the last 30 days. About 30 mL (2 tablespoons) of blood will be drawn for the following tests:

- Routine blood count and chemistry tests, HIV viral load, and hepatitis B test (a virus that can affect your liver).
- 10 mL of blood (about 2 teaspoons) will be stored indefinitely for future tests.
- You will be asked to give a urine specimen.

Entry

Only patients who have HIV below a certain level at the screening visit will be able to participate in this study. If you have met all the requirements to enter the study, you will come to the clinic at least 24 hours after your screening evaluation, but within 45 days of your screening visit, for entry evaluations. This visit will last about 30-60 minutes.

- You will be asked about any medicine changes you have had since screening.
- You will have a physical exam. The clinic staff will check your height and weight, and vital signs such as temperature, blood pressure, and pulse.
- You will have about 30 mL (2 tablespoons) of blood drawn for routine blood tests, HIV viral load, **hepatitis C test**, and CD4 and CD8 cell count (marker of how strong your immune system is). Lipid tests (blood fats and cholesterol) will be done, so you must not have anything to eat or drink, except water and required prescription medications, for at least 8 hours before coming to the clinic.
- About **30 mL (2 tablespoons**) of blood will be drawn for the HIV single copy assay
- About 20 ml (4 teaspoons) will be drawn and stored indefinitely for possible future studies to evaluate how changing to the two study drugs affects the immune system, bone, and kidneys.

- You will be randomly assigned (like the toss of a coin) to one of two study groups:
    - Arm 1: Switch your current HIV treatment to the study drugs:
      DTG plus 3TC.
    - Arm 2: Continue taking your current HIV regimen.

You and your study team will know which treatment arm you are on. There are no placebos (dummy pills). The study drugs DTG and 3TC will be given to you at this visit only if you are assigned to Arm 1; if you are on Arm 2, you will need to continue to provide your own medications. You will remain on the assigned study treatment and be followed to the Week 48 visit.

You will take dolutegravir and 3TC at the same time once a day by mouth. You can take the drugs with or without food. If you are taking some antacids, laxatives, or iron or calcium supplements you will need to take the DTG 2 hours before or 6 hours after these medications. Alternatively, you may take iron or calcium supplements at the same time as DTG if taken with food. It is essential that you disclose all the medications (prescribed or over-the-counter) and supplements that you are taking to your site investigator and discuss the best way to take DTG.

After Entry

After you start taking the study drugs, you will be asked to come to the clinic approximately 4, 12, 24, 36, and 48 later. Most visits will last about 30 to 60 minutes.

At most visits, you will:

- Be asked about how you are feeling; if needed, a brief physical exam will be done.
- You will also be asked about how you are taking the study drugs and about changes to any other medicines that you may be taking.
- About 30 mL (2 tablespoons) of blood will be collected for routine blood tests, HIV viral load, and CD4 and CD8 cell count.
- In addition, about 20 mL (4 teaspoons) of blood will be stored indefinitely for future virology and immunology tests.
- At Weeks 24, and 48, you will have an additional **30 mL (about 2 tablespoons**) of blood drawn for single copy assay, and for lipid tests, so you must not have anything to eat or drink, except water and required prescription medications, for at least 8 hours before coming to the clinic at those visits.

If at any point during the study your viral load increases above 50 copies/mL, you will be asked to come back in for some additional tests within 35 days. You will also have another viral load test to make sure the first one was correct. This visit will last about 30-60 minutes.

- You will be asked about any medicine changes you have had since your last visit.
- You will have a brief physical exam.
- You will have about 30 mL (2 tablespoons) of blood drawn for HIV viral load, and resistance testing.
- Blood 40 mL (about 3 tablespoons) will be drawn and stored indefinitely for possible future virology, immunology, and study drug level tests.
- You will be asked about how well you are remembering to take your study drugs. You may be asked to undergo counseling to improve how well you take your medications

If the repeat blood test is again greater than 50 copies/mL, this will be taken to indicate failure of treatment. You may be asked to stop taking the study medications at this point. You doctor will be responsible for deciding the best course of treatment for you based on the results of resistance tests (how well the virus responds to certain drugs) and other factors.

Early study drug or study discontinuation

If you stop taking the study drugs before the end of the study, you will be asked to continue to be part of the study and attend study visits and complete evaluations for the duration of the study.

If you are taken off study early or decide to leave the study early, you will be asked to return to the clinic for a final visit. This visit will last about 30-60 minutes. You will have a brief physical exam, and

have blood drawn (total of about 60 mL, 4 tablespoons) for routine tests, HIV viral load, CD4 and CD8 cell count, and future tests.

Other

You will be told the results of HIV viral load tests, CD4 and CD8 cell counts, pregnancy tests, and routine blood tests done on this study.

Some of your blood will be stored (with usual steps taken to protect your confidentiality) at the study repository at Northwestern University and used for possible future testing to evaluate how changing to the two study drugs affects the immune system, bone, and kidneys. The stored sample may also be used for other tests to help understand what we find in the study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 90 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be on the study for 48 weeks.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- The study is cancelled by Northwestern University, FDA, the drug company supporting this study (ViiV), or the site's Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research participants.)
- A safety monitoring committee recommends that the study be stopped early.

The study doctor may also need to take you off the study drug(s) without your permission if:
- Continuing the study drugs may be harmful to you.
- You need a treatment that you may not take while on the study.
- You become pregnant or are breast-feeding.
- You are not able to attend the study visits as required by the study

If I have to permanently stop taking study-provided drug, or once I leave the study, how would the drug be provided?

During the study:
If you must permanently stop taking study-provided drug before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:
After you have completed your study participation, the study will not be able to continue to provide you with drug you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking (including nutritional supplements and herbal medications) before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks Associated with the Study Drugs

Dolutegravir (Tivicay®)
The following serious side effects have been associated with the use of dolutegravir :

Allergic reactions. Call your healthcare provider right away if you develop a rash with dolutegravir. Stop taking dolutegravir and get medical help right away if you:

- Develop a rash with any of the following signs or symptoms**:**
  - Fever
  - Generally ill feeling
  - Extreme tiredness
  - Muscle or joint aches
  - Blisters or sores in mouth
  - Blisters or peeling of the skin
  - Redness or swelling of the eyes
  - Swelling of the mouth, face, lips, or tongue
  - Problems breathing
- Develop any of the following signs or symptoms of liver problems:
  - Yellowing of the skin or whites of the eyes
  - Dark or tea-colored urine
  - Pale-colored stools -- bowel movements
  - Nausea or vomiting
  - Loss of appetite
  - Pain, aching, or tenderness on the right side below the ribs
  - If your healthcare provider informs you of changes in liver tests. People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with dolutegravir. Your healthcare provider may do tests to check your liver function before and during treatment with dolutegravir.

The most common side effects of dolutegravir include:

- trouble sleeping
- headache

Lamivudine (3TC, Epivir®)

The following side effects have also been associated with use of lamivudine:

If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if lamivudine is stopped. Although most of these cases have resolved without treatment, some deaths have been reported.

- Headache
- Feeling tired
- Dizziness
- Numbness, tingling, and pain in the hands or feet
- Depression
- Trouble sleeping
- Rash
- Upset stomach, vomiting, nausea, loose or watery stools
- Pancreatitis (inflammation of the pancreas), which may cause death. If you develop pancreatitis, you may have one or more of the following: stomach pain, nausea, and vomiting.
- Abnormal pancreatic and liver function blood tests

These are not all the possible side effects of the study drugs. For more information, ask your healthcare provider or pharmacist.

Risks of Drawing Blood

Taking blood may cause discomfort, bleeding, and bruising where the blood is drawn. Occasionally, there is swelling in the area where the needle enters the body and there is a small risk of infection. There is also a risk of lightheadedness, fainting, and blood clots.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known whether the drug or drug combinations in this study harm unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or make someone else pregnant. Because of the risk involved, you and your partner must use at least one method of birth control. You must continue to use birth control until 2 weeks after the study ends. You must choose one of the birth control methods listed below:

- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- IUD
- Hormone-based contraception

Some HIV medications can make oral contraceptives less effective. You should discuss this possibility with the study staff as you may need a back-up method.

If you can become pregnant, you must have a pregnancy test before you enter this study and before you begin study medications (1 teaspoon of blood or a urine specimen will be collected). You will be told the results of the test. The test must show that you are not pregnant.

Breast-feeding

It is unknown whether the study drugs pass through the breast-milk and may cause harm to your infant. You must not breast-feed if you are in this study.

WHAT IF I BECOME PREGNANT DURING THIS STUDY?

If you become pregnant or think you may be pregnant at any time during the study, tell your study staff right away. You will be asked to come in for a clinical assessment and have blood drawn (1 tablespoon, 15 mL) for a pregnancy test, other routine tests, and an HIV viral load. The study staff will talk to you about your choices and refer you to a provider of prenatal care if you do not have one. You will be told to stop taking the study medications, and you will be asked to continue to be part of the study and attend study visits and complete evaluations for the duration of the study. You will not need to have blood draws for storage.

You and your physician will decide what anti-HIV drug combination would be best for you to continue. These medications will not be provided by the study. This study will not provide care related to your pregnancy, the delivery of your baby, or the care of your baby. You must arrange for your care and your baby's care outside of this study. This study will not provide your baby any anti-HIV drugs. Long-term follow-up is recommended for a baby whose mother takes anti-HIV drugs during pregnancy. The study staff will talk to you about your choices for long-term follow up. The pregnancy will be reported to federal monitoring agencies.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study, you have the choice of:
- treatment with prescription drugs available to you
- treatment with experimental drugs, if there is another study available to you and you qualify for that study
- no treatment

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?
We will do everything we can to protect your privacy. Any publication of this study will not use your name or identify you personally.

People who may review your records include the sponsor, Northwestern University, OHRP, U.S. FDA, (insert name of site) IRB, study staff, study monitors, drug company supporting this study (ViiV Healthcare), and their designees.

ClinicalTrials.gov
A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Website at any time.

WHAT ARE THE COSTS TO ME?

DTG and 3TC will be provided by the study. Clinic visits, evaluations and tests required by the study will be provided by the study. The study will not provide your HIV medications if you are randomly assigned to the group that will remain on their current HIV drugs.

Taking part in this study may lead to added costs to you and your insurance company. In some cases it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WHAT HAPPENS IF I AM INJURED?

If you become ill or get an injury or illness as a result of study procedures, you should seek medical treatment through your doctor or treatment center of choice. You should promptly tell the study doctor about any illness or injury.

The hospital [university, researchers] will not pay for medical care required because of a bad outcome resulting from your participation in this research study. There is no program for compensation through Northwestern University, or ViiV Healthcare. This does not keep you from seeking to be paid back for care required because of a bad outcome. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. You will be treated the same no matter what you decide.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

Consent for Future Use of Stored Samples
Any blood leftover after all required study testing is done may be stored (with no information that will identify you) and used for future ASPIRE team-approved research. These blood samples may be stored for an unknown period of time. Results of testing done on these samples may not be given to you because they will be done in the future.

Please initial below if you agree to have any of your leftover blood used for future ASPIRE-approved research. You may change your mind at any time and reasonable efforts will be made to destroy your samples, though this may not always be possible.

_____ (initial) I agree to have my blood and any of my leftover blood stored and used for future ASPIRE-approved research
_____ (initial) I do NOT agree to have any of my blood and any leftover blood stored and used for future ASPIRE-approved research

_____ _____
Witness' Name (print) Witness' Signature and Date
(As appropriate)

Additional Consent for Subjects Enrolled at Northwestern University ONLY
About 20 ml (4 teaspoons) of blood will be obtained and stored at the entry, Week 24 and Week 48 visits for possible evaluation of changes in the amount of HIV that remain hidden in specific blood cells called peripheral blood mononuclear cells (PBMCs). This will give us a clue about how changing to the two study drugs may affect the ability of HIV to hide in places called HIV reservoirs.

Please initial one of the following to indicate your choice:
_____ (initial) I agree to complete the extra visits.
_____ (initial) I do not agree to complete the extra visits.

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____ _____
Participant's Name (print) Participant's Signature and Date

_____ _____
Study Staff Conducting Study Staff's Signature and Date
Consent Discussion (print)